

Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms

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Abstract | Inflammation is a fundamental innate immune response to perturbed tissue homeostasis. Chronic inflammatory processes affect all stages of tumour development as well as therapy. In this Review, we outline the principal cellular and molecular pathways that coordinate the tumour-promoting and tumour-antagonizing effects of inflammation and we discuss the crosstalk between cancer development and inflammatory processes. In addition, we discuss the recently suggested role of commensal microorganisms in inflammation-induced cancer and we propose that understanding this microbial influence will be crucial for targeted therapy in modern cancer treatment.

Less than 10% of all cancers are caused by germline mutations; the remainder are caused by acquired somatic mutations and environmental factors. In many cases, tumour development is linked to chronic infection, dietary factors, obesity, inhaled pollutants, tobacco use or autoimmunity¹. The unifying principle that underlies these processes is chronic inflammation, which is an aberrantly prolonged form of a protective response to a loss of tissue homeostasis². Similarly, cancer development can, in many cases, be viewed as a dysregulated form of protective tissue repair and growth response. Hence, inflammatory and neoplastic processes may co-develop into aberrant “wounds that do not heal” (REF. 3). The first observations that linked inflammation to tumour growth were made by the German physician Rudolf Virchow in the nineteenth century⁴. Virchow described leukocyte infiltrates within tumours, which provided the first evidence for what is now commonly considered a hallmark of cancer⁵. These leukocyte infiltrates were initially thought to be solely indicative of tumour immune surveillance and antitumour immune responses but it is now clear that they can exert both tumour-suppressive and tumour-promoting effects, and the underlying mechanisms are starting to be understood.

Of the multiple inflammatory causes of cancer susceptibility (TABLE 1), infection has gradually been accepted as a major driver of inflammation-induced tumorigenesis. Indeed, up to 20% of all cases of cancer worldwide are associated with microbial

infection⁶. Although the origin and molecular signals that drive inflammation during infection may be distinct from inflammation that is caused by other factors, such as obesity, noxious inhalants and autoimmunity, many of the biological concepts that drive and regulate inflammation-associated cancer are similar across the various aetiologies. Even more intriguing is the emerging possibility that variation in the commensal microbial ecosystems (the microbiota) among individuals may be related to the considerable degree of variability noted in the manifestation of inflammation-associated cancer both among different inflammatory diseases and among individuals with the same inflammatory disease. Indeed, commensal microbial elements have recently been associated with inflammation and cancer development^{7–10}. The first members of the microbiota to be involved in cancer development have been identified; they potentially represent only the ‘tip of the iceberg’ of a so-far underappreciated part of the interplay between inflammation and cancer.

In this Review, we outline the major molecular and cellular pathways that participate in the crosstalk between cancer cells and inflammatory mediators. We focus on emerging mechanisms of inflammation-induced carcinogenesis and describe the cellular and molecular pathways that are involved in inflammation-driven incipient neoplasia. We also discuss the new perspectives gained from recent studies on the role of the commensal microbiota in inflammation-mediated tumour development.

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doi:10.1038/nrc3611

Key points

- Inflammation is causally related to cancer development, through processes that involve genotoxicity, aberrant tissue repair, proliferative responses, invasion and metastasis.
- Major inflammatory pathways that are involved in inflammation-induced carcinogenesis converge at the level of the transcription factors signal transducer and activator of transcription 3 (STAT3) and nuclear factor- κ B (NF- κ B).
- Tumours modulate the inflammatory environment by the secretion of soluble growth factors and chemoattractants, which render inflammatory cells suppressive against anticancer T cell responses.
- In around 20% of all cases, microbial organisms are the causative agents of cancer-inducing inflammation.
- In addition to bona fide pathogens, pathobionts of the commensal microbiota have recently been recognized as being involved in inflammatory processes that promote tumour growth.
- A better understanding of the role of the microbiota in inflammation-induced cancer might prospectively lead to targeted antimicrobial therapies against cancer initiation or progression.

Outside-in: cancer promotion by inflammation

Carcinogenesis is the result of the interplay of multiple cell-intrinsic and cell-extrinsic processes, which include genomic instability, proliferative abnormality, reprogramming of the stromal environment, and aberrant differentiation between epithelial and mesenchymal states. A remarkable characteristic of inflammation is its ability to enable most, if not all, of the core cellular and molecular capabilities that are required for tumorigenesis⁵. Although the mechanisms by which inflammatory cells promote neoplastic transformation are not fully understood, we discuss below the major mechanistic principles of inflammation-induced cancer on the basis of recent research advances and the current understanding of the tumorigenic process, and pay particular attention to the development of incipient neoplasia (FIG. 1).

Promoting proliferative and survival signalling. Cancer growth results in loss of homeostatic tissue architecture. The control of tissue architecture and function is mostly governed by the regulation of soluble growth factors and their receptors that convey proliferative, homeostatic and survival signals. Cancer cells exploit growth factor signalling by several common strategies: altering endocytosis and receptor cycling; inhibiting negative-feedback mechanisms that attenuate growth; and enabling redundant proliferative pathways downstream of receptor tyrosine kinase signalling^{11–15}. Growth factor receptor tyrosine kinases integrate a wide range of input signals that converge on a few major intracellular signalling cascades. This leads to cell proliferation and survival, as well as to cellular differentiation, adhesion, migration and metabolism¹⁶. Among these pathways, the activation of signal transducer and activator of transcription (STAT) family members, in particular STAT3, is broadly implicated in tumorigenesis in multiple tissues, and is closely linked to inflammatory processes in gastric, colon, liver, lung and pancreatic cancers^{17–22}. Activation of STAT3 by interleukin-6 (IL-6) that is produced by myeloid cells was crucial in the early tumorigenesis of colitis-associated colorectal cancer (CAC) in which STAT3 increased

pre-malignant cell proliferation and inhibited apoptosis *in vivo*^{19,20,23}. Mechanistically, STAT3 promotes cell proliferation by upregulating the expression of the cell cycle regulators cyclin D1, cyclin D2 and cyclin B, as well as the proto-oncogene *MYC*, and it increases cell survival by upregulating the expression of the anti-apoptotic genes *BCL2* and *BCL2*-like 1 (*BCL2L1*; which encodes *BCL-X_L*)^{19,20,24}.

Another layer of STAT3 regulation was recently uncovered. Deletion of sphingosine kinase 2 (*Sphk2*) in mice identified an important module of CAC development in which the production of sphingosine-1-phosphate (S1P) leads to the activation of nuclear factor- κ B (NF- κ B)-IL-6-STAT3 signalling, which in turn upregulates S1P receptor 1 (S1PR1). This establishes a feedforward amplification loop that maintains chronic inflammation and leads to CAC²⁵. Remarkably, in many cases, excessive STAT3 activation during incipient neoplasia is the result of immune cell signalling in the tumour microenvironment. Recent evidence from *Kras*-driven pancreatic cancer models suggests that STAT3 signalling has an intrinsic role in pancreatic intra-epithelial neoplasia development, even in the absence of inflammatory insults¹⁷. However, in many cases, epithelial STAT3 functions in transducing myeloid cell-derived IL-6 pro-tumorigenic signals; for example, STAT3 functions in the progression of pancreatic intra-epithelial neoplasia to pancreatic ductal adenocarcinoma but does not function in its initiation¹⁸. Similarly, in the liver, low-grade inflammation induced by obesity in the diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) model was also shown to activate tumorigenic STAT3 signalling via production of IL-6 and tumour necrosis factor (TNF)²⁶. A regulatory mechanism that may further elucidate the role of the IL-6-STAT3 axis in tumour initiation and progression was shown in immortalized mammary cells where transient activation of the oncoprotein SRC triggered an epigenetic switch to a constant transformed state induced by STAT3 activation²⁷. SRC activation induced an NF- κ B-dependent inflammatory response that mediated increased IL-6 expression by decreasing the transcription of its negative regulator microRNA *let-7*. Increased IL-6 levels activated STAT3 transcription, which was necessary for cell transformation, and in parallel activated NF- κ B. This established a positive feedback loop that persisted in the absence of the inducing signal²⁷. Altogether, these data suggest that an inflammatory process that is accompanied by oncogenic activation may lead to amplification of the NF- κ B-IL-6-STAT3 signalling cascade, which results in cancer initiation or progression, thus providing a bona fide example of the effect that immune cell signalling has on cancer cell proliferative behaviour.

A conceptually similar model can be applied to NF- κ B signalling. NF- κ B activation occurs in most tumours by inflammatory stimuli or oncogenic mutations, and results in pro-inflammatory, proliferative and pro-survival gene expression^{28–30}. Its identification as the first molecular link between inflammation and cancer in the liver³¹ and the colon³² has highlighted the important role of the tissue microenvironment as a source of

Tumour microenvironment

Cellular and non-cellular components of the tissue that surrounds and influences tumour growth. Crucial components of the tumour microenvironment are immune cells, blood vessels, fibroblasts, extracellular matrix and other stromal cells.

Inflammasome

An intracellular multiprotein complex of the innate immune system, consisting of sensor proteins of the NOD-like receptor (NLR) family, adaptor proteins and the pro-inflammatory serine protease caspase 1. The function of the inflammasome is to cleave the cytokines pro-interleukin-1 β and pro-interleukin-18 into their biologically active forms.

pro-tumorigenic inflammatory cytokines, many of them being both potent NF- κ B activators and target genes. In a mouse model of inflammation-associated HCC (*Abcb4*^{-/-} mice; *Abcb4* encodes multidrug resistance protein 2 (MDR2)), production of TNF by tissue endothelial and inflammatory cells induced NF- κ B in hepatocytes, and this was shown to be required for progression to HCC but not for hepatocyte transformation³¹. In a CAC model, inactivation of canonical NF- κ B signalling by epithelial cell-specific ablation of inhibitor of NF- κ B kinase- β (IKK β) reduced CAC incidence, whereas deletion of *Ikkkb* (which encodes IKK β) in myeloid cells resulted in reduced tumour size³². Again, TNF production by leukocytes that infiltrate the colonic lamina propria and submucosal sites was later shown to mediate CAC initiation and progression³³. Interestingly, NF- κ B activation can promote tumorigenic autocrine signalling in the transformed cells themselves (as mentioned above). Specifically, the oncogenic effects of RAS in keratinocytes required the establishment of an autocrine loop through IL-1 α , IL-1R and myeloid differentiation primary response 88 (MYD88), which leads to NF- κ B activation³⁴. MYD88 was also found to regulate colonic macrophage production of cytokines such as IL-6 and transforming growth factor- β (TGF β) that were in turn found to be required for CAC development³⁵. This provides a possible link to NF- κ B intrinsic and extrinsic tumorigenic functions during inflammation. This idea is further supported by the role of Toll-like receptor 2 (TLR2) in gastric tumorigenesis via STAT3 activation³⁶.

If myeloid cell-derived inflammatory cytokines function as major activators of proliferative responses during the initiation of neoplasia, then tissue conditions that lead to inflammatory cytokine release are of crucial importance. Responses to tissue damage elicit the production of multiple inflammatory cytokines, among which IL-22 is pivotal for the induction of

epithelial cell proliferation and survival^{37,38}. Recent data show that IL-22 produced by CD11c⁺ cells mediates wound-healing responses by activating STAT3 in intestinal epithelial cells after intestinal damage and colitis induced by dextran sodium sulphate (DSS) treatment³⁹. An important role for IL-22 in CAC development was recently shown in mice that lack the IL-22 neutralizing receptor IL-22-binding protein (IL-22BP; also known as IL22Ra2), demonstrating that IL-22BP (which is mainly produced by CD11c⁺ cells downstream of inflammasome signalling) inhibits CAC⁴⁰. Similarly, IL-22 that is produced by HCC-infiltrating leukocytes promotes HCC by activating STAT3 and its downstream survival genes⁴¹. Consistent with a direct tumour-promoting function, hepatocyte-specific expression of IL-22 in transgenic mice resulted in the promotion of HCC by increasing cell survival and proliferation without substantially affecting liver inflammation⁴².

Apart from proliferative responses downstream of inflammatory cytokine signalling, enhanced cell proliferation and survival-enabling tumour capabilities may also be achieved by dedifferentiation of pre-malignant cells and by the acquisition of stem-cell-like properties. In a model of constitutive WNT activation, elevated NF- κ B signalling in epithelial cells enhanced WNT- β -catenin activation and induced dedifferentiation of intestinal non-stem cells that acquired tumour-initiating capacity, which resulted in intestinal tumorigenesis⁴³. Alternatively, loss of the tumour suppressor adenomatous polyposis coli (APC) may lead to activation of the GTPase RAC1 and to hyperproliferation of leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5)-expressing intestinal stem cells, which is mediated by RAC1 control of reactive oxygen species (ROS) production and NF- κ B activation⁴⁴. With respect to the roles discussed above, STAT3 has been shown to regulate tumour-promoting

Table 1 | **Examples of inflammatory insults or conditions that are associated with malignancy**

Inflammation that causes insults or pathological conditions	Associated malignancy
Silica, asbestos, smoking-associated silicosis and bronchitis	Lung carcinoma
Pelvic inflammatory disease	Ovarian carcinoma
Chronic indwelling urinary catheter	Bladder carcinoma
<i>TRYP1</i> mutation-associated pancreatitis and alcoholism-associated pancreatitis	Pancreatic carcinoma
UV irradiation-associated skin inflammation	Melanoma
Asbestos	Mesothelioma
Bile acids	Cholangiosarcoma and colorectal carcinoma
Gastric acid-associated Barrett's metaplasia and reflux oesophagitis	Oesophageal carcinoma
Gall bladder stone-associated cholecystitis	Gall bladder carcinoma
Lichen sclerosus (a skin condition)	Vulvar carcinoma
Inflammatory bowel disease	Colorectal carcinoma
Hashimoto's thyroiditis (an autoimmune disease of the thyroid) and Sjögren's syndrome (an autoimmune disease of exocrine glands)	Mucosa-associated lymphoid tissue lymphoma
Gingivitis (inflammation of the gum tissue) and lichen planus	Oral squamous cell carcinoma
Sialadenitis (inflammation of the salivary gland)	Salivary gland carcinoma

TRYP1, trypsinogen 1; UV, ultraviolet.

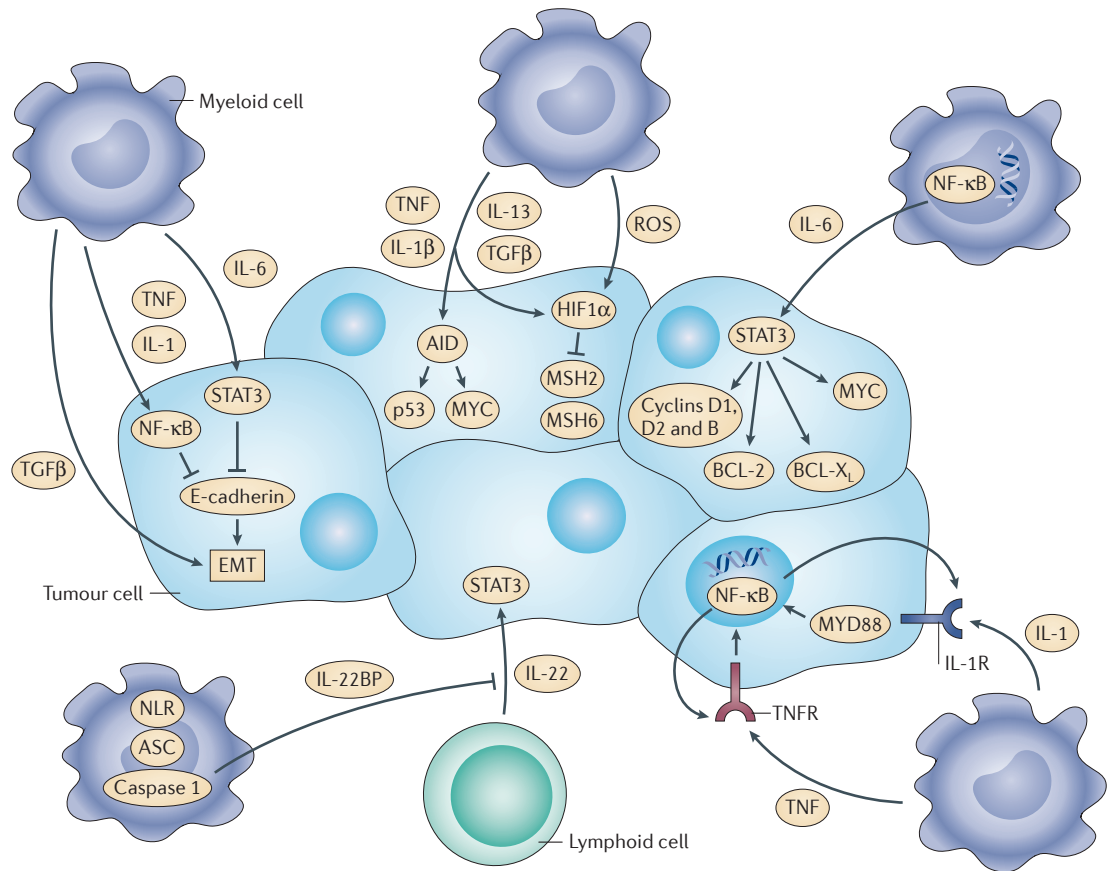


Figure 1 | Influence of inflammatory signalling on carcinogenesis. Tumour-infiltrating myeloid cells contribute to carcinogenesis in various ways. Pro-inflammatory cytokines induce signal transducer and activator of transcription 3 (STAT3) and nuclear factor-κB (NF-κB) signalling in cancer cells, which leads to the suppression of apoptosis and the promotion of cell cycle progression. Inflammasome-dependent interleukin-22 binding protein (IL-22BP) secretion inhibits IL-22-driven STAT3 induction. Genomic destabilization can be promoted by cytokine-mediated ectopic expression of activation-induced cytidine deaminase (AID) and by hypoxia-dependent suppression of DNA repair mechanisms. In addition, STAT3 and NF-κB signalling also induces epithelial–mesenchymal transition (EMT) by downregulating the expression of epithelial differentiation markers. ASC, apoptosis-associated speck-like protein containing a CARD; HIF1α, hypoxia-inducible factor 1α; IL-1R, IL-1 receptor; MYD88, myeloid differentiation primary response 88; NLR, NOD-like receptor; ROS, reactive oxygen species; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor; TNFR, TNF receptor.

properties of cancer stem cells in various tissues^{45–48}. In addition, it has been shown that IL-1β-dependent and IL-6-dependent inflammation can induce the activation and migration of gastric cardia progenitor cells, which results in malignant transformation in a mouse model of Barrett’s oesophagus and oesophageal adenocarcinoma⁴⁹. Thus, the control of tissue stem cell expansion and acquisition of stem-like properties that are driven by inflammatory transcriptional programmes may foster incipient neoplasia.

Although all of the scenarios discussed above provide evidence for the concept that inflammatory signalling promotes proliferative responses, conversely, disruption of anti-proliferative mechanisms that regulate the cell cycle may also result in tumour-promoting activity. Cellular senescence is one such anti-proliferative programme that mediates RB-dependent and p53-dependent stable cell cycle arrest^{50,51}. Therefore, oncogene-induced senescence

may limit the proliferation of damaged cells that are at risk of neoplastic transformation. The senescent state is reinforced by a senescence-associated secretory phenotype (SASP), which was regulated by NF-κB in a mouse lymphoma model and NF-κB was required to maintain chemosensitivity and tumour suppression⁵². Pre-malignant senescent hepatocytes are immunogenic and elicit clearance by antitumorigenic T cell surveillance, the absence of which results in the development of HCC⁵³. In contrast to oncogene-induced senescence, TNF and interferon-γ (IFNγ) were recently shown to induce cytokine-induced senescence through TNF receptor 1 (TNFR1; also known as TNFRSF1A)–STAT1 signalling⁵⁴. The capacity of senescent cells to mediate antitumour immune responses is regulated by p53; in the absence of p53, senescence-associated low-grade inflammation in stressed colonic epithelial cells promotes tumorigenesis⁵⁵. These data further exemplify the delicate balance between tumour-promoting and

Senescence-associated secretory phenotype (SASP). A common profile of secreted factors, induced during cellular senescence. These factors include pro-inflammatory cytokines, such as interleukin-1 and interleukin-6, and chemoattractants, such as CXC-chemokine ligand 8.

tumour-antagonizing inflammatory responses and the dependency of tumour-neutralizing immune responses on the proper function of key transcription factors and tumour suppressors.

Genomic destabilization. In addition to the aberrant proliferative and anti-apoptotic behaviour of tumour cells, increased genomic instability accompanied by genomic mutagenesis is believed to be a crucial driving force of cancer. Once again, inflammation may have a prominent role in initiating neoplastic transformation by increasing the rates of DNA damage while compromising DNA repair mechanisms that are required to maintain genomic integrity, which leads to increased genomic instability. Somatic mutation that is induced during inflammation has various sources, which may function on epithelial cells directly or indirectly, in a cell-intrinsic or a cell-extrinsic manner. First, ROS and reactive nitrogen species (RNS) that are released by tissue macrophages and neutrophils, or that are induced intracellularly in pre-malignant cells by inflammatory cytokines, cause DNA breaks, single base mutations or more complex DNA lesions^{56–58}. Second, several cytokines, including TNF, IL-1 β , IL-4, IL-13 and TGF β , have been shown to induce ectopic expression of activation-induced cytidine deaminase (AID; also known as AICDA), a member of the DNA and RNA cytosine deaminase family, which introduces mutations in crucial cancer-associated genes such as *TP53* (which encodes p53) and *MYC* and thereby promotes oncogenesis^{59–62}. In addition, it was recently found that inflammation can alter the intestinal microbial composition and can induce expansion of microorganisms with genotoxic capabilities that promote intestinal tumorigenesis (as detailed below)¹⁰. Intriguingly, inflammation may also directly increase cellular susceptibility to mutagenesis and indirectly increase genomic destabilization by downregulation of DNA repair pathways and disruption of cell cycle checkpoints, which leads to the accumulation of random genetic alterations^{57,63–65}. In this regard, mismatch repair (MMR) proteins are important to prevent genetic instability that results from microsatellite instability, and inflammation can repress MMR via various mechanisms to increase the rate of DNA replication errors throughout the genome: multiple inflammatory mediators (TNF, IL-1 β , prostaglandin E2 (PGE2) and ROS) induce hypoxia-inducible factor 1 α (HIF1 α) to downregulate the expression of the MMR genes *MSH2* and *MSH6* (REF. 63), whereas ROS can reduce the enzymatic activity of MMR proteins⁶⁴. Inflammation-induced DNA hypermethylation can also cause epigenetic silencing of the MMR protein MLH1 and other tumour suppressors, such as p53 (REFS 64,66). Furthermore, inflammation can induce inactivation of the p53-mediated genomic surveillance and overexpression of BCL-2 and MYC, which results in the suppression of DNA repair and in the acceleration of the mutation rate in cancer cells^{56,64}. It is probable that multiple pathways converge to contribute to inflammation-induced genetic instability; for example, ectopic expression of IL-15 initiates large granular lymphocytic leukaemia through the induction of MYC

and NF- κ B, leading to repression of miR-29b, which is a repressor of DNA methyltransferase 3B (DNMT3B) expression — this results in DNA hypermethylation and chromosomal instability⁶⁷.

Induction of invasion and metastasis. Although genomic instability and aberrant proliferative responses characterize the initial stages of neoplastic aberrations, such a loss of tissue homeostasis has not yet been associated with morbidity and mortality in most cases. Around 90% of cancer mortality is caused by tumour metastasis. Metastasis is a multistage process that involves local invasion of primary cancer cells, intravasation of cancer cells into nearby blood and lymphatic vessels, transit and survival of cancer cells in the circulatory system, and ultimately dissemination and colonization of escaped cancer cells at distant sites^{5,68}. Notably, it has long been recognized that various inflammatory mediators substantially contribute to metastasis, and myeloid-derived monocytes and macrophages strongly facilitate tumour cell invasion, extravasation and metastatic outgrowth^{69,70}, but the underlying mechanisms have long remained elusive. First, cancer cells undergo epithelial–mesenchymal transition (EMT), in which they are polarized towards acquiring mesenchymal cell characteristics such as an increased migratory capacity and invasiveness to basal membranes⁷¹. TGF β , despite suppressing cell proliferation and tumour growth at an early stage, is a potent stimulator of EMT^{71–73}. Activation of NF- κ B and STAT3 by TNF, IL-6 and IL-1 also enhances EMT by downregulating E-cadherin expression^{73,74} and upregulating the production and activity of matrix metalloproteinases (MMPs)^{75,76}. IL-4-activated tumour-associated macrophages (TAMs)^{77,78} and CC-chemokine receptor 1 (CCR1)⁺ immature myeloid cells⁷⁹ at the tumour periphery are essential for local invasion of tumour cells, because they supply matrix-degrading enzymes such as MMPs, cathepsins and heparanase^{68,70,71,80,81}.

Following EMT, intravasation of cancer cells into blood vessels and lymphatics is facilitated by direct interactions between tumour cells and TAMs⁸². Inflammation promotes this process through a TNF-induced increase in vascular permeability⁸³, cyclooxygenase 2 (COX2)-dependent prostaglandin production and MMP-mediated tissue remodelling⁸⁴. Furthermore, inflammatory mediators enhance the survival of circulating metastatic ‘seeds’ (REF. 84) and promote the extravasation of circulating cancer cells by upregulation of adhesion molecules^{56,85}. In particular, CC- and CXC-chemokine receptors (including CCR1, CCR4, CCR7, CCR9, CCR10, CXCR1–5 and CXCR7) are expressed by malignant cells from various tissues in response to pro-inflammatory cytokines; they sense chemokine gradients to direct the organ-specific migration of cancer cells⁵⁶. In addition, CCL18 promotes mammary tumour migration by enhancing the adherence of metastatic cells to the extracellular matrix⁸⁶. Recently, CC-chemokine ligand 2 (CCL2) has been identified as a crucial factor that facilitates the metastasis and dissemination of breast cancer cells and colon carcinoma cells^{87,88}. Tumour-derived CCL2 activates the CCR2⁺ endothelium to

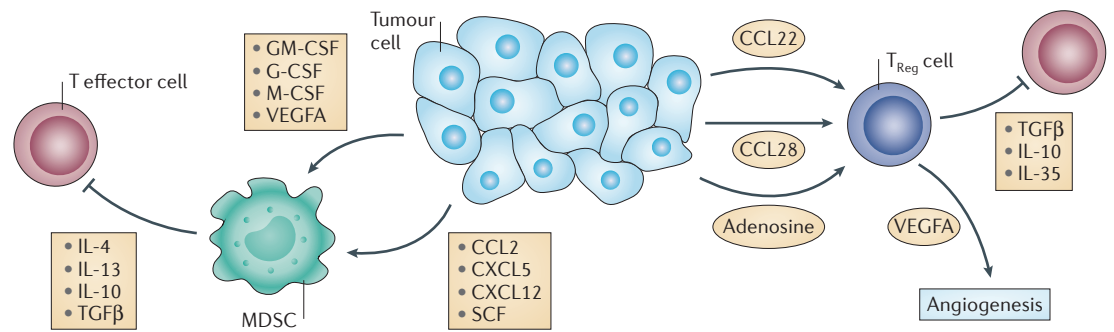


Figure 2 | Influence of cancer cells on inflammatory signalling. Tumours recruit T regulatory (T_{Reg}) cells and manipulate their function. CC-chemokine ligand 22 (CCL22) and CCL28 attract T_{Reg} cells that express the respective receptors CC-chemokine receptor 4 (CCR4) and CCR10 to the site of tumour growth. There, T_{Reg} cells suppress effector T cells by the secretion of soluble mediators and induce an angiogenesis programme. Tumours also promote the generation of myeloid-derived suppressor cells (MDSCs) via the secretion of growth factors and chemoattractants. MDSCs suppress antitumour T cell responses by the secretion of cytokines such as interleukin-4 (IL-4), IL-13, IL-10 and transforming growth factor- β (TGF β). CXCL, CXC-chemokine ligand; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; M-CSF, macrophage colony-stimulating factor; SCF, stem cell factor; VEGFA, vascular endothelial growth factor A.

increase vascular permeability and recruits inflammatory monocytes to promote the extravasation and seeding of metastatic tumour cells^{87,88}.

In summary, the tissue microenvironment is a source of multiple inflammatory mediators that may function individually or cumulatively to trigger and sustain cellular transformation and tumorigenesis. Cytokines activate inflammatory transcription factors that relay tumorigenic signalling. These relays often involve the establishment of feedforward signal amplification loops, which ultimately promote cell proliferation and resistance to cell death and possibly promotes dedifferentiation to a stem-like state. The induction of genomic instability is central to the role of inflammation in neoplastic transformation, because inflammation increases the production of DNA-damaging agents while compromising genomic maintenance and repair mechanisms. At later stages of tumour development, myeloid cells facilitate the multistep metastatic process by producing the inflammatory milieu that is required for EMT, intravasation and for seeding of metastatic cancer cells.

Inside-out: immune modulation by cancer

For many years, cancer was predominantly considered to be a cell-autonomous process. The prevailing concept centred on genetically transformed cells and their progression to malignant neoplasms. However, the study of the tumour microenvironment has given rise to the emerging concept that tumour progression is dependent on a dense network of interactions among cancer cells and the surrounding stroma, niche-defining cells and the vasculature. Perhaps one of the most important aspects of the tumour–microenvironment crosstalk is the ability of cancer cells to modulate the inflammatory response by way of soluble mediators. The effect of cancer cell activity on both the innate and the adaptive immune systems is manifold and includes a skew of the acquired T cell response from

the T helper 1 (T_H1) cell subset to the T_H2 cell subset, the induction of immunosuppressive T regulatory (T_{Reg}) cells, a skewing of the phenotype of macrophages and neutrophils to a type 2 differentiation state and the induction of myeloid-derived suppressor cells (MDSCs)⁸⁹. Recent studies have shed light on the mechanisms that underlie this considerable tumour–immune system crosstalk. We highlight below the ways by which tumours modulate the antitumour immune response. The overarching theme of tumour-mediated immunomodulation is that cancer cells are able to interfere with every step of the antitumour inflammatory response by secreting soluble mediators that block the effector function of the involved immune cells and reprogramme them into cells that are characterized by a regulatory (immunosuppressive) phenotype (FIG. 2).

Inflammatory responses to tumour growth begin with the uptake of tumour antigen by antigen-presenting cells. Immunostimulatory antigens can be differentiation antigens that are indicative of the origin of the tumour, of overexpressed antigens or of mutated neo-antigens⁹⁰. Tumours exert manifold effects on the function of antigen-presenting cells. Gabrilovich *et al.*⁹¹ were the first to describe a mechanism of direct tumour-mediated regulation of myeloid cell function. They identified tumour-derived vascular endothelial growth factor A (VEGFA) as a suppressor of dendritic cell function and maturation. VEGFA treatment of peripheral myeloid cells induces the expression of programmed cell death 1 ligand 1 (PDL1; also known as CD274), an inhibitory ligand of the B7 family⁹². Similarly, tumours have been reported to influence antigen-presenting cell function by secretion of TGF β ⁹³, IL-10 (REF. 94) and IL-6 (REF. 95). As a result, the tumour manipulates the ability of the immune system to elicit an antitumour T cell response. In a mouse model of pancreatic ductal adenocarcinoma (PDA), it was recently found that tumour-derived granulocyte–macrophage colony-stimulating factor (GM-CSF) promotes the development and recruitment of granulocyte

differentiation antigen 1 (GR1)⁺CD11b⁺ myeloid cells. These cells suppress antigen-specific T cells at the site of the tumour⁹⁶.

Myeloid cells with regulatory capacity that accumulate in the tumour microenvironment and in the peripheral blood of cancer patients have been designated as MDSCs. Tumours recruit MDSCs via the secretion of CCL2, CXCL5, CXCL12 and stem cell factor (SCF; also known as KIT ligand)⁸⁰. Once they are at the site of the tumour, MDSCs exert their T cell-suppressive function via the secretion of IL-10, TGF β and arginase⁹⁷.

Tumours also modulate the inflammatory microenvironment by actively recruiting T_{Reg} cells. Hodgkin's lymphoma cells and ovarian cancer cells secrete CCL22 — which is the chemokine ligand for CCR4 — and thereby recruit T_{Reg} cells to the tumour stroma⁹⁸. Facciabene *et al.*⁹⁹ recently found that, under hypoxic conditions, ovarian cancer cells secrete CCL28. This chemokine binds to CCR10, which is preferentially expressed by T_{Reg} cells. In addition to suppressing anti-tumour T cell responses by means of soluble mediators, such as TGF β , IL-10 and IL-35, recruited T_{Reg} cells also reprogrammed the tumour microenvironment towards angiogenic mechanisms¹⁰⁰. Thus, tumours actively exploit the capacities of T_{Reg} cells to redirect anti-tumour T cell responses and to promote oxygen supply. Furthermore, once recruited, T_{Reg} cell populations are actively maintained by the secretion of TGF β and adenosine by tumour cells¹⁰¹.

Taken together, although inflammatory processes that accompany carcinogenesis exert multiple effects on all stages of tumour development, the tumour itself is actively involved in the modulation of immune reactions that take place in its microenvironment and beyond. Nonetheless, the difficulty in translating our knowledge about the tumour–inflammatory crosstalk into therapeutic modalities has highlighted the many gaps in our understanding of this complex process, one of which we focus on below.

Outside control of the inside: the microbiota

Despite all the knowledge gathered so far about the importance of the inflammatory pathways and cell types that are mentioned above, in many cases it remains unclear what initially instigates the inflammatory response. During the past decade, evidence has accumulated that this stimulus can be due to aberrant pathogenic or pathobiont microbial colonization. In around one-fifth of all cases of cancer there is a direct link to an infectious cause. Knowledge of the cancer-promoting activity of microorganisms is especially well-established for oncoviruses, but bacteria and parasites have also been associated with increased tumour development. Whether a similar association occurs for fungi remains unclear. In many cases, it is now clear that it is the host inflammatory response to the pathogenic infection that links the presence of a pathogen to cancer development. In some cases, cancer development and progression is linked to 'sterile' inflammatory causes that are not directly associated with infectious causes, and that are believed to initiate from chronic uncontrolled

inflammatory irritation and tissue damage that leads to malignant transformation in the chronic inflammatory milieu. Nevertheless, even in these instances, commensal or pathogenic infectious agents are suggested to have modulatory roles in cancer development and progression^{102,103}. The contribution of pathogens to inflammation-induced cancer has been firmly established and summarized in recent reviews¹⁰⁴. We highlight below the recently emerging role of bacterial members of the commensal microbiota.

The association of bacterial infection and tumorigenesis has long remained controversial. Beginning in the 1890s, numerous reports have described the presence of bacteria in cancerous tissue^{105,106}. However, in many cases it has remained unclear whether this represents a causal relationship, or whether bacterial accumulation in tumours is simply because of the high vascularization and metabolic activity of cancer cells. In the 1960s, the American physician Virginia Livingston claimed to have identified a bacterial species, '*Progenitor cryptocides*', as a causative agent in human cancer¹⁰⁷. However, this theory was later refuted¹⁰⁸. The best evidence for causal bacterial involvement in inflammation-induced cancer comes from infections with *Helicobacter pylori*. Infection with *H. pylori* is the strongest known risk factor for gastric adenocarcinoma¹⁰⁹. Mechanistically, chronic gastric inflammation caused by *H. pylori* leads to aberrant β -catenin signalling in epithelial cells, which augments the risk of malignant transformation¹¹⁰. Moreover, *Salmonella enterica* subsp. *enterica* serovar Typhi infection is also associated with gall bladder cancer¹¹¹. The underlying mechanism is not entirely clear, but it might involve the production of β -glucuronidase, leading to local deconjugation of toxins and bile acids, which in turn exert potentially carcinogenic actions on the gall bladder epithelium¹¹².

Although the above examples all provide evidence for the involvement of pathogenic infections in cancer development, it has recently become apparent that members of the commensal community of microorganisms are crucially involved in tumour-promoting inflammation (FIG. 3). The human body is colonized by trillions of bacteria, viruses, parasites and fungi on the skin, respiratory tract, oral cavity, gastrointestinal tract and the urogenital system¹¹³. Although these commensal microorganisms have functions that are essential for human physiology under homeostatic conditions, they also contribute to aberrations in inflammatory processes that have ensuing pathologies¹¹⁴. However, until recently it remained unclear whether these microbiota-dependent inflammatory processes promote tumour growth in a way that is similar to the inflammation provoked by pathogenic infection.

The first evidence for microbiota-induced inflammatory tumorigenesis came from a study showing that the TLR-signalling adaptor protein MYD88 contributes to cancer progression in the *Apc*^{Min/+} mouse model of spontaneous intestinal tumorigenesis and in mice treated with multiple injections of azoxymethane (AOM)¹¹⁵. This suggests that innate sensing of microorganisms in the intestine is necessary for the regulation of

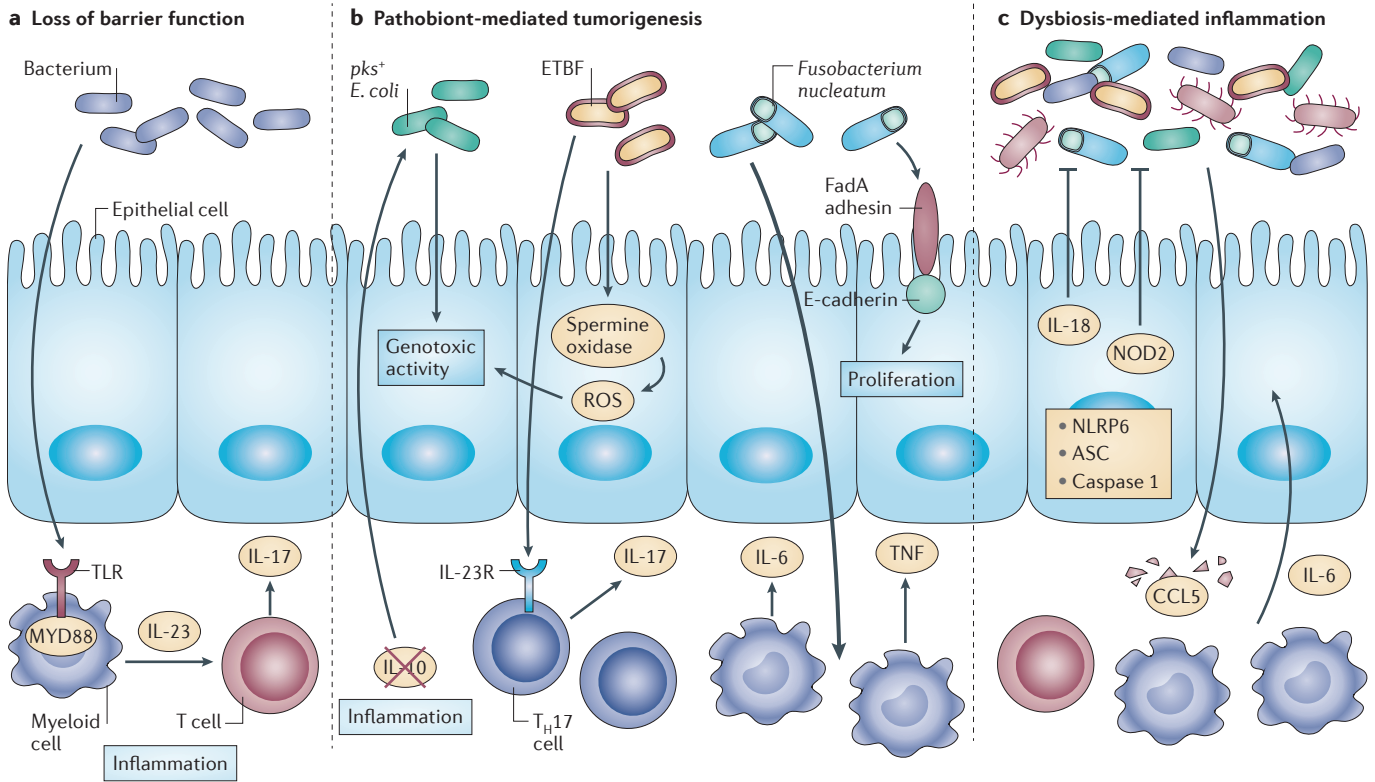


Figure 3 | Commensals and pathobionts as inducers of cancer development. The interactions of the host with its environment, and in particular with microorganisms that inhabit distinct environmental niches, have been recently suggested to have fundamental roles in tumour initiation and progression. Examples include tumour-associated loss of barrier function that results in increased commensal penetration and inflammation induction, which in turn results in enhanced tumour growth (part **a**); pathobiont-mediated tumorigenesis, by which potentially pathogenic commensal strains induce a tumorigenic environment by secretion of mediators (part **b**) and dysbiosis-mediated inflammation, in which loss of host-related innate sensing platforms results in perturbation of the microbiota composition and function (part **c**). Expansion of normally suppressed taxa induces local inflammation in the host and ensuing tumorigenesis. ASC, apoptosis-associated speck-like protein containing a CARD; CCL5, CC-chemokine ligand 5; *E. coli*, *Escherichia coli*; ETBF, enterotoxigenic *Bacteroides fragilis*; IL, interleukin; IL-23R, IL-23 receptor; MDSC, myeloid-derived suppressor cell; MYD88, myeloid differentiation primary response 88; NLRP6, NLR family, pyrin domain-containing 6; NOD2, nucleotide-binding oligomerization domain-containing 2; *pks*, polyketide synthase; ROS, reactive oxygen species; T_H17 , T helper 17; TLR, Toll-like receptor; TNF, tumour necrosis factor.

inflammation and cancer development. Downstream of MYD88, ERK activation drives intestinal tumorigenesis in *Apc^{Min/+}* mice¹¹⁶. A role for MYD88 in intestinal tumorigenesis was confirmed in colitis-susceptible *Il10^{-/-}* mice¹¹⁷. By contrast, in the DSS-AOM model of inflammation-induced colorectal cancer, *Myd88^{-/-}* mice exhibited increased susceptibility to the development of intestinal tumours¹¹⁸. Unlike *Myd88^{-/-}* mice, *Tlr4^{-/-}* mice are protected from DSS-AOM-induced intestinal tumour development¹¹⁹. Conversely, *Tlr2^{-/-}* mice show enhanced intestinal tumorigenesis in this model¹²⁰. These seemingly contradictory effects may be related to differences in the microbiota composition in innate immune-deficient mice; these differences result in a distinct and — in some cases — even an opposite response to microbiota elements in the tumorigenic cascade. Alternatively, they may reflect an integrative type of host sensing of bacterial-associated molecular patterns, as part of host regulation of cell division.

As such, disruption of some — but not of other — innate sensing pathways may result in different responses to tumorigenic stimuli.

The seemingly contradictory roles of TLR signalling has led researchers to consider the second branch of innate immune signalling, which is also dependent on MYD88: signal transduction through the receptors for IL-1 and IL-18. Remarkably, when compared with *Myd88^{-/-}* mice, *Il18^{-/-}* mice show a similar susceptibility to intestinal polyp formation¹¹⁸. IL-18 is released from cells following the activation of inflammasomes, which are an innate immune platform consisting of an upstream NOD-like receptor (NLR), the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC; also known as PYCARD) and caspase 1 (REF. 121). Consistently, mice that are deficient in caspase 1 or in the inflammasome-forming NLRs, NLRP3 and NLRP6, show a greatly increased susceptibility to colorectal carcinoma^{122–125}, because of a lack of protective IL-18 (FIG. 4).

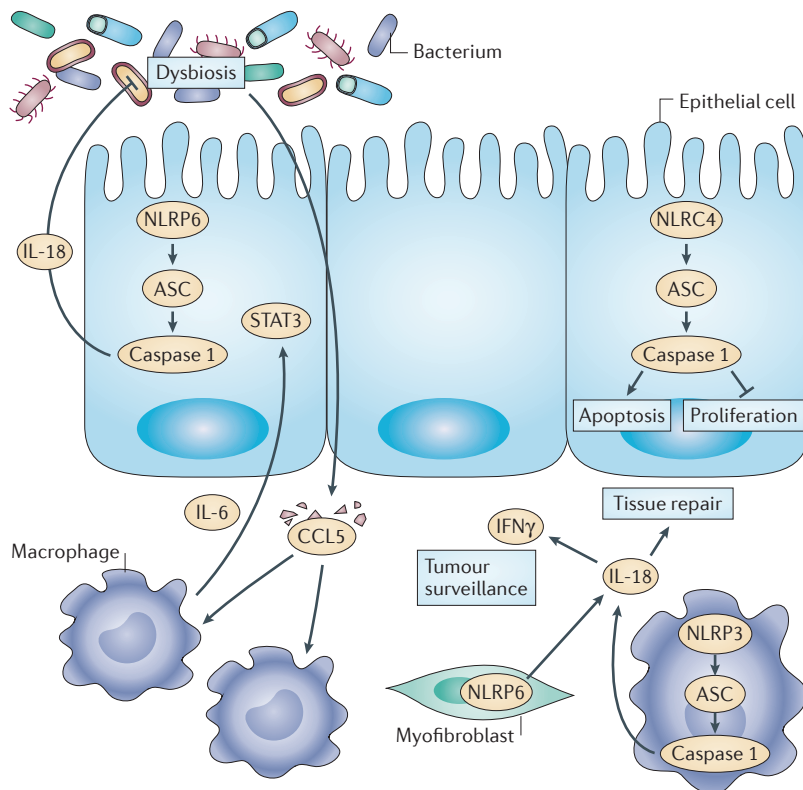


Figure 4 | The multifaceted role of inflammasomes in cancer development.

Inflammasome-derived interleukin-18 (IL-18) is necessary for tissue repair and tumour surveillance at the intestinal mucosal surface. In addition, decreased levels of IL-18 decrease the antitumour immune response mediated by interferon- γ (IFN γ). Inflammasome deficiency also leads to aberrations in microbial ecology, which results in the outgrowth of bacterial strains with potentially tumorigenic activity. This dysbiotic microbiota induces chronic inflammation of the mucosa, enhanced IL-6 signalling and epithelial neoplasia. The NLR family, CARD domain-containing 4 (NLRC4) inflammasome controls epithelial cell homeostasis by balancing proliferation and cell death. Note the compartmentalization and cell type specificity of inflammasome activation and its consequences. ASC, apoptosis-associated speck-like protein containing a CARD; CCL5, CC-chemokine ligand 5; NLRP, NLR family, pyrin domain containing; NOD2, nucleotide-binding oligomerization domain-containing 2; STAT3, signal transducer and activator of transcription 3.

Notably, these mice also have altered community representation and function of microbial species in the gut ecosystem, a state that is called dysbiosis, which exerts pro-inflammatory properties on the gut mucosa^{126,127}. The microflora associated with inflammasome deficiency in mice was recently shown to contribute to inflammation-induced colorectal cancer through inflammatory stimuli-mediated activation of epithelial IL-6 signalling, and this activation of epithelial IL-6 signalling was transferable to cohabitant wild-type mice (from the same cage)¹²⁸. Thus, it is conceivable that alterations in the microbiota composition may function as a prime driver of intestinal tumorigenesis (FIG. 3).

Indeed, intestinal dysbiosis has been associated with colorectal cancer, first in the *Tbet*^{-/-} (also known as *Tbx21*^{-/-}) recombination activating gene 2 (*Rag2*)^{-/-} ulcerative colitis (TRUC) mouse model¹⁰², and subsequently in humans^{129,130}. Interestingly, inflammation-induced colorectal cancer that is associated with

intestinal dysbiosis is transmissible between mice, as shown in nucleotide-binding oligomerization domain-containing 2 (*Nod2*)^{-/-} mice¹⁰³ and in mice deficient in the NLR family, pyrin domain containing 6 (NLRP6) pathway¹²⁸, which indicates an infectious component of colorectal cancer that cannot be ascribed to known pathogenic species. Rather, the aberrant outgrowth and activity of normally symbiotic but — in the context of dysbiosis — pathogenic species ('pathobionts') is responsible for exacerbating inflammation and the neoplastic growth that ensues (FIG. 3). Although in these examples the development of dysbiosis seems to be the primary cause of inflammation-associated tumour growth, thus providing an example of microorganism-driven tumour-initiating inflammation, there are also cases of microorganism-driven tumour-elicited inflammation. In these cases, dysbiosis and enhanced microbial translocation across the intestinal barrier arises secondary to chronic inflammatory conditions or neoplasia, and fosters cancer development. Colorectal cancers show defective mucin production and aberrant expression of proteins that are involved in intestinal barrier maintenance. This leads to increased microbial translocation to the site of tumour growth and upregulation of IL-23 and IL-17, which perpetuates local tumour-elicited inflammation⁷. In AOM-treated colitis-susceptible *Il10*^{-/-} mice, the structure of the intestinal microbial community is altered, and commensal *Escherichia coli* can promote invasive carcinoma in a manner that is dependent on a polyketide synthase (*pks*) genotoxic island. Similarly, patients with inflammatory bowel disease (IBD) and colorectal cancer show a higher representation of *pks*⁺ *E. coli* than healthy controls¹⁰, which implies that a single aberrantly represented bacterial species might contribute to enhanced neoplastic growth. In accordance with this hypothesis, three studies have recently identified a high prevalence of the obligate anaerobe *Fusobacterium nucleatum* in human colorectal carcinoma samples^{131–133}. *F. nucleatum* has been demonstrated to enhance colorectal neoplasia progression through recruitment of tumour-infiltrating myeloid cells¹³⁴. Mechanistically, *F. nucleatum* binds to E-cadherin on epithelial cells and activates β -catenin signalling, thereby driving epithelial cell proliferation¹³⁵. Enterotoxigenic *Bacteroides fragilis* (ETBF) has also been associated with inflammation-induced colon cancer¹³⁶; in particular, ETBF has a role in inducing spermine oxidase-dependent ROS production⁸. Together, these studies establish a role for the bacterial microbiota in the inflammatory processes that are associated with cancer development. Whether viral, fungal or parasitic members of the microbiota can have a similarly crucial role in inflammation-induced cancer remains to be investigated.

The liver represents the 'first pass' organ for microbial products that drain from the gut via the portal vein, and an increased translocation of bacterial products to the liver is a hallmark of chronic liver disease¹²⁷. The intestinal microbiota also contributes to the development of HCC by triggering TLR4 signalling on non-haematopoietic cells in the liver¹³⁷. Downstream of

Genotoxic island

A genomic island in bacteria that encodes proteins with potentially genotoxic — that is, genome-damaging — properties.

TLR4, the hepatomitogen epiregulin promotes hepatocarcinogenesis. Importantly, the late-stage administration of antibiotics reduces the anti-apoptotic effect of microbiota-triggered TLR4 signalling and ameliorates HCC¹³⁷. A connection was recently established between the microbiota, pro-inflammatory cytokines, signalling, SASP and HCC. Obesity induces alterations in the gut microbial ecology, which were linked to enhanced levels of deoxycholic acid (DCA) and ensuing DNA damage. Increased levels of DCA in the enterohepatic circulation elicited SASP and cytokine production by hepatic stellate cells, and this drove hepatic carcinogenesis¹³⁸. These findings show that the cancer-promoting inflammatory response to commensal microbial elements is not restricted to sites of direct contact between the tumour and microorganisms. Whether a similar concept applies to other extraintestinal sites — such as the skin or lung — remains to be established, but a contribution of MYD88 and TLR4 to cutaneous carcinogenesis has already been shown^{139,140}.

Future directions

The concept of inflammation-induced cancer has been firmly established during the past decade, but many of the mechanisms that link inflammatory processes to their considerable modulatory effects on various stages of tumour development remain elusive. Some of the molecular events that coordinate the crosstalk between cancer cells and their inflammatory microenvironment have been determined, and we have learned a great deal about the cell types and pathways that are involved in the interplay of inflammation, genetic instability, neoplasia and chemotherapy. Nonetheless, fundamental questions remain to be answered, and this limits our ability to exploit the growing knowledge of cancer-associated inflammation for the development of novel therapeutic approaches. For example, not all chronic inflammatory diseases increase the risk of cancer; on the contrary, some of them, including psoriasis, have been associated with a reduced incidence of cancer¹⁴¹. One possible explanation for such seemingly counterintuitive observations can be found in the growing literature concerning the overly simplified paradigm that is related to the different branches of the immune response. Classically, immune responses have been categorized into parallel and functionally distinct phylogenetic types, such as T_H1, T_H2 and T_H17 responses. However, it is increasingly being appreciated that a highly dynamic interchange occurs between the cellular subsets that represent these branches. Thus, different facets of inflammation may occur and dynamically evolve — within and around the tumour microenvironment — which induce tumorigenic and antitumorigenic effects that depend on the integrative nature of a given set of signals. Furthermore, cells of non-haematopoietic lineages harbour immunological functions; for example, they have crucial roles in interactions with commensal microorganisms and in antigen presentation.

As such, these cells might have modulatory roles in promoting an infectious and immune response towards a tumorigenic or an antitumorigenic effect.

The distinction between organs in which inflammation clearly drives cancer development (such as the gastrointestinal tract, liver and lung) and organs that can harbour severe chronic inflammation that carries no increased risk of cancer (such as the joints in rheumatoid arthritis) may be related to the presence or function of commensal microbial populations. As such, regions that are characterized by intense epithelial–microbial interactions (such as the intestine, lung and — to a lesser extent — the liver, which is constantly exposed to gut-derived microbial products) may show an inflammation-induced tumour propensity that is distinct from organs that feature near-sterility (such as joints and the brain). Hence, the commensal microbiota may represent the missing link between inflammatory preconditioning and the risk of tumour development. Metagenome-wide association studies of cancer patients might reveal a so-far unexpected role of microbial communities and genomes in cancer predisposition, whereas studies in mice may help to decipher the molecular mechanisms that link dysbiosis and its functional consequences to the propensity towards tumorigenesis.

Furthermore, the recognition that not only pathogenic but also commensal and pathobiont microorganisms can influence the inflammatory processes that are associated with cancer development may lead a new phase in the treatment of cancer. In the future, the targeted elimination of cancer-associated microorganisms might provide a new therapy option which, if effective, seems very attractive because of its minimal expected side effects and the possibility of its preventive application. Furthermore, probiotic approaches in the treatment of colorectal cancer should be considered, and the first studies in this area have aimed to identify potentially promising probiotic strains¹⁴². *Lactobacillus acidophilus* was used in an *in vivo* model of breast cancer to alter T cell responses towards a protective T_H1 response¹⁴³. By contrast, VSL#3 probiotic bacteria and conjugated linoleic acid (a polyunsaturated fatty acid) were shown to increase T_{Reg} cell and T_H17 cell responses and were effective in suppressing colon carcinogenesis¹⁴⁴. The kinetics of probiotic colonization of the gut are complex and probably not stable. This means that probiotic strains do not persist as stable members of the microbial community¹⁴⁵. *Lactobacillus rhamnosus* GG was found to decrease the proliferation of cancer cell lines, with the cytoplasmic fraction of the bacteria being responsible for the exerted effect¹⁴⁶. In another study, *Bifidobacterium adolescentis* SPM0212 was shown to inhibit the division of cell lines that were derived from the human colon¹⁴⁷. *In vivo* studies have assessed the effect of *Lactobacillus acidophilus* and *Bifidobacterium lactis* administration on intestinal carcinogen-induced apoptosis and found reduced dysplasia in animals that were treated with probiotics^{148,149}. It will be interesting to determine whether dietary approaches that use prebiotics can be used to modulate the microbiota to prevent or ameliorate cancer development.

Probiotic

Pertaining to microbial species that are introduced into the intestinal microbial ecosystem to exert beneficial effects on the host.

Prebiotics

Interventions (not live microorganisms) that function to stabilize a particular microbial community with a beneficial effect.

However, the development of new rational therapy that is directed towards the microbial elements of inflammation-induced cancer necessitates a mechanistic understanding of the processes that link the development of dysbiosis and increased microbial translocation to tumour development. Primarily, it will be essential to address several important questions. Which pathobionts can be unequivocally linked with cancer-associated inflammation? Are these microorganisms causally involved in tumorigenesis, or do they benefit from the consequences of tumour growth and, in turn, promote tumour progression? Which of the mechanisms that are driven by members of the commensal microbiota result

in inflammation-induced cancer development? Can cancer-associated pathobionts be selectively eliminated by targeted therapy? If so, will their pathogenic activity be replaced by other members of the commensal microbiota, or is the cancer-promoting activity an intrinsic and specific characteristic of certain pathobiont members of the microbiota? Does microorganism-driven inflammation affect only incipient neoplasia and tumour progression, or is there a similarly important effect on metastasis and chemotherapy? If these questions can be answered by future research, we might witness the start of a new era of antimicrobial therapy in cancer biology.

- Jemal, A., Siegel, R., Xu, J. & Ward, E. Cancer statistics, 2010. *CA Cancer J. Clin.* **60**, 277–300 (2010).
- Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, 428–435 (2008).
- 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).
- Virchow, R. An address on the value of pathological experiments. *Br. Med. J.* **2**, 198–203 (1881). **This is the first account of inflammatory processes that accompany cancer development in tissues.**
- Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
- Kuper, H., Adami, H. O. & Trichopoulos, D. Infections as a major preventable cause of human cancer. *J. Intern. Med.* **248**, 171–183 (2000).
- 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). **This paper shows a role for products derived from the commensal microbiota in tumour-induced inflammation and tumour promotion.**
- Goodwin, A. C. *et al.* Polyamine catabolism contributes to enterotoxigenic *bacteroides fragilis*-induced colon tumorigenesis. *Proc. Natl Acad. Sci. USA* **108**, 15354–15359 (2011).
- Abdulmir, A. S., Hafidh, R. R. & Abu Bakar, F. The association of *streptococcus bovis/gallolyticus* with colorectal tumors: the nature and the underlying mechanisms of its etiological role. *J. Exp. Clin. Cancer Res.* **30**, 11 (2011).
- Arthur, J. C. *et al.* Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* **338**, 120–123 (2012). **This article shows the genotoxic and tumour-promoting potential of a pathobiont of the commensal microflora that blooms under inflammatory conditions.**
- Amit, I. *et al.* A module of negative feedback regulators defines growth factor signaling. *Nature Genet.* **39**, 503–512 (2007).
- Mosesson, V., Mills, G. B. & Yarden, Y. Derailed endocytosis: an emerging feature of cancer. *Nature Rev. Cancer* **8**, 835–850 (2008).
- Wilson, T. R. *et al.* Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature* **487**, 505–509 (2012).
- Straussman, R. *et al.* Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* **487**, 500–504 (2012).
- Prahalad, A. *et al.* Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* **483**, 100–103 (2012).
- Casaletto, J. B. & McClatchey, A. I. Spatial regulation of receptor tyrosine kinases in development and cancer. *Nature Rev. Cancer* **12**, 387–400 (2012).
- Fukuda, A. *et al.* Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression. *Cancer Cell* **19**, 441–455 (2011).
- 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).
- 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).
- 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).
- Bronte-Tinkew, D. M. *et al.* *Helicobacter pylori* cytotoxin-associated gene A activates the signal transducer and activator of transcription 3 pathway *in vitro* and *in vivo*. *Cancer Res.* **69**, 632–639 (2009).
- Gao, S. P. *et al.* Mutations in the EGFR kinase domain mediate STAT3 activation via IL-6 production in human lung adenocarcinomas. *J. Clin. Invest.* **117**, 3846–3856 (2007).
- Waldner, M. J., Foersch, S. & Neurath, M. F. Interleukin-6 — a key regulator of colorectal cancer development. *Int. J. Biol. Sci.* **8**, 1248–1253 (2012).
- Yu, H., Pardoll, D. & Jove, R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nature Rev. Cancer* **9**, 798–809 (2009).
- Liang, J. *et al.* Sphingosine-1-phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer. *Cancer Cell* **23**, 107–120 (2013).
- 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).
- Iliopoulos, D., Hirsch, H. A. & Struhl, K. An epigenetic switch involving NF- κ B, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. *Cell* **139**, 695–706 (2009).
- Grivennikov, S. I., Greten, F. R. & Karin, M. Immunity, inflammation, and cancer. *Cell* **140**, 885–899 (2010).
- Karin, M. & Greten, F. R. NF- κ B: linking inflammation and immunity to cancer development and progression. *Nature Rev. Immunol.* **5**, 749–759 (2005).
- Ben-Neriah, Y. & Karin, M. Inflammation meets cancer, with NF- κ B as the matchmaker. *Nature Immunol.* **12**, 715–723 (2011).
- Pikarsky, E. *et al.* NF- κ B functions as a tumour promoter in inflammation-associated cancer. *Nature* **431**, 461–466 (2004).
- Greten, F. R. *et al.* IKK β links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* **118**, 285–296 (2004). **This paper and reference 31 first showed a connection between inflammation and cancer growth through the transcription factor NF- κ B.**
- Popivanova, B. K. *et al.* Blocking TNF- α in mice reduces colorectal carcinogenesis associated with chronic colitis. *J. Clin. Invest.* **118**, 560–570 (2008).
- Cataisson, C. *et al.* IL-1R-MyD88 signaling in keratinocyte transformation and carcinogenesis. *J. Exp. Med.* **209**, 1689–1702 (2012).
- Schiechl, G. *et al.* Tumor development in murine ulcerative colitis depends on MyD88 signaling of colonic F4/80 + CD11b^{high}Cr1^{low} macrophages. *J. Clin. Invest.* **121**, 1692–1708 (2011).
- Tye, H. *et al.* STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation. *Cancer Cell* **22**, 466–478 (2012).
- Zenewicz, L. A. *et al.* Innate and adaptive interleukin-22 protects mice from inflammatory bowel disease. *Immunity* **29**, 947–957 (2008).
- Sonnenberg, G. F., Fouser, L. A. & Artis, D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. *Nature Immunol.* **12**, 383–390 (2011).
- Pickert, G. *et al.* STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. *J. Exp. Med.* **206**, 1465–1472 (2009).
- Huber, S. *et al.* IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. *Nature* **491**, 259–263 (2012).
- Jiang, R. *et al.* Interleukin-22 promotes human hepatocellular carcinoma by activation of STAT3. *Hepatology* **54**, 900–909 (2011).
- Park, O. *et al.* *In vivo* consequences of liver-specific interleukin-22 expression in mice: Implications for human liver disease progression. *Hepatology* **54**, 252–261 (2011).
- Schwitalla, S. *et al.* Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties. *Cell* **152**, 25–38 (2013).
- Myant, K. B. *et al.* ROS production and NF- κ B activation triggered by RAC1 facilitate WNT-driven intestinal stem cell proliferation and colorectal cancer initiation. *Cell Stem Cell* **12**, 761–773 (2013).
- Marotta, L. L. *et al.* The JAK2/STAT3 signaling pathway is required for growth of CD44⁺CD24⁻ stem cell-like breast cancer cells in human tumors. *J. Clin. Invest.* **121**, 2723–2735 (2011).
- Ho, P. L., Lay, E. J., Jian, W., Parra, D. & Chan, K. S. Stat3 activation in urothelial stem cells leads to direct progression to invasive bladder cancer. *Cancer Res.* **72**, 3135–3142 (2012).
- Zhou, J. *et al.* Activation of the PTEN/mTOR/STAT3 pathway in breast cancer stem-like cells is required for viability and maintenance. *Proc. Natl Acad. Sci. USA* **104**, 16158–16163 (2007).
- Scheitz, C. J., Lee, T. S., McDermitt, D. J. & Tumber, T. Defining a tissue stem cell-driven Runx1/Stat3 signalling axis in epithelial cancer. *EMBO J.* **31**, 4124–4139 (2012).
- Quante, M. *et al.* Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. *Cancer Cell* **21**, 36–51 (2012).
- Campisi, J. & d'Adda di Fagagna, F. Cellular senescence: when bad things happen to good cells. *Nature Rev. Mol. Cell Biol.* **8**, 729–740 (2007).
- Xue, W. *et al.* Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature* **445**, 656–660 (2007).
- Chien, Y. *et al.* Control of the senescence-associated secretory phenotype by NF- κ B promotes senescence and enhances chemosensitivity. *Genes Dev.* **25**, 2125–2136 (2011).
- Kang, T. W. *et al.* Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. *Nature* **479**, 547–551 (2011).
- Braumuller, H. *et al.* Helper-1-cell cytokines drive cancer into senescence. *Nature* **494**, 361–365 (2013).
- Pribluda, A. *et al.* A senescence-inflammatory switch from cancer-inhibitory to cancer-promoting mechanism. *Cancer Cell* **24**, 242–256 (2013).
- Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. Cancer-related inflammation. *Nature* **454**, 436–444 (2008).

57. Campregher, C., Luciani, M. G. & Gasche, C. Activated neutrophils induce an HMSH2-dependent G2/M checkpoint arrest and replication errors at a (CA)13-repeat in colon epithelial cells. *Gut* **57**, 780–787 (2008).
58. Mills, K. D., Ferguson, D. O. & Alt, F. W. The role of DNA breaks in genomic instability and tumorigenesis. *Immunol. Rev.* **194**, 77–95 (2003).
59. Takai, A. *et al.* A novel mouse model of hepatocarcinogenesis triggered by AID causing deleterious p53 mutations. *Oncogene* **28**, 469–478 (2009).
60. Okazaki, I. M., Kotani, A. & Honjo, T. Role of AID in tumorigenesis. *Adv. Immunol.* **94**, 245–273 (2007).
61. Endo, Y. *et al.* Activation-induced cytidine deaminase links between inflammation and the development of colitis-associated colorectal cancers. *Gastroenterology* **135**, 889–898 (2008).
62. Komori, J. *et al.* Activation-induced cytidine deaminase links bile duct inflammation to human cholangiocarcinoma. *Hepatology* **47**, 888–896 (2008).
63. 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).
64. Schetter, A. J., Heegaard, N. H. & Harris, C. C. Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. *Carcinogenesis* **31**, 37–49 (2010).
65. Singh, B., Vincent, L., Berry, J. A., Multani, A. S. & Lucci, A. Cyclooxygenase-2 expression induces genomic instability in MCF10A breast epithelial cells. *J. Surg. Res.* **140**, 220–226 (2007).
66. Hahn, M. A. *et al.* Methylation of polycomb target genes in intestinal cancer is mediated by inflammation. *Cancer Res.* **68**, 10280–10289 (2008).
67. Mishra, A. *et al.* Aberrant overexpression of IL-15 initiates large granular lymphocyte leukemia through chromosomal instability and DNA hypermethylation. *Cancer Cell* **22**, 645–655 (2012).
68. Talmadge, J. E. & Fidler, I. J. AACR centennial series: the biology of cancer metastasis: historical perspective. *Cancer Res.* **70**, 5649–5669 (2010).
69. Peinado, H., Lavotshkin, S. & Lyden, D. The secreted factors responsible for pre-metastatic niche formation: old sayings and new thoughts. *Semin. Cancer Biol.* **21**, 139–146 (2011).
70. Qian, B. Z. & Pollard, J. W. Macrophage diversity enhances tumor progression and metastasis. *Cell* **141**, 39–51 (2010).
71. Kalluri, R. & Weinberg, R. A. The basics of epithelial-mesenchymal transition. *J. Clin. Invest.* **119**, 1420–1428 (2009).
72. Bates, R. C. & Mercurio, A. M. Tumor necrosis factor- α stimulates the epithelial-to-mesenchymal transition of human colonic organoids. *Mol. Biol. Cell* **14**, 1790–1800 (2003).
73. Sullivan, N. J. *et al.* Interleukin-6 induces an epithelial-mesenchymal transition phenotype in human breast cancer cells. *Oncogene* **28**, 2940–2947 (2009).
74. Wu, Y. *et al.* Stabilization of snail by NF- κ B is required for inflammation-induced cell migration and invasion. *Cancer Cell* **15**, 416–428 (2009).
75. Voronov, E. *et al.* IL-1 is required for tumor invasiveness and angiogenesis. *Proc. Natl Acad. Sci. USA* **100**, 2645–2650 (2003).
76. Grivennikov, S. I. & Karin, M. Inflammation and oncogenesis: a vicious connection. *Curr. Opin. Genet. Dev.* **20**, 65–71 (2010).
77. Gocheva, V. *et al.* IL-4 induces cathepsin protease activity in tumor-associated macrophages to promote cancer growth and invasion. *Genes Dev.* **24**, 241–255 (2010).
78. DeNardo, D. G. *et al.* CD4⁺ T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. *Cancer Cell* **16**, 91–102 (2009).
79. Kitamura, T. *et al.* SMAD4-deficient intestinal tumors recruit CCR1⁺ myeloid cells that promote invasion. *Nature Genet.* **39**, 467–475 (2007).
80. Murdoch, C., Muthana, M., Coffelt, S. B. & Lewis, C. E. The role of myeloid cells in the promotion of tumour angiogenesis. *Nature Rev. Cancer* **8**, 618–631 (2008).
81. Lerner, I. *et al.* Heparanase powers a chronic inflammatory circuit that promotes colitis-associated tumorigenesis in mice. *J. Clin. Invest.* **121**, 1709–1721 (2011).
82. Wyckoff, J. B. *et al.* Direct visualization of macrophage-assisted tumor cell intravasation in mammary tumors. *Cancer Res.* **67**, 2649–2656 (2007).
83. Grivennikov, S. I., Kuprash, D. V., Liu, Z. G. & Nedospasov, S. A. Intracellular signals and events activated by cytokines of the tumor necrosis factor superfamily: From simple paradigms to complex mechanisms. *Int. Rev. Cytol.* **252**, 129–161 (2006).
84. Nguyen, D. X., Bos, P. D. & Massague, J. Metastasis: from dissemination to organ-specific colonization. *Nature Rev. Cancer* **9**, 274–284 (2009).
85. McDonald, B. *et al.* Systemic inflammation increases cancer cell adhesion to hepatic sinusoids by neutrophil mediated mechanisms. *Int. J. Cancer* **125**, 1298–1305 (2009).
86. Chen, J. *et al.* CCL18 from tumor-associated macrophages promotes breast cancer metastasis via P1TPNMS3. *Cancer Cell* **19**, 541–555 (2011).
87. Qian, B. Z. *et al.* CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature* **475**, 222–225 (2011).
88. Wolf, M. J. *et al.* Endothelial CCR2 signaling induced by colon carcinoma cells enables extravasation via the JAK2-Stat5 and p38MAPK pathway. *Cancer Cell* **22**, 91–105 (2012).
89. Motz, G. T. & Coukos, G. Deciphering and reversing tumor immune suppression. *Immunity* **39**, 61–73 (2013).
90. Robbins, P. F. *et al.* Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. *Nature Med.* **19**, 747–752 (2013).
91. Gabrilovich, D. I. *et al.* Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nature Med.* **2**, 1096–1103 (1996).
92. Curiel, T. J. *et al.* Blockade of B7-H1 improves myeloid dendritic cell-mediated antitumor immunity. *Nature Med.* **9**, 562–567 (2003).
93. Geissmann, F. *et al.* TGF- β 1 prevents the noncognate maturation of human dendritic Langerhans cells. *J. Immunol.* **162**, 4567–4575 (1999).
94. Steinbrink, K. *et al.* Interleukin-10-treated human dendritic cells induce a melanoma-antigen-specific energy in CD8⁺ T cells resulting in a failure to lyse tumor cells. *Blood* **93**, 1634–1642 (1999).
95. Menetrier-Caux, C. *et al.* Inhibition of the differentiation of dendritic cells from CD34⁺ progenitors by tumor cells: role of interleukin-6 and macrophage colony-stimulating factor. *Blood* **92**, 4778–4791 (1998).
96. Bayne, L. J. *et al.* Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. *Cancer Cell* **21**, 822–835 (2012).
97. Gabrilovich, D. I. & Nagaraj, S. Myeloid-derived suppressor cells as regulators of the immune system. *Nature Rev. Immunol.* **9**, 162–174 (2009).
98. Curiel, T. J. *et al.* Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nature Med.* **10**, 942–949 (2004).
99. Facciabene, A. *et al.* Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and Treg cells. *Nature* **475**, 226–230 (2011).
100. Facciabene, A., Motz, G. T. & Coukos, G. T-regulatory cells: key players in tumor immune escape and angiogenesis. *Cancer Res.* **72**, 2162–2171 (2012).
101. Zarek, P. E. *et al.* A2A receptor signaling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. *Blood* **111**, 251–259 (2008).
102. Garrett, W. S. *et al.* Colitis-associated colorectal cancer driven by Tbet deficiency in dendritic cells. *Cancer Cell* **16**, 208–219 (2009).
103. Couturier-Maillard, A. *et al.* NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. *J. Clin. Invest.* **123**, 700–711 (2013).
104. Moore, P. S. & Chang, Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nature Rev. Cancer* **10**, 878–889 (2010).
105. Russell, W. An address on a characteristic organism of cancer. *Br. Med. J.* **2**, 1356–1360 (1890).
106. Wuerthele-Caspe, V. *et al.* Cultural properties and pathogenicity of certain microorganisms obtained from various proliferative and neoplastic diseases. *Am. J. Med. Sci.* **220**, 638–646 (1950).
107. Livingston, V. W. & Alexander-Jackson, E. An experimental biologic approach to the treatment of neoplastic disease; determination of actinomycin in urine and cultures as an aid to diagnosis and prognosis. *J. Am. Med. Womens Assoc.* **20**, 858–866 (1965).
108. Unproven methods of cancer management. Livingston-Wheeler therapy. *CA Cancer J. Clin.* **41**, A7–A12 (1991).
109. Polk, D. B. & Peek, R. M. Jr. *Helicobacter pylori*: gastric cancer and beyond. *Nature Rev. Cancer* **10**, 403–414 (2010).
110. Franco, A. T. *et al.* Activation of β -catenin by carcinogenic *Helicobacter pylori*. *Proc. Natl Acad. Sci. USA* **102**, 10646–10651 (2005).
111. Samaras, V., Rafailidis, P. I., Mourtzoukou, E. G., Peppas, G. & Falagas, M. E. Chronic bacterial and parasitic infections and cancer: a review. *J. Infect. Dev. Ctries* **4**, 267–281 (2010).
112. Hill, M. J. Chronic bacterial infection and subsequent human carcinogenesis. *Eur. J. Cancer Prev.* **4**, 127–128 (1995).
113. Structure, function and diversity of the healthy human microbiome. *Nature* **486**, 207–214 (2012).
114. Gordon, J. I. Honor thy gut symbionts redux. *Science* **336**, 1251–1253 (2012).
115. Rakoff-Nahoum, S. & Medzhitov, R. Regulation of spontaneous intestinal tumorigenesis through the adaptor protein MyD88. *Science* **317**, 124–127 (2007).
116. Lee, S. H. *et al.* ERK activation drives intestinal tumorigenesis in Apc^{cmv/+} mice. *Nature Med.* **16**, 665–670 (2010).
117. Uronis, J. M. *et al.* Modulation of the intestinal microbiota alters colitis-associated colorectal cancer susceptibility. *PLoS ONE* **4**, e6026 (2009).
118. Salcedo, R. *et al.* MyD88-mediated signaling prevents development of adenocarcinomas of the colon: role of interleukin 18. *J. Exp. Med.* **207**, 1625–1636 (2010).
119. Fukata, M. *et al.* Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. *Gastroenterology* **133**, 1869–1881 (2007).
120. Lowe, E. L. *et al.* Toll-like receptor 2 signaling protects mice from tumor development in a mouse model of colitis-induced cancer. *PLoS ONE* **5**, e13027 (2010).
121. Elinav, E., Henao-Mejia, J. & Flavell, R. A. Integrative inflammasome activity in the regulation of intestinal mucosal immune responses. *Mucosal Immunol.* **6**, 4–13 (2013).
122. Hu, B. *et al.* Inflammation-induced tumorigenesis in the colon is regulated by caspase-1 and NLRP4. *Proc. Natl Acad. Sci. USA* **107**, 21635–21640 (2010).
123. Zaki, M. H., Vogel, P., Body-Malapel, M., Lamkanfi, M. & Kanneganti, T. D. IL-18 production downstream of the Nlrp3 inflammasome confers protection against colorectal tumor formation. *J. Immunol.* **185**, 4912–4920 (2010).
124. Chen, G. Y., Liu, M., Wang, F., Bertin, J. & Nunez, G. A functional role for Nlrp6 in intestinal inflammation and tumorigenesis. *J. Immunol.* **186**, 7187–7194 (2011).
125. Normand, S. *et al.* Nod-like receptor pyrin domain-containing protein 6 (NLRP6) controls epithelial self-renewal and colorectal carcinogenesis upon injury. *Proc. Natl Acad. Sci. USA* **108**, 9601–9606 (2011).
126. Elinav, E. *et al.* NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. *Cell* **145**, 745–757 (2011).
127. Henao-Mejia, J. *et al.* Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* **482**, 179–185 (2012).
128. Hu, B. *et al.* Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. *Proc. Natl Acad. Sci. USA* <http://dx.doi.org/10.1073/pnas.1307571110> (2013). **This paper, together with reference 103, shows that the intestinal dysbiosis that results from innate immune deficiency leads to transmissible colon cancer.**
129. Sobhani, I. *et al.* Microbial dysbiosis in colorectal cancer (CRC) patients. *PLoS ONE* **6**, e16393 (2011).
130. Marchesi, J. R. *et al.* Towards the human colorectal cancer microbiome. *PLoS ONE* **6**, e20447 (2011).
131. Castellarin, M. *et al.* Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. *Genome Res.* **22**, 299–306 (2012).
132. Kostic, A. D. *et al.* Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. *Genome Res.* **22**, 292–298 (2012).

133. Strauss, J. *et al.* Invasive potential of gut mucosa-derived *Fusobacterium nucleatum* positively correlates with IBD status of the host. *Inflamm. Bowel Dis.* **17**, 1971–1978 (2011).
134. Kostic, A. D. *et al.* *Fusobacterium nucleatum* Potentiates Intestinal Tumorigenesis and Modulates the Tumor-Immune Microenvironment. *Cell Host Microbe*. **14**, 207–215 (2013).
135. Rubinstein, M. R., *et al.* *Fusobacterium nucleatum* Promotes Colorectal Carcinogenesis by Modulating E-Cadherin/ β -Catenin Signaling via its FadA Adhesin. *Cell Host Microbe*. **14**, 195–206 (2013).
136. Wu, S. *et al.* A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nature Med.* **15**, 1016–1022 (2009).
- This paper shows the direct involvement of a member of the commensal microflora in inflammation and tumorigenesis.**
137. Dapito, D. H. *et al.* Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. *Cancer Cell* **21**, 504–516 (2012).
138. Yoshimoto, S. *et al.* Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* **499**, 97–101 (2013).
- This report links microbiota-derived products to carcinogenesis and cellular senescence.**
139. Yusuf, N. *et al.* Protective role of Toll-like receptor 4 during the initiation stage of cutaneous chemical carcinogenesis. *Cancer Res.* **68**, 615–622 (2008).
140. Swann, J. B. *et al.* Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. *Proc. Natl Acad. Sci. USA* **105**, 652–656 (2008).
141. Nickoloff, B. J., Ben-Neriah, Y. & Pikarsky, E. Inflammation and cancer: is the link as simple as we think?. *J. Invest Dermatol.* **124**, 10–14 (2005).
142. Sanders, M. E. *et al.* An update on the use and investigation of probiotics in health and disease. *Gut* **62**, 787–796 (2013).
143. Maroof, H., Hassan, Z. M., Mobarez, A. M. & Mohamadabadi, M. A. *Lactobacillus acidophilus* could modulate the immune response against breast cancer in murine model. *J. Clin. Immunol.* **32**, 1353–1359 (2012).
144. Bassaganya-Riera, J., Viladomiu, M., Pedragosa, M., De Simone, C. & Hontecillas, R. Immunoregulatory mechanisms underlying prevention of colitis-associated colorectal cancer by probiotic bacteria. *PLoS ONE* **7**, e34676 (2012).
145. Corthesy, B., Gaskins, H. R. & Mercenier, A. Cross-talk between probiotic bacteria and the host immune system. *J. Nutr.* **137**, 781S–790S (2007).
146. Orlando, A., Messa, C., Linsalata, M., Cavallini, A. & Russo, F. Effects of *Lactobacillus rhamnosus* GG on proliferation and polyamine metabolism in HGC-27 human gastric and DLD-1 colonic cancer cell lines. *Immunopharmacol. Immunotoxicol* **31**, 108–116 (2009).
147. Kim, Y. *et al.* Inhibition of proliferation in colon cancer cell lines and harmful enzyme activity of colon bacteria by *Bifidobacterium adolescentis* SPM0212. *Arch. Pharm. Res.* **31**, 468–473 (2008).
148. Le Leu, R. K. *et al.* A synbiotic combination of resistant starch and *Bifidobacterium lactis* facilitates apoptotic deletion of carcinogen-damaged cells in rat colon. *J. Nutr.* **135**, 996–1001 (2005).
149. Pool-Zobel, B. L. *et al.* *Lactobacillus*- and bifidobacterium-mediated antigenotoxicity in the colon of rats. *Nutr. Cancer* **26**, 365–380 (1996).

Acknowledgements

The authors thank all members of the Elinav and Flavell laboratories for scientific suggestions and discussion. This work was supported by the Marie Curie Integration and Helmsley Charitable Foundation grants (to E.E.), by the Howard Hughes Medical Institute and a grant from the US Department of Defense 11-1-0745 (to R.A.F.) and a United States–Israel Binational Foundation grant (to E.E. and R.A.F.). C.A.T. receives a Boehringer Ingelheim Fonds Ph.D. Fellowship. R.N. is supported by a fellowship from the Jane Coffin Childs Memorial Fund, and C.J. was a recipient of a Trudeau Fellowship from Yale University, USA.

Competing interests statement

The authors declare no competing financial interests.