NF-κB, inflammation, immunity and cancer: coming of age

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Abstract | Fourteen years have passed since nuclear factor-κB (NF-κB) was first shown to serve as a molecular lynchpin that links persistent infections and chronic inflammation to increased cancer risk. The young field of inflammation and cancer has now come of age, and inflammation has been recognized by the broad cancer research community as a hallmark and cause of cancer. Here, we discuss how the initial discovery of a role for NF-κB in linking inflammation and cancer led to an improved understanding of tumour-elicited inflammation and its effects on anticancer immunity.

The idea that inflammation and cancer may be linked is not entirely new — in 1863, Rudolf Virchow proposed that chronic irritation and inflammation cause cancer[1,2]. In 1915, Virchow's student, Katsusaburō Yamagiwa, demonstrated experimentally that chronic inflammation can result in cancer[3]. However, the importance of inflammation in the onset of cancer and the mechanisms through which it exerts its pro-tumorigenic effects were not fully appreciated and understood until the 1990s, when many studies, using molecular biology techniques and genetically modified mice, revealed the importance of inflammatory cells, cytokines, chemokines and growth factors in cancer-related inflammation[1,2]. Subsequently, in 2004, two seminal studies demonstrated the critical role of nuclear factor-κB (NF-κB) in inflammation-driven colitis-associated cancer (CAC)[4] and hepatocellular carcinoma (HCC)[5]. These studies were supported by a body of circumstantial evidence showing that chronic inflammation due to persistent infections, such as hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV) and *Helicobacter pylori*, autoimmunity or exposure to noxious chemicals can increase cancer risk[2,6–8]. However, not all chronic inflammation leads to cancer; the site at which it occurs is also important. Whereas bowel or liver inflammation greatly increases cancer risk, joint or muscle inflammation rarely affects cancer development[8]. Nonetheless, persistent infections and chronic inflammation are estimated to be associated with at least 15–20% of cancer deaths worldwide[2,6–8], and obesity-associated inflammation may be responsible for another 15% of the death toll of cancer[9]. Inflammation can also be provoked after tumour initiation owing to the necrotic death of cancer cells subject to an insufficient blood supply or microbial invasion into the tumour bed caused by barrier deterioration[8]. Such 'tumour-elicited inflammation' appears to be a key driver of malignant progression in most solid malignancies[8]. Moreover, chemotherapy and radiotherapy, both of which induce necrotic cell death, can further enhance tumour-associated inflammation and thereby cause therapy resistance or induction of antitumour immunity[8]. Chronic inflammation can also augment tumour development and progression by triggering immunosuppression and compromising anticancer immunity[10]. Thus, inflammation is a relevant contributing factor in most solid and haematopoietic malignancies.

Correspondingly, the molecular mechanisms that connect inflammation to tumorigenesis have become a major branch of cancer research[11]. It has also become apparent that the tumorigenic function of inflammation is a grotesque manifestation of its essential role in tissue regeneration and repair[12]. In this Review, we focus on recent insights into the pro-tumorigenic functions of NF-κB and NF-κB-driven inflammation in cancer, which are closely related to all known hallmarks of cancer[11].

NF-κB signalling and its regulation

Discovered in 1986 by David Baltimore's group as a B cell-specific transcription factor[13,14], the NF-κB family consists of five different DNA-binding proteins that form a variety of homodimers and heterodimers[15,16]. The NF-κB proteins are key regulators of innate and adaptive immune responses that can accelerate cell proliferation, inhibit apoptosis, promote cell migration and invasion, and stimulate angiogenesis and metastasis[17] (FIG. 1). Activation of NF-κB is rapidly and transiently induced by viral and bacterial infections, necrotic cell products, DNA damage, oxidative stress and pro-inflammatory cytokines[17]. Notably, in many types of cancer, both in malignant cells and in the tumour microenvironment, NF-κB is constitutively active[17], and only rarely is such activation due to NF-κB-related genetic alterations[18,19].

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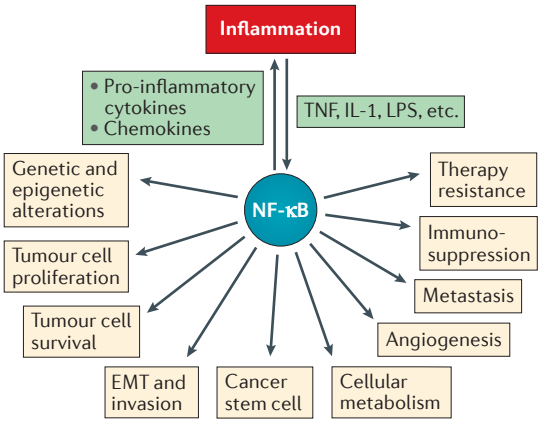

Figure 1 | **Roles of NF-κB in cancer.** Nuclear factor-κB (NF-κB) directly and indirectly controls inflammation, cancer cell proliferation and survival, epithelial-to-mesenchymal transition (EMT), invasive behaviour, angiogenesis and metastasis, as well as genetic and epigenetic alterations, cancer stem cell formation, cellular metabolism and therapy resistance. NF-κB activation also induces immunosuppression via several mechanisms. LPS, lipopolysaccharide; TNF, tumour necrosis factor.

The activation of NF-κB depends on the degradation of its specific inhibitors, the inhibitor of NF-κB (IκB) proteins, following their phosphorylation by the IκB kinase (IKK) complex[17]. Most of the increased NF-κB activity observed in solid malignancies is due to elevated production of IKK-activating cytokines, including tumour necrosis factor (TNF) and IL-1 (REFS 19,20).

Production of such cytokines by tissue macrophages and other immune cells is frequently induced by pathogen-associated or damage-associated molecular patterns (PAMPs and DAMPs, respectively), which act via a variety of pattern-recognition receptors, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs)[8,21]. Some of the cytokines produced by activated macrophages, such as IL-1, IL-6 and IL-23, often act on other immune cells, for instance, T cells, resulting in elevated production of pro-tumorigenic cytokines, such as IL-17A[22–25]. In some cases, loss of the tumour suppressor p53 (encoded by *TP53*) in epithelial cells, a common and early event in many cancers, can also support NF-κB activation[26].

There are two general types of NF-κB signalling pathways: the classical (also known as canonical) and the alternative (also known as noncanonical) pathways[17] (FIG. 2). The classical pathway is rapidly and transiently activated by pro-inflammatory cytokines, PAMPs and DAMPs that act via specific receptors and adaptor molecules[17]. Activation of the alternative pathway is considerably slower, as it depends on *de novo* synthesis of NF-κB-inducing kinase (NIK; also known as MAP3K14)[27]. The alternative pathway is activated by a small subset of cytokines that belong to the TNF family, including lymphotoxin (LT), receptor activator of NF-κB ligand (RANKL; also known as TNFSF11), CD40 ligand (CD40L) and B cell activating factor of the TNF family (BAFF; also known as TNFSF13B)[28–30]. Whereas the classical pathway mainly targets p50–p65 (encoded by *RELA*) dimers, the alternative pathway results in activation of p52–RELB dimers[17,28,29]. The IKK subunits involved in both pathways also differ; IKKα–IKKβ heterodimers are needed for activation of the classical pathway, whereas IKKα–IKKα homodimers participate in the alternative pathway[17,28,29,31]. In many cases, target gene activation by NF-κB dimers through binding to specific DNA-binding sites requires assistance from other transcription factors, including signal transducer and activator of transcription (STAT) and activator protein 1 (AP1) family members and interferon regulatory factors (IRFs)[32–34] (BOX 1). Typical targets for classical NF-κB signalling include genes encoding pro-inflammatory cytokines (such as TNF, IL-1 and IL-6), growth factors (such as granulocyte–macrophage colony-stimulating factor (GM-CSF)), chemokines (including IL-8 (in humans), CXC-chemokine ligand 1 (CXCL1; also known as KC in mice), CC-chemokine ligand 3 (CCL3; also known as MIP1α), CXCL2 (also known as MIP2α), CCL2 (also known as MCP1) and CCL5 (also known as RANTES)), matrix metalloproteinases (MMPs; such as MMP9), pro-proliferative proteins (such as cyclin D1 and MYC), anti-apoptotic proteins (such as BCL-X_L, BCL-2 and FLIP (also known as CFLAR)), pro-inflammatory enzymes (such as cyclooxygenase 2 (COX2; also known as PTGS2) and inducible nitric oxide synthase (iNOS; also known as NOS2)), angiogenic factors (such as vascular endothelial growth factor (VEGF)), adhesion molecules (such as vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1) and E-selectin) and inhibitors of NF-κB signalling (such as IκBα and A20 (also known as TNFAIP3))[15,35,36].

The classical IKK complex comprising the IKKα and IKKβ catalytic subunits and the IKKγ (also known as NEMO) regulatory subunit serves as a hub for many NF-κB activating inputs[15,17]. Structural studies suggest that IKK activation depends on *trans*-autophosphorylation of two adjacent IKK catalytic subunit dimers[37], as originally suggested by Rothwarf and Karin[38]. Induced proximity between the *trans*-phosphorylating IKK dimers depends on modification of their ubiquitin-binding IKKγ subunits by K63-linked polyubiquitin and M1-linked linear ubiquitin, the formation of which is catalysed by a number of K63-specific E3 ubiquitin ligases, such as TNF receptor-associated factor 6 (TRAF6)[39], and the linear ubiquitylation assembly complex (LUBAC)[40], respectively. NF-κB activity is further modulated, positively and negatively, by microRNAs (miRNAs) — such as miR-146, miR-155, miR-181b, miR-21 and miR-301a — that target mRNAs encoding NF-κB subunits, IκBα, IKK subunits and various upstream regulators[41–43]. Conversely, NF-κB can directly and indirectly regulate miRNA expression[43,44]. Exosomes can also activate NF-κB via TLR signalling, resulting in the induction of pro-inflammatory cytokines by human monocytic cells[45]. The classical NF-κB pathway in cancer cells increases telomerase expression at the transcriptional level, and in turn, telomerase binds p65 to enhance NF-κB-dependent transcription of TNF, IL-6 and other targets, thus establishing a feedforward

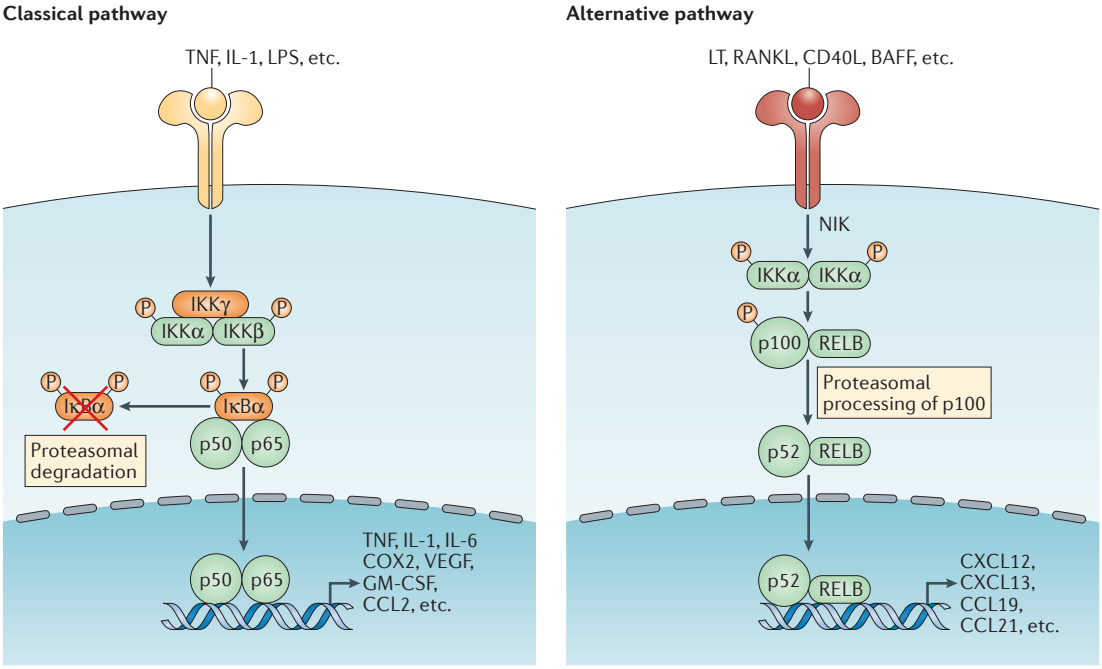

Figure 2 | **The two NF-κB signalling pathways.** The classical (also known as canonical) nuclear factor-κB (NF-κB) signalling pathway is activated by tumour necrosis factor (TNF), IL-1 and Toll-like receptor ligands, such as lipopolysaccharide (LPS), or by T cell receptor and B cell receptor engagement. This pathway plays an important role in the induction of genes involved in inflammation, cell proliferation and survival, epithelial-to-mesenchymal transition and invasion, angiogenesis and metastasis. The alternative (also known as noncanonical) pathway of NF-κB signalling is activated by lymphotoxin (LT), receptor activator of NF-κB ligand (RANKL), CD40 ligand (CD40L) and B cell activating factor of the TNF family (BAFF) and plays an essential role in the induction of genes associated with the development and maintenance of secondary lymphoid organs and related structures in the tumour microenvironment. LPS can also weakly activate the alternative pathway, whereas LT, RANKL, CD40L and BAFF can also activate the classical pathway. CCL, CC-chemokine ligand; COX2, cyclooxygenase 2; CXCL, CXC-chemokine ligand; GM-CSF, granulocyte–macrophage colony-stimulating factor; IκB, inhibitor of NF-κB; IKK, IκB kinase; NIK, NF-κB-inducing kinase; P, phosphate; VEGF, vascular endothelial growth factor.

loop[46]. Sequestosome 1 (SQSTM1; also known as ubiquitin-binding protein p62) is a scaffold protein that is upregulated by NF-κB and can promote further NF-κB activation in tumour cells via its TRAF6-binding motif, linking NF-κB to nuclear factor erythroid 2-related factor 2 (NRF2; also known as NFE2L2) activation and tumour promotion[47]. Curiously, NF-κB inhibition in myeloid cells, due to cell-type-specific IKKβ ablation or treatment with highly specific IKKβ inhibitors, can actually enhance inflammation by reducing SQSTM1 expression, as SQSTM1 has a crucial regulatory role in curtailing long-term NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome activation[48,49]. These results show that rather than being a simple innate activator of acute inflammation, NF-κB is responsible for orchestrating and coordinating the entire inflammatory response, initiating it when needed and making sure that it does not run amok, leading to irreparable damage.

NF-κB function in the tumour microenvironment

There are many cellular constituents of the tumour microenvironment, including tumour-associated macrophages (TAMs), dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), neutrophils, mast cells, natural killer (NK) cells, natural killer T (NKT) cells T cells, B cells, cancer-associated fibroblasts (CAFs) and endothelial cells. NF-κB functions in all these cells types and modulates inflammation, tumorigenesis and metastasis[8,21,50,51].

Myeloid cells and NF-κB. Macrophages or TAMs are typically the most abundant immune cells in the tumour microenvironment[8]. They often promote tumour development by producing cytokines, chemokines and growth factors, as well as proteases involved in cytokine and growth factor activation and extracellular matrix (ECM) remodelling[51]. Increased TAM density in tumours usually correlates with poor prognosis[8]. There are two major subsets of polarized TAMs: classically activated 'M1-type' macrophages induced by IFNγ and lipopolysaccharide (LPS) and alternatively activated 'M2-type' macrophages induced by IL-4, IL-10 and IL-13; however, neither phenotype represents an irreversible state[52–54]. M1 macrophages promote inflammation by producing pro-inflammatory cytokines, chemokines and enzymes, including TNF, IL-1, IL-6, IL-12, IL-23 and iNOS, whereas M2 macrophages can inhibit inflammation by releasing anti-inflammatory mediators, such as IL-10, transforming growth factor-β (TGFβ) and

Box 1 | **Crosstalk between NF-κB and other signalling pathways**

Part of the complexity and the variance in nuclear factor-κB (NF-κB) function between different cell and tumour types is due to its crosstalk with other transcription factors and signalling proteins, including signal transducer and activator of transcription 3 (STAT3), activator protein 1 (AP1), p53, interferon regulatory factors (IRFs), nuclear factor erythroid 2-related factor 2 (NRF2), glycogen synthase kinase 3β (GSK3β), mechanistic target of rapamycin (mTOR), extracellular signal-regulated kinase 1/2 (ERK1/2) JUN N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)–AKT, WNT–β-catenin, Notch and Hedgehog[32–34,259]. We discuss below how such crosstalk modulates the ability of NF-κB to control tumour-promoting inflammation and antitumour immunity.

NF-κB and STAT3

NF-κB and STAT3 can interact either positively or negatively[32]. In many cell types, NF-κB and STAT3 cooperatively regulate the expression of pro-proliferative proteins, such as cyclin D1 and MYC, and anti-apoptotic proteins, such as BCL-X_L and apoptosis regulator BCL-2, and interfere with p53 synthesis[19,32]. In glioma stem cells, constitutive activation of NF-κB and STAT3 induces upregulation of Notch pathway components, resulting in Notch activation[260]. NF-κB also accelerates STAT3-mediated expression of genes encoding different inflammatory mediators in immune cells of the tumour microenvironment and vice versa[32]. However, NF-κB and STAT3 can also exhibit antagonistic interactions, such as suppression of STAT3 activation by the inhibitor of NF-κB kinase-β (IKKβ)–NF-κB pathway in several types of cells, including hepatocytes[191]. NF-κB and STAT1, another member of the STAT family, can also cooperatively induce certain genes, such as inducible nitric oxide synthase (*iNOS*)[261].

NF-κB and p53

In most cases, NF-κB and tumour suppressor p53 antagonistically regulate each other's activity through different mechanisms[138,158,262]. IKKβ directly phosphorylates p53 and promotes its F-box/WD repeat-containing protein 1A (BTRC)-mediated K48 polyubiquitylation and degradation[263]. In a mouse colitis-associated cancer (CAC) model, chronic NF-κB activation in intestinal epithelial cells (IECs) was observed in response to a p53 loss-of-function mutant (p53R172H; the mouse equivalent of the human mutant p53R175H), which was also seen in human colitis-associated colorectal cancer[264]. Another paper reported that, in a mouse model of colorectal cancer, NF-κB in IECs and stromal cells is activated indirectly owing to loss of barrier function and enhanced microbial translocation in response to p53 loss in IECs[26]. This study shows that, similar to NF-κB[265], p53 is required for maintenance of barrier integrity, a function recently demonstrated for the key suppressor of intestinal tumorigenesis, adenomatous polyposis coli (APC)[24].

NF-κB and IRF

IRF transcription factors are important regulators of innate and adaptive immune responses[266]. The crosstalk between NF-κB and IRF family members takes place at the transcriptional level[33,267,268]. However, it was also reported that IKKβ can phosphorylate IRF3 (REF. 269) and that IRF3-dependent tumour necrosis factor (TNF) expression is required for NF-κB activation via an MYD88-independent pathway[270]. Because IRF activation can promote anticancer immunity through the induction of type I interferon[266,271], this crosstalk may be an important modulator and promoter of antitumour immunity.

NF-κB and NRF2

NRF2 is a key transcriptional regulator of the oxidative stress response, and its crosstalk with NF-κB is critical for integrating oxidative stress with the inflammatory response[47,272,273]. Ablation of NRF2 enhances NF-κB activity and cytokine production, whereas NF-κB can regulate NRF2 transcriptional activity positively or negatively[272]. NF-κB and NRF2 cooperatively maintain liver homeostasis and prevent development of hepatic adenomas[274], although under different circumstances both NRF2 (REF. 275) and NF-κB[201] promote liver carcinogenesis.

NF-κB and JNK

NF-κB downregulates JNK activation via upregulation of growth arrest and DNA damage-inducible protein GADD45β, XIAP, A20 and inhibitors of reactive oxygen species accumulation[276]. The negative crosstalk between NF-κB and JNK is reported to play an important role in the development of diethylnitrosamine (DEN)-induced hepatocellular carcinoma[123,277].

NF-κB and WNT–β-catenin

The WNT–β-catenin pathway exhibits both pro-inflammatory and anti-inflammatory functions by either activating or suppressing the NF-κB response[278]. Conversely, NF-κB either promotes or inhibits WNT–β-catenin signalling through multiple mechanisms[185,278]. Constitutive β-catenin activation in IECs induces TNF-mediated NF-κB activation in mice[279]. In turn, NF-κB enhances β-catenin activation, leading to de-differentiation of non-stem cells that acquire tumour-initiating abilities, a phenomenon that was also observed in patients with ulcerative colitis[22,279].

NF-κB and Notch

Crosstalk between NF-κB and Notch has been reported in some cancers[33,130,280]. Notch activation induces NF-κB activation via several different mechanisms, and, correspondingly, Notch inhibition can result in decreased NF-κB activity[33,130,280]. Conversely, NF-κB activates Notch by inducing Notch ligands and receptors, such as protein Jagged 1 (JAG1) and Notch1 (REFS 130,135,280).

arginase 1 (ARG1)[8]. Although M1 macrophages are thought to enhance antitumour immunity, this simplistic hypothesis is inconsistent with the fact that the cytokines produced by these cells are the most potent and ubiquitous tumour-promoting cytokines identified thus far[23]. By contrast, M2 macrophages are proposed to be pro-tumorigenic, but instead of tissue repair and angiogenesis, their most potent tumour-promoting activity could be IL-10-mediated and TGFβ-mediated immunosuppression[10]. NF-κB, especially the p50 subunit, has

been proposed to participate in macrophage polarization[19,54,55], and blocking NF-κB activation in TAMs can convert them from a tumour-promoting M2 phenotype to an M1-like cytotoxic phenotype, thereby enhancing tumour shrinkage[19,56].

DCs are also important regulators of antitumour immunity and may exert either pro-tumorigenic or antitumorigenic functions in a context-dependent manner[57]. Signalling via the immune checkpoint molecule programmed cell death protein 1 (PD1) inactivates the classical NF-κB pathway in DCs and inhibits their production of cytokines and expression of co-stimulatory molecules[58]. Finally, MDSCs, which can promote tumour growth by contributing to an immunosuppressive microenvironment, are activated through an IL-1β-induced NF-κB pathway[59].

NF-κB regulates lymphocyte functions in cancer. NK cells exert antitumorigenic activity, most notably against leukaemias and lymphomas, by directly killing malignant cells[60]. NF-κB activation in NK cells controls their lytic functions by promoting the expression of cytotoxic mediators, such as perforin[61] and granzyme B[62].

T and B lymphocytes are also recruited to tumours and can have either pro-tumorigenic or antitumorigenic functions[8,63]. Both the classical and the alternative NF-κB pathways play essential roles in T cell and B cell activation downstream of T cell receptor (TCR) and B cell receptor (BCR) engagement as well as in T cell and B cell development[64,65]. A recent paper reported that both the p65 and REL NF-κB subunits promote the development and suppressor functions of $CD4^+CD25^+$ regulatory T (T_{reg}) cells[66], the infiltration of which into the tumour bed is often a poor prognostic marker, especially in breast, cervical and renal cancers[67]. Canonical NF-κB signalling also supports conventional effector T cell activation and function[64,65], suggesting that interference with this pathway compromises antitumour immunity. However, deletion or inhibition of REL, but not p65, in peripherally induced T_{reg} cells impairs their immunosuppressive activity and potentiates the effectiveness of anti-PD1 immune checkpoint inhibitors[68], demonstrating that different NF-κB subunits have overlapping but distinct functions[16,69]. Canonical NF-κB activation in T cells increases the number of tumour-specific IFNγ-producing $CD8^+$ T cells and is required for tumour elimination[70]. Similarly, NF-κB activation in lung cancer cells induces T cell-mediated immune surveillance and results in tumour rejection owing to the expression of T cell-recruiting chemokines, including CCL2 (REF. 71). Under certain conditions, such as the induction of mitochondrial outer membrane permeabilization, NF-κB activation in tumour cells can also induce anticancer immune responses, including T cell infiltration and macrophage activation[72].

The tumour microenvironment also harbours a different B cell subset for which exposure to CXCL13 leads to NF-κB activation and subsequent production of LT, a cytokine that activates an IKKα–Polycomb complex protein BMI1 pathway that supports the expansion of prostate cancer stem cells, especially after androgen ablation[73–75]. Another subset of B cells, also identified in treatment-refractory prostate cancer, is IgA^+ immunosuppressive plasmocytes, which express high amounts of programmed cell death 1 ligand 1 (PDL1) and IL-10 and block the activation of cytotoxic T lymphocytes (CTLs)[76].

Cancer-associated fibroblasts and NF-κB. Fibroblasts in the tumour microenvironment are activated by tumour-induced alterations in tissue structure or in response to TGFβ and hypoxia[75]; once activated, these fibroblasts are referred to as CAFs[77,78]. CAFs maintain a pro-inflammatory transcriptional signature, expressing genes encoding TNF, IL-1β, IL-6, osteopontin, VEGF, CXCL12 (also known as SDF1), CXCL1, CXCL2 and many other chemokines, thereby enhancing tumorigenesis and metastasis via ECM deposition and remodelling, cancer cell proliferation, angiogenesis and inflammation, partly in an NF-κB-dependent manner[77–79]. IL-11 secreted from TGFβ-stimulated CAFs initiates colorectal cancer metastasis by activating STAT3 in cancer cells[80], whereas CXCL13 production by prostate cancer CAFs results in the recruitment and stimulation of LT-producing B cells[73,75]. Despite its important role in the production of inflammatory cytokines and chemokines, IKKβ activation in CAFs was reported to inhibit hepatocyte growth factor (HGF; also known as scatter factor) secretion and intestinal tumorigenesis through the induction of negative regulators of TGFβ signalling, including SMAD7 and E3 ubiquitin-protein ligase SMURF1 (REF. 81). However, IKKβ in CAFs was also shown to promote CAC initiation through the production of IL-6 and other pro-tumorigenic factors[82]. Undoubtedly, the specific effect of IKKβ inhibition on components of the tumour microenvironment is highly context dependent.

Cellular processes regulated by NF-κB

Cytokines and chemokines as mediators of NF-κB action. TNF and IL-6 are two of the best-studied pro-tumorigenic cytokines, the expression of which is elevated in many different cancers[83], often correlating with poor prognosis[84,85]. In addition to being an NF-κB target, TNF is a potent activator of both NF-κB and AP1, whereas IL-6 links NF-κB to STAT3 (REF. 83). All three of these transcription factors are important activators of cancer-related inflammation and other pathologies[8,21,32].

TNF signalling entails activation of NF-κB and mitogen-activated protein kinases (MAPKs) and can either promote cell death or increase cell survival in a context-dependent manner[84,86–88]. TNF is mainly produced by activated macrophages and neutrophils and can induce other pro-inflammatory cytokines, including IL-1 and IL-6, and can accelerate tumorigenesis[84]. IL-1α and IL-1β are important pro-inflammatory cytokines that are produced by cancer cells and immune cells and promote activation of the NF-κB and MAPK pathways and tumorigenesis[89,90]. IL-33, a member of the IL-1 family, is mainly expressed in the nucleus of epithelial cells, fibroblasts, endothelial cells and activated myeloid cells, as well as in tumour cells, and plays an important role in allergy, autoimmunity, inflammation and

cancer[91,92]. IL-33 is released from necrotic cells and functions as an alarmin, resulting in the activation of NF-κB and MAPKs via its unique receptor protein ST2 (also known as IL1RL1); this occurs mainly in immune cells, including group 2 innate lymphoid cells (ILC2s), T_{reg} cells and $CD8^+$ T cells[91,92]. In addition, nuclear IL-33 is reported to suppress NF-κB function through the interaction with p65[93], although nuclear IL-33 upregulates the expression of p65 in endothelial cells[94]. IL-12 and IL-23 are two other NF-κB-induced cytokines that are produced by antigen-presenting cells and are important regulators of T cell responses[95]. IL-17A, which is mainly produced by T helper 17 (T_H17) cells, γδ T cells and group 3 innate lymphoid cells (ILC3s), provides protection against extracellular bacteria and fungi and can further increase expression of TNF, IL-1β and IL-6 owing to its ability to activate NF-κB and MAPK signalling, resulting in tumour promotion[23,25,96,97].

IL-6, which is produced by macrophages and other cell types, was the first NF-κB target demonstrated to link inflammation and tumorigenesis[4,85,98]. Small amounts of IL-6 are also produced by malignant cells and act in an autocrine manner to initiate cancer-associated inflammation and stem cell expansion[85,99]. IL-6, as well as other IL-6 family cytokines including IL-11, leukaemia inhibitory factor (LIF) and oncostatin M (OSM), activates JAK–STAT3, RAS–MAPK and phosphoinositide 3-kinase (PI3K)–AKT signalling through their common receptor membrane glycoprotein 130 (gp130; also known as IL6ST)[85]. IL-6 family members also activate YAP and downstream Notch signalling, via a SRC family kinase (SFK)-dependent pathway, and this has been shown to be important in intestinal regeneration and tumorigenesis[100,101]. IL-10 also activates JAK–STAT3 signalling and is mostly expressed in immune cells, but unlike IL-6, IL-10 has potent anti-inflammatory activity, mediated in part via NF-κB inhibition[102]. By contrast, IL-22, a relative of IL-10, is a pro-inflammatory, regenerative and tissue-protective cytokine that also activates JAK–STAT3 signalling[103]. IL-22 is mostly produced by $CD4^+$ T cells and ILC3s and acts mainly on epithelial cells[23]. Another potent anti-inflammatory cytokine is TGFβ, which is produced by cancer cells, myeloid cells, T cells and fibroblasts[8]. Although TGFβ is a potent inhibitor of cell proliferation, its ability to regulate T_{reg} and T_H17 cell differentiation makes it a tumour promoter as well as a strong inducer of invasion and metastasis[104]. Both IL-10 and TGFβ are potent immunosuppressive cytokines, and part of their tumour-promoting ability depends on the inhibition of CTL activity[10].

Cytokines produced by immune cells and cancer cells are some of the key effectors in inflammation-enhanced tumorigenesis and metastasis[8]. Several cytokine antagonists and inhibitors are already in clinical use in inflammatory and autoimmune diseases[22,85]. Therefore, most of these drugs, as long as they are not immunosuppressive, should also be tested for cancer prevention and treatment. Indeed, several ongoing cancer treatment trials include tocilizumab (an anti-IL-6 receptor antibody) and ruxolitinib (a JAK inhibitor)[22,85].

In addition to cytokines, NF-κB induces numerous chemokines both in malignant cells and in constituents of the tumour microenvironment[105,106], especially CAFs[75,77,78]. Chemokines are important not only for recruiting immune cells into the tumour bed but also in stimulating primary tumour growth, growth factor synthesis, angiogenesis and metastasis, and so chemokines are potential targets for cancer immunotherapy[50,105,106]. However, as chemokines can have both positive and negative roles during tumorigenesis and metastasis and because quite a few of them have redundant functions, the targeting of chemokines and their receptors is not always straightforward[106]. Currently, a few chemokine-targeting drugs are in clinical trials, including maraviroc (a CC-chemokine receptor 5 (CCR5) antagonist) and plerixafor (a CXC-chemokine receptor 4 (CXCR4) antagonist)[107]. The sources and target cells of cytokines and chemokines have been summarized[23,50] (FIG. 3).

NF-κB and autophagy. Autophagy is a self-digesting system that disposes of cellular debris to maintain cellular homeostasis and well-being[47,108]. Although autophagy may be needed for cancer cell survival, it directly and indirectly suppresses tumour initiation[47,109,110]. Autophagy inhibits tumour-enhancing inflammation by downregulating NLRP3 inflammasome activation and cell death, whereas autophagy potentiates antitumour immunity by enhancing the processing and presentation of tumour antigens[49,110]. Therefore, drugs that stimulate autophagy may be effective cancer-preventing agents[109,110]. NF-κB and autophagy intricately regulate each other's activity[111,112]. For example, NF-κB induces expression of beclin 1 (BECN1), SQSTM1 and other autophagy-associated proteins to enhance autophagy, whereas autophagy degrades IKK subunits and inhibits NF-κB signalling[111–113]. Further studies are needed to fully appreciate the intricate mechanisms through which autophagy and inflammation interact and to be able to use this information to improve cancer therapy.

NF-κB and cellular senescence. It was originally thought that irreversible cellular senescence, which is triggered by DNA damage or oncogene activation, forms a protective barrier to cancer initiation[114]. However, senescent cells can produce pro-inflammatory cytokines and chemokines, such as IL-1, IL-6 and IL-8, that affect neighbouring cells[114,115]. A programme known as the senescence-associated secretory phenotype (SASP) maintains senescence and facilitates the elimination of senescent cancer cells through activation of phagocytic cells[114,115]. However, most SASP cytokines are also tumour promoters, suggesting that cellular senescence is a double-edged sword that can either inhibit or stimulate tumorigenesis[114–116]. NF-κB is activated in senescent cells and functions as a key SASP regulator[115,117,118]. NF-κB promotes cellular senescence together with p53 in cultured fibroblasts and increases cellular senescence and chemosensitivity in murine lymphomas, suggesting a tumour-suppressive function[118]. NF-κB activation also suppresses the generation of induced pluripotent

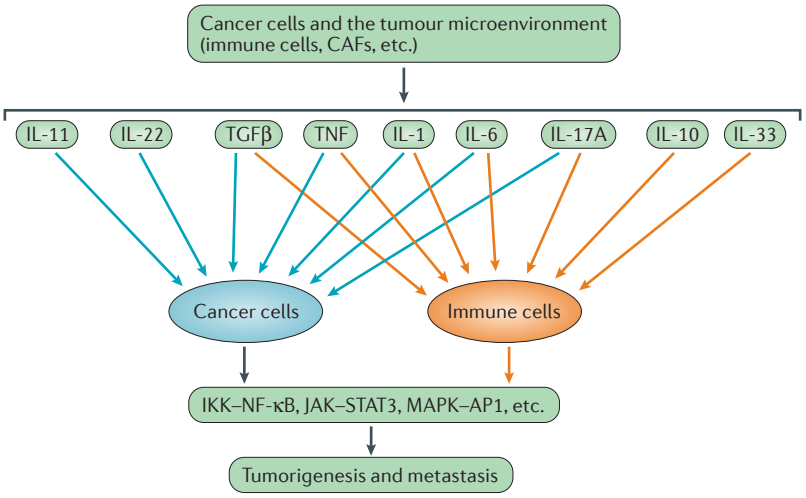

Figure 3 | **Mode of action of cytokines on cancer and immune cells.** Cytokines such as tumour necrosis factor (TNF), IL-1, IL-6, IL-17A and transforming growth factor-β (TGFβ) target both cancer and immune cells and activate the IKK–NF-κB (IκB kinase– nuclear factor-κB), JAK–STAT3 (signal transducer and activator of transcription 3) and MAPK–AP1 (mitogen-activated protein kinase–activator protein 1) signalling pathways. IL-11 and IL-22 mostly target cancer cells, whereas IL-10 and IL-33 mainly act on immune cells. CAFs, cancer-associated fibroblasts.

stem cells by inducing the reprogramming repressor histone–lysine *N*-methyltransferase, H3 lysine-79-specific (encoded by *DOT1L*) to promote cellular senescence[119]. However, NF-κB also acts as a tumour promoter by inducing SASP-related factors, such as IL-1 and IL-6 (REFS 114,115).

NF-κB and tissue regeneration and repair. Inflammation, especially acute inflammation, is critical for tissue regeneration and repair, acting through numerous signalling pathways, including IKK–NF-κB, JAK–STAT3, MAPKs, SFKs, YAP, WNT–β-catenin and Notch, all of which are also closely associated with cancer[12,100,120]. IL-6 family members and IL-22 activate several of these pathways, thereby enhancing intestinal and liver regeneration[12,100]. Overexpression of constitutively active YAP was found insufficient to promote hepatocyte growth in the absence of a second signal, provided by inflammation and IL-6 (REFS 121,122), underscoring the importance of inflammation. TNF also promotes intestinal and liver regeneration by inhibiting intestinal epithelial cell (IEC) and hepatocyte death through NF-κB activation and enhances epithelial regeneration through Notch activation[12]. Moreover, activation of NF-κB in myeloid cells stimulates hepatocyte proliferation and liver regeneration via TNF, IL-6, LT and other cytokines[12,123]. Correspondingly, TNFR1-deficient or IL-6-deficient mice exhibit impaired liver regeneration after partial hepatectomy[124,125]. Cancer is referred to as a 'wound that does not heal' and often utilizes signalling pathways and programmes that control tissue regeneration and repair[126]. The basal activity of these pathways in normal tissues is low, and knockout mice deficient in their key components exhibit almost no phenotype when kept unchallenged. Therefore, regenerative signalling pathways that are dysregulated in cancer represent attractive targets for therapeutic application, although it will be important not to combine such approaches with injury-provoking chemotherapies and radiotherapy.

NF-κB and cancer stem cells. Cancer stem cells (CSCs) are malignant cells that possess self-renewal capacity and the ability to differentiate into more differentiated malignant cells[127–129]. CSCs are thought to mediate cancer metastasis and therapy resistance[127–129]. Inflammation and numerous signalling pathways, including NF-κB and STAT3, play important roles in CSC generation and maintenance[127–129]. NF-κB is constitutively activated in many types of CSC and stimulates their proliferation, survival, maintenance and expansion[130]. Both NF-κB and STAT3 promote CSC development and maintenance through the induction of SLUG (also known as SNAI2), TWIST1 and SNAIL (also known as SNAI1)[127,131–134]. In breast cancer, NF-κB expands the CSC population by activating Notch signalling in a cell-non-autonomous manner[135]. In pancreatic CSCs, the classical NF-κB pathway increases the expression of transcription factor SOX9, which is associated with enhanced stemness and invasiveness[136].

NF-κB and cellular metabolism. Reprogramming energy metabolism is now recognized as a hallmark of cancer[11]. Inflammation and NF-κB also modulate cancer cell metabolism, stimulating the so-called Warburg effect, and affect whole-body metabolism, including obesity and type 2 diabetes[137–139]. Curiously, however, IKKβ-mediated hepatic inflammation was recently shown to have a beneficial effect on glucose homeostasis[140]. The crosstalk between NF-κB and p53 is crucial for the regulation of cancer cell metabolism[138,139,141]. In p53 wild-type cells, NF-κB stimulates mitochondrial respiration through the upregulation of SCO2 (synthesis of cytochrome c oxidase 2) in mitochondria, whereas in p53-deficient cells, NF-κB suppresses mitochondrial oxidative phosphorylation and promotes glycolysis through the induction of genes such as *GLUT3* (also known as *SLC2A3*), the products of which stimulate the Warburg effect[138,139,141]. In turn, glycolysis activates NF-κB through *O*-linked β-*N*-acetyl glucosamine modification of IKKβ, forming a positive feedback loop[142,143].

NF-κB in tumorigenesis and metastasis

Tumorigenesis is a multistage process that is generally divided into three steps: tumour initiation (that is, acquisition of oncogenic mutations by tumour-initiating cells); tumour promotion (involving the clonal expansion of tumour-initiating cells); and tumour progression (in which tumour cells acquire further oncogenic mutations and malignant traits)[144]. Evolution of the tumour microenvironment may also occur in three phases: first, niche construction; second, expansion; and third, maturation, thereby corresponding to the three steps of the tumorigenic process[145]. Notably, NF-κB plays important roles in each of these steps.

NF-κB and tumour initiation. Between three to five genetic alterations are needed for tumour initiation[8,146]. Because only a minority of all cancers are linked to

germline mutations, most cancer-causing mutations are acquired *de novo*[8]. Inflammation and NF-κB affect tumour initiation by promoting the production of reactive oxygen species and reactive nitrogen species, which induce DNA damage and oncogenic mutations[8]. By stimulating cell cycle entry in cells in which only one DNA strand has been damaged, NF-κB activation ensures the incorporation of mutations into both DNA strands and their transmission to daughter cells[147,148]. Mutations in mismatch repair genes further enhance genomic instability and lead to inactivation of critical tumour suppressor genes, such as those encoding TGFβ receptor type II (TGFR2), insulin-like growth factor 2 receptor (IGF2R; also known as M6PR) or apoptosis regulator BAX, which all contain microsatellite sequences[8,149]. Chronic inflammation and NF-κB can also induce chromosomal instability and aneuploidy as well as epigenetic changes, leading to tumour initiation, promotion and progression[8,149,150,151,152]. Another mechanism through which NF-κB may stimulate tumour initiation is through the induction of the mutator enzyme activation-induced cytidine deaminase (AID), which deaminates cytosine residues to cause cytosine-to-thymine transitions[153]. AID overexpression was suggested to contribute to gastric cancer, HCC and lymphomas[153]. AID belongs to the apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) family of DNA-modifying enzymes[154], which has been suggested to contribute to human cancer-associated mutations[155]. Expression of APOBEC3, the main mutagenic member of this family, is induced by NF-κB[156,157]. Inflammation may also promote tumour initiation by conferring a stem-cell-like phenotype upon tumour-initiating cells and/or expanding stem cell pools, thereby increasing targets for mutagenesis[8]. In addition, by preventing p53-induced apoptosis, NF-κB activation increases the number of DNA-damaged cells that accumulate oncogenic mutations[158].

NF-κB and tumour promotion. The major tumorigenic effect of NF-κB is exerted at the tumour promotion stage through enhancement of cancer cell proliferation and survival[17]. By stimulating the production of regeneration-enhancing inflammatory cytokines and growth factors, NF-κB enhances the proliferation of initiated tumour progenitor cells[8,17]. In addition, by inhibiting apoptosis, NF-κB blocks the cell death that is induced in response to the activation of oncogenes such as GTPase HRAS[159] and MYC[160]. NF-κB is activated by mutant GTPase KRAS, which is associated with enhanced proliferation and decreased apoptosis and plays an important role in $KRAS^{G12D}$-induced tumorigenesis[139,161]. NF-κB can also increase the expression of various cell cycle proteins, especially cyclin D1 (REF. 147).

NF-κB and tumour spread. By chronically stimulating cancer cell proliferation, inhibiting cell death and promoting the accumulation of mutations, inflammation and NF-κB can drive malignant progression[17,132]. NF-κB, STAT3 and other inflammatory transcription factors can directly stimulate the expression of genes, the products of which contribute to the malignant phenotype and trigger epithelial-to-mesenchymal transition (EMT), invasive behaviour and neoangiogenesis[32,132]. For example, NF-κB stimulates the transcription of SLUG, TWIST1 and SNAIL[132,162], which initiate EMT and augment the malignant phenotype by enhancing cancer cell stemness and migratory behaviour[163]. Inflammation and NF-κB can directly stimulate metastatic dissemination through EMT, increase cancer cell extravasation into the blood and lymphatics and prevent the death of circulating tumour cells[8,164]. Inflammation also enhances metastatic seeding by supporting the survival and proliferation of metastasis-initiating cells and by preparing a highly supportive metastatic niche[165].

In addition to upregulating SLUG, TWIST1 and SNAIL, NF-κB activation can promote cell migration, invasion and EMT through other mechanisms[127,132], including NF-κB-mediated induction of matrix-degrading enzymes such as MMP9 (REF. 166). NF-κB also stimulates the expression of hypoxia-inducible factor 1α (HIF1α)[167] and thereby enhances hypoxic conditioning and early survival of metastasis-initiating cells[168]. HIF1α activation also contributes to EMT[169]. Furthermore, MMP family members induced by NF-κB contribute to the release of bioactive TGFβ, which strongly stimulates EMT and other processes that contribute to metastatic dissemination[104,132,170].

Inflammation stimulates tumour angiogenesis[8], although it was also reported that NF-κB activation in endothelial cells might result in the inhibition of angiogenesis[171,172]. First and foremost, activated macrophages produce VEGF family members and other angiogenesis-stimulating factors[173]. Production of proteases and nitric oxide due to NF-κB-dependent iNOS induction in inflammatory cells also plays an important role in the crosstalk between inflammation and angiogenesis[173]. Last but not least, inflammation stimulates the expression of motility-inducing factors, such as HGF[174], and chemokines that can directly stimulate cancer cell migration, such as CXCL12 (REF. 175).

NF-κB and gastrointestinal cancers

Gastric cancer and colorectal cancer are classical inflammation-dependent cancers[2,8] (BOX 2). Chronic gastrointestinal inflammation, such as that which occurs in gastritis and inflammatory bowel disease (IBD), greatly increases the risk of cancer via a process that involves the production of pro-tumorigenic cytokines, such as TNF, IL-1, IL-6, IL-17A and IL-23, and also involves NF-κB and STAT3 activation[22,23]. The roles of NF-κB and STAT3 in inflammation-driven colorectal cancer, known as CAC, were studied in mice subjected to treatment with azoxymethane and dextran sulfate sodium salt[4,176,177]. These studies were the first to show the critical roles of NF-κB and STAT3 in linking chronic inflammation and cancer[4,176,177]. Whereas the pro-tumorigenic function of STAT3 is mainly exerted in epithelial cells[176,177], NF-κB acts in both epithelial cells, where it suppresses cell death, and myeloid cells, where it controls the expression of tumour-promoting cytokines[4] (FIG. 4).

Box 2 | **Inflammation and the gut microbiota**

Microorganisms and microbial products are sensed by pattern-recognition receptors, leading to nuclear factor-κB (NF-κB) activation and inflammation[15,17] in addition to affecting tumorigenesis, metastasis, and the effectiveness and toxicity of cancer therapy[281–286]. The gastrointestinal tract is the largest reservoir of commensal microbiota in the human body[287], and dysbiosis that results in over-representation of inflammation-provoking colitogenic bacteria or in gut epithelial barrier loss accelerates colorectal cancer development[281,283,288]. Barrier disruption results in aberrant and promiscuous interactions between immune cells and the microbiota that can trigger chronic inflammation[22,24]. The inflammatory effect of dysbiosis can be attenuated by antibiotic treatment followed by the transplantation of normal, well-balanced microbiota[289]. Ingestion of anti-inflammatory probiotics or prebiotics can also result in the attenuation or resolution of dysbiosis-induced inflammation[289].

An association between gastrointestinal cancer and altered gut microbiota has been investigated in several epidemiological and clinical studies and experimental animal models[281]. Although a single gut bacterium that can initiate and accelerate colorectal cancer development remains to be identified, several microorganisms, including *Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis* and colibactin-producing *Escherichia coli*, were suggested to be associated with increased colorectal cancer risk[290]. By contrast, *Helicobacter pylori*, which resides in the stomach epithelium, was shown to cause gastritis, mucosa-associated lymphoid tissue lymphoma and gastric cancer, even when present at rather low concentrations[6–8]. This is entirely different from the nonphysiological situations caused by artificial monocolonization experiments[21]. Although certain bacteria other than *H. pylori* have been proposed to promote gastrointestinal tumorigenesis by inducing chronic inflammation, alteration of the tumour microenvironment and the promotion of DNA damage[281,290,291], it has never been shown that vaccination or the elimination of individual microorganisms can prevent cancer. It is equally probable that the tumour-promoting effects of microbial dysbiosis are due to the absence of protective species. Because of the ability of gut microbial products to reach the liver via the portal circulation, obesity-induced alteration of the gut microbiota may also enhance the development of HCC through upregulation of hepatic inflammation[116]. However, it is questionable whether individual bacteria or their specific metabolites are any more pathogenic than the inflammation-provoking endotoxins produced by most Gram-negative bacteria and bacterial nucleic acids, although, for example, a short-chain fatty acid, butyrate, derived from commensal microbiota induces the differentiation of $CD4^+CD25^+$ regulatory T cells in mouse colon[292–295].

More recently, it has become clear that inflammation also plays a critical role in the development and progression of sporadic colorectal cancer, which is not preceded by colonic inflammation[22,23]. Most cases of sporadic colorectal cancer are accompanied by elevated expression of IL-1, IL-6, IL-17A and IL-23 (REFS 178,179). Moreover, elevated expression of these tumorigenic cytokines in stage II patients predicts rapid progression to metastatic disease[179]. To understand the origin, mechanism and effects of this so-called tumour-elicited inflammation, we have used a mouse model of sporadic colorectal tumorigenesis, known as the CPC–APC (adenomatous polyposis coli) mouse, in which colorectal tumours are initiated by random allelic deletions of the *Apc* locus[180]. APC loss, which results in constitutive β-catenin activation, is the most common initiating event in sporadic human colorectal cancer[181]. We found that in addition to β-catenin activation, *Apc* loss in mice and *APC* loss in humans result in a rapid downregulation of mucin 2 production and an absence of tight junction proteins, resulting in intestinal epithelial barrier deterioration and localized translocation of microbial products that induce expression of IL-23 and other pro-inflammatory cytokines in adenoma-associated macrophages and DCs[24]. IL-23 expands the population of IL-17A-producing cells, and IL-17A directly stimulates the proliferation of APC-deficient IECs by activating NF-κB and MAPKs without affecting β-catenin signalling, resulting in the accelerated formation and growth of colorectal adenomas[24,25], thereby underscoring the tremendous importance of tumour-elicited inflammation.

Further evidence for the importance of tumour-elicited inflammation in colorectal cancer and other epithelial malignancies comes from the well-established cancer-preventing effect of long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and indomethacin, which suppress the enzymatic activity of COX2, a critical regulator of prostaglandin E2 (PGE_2) synthesis[182]. Another effect of tumour-elicited inflammation is provided by the NF-κB-dependent induction of iNOS, which promotes genetic instability and accelerates malignant progression through the accumulation of mutations[183,184]. Chronic NF-κB activation in IECs also potentiates β-catenin activation and expression of genes encoding intestinal stem-cell-related molecules, such as achaete-scute homologue 2 (ASH2), olfactomedin 4 (OLM4), DLK1 and BMI1, resulting in enhanced cell proliferation and spontaneous tumorigenesis[185]. APC loss enhances RAC1 GTPase activity, which induces reactive oxygen species production and NF-κB activation, resulting in expansion of the leucine-rich repeat-containing G-protein-coupled receptor 5 $(LGR5)^+$ intestinal stem cell signature and colorectal cancer growth[186].

NF-κB and liver cancer

Another malignancy highly dependent on inflammation is HCC, the most common type of liver cancer[187]. Most HCCs develop as a consequence of chronic viral hepatitis due to either HBV or HCV infection, but nonalcoholic steatohepatitis (NASH) and alcoholic steatohepatitis have been growing in their relative importance and will soon be the leading aetiologies[187].

Initially, inflammation-associated HCC was studied in multidrug resistance protein 2 (MDR2)-deficient ($Mdr2^{-/-}$) mice, for which hepatocytes cannot secrete phospholipids into bile, resulting in inflammatory cholangitis, which progresses to HCC within 8–10 months[5,15,188]. Although the mechanism of HCC progression in $Mdr2^{-/-}$ mice is poorly understood, inhibition of NF-κB through liver-specific expression of an IκBα-super-repressor variant enhances the death of pre-malignant hepatocytes and blocks HCC development[5]. NF-κB activation in hepatocytes seems to depend on TNF produced by nonparenchymal liver cells, such as Kupffer cells[5]. Indeed, inhibition of TNF signalling suppresses the expression of NF-κB-dependent prosurvival genes, resulting in enhanced hepatocyte apoptosis and reduced tumour multiplicity[5]. Ablation of IL-6 in monocytes also decreases spontaneous HCC development in $Mdr2^{-/-}$ mice[189], resembling what has been found in CAC[85,176].

However, NF-κB inactivation in a model of chemically induced HCC that is not accompanied by chronic inflammation results in enhanced tumorigenesis[123]. Liver-specific ablation of IKKβ strongly potentiates HCC induction by the carcinogen diethylnitrosamine (DEN),

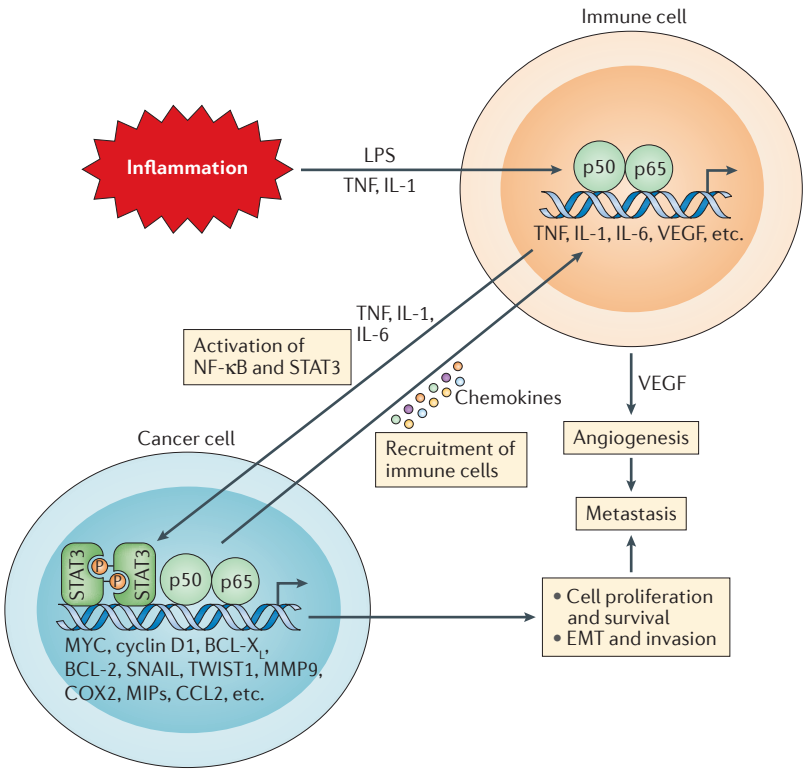

Figure 4 | **Chronic inflammatory crosstalk between cancer cells and immune cells.** Nuclear factor-κB (NF-κB) in immune cells is initially activated by tumour necrosis factor (TNF), IL-1 and various pathogen-associated or damage-associated molecular patterns, leading to the production of pro-inflammatory cytokines, chemokines and growth factors such as TNF, IL-1, IL-6 and vascular endothelial growth factor (VEGF). Pro-inflammatory cytokines activate NF-κB and signal transducer and activator of transcription 3 (STAT3) in cancer cells and in components of the tumour microenvironment, resulting in the stimulation of cancer cell proliferation and survival, epithelial-to-mesenchymal transition (EMT), invasion, angiogenesis and metastasis. Cancer cells can recruit more immune cells into the tumour microenvironment by producing chemokines and thereby augment and maintain the local inflammatory state, thus establishing a chronic feedforward loop that enhances tumorigenesis and metastasis. CCL2, CC-chemokine ligand 2; COX2, cyclooxygenase 2; LPS, lipopolysaccharide; MIPs, macrophage inflammatory proteins; MMP9, matrix metalloproteinase 9; P, phosphate.

an effect that has been attributed to elevated compensatory proliferation, which is triggered by excessive killing of NF-κB-deficient hepatocytes by DEN[123]. Hepatocyte death causes the release of IL-1α, which leads to activation of liver-resident myeloid cells and induction of TNF and IL-6 (REF. 190), both of which stimulate hepatocyte proliferation and HCC growth[191–193]. A more substantial decrease in hepatic NF-κB activity due to liver-specific deletion of IKKγ results in spontaneous steatohepatitis and HCC without exposure to DEN[194]. A follow-up study revealed that IKKγ inhibits hepatocyte cell death, steatohepatitis and HCC by suppressing receptor-interacting serine/threonine-protein kinase 1 (RIPK1) activity via NF-κB-dependent and NF-κB-independent mechanisms[195]. By contrast, inhibition of NF-κB in myeloid cells via cell-type-specific IKKβ deletion decreases cytokine expression, including TNF and IL-6, and inhibits DEN-induced HCC[123]. Whereas IL-6 from liver myeloid cells and HCC progenitor cells accelerates HCC development through STAT3 activation[99,191], TNF produced by myeloid cells stimulates TNFR1 signalling in HCC progenitor cells, leading to the activation of IKKβ–NF-κB and JUN N-terminal kinase (JNK), which in turn contributes to HCC development[192]. NF-κB activation in liver myeloid cells is inhibited by oestrogen, resulting in decreased IL-6 production and attenuated hepatocellular carcinogenesis[196–199], which partly accounts for the gender difference in HCC incidence.

Notably, IKKβ is not a real tumour suppressor, and its ablation in hepatocytes enhances HCC development only under conditions that result in elevated hepatocyte injury[17]. Under such conditions, even STAT3, which is an important mediator of hepatocellular carcinogenesis[191], can behave as a tumour suppressor[200]. Moreover, forced IKKβ activation in hepatocytes greatly enhances HCC development[201], an effect that has been attributed to the formation of ectopic lymphoid structures (ELSs), which consist of T cells, B cells and follicular dendritic cells[202]. ELSs develop at sites of inflammation and are often observed in cancer. In colorectal cancer, the presence of ELSs correlates with better prognosis, suggesting that ELSs also mediate immune surveillance[202]. However, in HCC, ELS formation is pro-tumorigenic because these structures provide a supportive immunopathological microniche for HCC progenitor cells[201]. ELS microniches exhibit localized production of various cytokines and chemokines, including LTβ, LIGHT (also known as TNFSF14), CCL17 and CCL20, the expression of which is abolished after T cell depletion[201]. Liver-specific overexpression of LTα and LTβ also induces hepatitis and spontaneous HCC, both of which depend on IKKβ activation in hepatocytes[203].

Obesity and insulin resistance increase the risk of many types of cancer, especially endometrial, ovarian and liver cancers[204–206]. The pro-tumorigenic effect of obesity in the liver is due to inflammation and the elevated production of cytokines, such as TNF and IL-6 (REF. 193). Initially, genetic and dietary obesity were shown to greatly enhance DEN-induced HCC formation[193], but the most critical cellular sites of TNF and IL-6 production were not genetically identified. A subsequent study suggested that IL-6 is part of the SASP in hepatic stellate cells (HSCs), which is also observed in human NASH-induced HCC[116]. It was also proposed that obesity-promoted chemical hepatic carcinogenesis depends on gut dysbiosis, which promotes SASP activation in HSCs[116]. Correspondingly, the treatment of mice with broad-spectrum antibiotics can attenuate obesity-promoted HCC induction[116].

Nonalcoholic fatty liver disease, which is tightly linked to metabolic syndrome, is one of the most prevalent liver diseases worldwide and spans a spectrum from bland steatosis to NASH[207]. To examine whether endoplasmic reticulum (ER) stress can control the transition from simple steatosis to NASH, we fed a high-fat diet (HFD) to MUP–uPA transgenic mice, which express urokinase-type plasminogen activator (uPA) from the hepatocyte-specific major urinary protein (MUP) promoter and therefore undergo liver-specific ER stress shortly after birth[192,208]. The ER stress response, however, is transient owing to silencing of the *MUP–uPA* transgene in newly generated hepatocytes[192,208]. However, upon HFD feeding,

MUP–uPA mice, unlike nontransgenic C57BL/6 controls, go on to develop classical signs of NASH, including hepatocyte ballooning, liver damage, accumulation of Mallory–Denk bodies, inflammatory infiltrates and a 'chicken-wire' pattern of liver fibrosis[192,207]. Most importantly, HFD-fed MUP–uPA mice show robust progression from NASH to HCC, which depends on TNF-activated NF-κB and JNK signalling in hepatocytes[192]. Both NASH and HCC development in these mice can be inhibited by treatment with TNF signalling inhibitors, which may also be useful for the treatment of human NASH[192]. In HFD-fed MUP–uPA mice, IgA^+ immunosuppressive plasmocytes are induced by hepatic inflammation and suppress anti-liver cancer immunity[209].

NF-κB and pancreatic cancer

Inflammation and NF-κB are also associated with pancreatic cancer, the major risk factors of which include tobacco smoking, alcohol consumption, obesity, type 2 diabetes, and chronic and hereditary pancreatitis[210–212]. Elevated expression of pro-inflammatory cytokines, including TNF, IL-1α and IL-6, correlates with poor prognosis in pancreatic ductal adenocarcinoma (PDAC), the predominant form of pancreatic cancer[213–216]. PDAC is usually initiated by *KRAS*-activating mutations, and the expression of $KRAS^{G12D}$ in pancreatic epithelial cells triggers PDAC in mice after a very long latency[217]. $KRAS^{G12D}$ induces IL-1α expression via AP1 activation, leading to NF-κB activation in tumour cells[214]. In turn, this NF-κB activation initiates the expression of IL-1α and SQSTM1, resulting in the establishment of IL-1α–SQSTM1 feed-forward loops to induce and maintain NF-κB activation in PDAC cells[214]. Once activated, NF-κB cooperates with Notch to inhibit the expression of the anti-inflammatory nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) and stimulate PDAC development[218]. In the $KRAS^{G12D}$-induced PDAC model, the progression of pancreatic intraepithelial neoplasia (PanIN) into PDAC and the development of PDAC depend on the activation of the IL-6–STAT3 pathway[219]. Similar to HCC, HFD feeding accelerates PanIN development, and this depends on TNFR1 signalling[220]. IKKα deletion in pancreatic epithelial cells induces the accumulation of SQSTM1 and spontaneous pancreatitis in mice, which is attenuated by SQSTM1 ablation[221]. Such spontaneous pancreatitis accelerates PDAC development via NF-κB-independent mechanisms[222].

NF-κB and prostate cancer

Another cancer type associated with inflammation and NF-κB is prostate cancer[223]. Prostate tumour-initiating stem-like cells show increased NF-κB activity[224], and the NF-κB gene signature predicts disease-specific and metastasis-free survival[225]. Although TNF exhibits both pro-tumorigenic and antitumorigenic roles in prostate cancer[226], IL-6 promotes prostate tumorigenesis and metastasis and plays an important role in the transition from hormone-dependent to castration-resistant prostate cancer (CRPC)[227]. In a mouse model of CRPC, IKKβ-mediated NF-κB signalling was found to be important for the production of LT[73], which activates an IKKα–BMI1 cascade in prostate epithelial cells[74]. IKKα blockade suppresses CRPC development, although IKKβ deletion in prostate cancer cells has no effect on disease development or recurrence[19,73]. Furthermore, IKKα, but not IKKβ, is necessary for metastatic progression through an effect on BMI1 and maspin (also known as serpin B5), both of which are NF-κB-independent[19,74,228]. An NF-κB-independent anti-inflammatory function of IKKα was also reported in the intestine[229].

NF-κB and lung cancer

Lung cancer is mainly initiated by environmental factors, such as tobacco smoking and asbestos exposure, and is associated with chronic inflammation and NF-κB activation[230,231]. Interstitial lung disease and chronic obstructive pulmonary disease, both of which are closely related to tobacco smoke, are linked to higher lung cancer risk[232]. NF-κB is upregulated in lung cancer and preneoplastic lesions[233], and its activation is correlated with poor prognosis in patients with non-small-cell lung cancer[230]. Tobacco smoke promotes $KRAS^{G12D}$-induced lung tumour development through the induction of lung inflammation, which depends on NF-κB activation in myeloid cells[234]. Activation of NF-κB (especially p65), mainly induced by p53 loss[235] or oncogenic KRAS-induced SQSTM1 expression[236], plays an important role in $KRAS^{G12D}$-induced lung tumorigenesis[161]. In addition, NF-κB activation is crucial in epidermal growth factor receptor (*EGFR*)-mutant lung cancer[237]. NF-κB activation is rapidly induced in response to EGFR oncogene inhibition in lung cancer and promotes resistance to therapy via IL-6 induction[238].

Therapeutic implications

Conventional therapies for solid malignancies include surgery, chemotherapy and radiation. Surgical resection of primary cancer causes tissue injury, necrotic cell death and subsequent inflammation, which might stimulate the growth and metastasis of residual malignant cells[50,239], and surgery-induced inflammation promotes the stem-like feature acquisition of cancer cells through STAT3 activation[240]. Both chemotherapy and radiation induce DNA damage and genotoxic stress, which also evoke a subsequent inflammatory response that results in NF-κB and STAT3 activation and the upregulation of cytokines and chemokines, which promote therapy resistance and tumour recurrence[8,241,242] and increase CSCs through activation of an IL-6 inflammatory feedback loop[243]. Nonetheless, inflammation can also induce cross-presentation of tumour antigens and stimulate antitumour immune responses[8,244]. In addition, chemotherapy induces NF-κB-dependent PDL1 overexpression and local immune suppression in ovarian cancer[245]. Moreover, pentoxifylline (a REL inhibitor)[246] and REL deficiency in T_{reg} cells can boost the effects of anti-PD1 immunotherapy[68]. Thus, NF-κB inhibition may augment the response to most conventional cancer therapies and immune checkpoint inhibitors, although inhibition of the NF-κB pathway for long periods may cause severe adverse effects, such as the impairment of immune responses and antitumour immunity[230,247].

Long-term consumption of anti-inflammatory drugs, such as aspirin or selective inhibitors of COX2, an NF-κB target, results in a considerable reduction in the risk and incidence of many cancers in addition to colorectal cancer[22,248]. In addition, NSAIDs can decrease mortality in patients with advanced colorectal cancer and breast cancer through COX2-dependent and COX2-independent mechanisms[22,248]. These results further underscore the importance of inflammation as a main driving force in tumorigenesis and malignant progression and suggest that NF-κB and STAT3 are attractive preventive and therapeutic targets to control cancer-related inflammation[8,32]. However, as mentioned above, the effects of both NF-κB and STAT3 are cell type specific, and it is hard to predict the net effect and outcome of systemic intervention. In addition, each NF-κB subunit has overlapping but distinct functions[16,69]. For example, REL and p65 play unique roles in T_{reg} cell development, identity and function[66]. Furthermore, systemic treatment with IKKβ inhibitors was found to potentiate inflammation, owing to enhanced activation of the IL-1-producing NLRP3 inflammasome[48,249]. Therefore, cell-type-specific and subunit-specific inhibition of NF-κB should be taken into consideration. It may also be worth trying to specifically inhibit the alternative NF-κB pathway or NF-κB-independent functions of IKK complex subunits because both promote tumorigenesis in different manners from the classical NF-κB pathway[33,250]. STAT3 inhibition in immune cells and/or tumour cells may actually activate antitumour immunity[251,252], although either hyperactivation or inactivation of STAT3 causes human immune disorders[253]. Perhaps some of the downstream mediators of NF-κB and STAT3 present better opportunities for preventive and therapeutic intervention, as they are less pleiotropic.

Several TNF, IL-1 and IL-6 antagonists and JAK inhibitors are clinically available and have been approved for the treatment of inflammatory and autoimmune diseases, such as IBD and rheumatoid arthritis[22,85]. So far, these drugs do not seem to increase cancer risk in patients with inflammatory and autoimmune diseases, although it was suspected that such treatments may increase cancer incidence owing to inhibition of antitumour immunity[254–256]. After 15 years of basic research in preclinical cancer models, it is time that such inhibitors be tested for their effectiveness in inflammation-dependent cancers. However, side effects of JAK inhibitors include infection, mucositis, anaemia, thrombocytopaenia and liver dysfunction[85,256]. Among these effects, mucositis is one of the principal dose-limiting factors in cancer chemotherapy and radiotherapy[257]; therefore, close attention should be taken when drugs that block the activity of regenerative cytokines and signalling molecules are combined with chemotherapeutic agents or radiation. In a similar vein, the inhibition of IL-6 signalling can lead to intestinal perforation[100,258]. Hence, to minimize such adverse side effects, novel strategies for targeting inflammatory signalling pathways in cell-type-specific and context-specific manners are needed.

Conclusions

Much progress has been made in understanding how inflammation and transcription factors such as NF-κB and STAT3 affect cancer. The general principles through which inflammation and inflammatory signalling promote cancer and modulate its response to therapy have been uncovered. Moreover, the detailed action of these factors in specific cancer types, especially colon and liver cancers, is now quite well understood. Although more remains to be discovered, especially concerning how to reproducibly convert tumour-promoting inflammation into tumour-rejecting immunity, it is time that some of the basic findings made in the past 15 years, reviewed above, be put into practice.

1. Balkwill, F. & Mantovani, A. Inflammation and cancer: back to Virchow? *Lancet* **357**, 539–545 (2001).
2. Coussens, L. M. & Werb, Z. Inflammation and cancer. *Nature* **420**, 860–867 (2002).
3. Fujiki, H. Gist of Dr. Katsusaburo Yamagiwa's papers entitled "Experimental study on the pathogenesis of epithelial tumors" (I to VI reports). *Cancer Sci.* **105**, 143–149 (2014).
4. Greten, F. R. *et al.* IKKβ links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* **118**, 285–296 (2004).
5. Pikarsky, E. *et al.* NF-κB functions as a tumour promoter in inflammation-associated cancer. *Nature* **431**, 461–466 (2004).
References 4 and 5 are the first reports to identify NF-κB as a central player that links inflammation to cancer.
6. Kuper, H., Adami, H. O. & Trichopoulos, D. Infections as a major preventable cause of human cancer. *J. Intern. Med.* **248**, 171–183 (2000).
7. Plummer, M. *et al.* Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob. Health* **4**, e609–e616 (2016).
8. Grivennikov, S. I., Greten, F. R. & Karin, M. Immunity, inflammation, and cancer. *Cell* **140**, 883–899 (2010).
Reference 8 is an excellent comprehensive review that describes the roles of inflammation and immunity in cancer.
9. Calle, E. E., Rodriguez, C., Walker-Thurmond, K. & Thun, M. J. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U. S. adults. *N. Engl. J. Med.* **348**, 1625–1638 (2003).
10. Shalapour, S. & Karin, M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J. Clin. Invest.* **125**, 3347–3355 (2015).
11. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
This review describes the ten hallmarks of cancer.
12. Karin, M. & Clevers, H. Reparative inflammation takes charge of tissue regeneration. *Nature* **529**, 307–315 (2016).
This review describes how inflammation regulates tissue regeneration.
13. Sen, R. & Baltimore, D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell* **46**, 705–716 (1986).
14. Zhang, Q., Lenardo, M. J. & Baltimore, D. 30 Years of NF-κB: a blossoming of relevance to human pathobiology. *Cell* **168**, 37–57 (2017).
15. Karin, M. Nuclear factor-κB in cancer development and progression. *Nature* **441**, 431–436 (2006).
16. Perkins, N. D. The diverse and complex roles of NF-κB subunits in cancer. *Nat. Rev. Cancer* **12**, 121–132 (2012).
17. Karin, M. & Greten, F. R. NF-κB: linking inflammation and immunity to cancer development and progression. *Nat. Rev. Immunol.* **5**, 749–759 (2005).
18. Staudt, L. M. Oncogenic activation of NF-κB. *Cold Spring Harb. Perspect. Biol.* **2**, a000109 (2010).
19. Ben-Neriah, Y. & Karin, M. Inflammation meets cancer, with NF-κB as the matchmaker. *Nat. Immunol.* **12**, 715–723 (2011).
20. DiDonato, J. A., Mercurio, F. & Karin, M. NF-κB and the link between inflammation and cancer. *Immunol. Rev.* **246**, 379–400 (2012).
21. Terzic, J., Grivennikov, S., Karin, E. & Karin, M. Inflammation and colon cancer. *Gastroenterology* **138**, 2101–2114 (2010).
22. Lasry, A., Zinger, A. & Ben-Neriah, Y. Inflammatory networks underlying colorectal cancer. *Nat. Immunol.* **17**, 230–240 (2016).
23. West, N. R., McCuaig, S., Franchini, F. & Powrie, F. Emerging cytokine networks in colorectal cancer. *Nat. Rev. Immunol.* **15**, 615–629 (2015).
References 22 and 23 are excellent Reviews that describe the roles of inflammation and cytokines in colorectal cancer.
24. Grivennikov, S. I. *et al.* Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature* **491**, 254–258 (2012).
25. Wang, K. *et al.* Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. *Immunity* **41**, 1052–1063 (2014).
References 24 and 25 reveal how 'tumour-elicited inflammation' is induced and promotes tumorigenesis in spontaneous colorectal cancer.
26. Schwitalla, S. *et al.* Loss of p53 in enterocytes generates an inflammatory microenvironment enabling invasion and lymph node metastasis of carcinogen-induced colorectal tumors. *Cancer Cell* **23**, 93–106 (2013).
This study shows that loss of p53 in IECs results in NF-κB activation.
27. Vallabhapurapu, S. & Karin, M. Regulation and function of NF-κB transcription factors in the immune system. *Annu. Rev. Immunol.* **27**, 693–733 (2009).

28. Sun, S. C. The non-canonical NF-κB pathway in immunity and inflammation. *Nat. Rev. Immunol.* **17**, 545–558 (2017).
29. Bonizzi, G. & Karin, M. The two NF-κB activation pathways and their role in innate and adaptive immunity. *Trends Immunol.* **25**, 280–288 (2004).
30. Vallabhapurapu, S. *et al.* Nonredundant and complementary functions of TRAF2 and TRAF3 in a ubiquitination cascade that activates NIK-dependent alternative NF-κB signaling. *Nat. Immunol.* **9**, 1364–1370 (2008).
31. Senftleben, U. *et al.* Activation by IKKα of a second, evolutionary conserved, NF-κB signaling pathway. *Science* **293**, 1495–1499 (2001).
32. Grivennikov, S. I. & Karin, M. Dangerous liaisons: STAT3 and NF-κB collaboration and crosstalk in cancer. *Cytokine Growth Factor Rev.* **21**, 11–19 (2010).
33. Oeckinghaus, A., Hayden, M. S. & Ghosh, S. Crosstalk in NF-κB signaling pathways. *Nat. Immunol.* **12**, 695–708 (2011).
34. Zhong, B., Tien, P. & Shu, H. B. Innate immune responses: crosstalk of signaling and regulation of gene transcription. *Virology* **352**, 14–21 (2006).
35. Ruland, J. Return to homeostasis: downregulation of NF-κB responses. *Nat. Immunol.* **12**, 709–714 (2011).
36. Luo, J. L., Kamata, H. & Karin, M. IKK/NF-κB signaling: balancing life and death — a new approach to cancer therapy. *J. Clin. Invest.* **115**, 2625–2632 (2005).
37. Xu, G. *et al.* Crystal structure of inhibitor of κB kinase β. *Nature* **472**, 325–330 (2011).
38. Rothwarf, D. M. & Karin, M. The NF-κB activation pathway: a paradigm in information transfer from membrane to nucleus. *Sci STKE* **1999**, RE1 (1999).
39. Chen, Z. J. Ubiquitination in signaling to and activation of IKK. *Immunol. Rev.* **246**, 95–106 (2012).
40. Tokunaga, F. & Iwai, K. LUBAC, a novel ubiquitin ligase for linear ubiquitination, is crucial for inflammation and immune responses. *Microbes Infect.* **14**, 563–572 (2012).
41. Ma, X., Becker Buscaglia, L. E., Barker, J. R. & Li, Y. MicroRNAs in NF-κB signaling. *J. Mol. Cell. Biol.* **3**, 159–166 (2011).
42. Boldin, M. P. & Baltimore, D. MicroRNAs, new effectors and regulators of NF-κB. *Immunol. Rev.* **246**, 205–220 (2012).
43. Taganov, K. D., Boldin, M. P., Chang, K. J. & Baltimore, D. NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc. Natl Acad. Sci. USA* **103**, 12481–12486 (2006).
44. Iliopoulos, D., Hirsch, H. A. & Struhl, K. An epigenetic switch involving NF-κB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. *Cell* **139**, 693–706 (2009).
45. Bretz, N. P. *et al.* Body fluid exosomes promote secretion of inflammatory cytokines in monocytic cells via Toll-like receptor signaling. *J. Biol. Chem.* **288**, 36691–36702 (2013).
46. Ghosh, A. *et al.* Telomerase directly regulates NF-κB-dependent transcription. *Nat. Cell Biol.* **14**, 1270–1281 (2012).
This study reveals the association between telomerase and NF-κB.
47. Taniguchi, K., Yamachika, S., He, F. & Karin, M. p62/SQSTM1 — Dr. Jekyll and Mr. Hyde that prevents oxidative stress but promotes liver cancer. *FEBS Lett.* **590**, 2375–2397 (2016).
48. Greten, F. R. *et al.* NF-κB is a negative regulator of IL-1β secretion as revealed by genetic and pharmacological inhibition of IKKβ. *Cell* **130**, 918–931 (2007).
49. Zhong, Z. *et al.* NF-κB restricts inflammasome activation via elimination of damaged mitochondria. *Cell* **164**, 896–910 (2016).
Reference 48 reports an unanticipated role of NF-κB as a negative regulator of inflammation, and reference 49 reveals the mechanism of how NF-κB suppresses inflammation.
50. Atretkhany, K. N., Drutskaya, M. S., Nedospasov, S. A., Grivennikov, S. I. & Kuprash, D. V. Chemokines, cytokines and exosomes help tumors to shape inflammatory microenvironment. *Pharmacol. Ther.* **168**, 98–112 (2016).
51. Quail, D. F. & Joyce, J. A. Microenvironmental regulation of tumor progression and metastasis. *Nat. Med.* **19**, 1423–1437 (2013).
52. Martinez, F. O. & Gordon, S. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep.* **6**, 13 (2014).
53. Sica, A. & Mantovani, A. Macrophage plasticity and polarization: *in vivo* veritas. *J. Clin. Invest.* **122**, 787–795 (2012).
54. Murray, P. J. Macrophage polarization. *Annu. Rev. Physiol.* **79**, 541–566 (2017).
55. Porta, C. *et al.* Tolerance and M2 (alternative) macrophage polarization are related processes orchestrated by p50 nuclear factor κB. *Proc. Natl Acad. Sci. USA* **106**, 14978–14983 (2009).
56. Hagemann, T. *et al.* "Re-educating" tumor-associated macrophages by targeting NF-κB. *J. Exp. Med.* **205**, 1261–1268 (2008).
57. Ma, Y., Shurin, G. V., Peiyuan, Z. & Shurin, M. R. Dendritic cells in the cancer microenvironment. *J. Cancer* **4**, 36–44 (2013).
58. Karyampudi, L. *et al.* PD-1 blunts the function of ovarian tumor-infiltrating dendritic cells by inactivating NF-κB. *Cancer Res.* **76**, 239–250 (2016).
59. Tu, S. *et al.* Overexpression of interleukin-1β induces gastric inflammation and cancer and mobilizes myeloid-derived suppressor cells in mice. *Cancer Cell* **14**, 408–419 (2008).
60. Vivier, E., Tomasello, E., Baratin, M., Walzer, T. & Ugolini, S. Functions of natural killer cells. *Nat. Immunol.* **9**, 503–510 (2008).
61. Zhou, J., Zhang, J., Lichtenheld, M. G. & Meadows, G. G. A role for NF-κB activation in perforin expression of NK cells upon IL-2 receptor signaling. *J. Immunol.* **169**, 1319–1325 (2002).
62. Huang, C. *et al.* A novel NF-κB binding site controls human granzyme B gene transcription. *J. Immunol.* **176**, 4173–4181 (2006).
63. Ward, J. P., Gubin, M. M. & Schreiber, R. D. The role of neoantigens in naturally occurring and therapeutically induced immune responses to cancer. *Adv. Immunol.* **130**, 25–74 (2016).
64. Gerondakis, S. & Siebenlist, U. Roles of the NF-κB pathway in lymphocyte development and function. *Cold Spring Harb. Perspect. Biol.* **2**, a000182 (2010).
65. Gerondakis, S., Fulford, T. S., Messina, N. L. & Grumont, R. J. NF-κB control of T cell development. *Nat. Immunol.* **15**, 15–25 (2014).
66. Oh, H. *et al.* An NF-κB transcription-factor-dependent lineage-specific transcriptional program promotes regulatory T cell identity and function. *Immunity* **47**, 450–465 (2017).
67. Shang, B., Liu, Y., Jiang, S. J. & Liu, Y. Prognostic value of tumor-infiltrating FoxP3$^+$ regulatory T cells in cancers: a systematic review and meta-analysis. *Sci. Rep.* **5**, 15179 (2015).
68. Grinberg-Bleyer, Y. *et al.* NF-κB c-Rel Is Crucial for the Regulatory T Cell Immune Checkpoint in Cancer. *Cell* **170**, 1096–1108 (2017).
Reference 68 shows that REL deletion or inhibition in T_{reg} cells potentiates anti-PD1 therapy and suppresses tumour growth.
69. Gerondakis, S. *et al.* NF-κB subunit specificity in hemopoiesis. *Immunol. Rev.* **246**, 272–285 (2012).
70. Evaristo, C. *et al.* Cutting edge: engineering active IKKβ in T cells drives tumor rejection. *J. Immunol.* **196**, 2933–2938 (2016).
71. Hopewell, E. L. *et al.* Lung tumor NF-κB signaling promotes T cell-mediated immune surveillance. *J. Clin. Invest.* **123**, 2509–2522 (2013).
72. Giampazolias, E. *et al.* Mitochondrial permeabilization engages NF-κB-dependent anti-tumour activity under caspase deficiency. *Nat. Cell Biol.* **19**, 1116–1129 (2017).
73. Ammirante, M., Luo, J. L., Grivennikov, S., Nedospasov, S. & Karin, M. B-Cell-derived lymphotoxin promotes castration-resistant prostate cancer. *Nature* **464**, 302–305 (2010).
74. Ammirante, M. *et al.* An IKKα-E2F1-BMI1 cascade activated by infiltrating B cells controls prostate regeneration and tumor recurrence. *Genes Dev.* **27**, 1435–1440 (2013).
75. Ammirante, M., Shalapour, S., Kang, Y., Jamieson, C. A. & Karin, M. Tissue injury and hypoxia promote malignant progression of prostate cancer by inducing CXCL13 expression in tumor myofibroblasts. *Proc. Natl Acad. Sci. USA* **111**, 14776–14781 (2014).
76. Shalapour, S. *et al.* Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. *Nature* **521**, 94–98 (2015).
This is the first report to describe IgA$^+$ immunosuppressive plasma cells, which suppress CTL activation.
77. Kalluri, R. The biology and function of fibroblasts in cancer. *Nat. Rev. Cancer* **16**, 582–598 (2016).
78. Koliaraki, V., Pallangyo, C. K., Greten, F. R. & Kollias, G. Mesenchymal cells in colon cancer. *Gastroenterology* **152**, 964–979 (2017).
79. Erez, N., Truitt, M., Olson, P., Arron, S. T. & Hanahan, D. Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-κB-dependent manner. *Cancer Cell* **17**, 135–147 (2010).
80. Calon, A. *et al.* Dependency of colorectal cancer on a TGF-β-driven program in stromal cells for metastasis initiation. *Cancer Cell* **22**, 571–584 (2012).
81. Pallangyo, C. K., Ziegler, P. K. & Greten, F. R. IKKβ acts as a tumor suppressor in cancer-associated fibroblasts during intestinal tumorigenesis. *J. Exp. Med.* **212**, 2253–2266 (2015).
82. Koliaraki, V., Pasparakis, M. & Kollias, G. IKKβ in intestinal mesenchymal cells promotes initiation of colitis-associated cancer. *J. Exp. Med.* **212**, 2235–2251 (2015).
83. Grivennikov, S. I. & Karin, M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann. Rheum. Dis.* **70**, i104–i108 (2011).
84. Balkwill, F. Tumour necrosis factor and cancer. *Nat. Rev. Cancer* **9**, 361–371 (2009).
Reference 84 is an excellent comprehensive Review on the role of TNF in cancer.
85. Taniguchi, K. & Karin, M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. *Semin. Immunol.* **26**, 54–74 (2014).
Reference 85 is a comprehensive review on the role of the IL-6 family of cytokines in solid malignancies.
86. Elmore, S. Apoptosis: a review of programmed cell death. *Toxicol. Pathol.* **35**, 495–516 (2007).
87. Vanden Berghe, T., Linkermann, A., Jouan-Lanhouet, S., Walczak, H. & Vandenabeele, P. Regulated necrosis: the expanding network of non-apoptotic cell death pathways. *Nat. Rev. Mol. Cell Biol.* **15**, 135–147 (2014).
88. Pasparakis, M. & Vandenabeele, P. Necroptosis and its role in inflammation. *Nature* **517**, 311–320 (2015).
89. Voronov, E. & Apte, R. N. IL-1 in colon inflammation, colon carcinogenesis and invasiveness of colon cancer. *Cancer Microenviron* **8**, 187–200 (2015).
90. Garlanda, C., Dinarello, C. A. & Mantovani, A. The interleukin-1 family: back to the future. *Immunity* **39**, 1003–1018 (2013).
91. Lu, B., Yang, M. & Wang, Q. Interleukin-33 in tumorigenesis, tumor immune evasion, and cancer immunotherapy. *J. Mol. Med.* **94**, 535–543 (2016).
92. Liew, F. Y., Girard, J. P. & Turnquist, H. R. Interleukin-33 in health and disease. *Nat. Rev. Immunol.* **16**, 676–689 (2016).
93. Ali, S. *et al.* The dual function cytokine IL-33 interacts with the transcription factor NF-κB to dampen NF-κB-stimulated gene transcription. *J. Immunol.* **187**, 1609–1616 (2011).
94. Choi, Y. S. *et al.* Nuclear IL-33 is a transcriptional regulator of NF-κB p65 and induces endothelial cell activation. *Biochem. Biophys. Res. Commun.* **421**, 305–311 (2012).
95. Croxford, A. L., Kulig, P. & Becher, B. IL-12-and IL-23 in health and disease. *Cytokine Growth Factor Rev.* **25**, 415–421 (2014).
96. Song, X. & Qian, Y. IL-17 family cytokines mediated signaling in the pathogenesis of inflammatory diseases. *Cell Signal.* **25**, 2335–2347 (2013).
97. Yang, B. *et al.* The role of interleukin 17 in tumour proliferation, angiogenesis, and metastasis. *Mediators Inflamm.* **2014**, 623759 (2014).
98. Chang, Q., Daly, L. & Bromberg, J. The IL-6 feed-forward loop: a driver of tumorigenesis. *Semin. Immunol.* **26**, 48–53 (2014).
99. He, G. *et al.* Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. *Cell* **155**, 384–396 (2013).
100. Taniguchi, K. *et al.* A gp130-Src-YAP module links inflammation to epithelial regeneration. *Nature* **519**, 57–62 (2015).
101. Taniguchi, K. *et al.* YAP-IL-6ST autoregulatory loop activated on APC loss controls colonic tumorigenesis. *Proc. Natl Acad. Sci. USA* **114**, 1643–1648 (2017).
References 100 and 101 reveal that the SRC–YAP pathway links inflammation to tissue regeneration and plays an important role in colorectal cancer.
102. Tian, G., Li, J. L., Wang, D. G. & Zhou, D. Targeting IL-10 in auto-immune diseases. *Cell Biochem. Biophys.* **70**, 37–49 (2014).
103. Lim, C. & Savan, R. The role of the IL-22/IL-22R1 axis in cancer. *Cytokine Growth Factor Rev.* **25**, 257–271 (2014).

104. Meulmeester, E. & Ten Dijke, P. The dynamic roles of TGF-β in cancer. *J. Pathol.* **223**, 205–218 (2011).
105. Richmond, A. Nf-κB, chemokine gene transcription and tumour growth. *Nat. Rev. Immunol.* **2**, 664–674 (2002).
106. Chow, M. T. & Luster, A. D. Chemokines in cancer. *Cancer Immunol. Res.* **2**, 1125–1131 (2014).
107. Weitzenfeld, P. & Ben-Baruch, A. The chemokine system, and its CCR5 and CXCR4 receptors, as potential targets for personalized therapy in cancer. *Cancer Lett.* **352**, 36–53 (2014).
108. Levine, B., Mizushima, N. & Virgin, H. W. Autophagy in immunity and inflammation. *Nature* **469**, 323–335 (2011).
109. White, E., Karp, C., Strohecker, A. M., Guo, Y. & Mathew, R. Role of autophagy in suppression of inflammation and cancer. *Curr. Opin. Cell Biol.* **22**, 212–217 (2010).
110. Zhong, Z., Sanchez-Lopez, E. & Karin, M. Autophagy, inflammation, and immunity: a troika governing cancer and its treatment. *Cell* **166**, 288–298 (2016).
111. Salminen, A., Hyttinen, J. M., Kauppinen, A. & Kaarniranta, K. Context-dependent regulation of autophagy by IKK-NF-κB signaling: impact on the aging process. *Int. J. Cell Biol.* **2012**, 849541 (2012).
112. Baldwin, A. S. Regulation of cell death and autophagy by IKK and NF-κB: critical mechanisms in immune function and cancer. *Immunol. Rev.* **246**, 327–345 (2012).
113. Copetti, T., Bertoli, C., Dalla, E., Demarchi, F. & Schneider, C. p65/RelA modulates BECN1 transcription and autophagy. *Mol. Cell. Biol.* **29**, 2594–2608 (2009).
114. Ren, J. L., Pan, J. S., Lu, Y. P., Sun, P. & Han, J. Inflammatory signaling and cellular senescence. *Cell Signal.* **21**, 378–383 (2009).
115. Capece, D. *et al.* Cancer secretome and inflammation: the bright and the dark sides of NF-κB. *Semin. Cell Dev. Biol.* http://dx.doi.org/10.1016/j.semcdb.2017.08.004 (2017).
116. Yoshimoto, S. *et al.* Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* **499**, 97–101 (2013).
117. Jing, H. & Lee, S. NF-κB in cellular senescence and cancer treatment. *Mol. Cells* **37**, 189–195 (2014).
118. Chien, Y. *et al.* Control of the senescence-associated secretory phenotype by NF-κB promotes senescence and enhances chemosensitivity. *Genes Dev.* **25**, 2125–2136 (2011).
119. Soria-Valles, C. *et al.* NF-κB activation impairs somatic cell reprogramming in ageing. *Nat. Cell Biol.* **17**, 1004–1013 (2015).
120. Pesic, M. & Greten, F. R. Inflammation and cancer: tissue regeneration gone awry. *Curr. Opin. Cell Biol.* **43**, 55–61 (2016).
121. Su, T. *et al.* Two-signal requirement for growth-promoting function of Yap in hepatocytes. *eLife* **4,** e02948 (2015).
122. Chen, Q. *et al.* Homeostatic control of Hippo signaling activity revealed by an endogenous activating mutation in YAP. *Genes Dev.* **29**, 1285–1297 (2015).
123. Maeda, S., Kamata, H., Luo, J. L., Leffert, H. & Karin, M. IKKβ couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. *Cell* **121**, 977–990 (2005).
124. Yamada, Y., Kirillova, I., Peschon, J. J. & Fausto, N. Initiation of liver growth by tumor necrosis factor: deficient liver regeneration in mice lacking type I tumor necrosis factor receptor. *Proc. Natl Acad. Sci. USA* **94**, 1441–1446 (1997).
125. Cressman, D. E. *et al.* Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. *Science* **274**, 1379–1383 (1996).
126. Dvorak, H. F. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N. Engl. J. Med.* **315**, 1650–1659 (1986).
127. Shigdar, S. *et al.* Inflammation and cancer stem cells. *Cancer Lett.* **345**, 271–278 (2014).
128. Tanno, T. & Matsui, W. Development and maintenance of cancer stem cells under chronic inflammation. *J. Nippon Med. Sch.* **78**, 138–145 (2011).
129. Blaylock, R. L. Cancer microenvironment, inflammation and cancer stem cells: A hypothesis for a paradigm change and new targets in cancer control. *Surg. Neurol. Int.* **6**, 92 (2015).
130. Vazquez-Santillan, K., Melendez-Zajgla, J., Jimenez-Hernandez, L., Martinez-Ruiz, G. & Maldonado, V. NF-κB signaling in cancer stem cells: a promising therapeutic target? *Cell Oncol.* **38**, 327–339 (2015).
131. Rinkenbaugh, A. L. & Baldwin, A. S. The NF-κB pathway and cancer stem cells. *Cells* **5,** 16 (2016).
132. Wu, Y. & Zhou, B. P. Inflammation: a driving force speeds cancer metastasis. *Cell Cycle* **8**, 3267–3273 (2009).
133. Miao, J. W., Liu, L. J. & Huang, J. Interleukin-6-induced epithelial-mesenchymal transition through signal transducer and activator of transcription 3 in human cervical carcinoma. *Int. J. Oncol.* **45**, 165–176 (2014).
134. Wendt, M. K., Balanis, N., Carlin, C. R. & Schiemann, W. P. STAT3 and epithelial-mesenchymal transitions in carcinomas. *JAKSTAT* **3**, e28975 (2014).
135. Yamamoto, M. *et al.* NF-κB non-cell-autonomously regulates cancer stem cell populations in the basal-like breast cancer subtype. *Nat. Commun.* **4**, 2299 (2013).
136. Sun, L. *et al.* Epigenetic regulation of *SOX9* by the NF-κB signaling pathway in pancreatic cancer stem cells. *Stem Cells* **31**, 1454–1466 (2013).
137. Baker, R. G., Hayden, M. S. & Ghosh, S. NF-κB, inflammation, and metabolic disease. *Cell Metab.* **13**, 11–22 (2011).
138. Johnson, R. F. & Perkins, N. D. Nuclear factor-κB, p53, and mitochondria: regulation of cellular metabolism and the Warburg effect. *Trends Biochem. Sci.* **37**, 317–324 (2012).
139. Xia, Y., Shen, S. & Verma, I. M. NF-κB, an active player in human cancers. *Cancer Immunol. Res.* **2**, 823–830 (2014).
140. Liu, J. *et al.* Inflammation Improves Glucose Homeostasis through IKKβ-XBP1s Interaction. *Cell* **167**, 1052–1066 (2016).
141. Mauro, C. *et al.* NF-κB controls energy homeostasis and metabolic adaptation by upregulating mitochondrial respiration. *Nat. Cell Biol.* **13**, 1272–1279 (2011).
This study shows that NF-κB plays an important role in metabolic adaptation in normal cells and in cancer cells.
142. Kawauchi, K. Araki, K., Tobiume, K. and Tanaka, N. p53 regulates glucose metabolism through an IKK-NF-κB pathway and inhibits cell transformation. *Nat. Cell Biol.* **10**, 611–618 (2008).
143. Kawauchi, K., Araki, K., Tobiume, K. & Tanaka, N. Loss of p53 enhances catalytic activity of IKKbeta through O-linked β-N-acetyl glucosamine modification. *Proc. Natl Acad. Sci. USA* **106**, 3431–3436 (2009).
144. Pitot, H. C., Goldsworthy, T. & Moran, S. The natural history of carcinogenesis: implications of experimental carcinogenesis in the genesis of human cancer. *J. Supramol. Struct. Cell Biochem.* **17**, 133–146 (1981).
145. Barcellos-Hoff, M. H., Lyden, D. & Wang, T. C. The evolution of the cancer niche during multistage carcinogenesis. *Nat. Rev. Cancer* **13**, 511–518 (2013).
146. Fearon, E. R. & Vogelstein, B. A genetic model for colorectal tumorigenesis. *Cell* **61**, 759–767 (1990).
147. Joyce, D. *et al.* NF-κB and cell-cycle regulation: the cyclin connection. *Cytokine Growth Factor Rev.* **12**, 73–90 (2001).
148. Kiraly, O., Gong, G., Olipitz, W., Muthupalani, S. & Engelward, B. P. Inflammation-induced cell proliferation potentiates DNA damage-induced mutations *in vivo*. *PLoS Genet.* **11**, e1004901 (2015).
149. Colotta, F., Allavena, P., Sica, A., Garlanda, C. & Mantovani, A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* **30**, 1073–1081 (2009).
150. Ren, J., Wang, Y., Gao, Y., Mehta, S.B. & Lee ,C.G. FAT10 mediates the effect of TNF-α in inducing chromosomal instability. *J. Cell Sci.* **124**, 3665–3675 (2011).
151. Vento-Tormo, R. *et al*. NF-κB directly mediates epigenetic deregulation of common microRNAs in Epstein–Barr virus-mediated transformation of B-cells and in lymphomas. *Nucleic Acids Res.* **42**, 11025–11039 (2014).
152. Nakshatri, H. *et al*. NF-κB-dependent and -independent epigenetic modulation using the novel anti-cancer agent DMAPT. *Cell Death Dis.* **6**, e1608 (2015).
153. Shimizu, T., Marusawa, H., Endo, Y. & Chiba, T. Inflammation-mediated genomic instability: roles of activation-induced cytidine deaminase in carcinogenesis. *Cancer Sci.* **103**, 1201–1206 (2012).
154. Park, S. R. Activation-induced cytidine deaminase in B cell immunity and cancers. *Immune Netw.* **12**, 230–239 (2012).
155. Seplyarskiy, V. B. *et al.* APOBEC-induced mutations in human cancers are strongly enriched on the lagging DNA strand during replication. *Genome Res.* **26**, 174–182 (2016).
156. Leonard, B. *et al.* The PKC/NF-κB signaling pathway induces APOBEC3B expression in multiple human cancers. *Cancer Res.* **75**, 4538–4547 (2015).
157. Maruyama, W. *et al.* Classical NF-κB pathway is responsible for APOBEC3B expression in cancer cells. *Biochem. Biophys. Res. Commun.* **478**, 1466–1471 (2016).
158. Gudkov, A. V., Gurova, K. V. & Komarova, E. A. Inflammation and p53: A Tale of Two Stresses. *Genes Cancer* **2**, 503–516 (2011).
159. Joneson, T. & Bar-Sagi, D. Suppression of Ras-induced apoptosis by the Rac GTPase. *Mol. Cell. Biol.* **19**, 5892–5901 (1999).
160. You, Z., Madrid, L. V., Saims, D., Sedivy, J. & Wang, C. Y. c-Myc sensitizes cells to tumor necrosis factor-mediated apoptosis by inhibiting nuclear factor κB transactivation. *J. Biol. Chem.* **277**, 36671–36677 (2002).
161. Basseres, D. S., Ebbs, A., Levantini, E. & Baldwin, A. S. Requirement of the NF-κB subunit p65/RelA for K-Ras-induced lung tumorigenesis. *Cancer Res.* **70**, 3537–3546 (2010).
162. Pires, B. R. *et al.* NF-κB Is Involved in the regulation of EMT genes in breast cancer cells. *PLoS ONE* **12**, e0169622 (2017).
163. Scheel, C. & Weinberg, R. A. Cancer stem cells and epithelial-mesenchymal transition: concepts and molecular links. *Semin. Cancer Biol.* **22**, 396–403 (2012).
164. Huber, M. A. *et al.* NF-κB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. *J. Clin. Invest.* **114**, 569–581 (2004).
165. Psaila, B. & Lyden, D. The metastatic niche: adapting the foreign soil. *Nat. Rev. Cancer* **9**, 285–293 (2009).
166. Huang, S., Pettaway, C. A., Uehara, H., Bucana, C. D. & Fidler, I. J. Blockade of NF-κB activity in human prostate cancer cells is associated with suppression of angiogenesis, invasion, and metastasis. *Oncogene* **20**, 4188–4197 (2001).
167. Gorlach, A. & Bonello, S. The cross-talk between NF-κB and HIF-1: further evidence for a significant liaison. *Biochem. J.* **412**, e17–19 (2008).
168. Gilkes, D. M. & Semenza, G. L. Role of hypoxia-inducible factors in breast cancer metastasis. *Future Oncol.* **9**, 1623–1636 (2013).
169. Zhang, W. *et al.* HIF-1α promotes epithelial-mesenchymal transition and metastasis through direct regulation of ZEB1 in colorectal cancer. *PLoS ONE* **10**, e0129603 (2015).
170. Drabsch, Y. & ten Dijke, P. TGF-β signalling and its role in cancer progression and metastasis. *Cancer Metastasis Rev.* **31**, 553–568 (2012).
171. Kisseleva, T. *et al.* NF-κB regulation of endothelial cell function during LPS-induced toxemia and cancer. *J. Clin. Invest.* **116**, 2955–2963 (2006).
172. Tabruyn, S. P. & Griffioen, A. W. NF-κB: a new player in angiostatic therapy. *Angiogenesis* **11**, 101–106 (2008).
173. Costa, C., Incio, J. & Soares, R. Angiogenesis and chronic inflammation: cause or consequence? *Angiogenesis* **10**, 149–166 (2007).
174. Spina, A. *et al.* HGF/c-MET axis in tumor microenvironment and metastasis formation. *Biomedicines* **3**, 71–88 (2015).
175. Balkwill, F. Cancer and the chemokine network. *Nat. Rev. Cancer* **4**, 540–550 (2004).
176. Grivennikov, S. *et al.* IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell* **15**, 103–113 (2009).
177. Bollrath, J. *et al.* gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. *Cancer Cell* **15**, 91–102 (2009).
178. Tosolini, M. *et al.* Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, Th2, Treg, Th17) in patients with colorectal cancer. *Cancer Res.* **71**, 1263–1271 (2011).
179. Schetter, A. J. *et al.* Association of inflammation-related and microRNA gene expression with cancer-specific mortality of colon adenocarcinoma. *Clin. Cancer Res.* **15**, 5878–5887 (2009).
180. Hinoi, T. *et al.* Mouse model of colonic adenoma-carcinoma progression based on somatic Apc inactivation. *Cancer Res.* **67**, 9721–9730 (2007).
181. Fearnhead, N. S., Britton, M. P. & Bodmer, W. F. The ABC of APC. *Hum. Mol. Genet.* **10**, 721–733 (2001).

182. Ulrich, C. M., Bigler, J. & Potter, J. D. Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics. *Nat. Rev. Cancer* **6**, 130–140 (2006).
183. Guma, M. *et al.* Constitutive intestinal NF-κB does not trigger destructive inflammation unless accompanied by MAPK activation. *J. Exp. Med.* **208**, 1889–1900 (2011).
184. Shaked, H. *et al.* Chronic epithelial NF-κB activation accelerates APC loss and intestinal tumor initiation through iNOS up-regulation. *Proc. Natl Acad. Sci. USA* **109**, 14007–14012 (2012).
185. Vlantis, K. *et al.* Constitutive IKK2 activation in intestinal epithelial cells induces intestinal tumors in mice. *J. Clin. Invest.* **121**, 2781–2793 (2011).
186. Myant, K. B. *et al.* ROS production and NF-κB activation triggered by RAC1 facilitate WNT-driven intestinal stem cell proliferation and colorectal cancer initiation. *Cell Stem Cell* **12**, 761–773 (2013).
187. Mittal, S. & El-Serag, H. B. Epidemiology of hepatocellular carcinoma: consider the population. *J. Clin. Gastroenterol.* **47** (Suppl.), S2–S6, (2013).
188. Mauad, T. H. *et al.* Mice with homozygous disruption of the mdr2 P-glycoprotein gene. A novel animal model for studies of nonsuppurative inflammatory cholangitis and hepatocarcinogenesis. *Am. J. Pathol.* **145**, 1237–1245 (1994).
189. Kong, L. *et al.* Deletion of interleukin-6 in monocytes/macrophages suppresses the initiation of hepatocellular carcinoma in mice. *J. Exp. Clin. Cancer Res.* **35**, 131 (2016).
190. Sakurai, T. *et al.* Hepatocyte necrosis induced by oxidative stress and IL-1 alpha release mediate carcinogen-induced compensatory proliferation and liver tumorigenesis. *Cancer Cell* **14**, 156–165 (2008).
191. He, G. *et al.* Hepatocyte IKKbeta/NF-κB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. *Cancer Cell* **17**, 286–297 (2010).
192. Nakagawa, H. *et al.* ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. *Cancer Cell* **26**, 331–343 (2014).
193. Park, E. J. *et al.* Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell* **140**, 197–208 (2010).
References 192 and 193 reveal the importance of TNF-mediated NF-κB signalling in obesity-associated HCC.
194. Luedde, T. *et al.* Deletion of NEMO/IKKgamma in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma. *Cancer Cell* **11**, 119–132 (2007).
195. Kondylis, V. *et al.* NEMO prevents steatohepatitis and hepatocellular carcinoma by inhibiting RIPK1 kinase activity-mediated hepatocyte apoptosis. *Cancer Cell* **28**, 582–598 (2015).
196. Naugler, W. E. *et al.* Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* **317**, 121–124 (2007).
197. Stein, B. & Yang, M. X. Repression of the interleukin-6 promoter by estrogen receptor is mediated by NF-κB and C/EBPβ. *Mol. Cell. Biol.* **15**, 4971–4979 (1995).
198. Galien, R. & Garcia, T. Estrogen receptor impairs interleukin-6 expression by preventing protein binding on the NF-κB site. *Nucleic Acids Res.* **25**, 2424–2429 (1997).
199. Liu, H., Liu, K. & Bodenner, D. L. Estrogen receptor inhibits interleukin-6 gene expression by disruption of nuclear factor κB transactivation. *Cytokine* **31**, 251–257 (2005).
200. Wang, H. *et al.* Hepatoprotective versus oncogenic functions of STAT3 in liver tumorigenesis. *Am. J. Pathol.* **179**, 714–724 (2011).
201. Finkin, S. *et al.* Ectopic lymphoid structures function as microniches for tumor progenitor cells in hepatocellular carcinoma. *Nat. Immunol.* **16**, 1235–1244 (2015).
This study shows that constitutive activation of NF-κB in hepatocytes results in HCC development.
202. Pitzalis, C., Jones, G. W., Bombardieri, M. & Jones, S. A. Ectopic lymphoid-like structures in infection, cancer and autoimmunity. *Nat. Rev. Immunol.* **14**, 447–462 (2014).
203. Haybaeck, J. *et al.* A lymphotoxin-driven pathway to hepatocellular carcinoma. *Cancer Cell* **16**, 295–308 (2009).
204. Khandekar, M. J., Cohen, P. & Spiegelman, B. M. Molecular mechanisms of cancer development in obesity. *Nat. Rev. Cancer* **11**, 886–895 (2011).
205. Deng, T., Lyon, C. J., Bergin, S., Caligiuri, M. A. & Hsueh, W. A. Obesity, inflammation, and cancer. *Annu. Rev. Pathol.* **11**, 421–449 (2016).
206. Gilbert, C. A. & Slingerland, J. M. Cytokines, obesity, and cancer: new insights on mechanisms linking obesity to cancer risk and progression. *Annu. Rev. Med.* **64**, 45–57 (2013).
207. Bettermann, K., Hohensee, T. & Haybaeck, J. Steatosis and steatohepatitis: complex disorders. *Int. J. Mol. Sci.* **15**, 9924–9944 (2014).
208. Weglarz, T. C., Degen, J. L. & Sandgren, E. P. Hepatocyte transplantation into diseased mouse liver. Kinetics of parenchymal repopulation and identification of the proliferative capacity of tetraploid and octaploid hepatocytes. *Am. J. Pathol.* **157**, 1963–1974 (2000).
209. Shalapour, S. *et al.* Inflammation-induced IgA$^+$ cells dismantle anti-liver cancer immunity. *Nature* **551**, 340–345 (2017).
210. Prabhu, L., Mundade, R., Korc, M., Loehrer, P. J. & Lu, T. Critical role of NF-κB in pancreatic cancer. *Oncotarget* **5**, 10969–10975 (2014).
211. Greer, J. B. & Whitcomb, D. C. Inflammation and pancreatic cancer: an evidence-based review. *Curr. Opin. Pharmacol.* **9**, 411–418 (2009).
212. Fujioka, S. *et al.* Function of nuclear factor κB in pancreatic cancer metastasis. *Clin. Cancer Res.* **9**, 346–354 (2003).
213. Dima, S. O. *et al.* An exploratory study of inflammatory cytokines as prognostic biomarkers in patients with ductal pancreatic adenocarcinoma. *Pancreas* **41**, 1001–1007 (2012).
214. Ling, J. *et al.* KrasG12D-induced IKK2/β/NF-κB activation by IL-α and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. *Cancer Cell* **21**, 105–120 (2012).
215. Ebrahimi, B., Tucker, S. L., Li, D., Abbruzzese, J. L. & Kurzrock, R. Cytokines in pancreatic carcinoma: correlation with phenotypic characteristics and prognosis. *Cancer* **101**, 2727–2736 (2004).
216. Bellone, G. *et al.* Cytokine expression profile in human pancreatic carcinoma cells and in surgical specimens: implications for survival. *Cancer Immunol. Immunother.* **55**, 684–698 (2006).
217. Bryant, K. L., Mancias, J. D., Kimmelman, A. C. & Der, C. J. KRAS: feeding pancreatic cancer proliferation. *Trends Biochem. Sci.* **39**, 91–100 (2014).
218. Maniati, E. *et al.* Crosstalk between the canonical NF-κB and Notch signaling pathways inhibits Pparγ expression and promotes pancreatic cancer progression in mice. *J. Clin. Invest.* **121**, 4685–4699 (2011).
219. Lesina, M. *et al.* Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. *Cancer Cell* **19**, 456–469 (2011).
220. Khasawneh, J. *et al.* Inflammation and mitochondrial fatty acid beta-oxidation link obesity to early tumor promotion. *Proc. Natl Acad. Sci. USA* **106**, 3354–3359 (2009).
221. Li, N. *et al.* Loss of acinar cell IKKalpha triggers spontaneous pancreatitis in mice. *J. Clin. Invest.* **123**, 2231–2243 (2013).
222. Todoric, J. A. *et al.* Stress activated NRF2-MDM2 cascade controls neoplastic progression in pancreas. *Cancer Cell* **32**, 824–839 (2017).
223. Sfanos, K. S. & De Marzo, A. M. Prostate cancer and inflammation: the evidence. *Histopathology* **60**, 199–215 (2012).
224. Rajasekhar, V. K., Studer, L., Gerald, W., Socci, N. D. & Scher, H. I. Tumour-initiating stem-like cells in human prostate cancer exhibit increased NF-κB signalling. *Nat. Commun.* **2**, 162 (2011).
225. Jin, R. *et al.* NF-κB gene signature predicts prostate cancer progression. *Cancer Res.* **74**, 2763–2772 (2014).
226. Tse, B. W., Scott, K. F. & Russell, P. J. Paradoxical roles of tumour necrosis factor-alpha in prostate cancer biology. *Prostate Cancer* **2012**, 128965 (2012).
227. Nguyen, D. P., Li, J. & Tewari, A. K. Inflammation and prostate cancer: the role of interleukin 6 (IL-6). *BJU Int.* **113**, 986–992 (2014).
228. Luo, J. L. *et al.* Nuclear cytokine-activated IKKalpha controls prostate cancer metastasis by repressing Maspin. *Nature* **446**, 690–694 (2007).
229. Diamanti, M. A. *et al.* IKKalpha controls ATG16L1 degradation to prevent ER stress during inflammation. *J. Exp. Med.* **214**, 423–437 (2017).
230. Chen, W., Li, Z., Bai, L. & Lin, Y. NF-κB in lung cancer, a carcinogenesis mediator and a prevention and therapy target. *Front. Biosci.* **16**, 1172–1185 (2011).
231. Cai, Z., Tchou-Wong, K. M. & Rom, W. N. NF-κB in lung tumorigenesis. *Cancers* **3**, 4258–4268 (2011).
232. Mizuno, S. *et al.* Chronic obstructive pulmonary disease and interstitial lung disease in patients with lung cancer. *Respirology* **14**, 377–383 (2009).
233. Tang, X. *et al.* Nuclear factor-κB (NF-κB) is frequently expressed in lung cancer and preneoplastic lesions. *Cancer* **107**, 2637–2646 (2006).
234. Takahashi, H., Ogata, H., Nishigaki, R., Broide, D. H. & Karin, M. Tobacco smoke promotes lung tumorigenesis by triggering IKKβ- and JNK1-dependent inflammation. *Cancer Cell* **17**, 89–97 (2010).
235. Meylan, E. *et al.* Requirement for NF-κB signalling in a mouse model of lung adenocarcinoma. *Nature* **462**, 104–107 (2009).
236. Duran, A. *et al.* The signaling adaptor p62 is an important NF-κB mediator in tumorigenesis. *Cancer Cell* **13**, 343–354 (2008).
237. Bivona, T. G. *et al.* FAS and NF-κB signalling modulate dependence of lung cancers on mutant EGFR. *Nature* **471**, 523–526 (2011).
238. Blakely, C. M. *et al.* NF-κB-activating complex engaged in response to EGFR oncogene inhibition drives tumor cell survival and residual disease in lung cancer. *Cell Rep.* **11**, 98–110 (2015).
239. Tohme, S., Simmons, R. L. & Tsung, A. Surgery for cancer: a trigger for metastases. *Cancer Res.* **77**, 1548–1552 (2017).
This is an excellent review that explains how surgery affects cancer metastasis.
240. Segatto, I. *et al.* Surgery-induced wound response promotes stem-like and tumor-initiating features of breast cancer cells, via STAT3 signaling. *Oncotarget* **5**, 6267–6279 (2014).
241. Godwin, P. *et al.* Targeting nuclear factor-kappa B to overcome resistance to chemotherapy. *Front. Oncol.* **3**, 120 (2013).
242. Wang, W., Mani, A. M. & Wu, Z. H. DNA damage-induced nuclear factor-kappa B activation and its roles in cancer progression. *J. Cancer Metastasis Treat.* **3**, 45–49 (2017).
243. Korkaya, H. *et al.* Activation of an IL6 inflammatory loop mediates trastuzumab resistance in HER2$^+$ breast cancer by expanding the cancer stem cell population. *Mol. Cell* **47**, 570–584 (2012).
244. Zitvogel, L., Apetoh, L., Ghiringhelli, F. & Kroemer, G. Immunological aspects of cancer chemotherapy. *Nat. Rev. Immunol.* **8**, 59–73 (2008).
245. Peng, J. *et al.* Chemotherapy induces programmed cell death-ligand 1 overexpression via the nuclear factor-κB to foster an immunosuppressive tumor microenvironment in ovarian cancer. *Cancer Res.* **75**, 5034–5045 (2015).
246. Wang, W., Tam, W. F., Hughes, C. C., Rath, S. & Sen, R. c-Rel is a target of pentoxifylline-mediated inhibition of T lymphocyte activation. *Immunity* **6**, 165–174 (1997).
247. Lin, Y., Bai, L., Chen, W. & Xu, S. The NF-κB activation pathways, emerging molecular targets for cancer prevention and therapy. *Expert Opin. Ther. Targets* **14**, 45–55 (2010).
248. Gurpinar, E., Grizzle, W. E. & Piazza, G. A. NSAIDs inhibit tumorigenesis, but how? *Clin. Cancer Res.* **20**, 1104–1113 (2014).
249. Hsu, L. C. *et al.* IL-1β-driven neutrophilia preserves antibacterial defense in the absence of the kinase IKKβ. *Nat. Immunol.* **12**, 144–150 (2011).
250. Storz, P. Targeting the alternative NF-κB pathway in pancreatic cancer: a new direction for therapy? *Expert Rev. Anticancer Ther.* **13**, 501–504 (2013).
251. Yu, H., Kortylewski, M. & Pardoll, D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. *Nat. Rev. Immunol.* **7**, 41–51 (2007).
252. Ferguson, S. D., Srinivasan, V. M. & Heimberger, A. B. The role of STAT3 in tumor-mediated immune suppression. *J. Neurooncol.* **123**, 385–394 (2015).
253. Hillmer, E. J., Zhang, H., Li, H. S. & Watowich, S. S. STAT3 signaling in immunity. *Cytokine Growth Factor Rev.* **31**, 1–15 (2016).
254. Haynes, K. *et al.* Tumor necrosis factor α inhibitor therapy and cancer risk in chronic immune-mediated diseases. *Arthritis Rheum.* **65**, 48–58 (2013).
255. Rubbert-Roth, A. *et al.* Malignancy rates in patients with rheumatoid arthritis treated with tocilizumab. *RMD Open* **2**, e000213 (2016).
256. Winthrop, K. L. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat. Rev. Rheumatol* **13**, 234–243 (2017).
257. Wardill, H. R., Bowen, J. M. & Gibson, R. J. New pharmacotherapy options for chemotherapy-induced alimentary mucositis. *Expert Opin. Biol. Ther.* **14**, 347–354 (2014).

258. Tanaka, T., Narazaki, M. & Kishimoto, T. Therapeutic targeting of the interleukin-6 receptor. *Annu. Rev. Pharmacol. Toxicol.* **52**, 199–219 (2012).
259. Hoesel, B. & Schmid, J. A. The complexity of NF-κB signaling in inflammation and cancer. *Mol. Cancer* **12**, 86 (2013).
260. Garner, J. M. *et al.* Constitutive activation of signal transducer and activator of transcription 3 (STAT3) and nuclear factor κB signaling in glioblastoma cancer stem cells regulates the Notch pathway. *J. Biol. Chem.* **288**, 26167–26176 (2013).
261. Hagemann, T., Biswas, S. K., Lawrence, T., Sica, A. & Lewis, C. E. Regulation of macrophage function in tumors: the multifaceted role of NF-kappaB. *Blood* **113**, 3139–3146 (2009).
262. Gudkov, A. V. & Komarova, E. A. p53 and the carcinogenicity of chronic inflammation. *Cold Spring Harb. Perspect. Med.* http://dx.doi.org/10.1101/cshperspect.a026161 (2016).
263. Xia, Y. *et al.* Phosphorylation of p53 by IκB kinase 2 promotes its degradation by β-TrCP. *Proc. Natl Acad. Sci. USA* **106**, 2629–2634 (2009).
264. Cooks, T. *et al.* Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. *Cancer Cell* **23**, 634–646 (2013).
265. Pasparakis, M. Role of NF-κB in epithelial biology. *Immunol. Rev.* **246**, 346–358 (2012).
266. Honda, K. & Taniguchi, T. IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. *Nat. Rev. Immunol.* **6**, 644–658 (2006).
267. Iwanaszko, M. & Kimmel, M. NF-κB and IRF pathways: cross-regulation on target genes promoter level. *BMC Genomics* **16**, 307 (2015).
268. Wietek, C., Miggin, S. M., Jefferies, C. A. & O'Neill, L. A. Interferon regulatory factor-3-mediated activation of the interferon-sensitive response element by Toll-like receptor (TLR) 4 but not TLR3 requires the p65 subunit of NF-kappa. *J. Biol. Chem.* **278**, 50923–50931 (2003).
269. Han, K. J. *et al.* Mechanisms of the TRIF-induced interferon-stimulated response element and NF-κB activation and apoptosis pathways. *J. Biol. Chem.* **279**, 15652–15661 (2004).
270. Covert, M. W., Leung, T. H., Gaston, J. E. & Baltimore, D. Achieving stability of lipopolysaccharide-induced NF-κB activation. *Science* **309**, 1854–1857 (2005).
271. Zitvogel, L., Galluzzi, L., Kepp, O., Smyth, M. J. & Kroemer, G. Type I interferons in anticancer immunity. *Nat. Rev. Immunol.* **15**, 405–414 (2015).
272. Wardyn, J. D., Ponsford, A. H. & Sanderson, C. M. Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways. *Biochem. Soc. Trans.* **43**, 621–626 (2015).
273. Buelna-Chontal, M. & Zazueta, C. Redox activation of Nrf2 and NF-κB: a double end sword? *Cell Signal.* **25**, 2548–2557 (2013).
274. Kohler, U. A. *et al.* NF-κB/RelA and Nrf2 cooperate to maintain hepatocyte integrity and to prevent development of hepatocellular adenoma. *J. Hepatol.* **64**, 94–102 (2016).
275. Umemura, A. *et al.* p62, upregulated during preneoplasia, induces hepatocellular carcinogenesis by maintaining survival of stressed HCC-initiating cells. *Cancer Cell* **29**, 935–948 (2016).
276. Papa, S., Zazzeroni, F., Pham, C. G., Bubici, C. & Franzoso, G. Linking JNK signaling to NF-κB: a key to survival. *J. Cell Sci.* **117**, 5197–5208 (2004).
277. Sakurai, T., Maeda, S., Chang, L. & Karin, M. Loss of hepatic NF-κB activity enhances chemical hepatocarcinogenesis through sustained c-Jun N-terminal kinase 1 activation. *Proc. Natl Acad. Sci. USA* **103**, 10544–10551 (2006).
278. Ma, B. & Hottiger, M. O. Crosstalk between Wnt/β-catenin and NF-κB signaling pathway during inflammation. *Front. Immunol.* **7**, 378 (2016).
279. Schwitalla, S. *et al.* Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties. *Cell* **152**, 25–38 (2013).
280. Ang, H. L. & Tergaonkar, V. Notch and NFκB signaling pathways: Do they collaborate in normal vertebrate brain development and function? *Bioessays* **29**, 1039–1047 (2007).
281. Francescone, R., Hou, V. & Grivennikov, S. I. Microbiome, inflammation, and cancer. *Cancer J.* **20**, 181–189 (2014).
282. Roy, S. & Trinchieri, G. Microbiota: a key orchestrator of cancer therapy. *Nat. Rev. Cancer* **17**, 271–285 (2017).
283. Dzutsev, A. *et al.* Microbes and cancer. *Annu. Rev. Immunol.* **35**, 199–228 (2017).
284. Dzutsev, A., Goldszmid, R. S., Viaud, S., Zitvogel, L. & Trinchieri, G. The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. *Eur. J. Immunol.* **45**, 17–31 (2015).
285. Gopalakrishnan, V. *et al.* Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* http://dx.doi.org/10.1126/science.aan4236 (2017).
286. Routy, B. *et al.* Gut microbiome influences efficacy of PD-1 based immunotherapy against epithelial tumors. *Science* http://dx.doi.org/10.1126/science.aan3706 (2017).
287. Yu, L. C., Wang, J. T., Wei, S. C. & Ni, Y. H. Host-microbial interactions and regulation of intestinal epithelial barrier function: from physiology to pathology. *World J. Gastrointestinal Pathophysiol.* **3**, 27–43 (2012).
288. Schwabe, R. F. & Jobin, C. The microbiome and cancer. *Nat. Rev. Cancer* **13**, 800–812 (2013).
289. Vemuri, R. C., Gundamaraju, R., Shinde, T. & Eri, R. Therapeutic interventions for gut dysbiosis and related disorders in the elderly: antibiotics, probiotics or faecal microbiota transplantation? *Benef Microbes* **8**, 179–192 (2017).
290. Brennan, C. A. & Garrett, W. S. Gut Microbiota, Inflammation, and Colorectal Cancer. *Annu. Rev. Microbiol.* **70**, 395–411 (2016).
291. Sun, J. & Kato, I. Gut microbiota, inflammation and colorectal cancer. *Genes Dis.* **3**, 130–143 (2016).
292. Furusawa, Y. *et al.* Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504**, 446–450 (2013).
293. Arpaia, N. *et al.* Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **504**, 451–455 (2013).
294. Tanoue, T., Atarashi, K. & Honda, K. Development and maintenance of intestinal regulatory T cells. *Nat. Rev. Immunol.* **16**, 295–309 (2016).
295. Honda, K. & Littman, D. R. The microbiota in adaptive immune homeostasis and disease. *Nature* **535**, 75–84 (2016).

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