OPINION

Toll-like receptors and cancer

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Abstract | Toll-like receptors (TLRs) are a family of pattern recognition receptors that are best-known for their role in host defence from infection. Emerging evidence also suggests that TLRs have an important role in maintaining tissue homeostasis by regulating the inflammatory and tissue repair responses to injury. The development of cancer has been associated with microbial infection, injury, inflammation and tissue repair. Here we discuss how the function of TLRs may relate to these processes in the context of carcinogenesis.

The inflammatory response can promote carcinogenesis by multiple mechanisms. These include the anti-apoptotic effect of nuclear factor-κB (NF-κB; a transcription factor commonly engaged in inflammatory conditions), induction of oxidative damage to DNA and the induction of the tissue repair response[1–3]. One of the major challenges in understanding the connection between inflammation and cancer is to identify the triggering events that lead to the inflammatory responses that can promote tumorigenesis.

Inflammation is an adaptive response that is triggered by a variety of abnormal conditions, including infection and tissue injury as well as more subtle alterations of tissue homeostasis. Infection is the best-understood trigger of inflammation, with recognition of microbial pathogens by the host innate immune system initiating a potent inflammatory response[4,5]. Although this response can be initiated by several types of pattern-recognition receptors (PRRs), the Toll-like receptors (TLRs) are the best-characterized. Here we will discuss TLRs and their role in cancer development.

TLRs recognize microbial ligands

Toll-like receptors are a family of transmembrane receptors that recognize conserved molecular patterns of microbial origin. Accumulating evidence indicates that TLRs also have an important role in tissue repair and tissue injury-induced inflammation. TLR ligands in this case can be either microbial (exogenous) or host-derived (endogenous).

TLRs are best-known for their ability to recognize conserved microbial structures that were originally named PAMPs (pathogen-associated molecular patterns) by Janeway[6]. Despite their name, PAMPs are common to all microorganisms regardless of their pathogenicity.

The best-characterized TLR microbial ligands are as follows: lipopolysaccharide (LPS; endotoxin) from Gram-negative bacteria, which stimulates TLR4; bacterial lipoproteins and lipotechoic acid and fungal zymosan, which stimulate TLR1, TLR2 and TLR6; bacterial flagellin, which activates TLR5; a profilin-like molecule from the protozoan *Toxoplasma gondii*, which activates TLR11; unmethylated CpG motifs present in DNA that function as stimulators of TLR9; double-stranded RNA that activates TLR3; and single-stranded RNA that can stimulate TLR7 and TLR8 (FIG. 1).

In addition to microbial ligands, an increasing number of endogenous ligands are being reported as candidate stimulators of TLRs, in particular of TLR2 and TLR4. These include heat shock proteins (HSP60, HSP70, endoplasmin, HSPB8 and α-crystallin A chain)[7–13], high mobility group box 1 (HMGB1)[14,15], uric acid crystals[16,17], surfactant protein A[18], and various products of the extracellular matrix such as fibronectin[19], heparan sulphate[20], biglycan[21], fibrinogen[22], oligosaccharides of hyaluronan[23] and hyaluronan breakdown fragments[24–26].

TLRs control host defence from infection

The most evolutionarily conserved role of TLRs in host defence is the regulation of antimicrobial responses by epithelial cells, the first line of defence at mucosal sites such as the respiratory, gastrointestinal and genitourinary tracts, and the skin. TLRs are involved in the transcriptional and post-transcriptional regulation (proteolytic processing and secretion) of potent antimicrobial factors such as defensins (α and β), phospholipase A_2, lysozyme and the regeneration (Reg) family of molecules[27–29].

TLRs enhance the uptake of microorganisms by phagocytic cells[30] and optimize microbial killing through the generation of reactive oxygen and nitrogen intermediates and stimulation of the neutrophil oxidative burst[31]. Recognition of PAMPs by TLRs leads to the induction of inducible nitric oxide synthetase[32] and activation of the NADPH oxidase complex[33–35], which is important for the production of reactive oxygen and nitrogen intermediates.

TLRs also have a crucial role in mediating leukocyte recruitment to infected tissues. Activation of TLRs on endothelium, either directly or indirectly, leads to the surface expression of E-selectin and intercellular adhesion molecule 1 (ICAM1). These molecules are crucial for leukocyte rolling and adhesion[36] and the induction of chemokines that lead to the adhesion of leukocytes to endothelium[37].

TLRs are central to the regulation of host protective adaptive immune responses. The stimulation of both T- and B-cell-mediated immune responses by adjuvants containing microbial lysates or products, such as complete Freund's adjuvant, is due mostly to ligation of TLRs[38]. Activation by TLRs of professional antigen-presenting cells such as dendritic cells is crucial for several processes: T-cell activation[39–42]; the processing and presentation of microbial antigens[43]; upregulation of co-stimulatory molecules such as CD80 and CD86, which are necessary for the activation of naive CD4 T cells[44]; and the inhibition of regulatory T-cell activity by the production of factors such as interleukin 6 (IL-6)[45]. TLRs are also crucial for the activation and maturation of the B-cell response during infection and vaccination. Through both

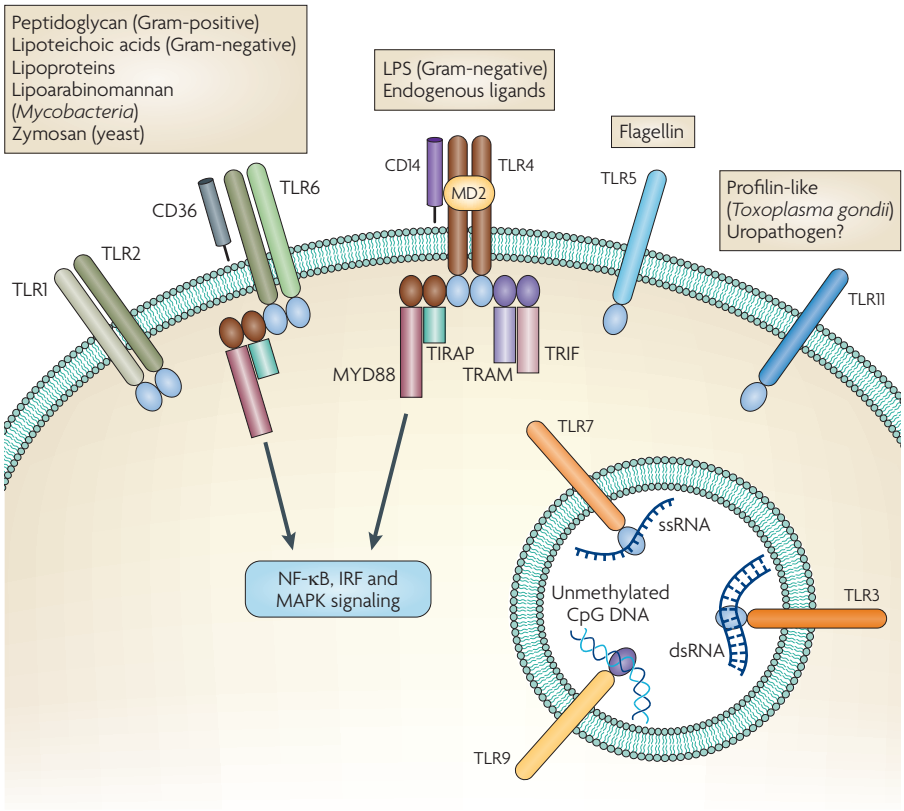

Figure 1 | **Physiological functions of Toll-like receptors (TLRs).** TLRs are involved in recognition of microbial and endogenously derived molecular patterns. This occurs both at the plasma membrane and at intracellular compartments. After ligation of TLR ligands either directly or with the help of accessory molecules such as CD14, MD2 (also known as LY96) and CD36, TLRs dimerize and transmit signals throughout the cell by means of adaptor molecules such as myeloid differentiation factor 88 (MYD88) and TRIF. This leads to the activation of multiple cellular phenomena, the best-described of which being the activation signal transduction to the nucleus (such as through activation of nuclear factor-κB (NF-κB), MAPKs and interferon regulatory factors (IRFs). TLR activation leads to regulation of innate and adaptive immune responses, inflammation and tissue repair. LPS, lipopolysaccharide.

T-cell-dependent and T-cell-independent pathways, TLRs regulate the B-cell response by inducing B-cell proliferation, immunoglobulin isotype class switching and somatic hypermutation[46]. TLRs can also regulate the differentiation and maintenance of T and B cells by the production of IL-12, IL-23 and IL-27. These cytokines induce T-helper type 1 (T_H1) and T_H17 cell development[47], and so help to promote the cell-mediated immune response.

TLR signalling

TLRs localize to several different subcellular compartments and their localization corresponds to the macromolecular nature of the ligands they recognize. Thus, TLRs that recognize lipid and protein ligands are expressed on the plasma membrane (TLR1, TLR2, TLR4, TLR5 and TLR6), whereas TLRs that detect viral nucleic acids are localized to endolysosomal compartments (TLR3, TLR7 and TLR9). TLRs transmit signals through one or more of four adaptor proteins: myeloid differentiation factor 88 (MYD88), TICAM1 (also known as TRIF), TIRAP (also known as MAL), and TICAM2 (also known as TRAM and TIRP). All TLRs (except for TLR3) and IL-1 receptor family members signal through MYD88. TLR3 signals through TICAM1 and TLR4 signals through both the MYD88 and the TICAM1 pathways[4].

Stimulation of TLRs leads to activation of NF-κB, MAPKs, JUN N-terminal kinases (JNKs), p38 and ERKs, and interferon regulatory factor (IRF3, IRF5 and IRF7) signalling pathways[5]. These signals are essential for the classical outcomes of TLR activation: the orchestration of host innate and adaptive immune responses.

TLRs have also been shown to regulate cell death. Activation of the PI3K–Akt signalling pathway by TLRs[48–50] promotes cell survival, and TLR signalling has also been associated with the increased expression of the anti-apoptotic proteins Bcl-2-related protein A1 (BCL2A1), inhibitor of apoptosis 1 (cIAP1), cIAP2, XIAP and Bcl-2 family members[51]. However, in the face of obligate intracellular bacteria and viruses, TLRs can induce cell-autonomous apoptosis through TICAM1, FADD, caspase 8 and protein kinase R (PKR)[52–55] or through the induction of type I interferons. In addition, TLRs assist natural killer (NK) cells in the killing of infected cells either by direct stimulation of TLRs on NK cells or the induction of factors such as type I interferons and IL-15 (REF. 56).

TLRs, tissue repair and regeneration

In addition to their role in mammalian host defence from microbial infection, TLRs are involved in various aspects of tissue homeostasis, including tissue repair and regeneration[57,58]. Tissue repair involves the restoration of lost cell populations, tissue architecture, blood supply and innervation, and TLRs appear to be involved in this though multiple mechanisms. By providing pro-survival signals and by inhibiting apoptosis, TLRs may dictate the threshold of injury and cell death, thereby limiting the extent of initial tissue injury. In addition, signalling induced after injury, such as the TLR-dependent production of prostaglandins (through cyclooxygenase 2 (COX2) induction) in tissue stroma[59,60] or the upregulation of anti-apoptotic factors may provide signals to keep both differentiated and progenitor cells within the tissue alive.

In the nervous system, TLRs regulate neuronal homeostasis by controlling the proliferation and differentiation of adult hippocampal neurons in the brain[61]. In this context, TLRs have also been shown to inhibit neurite outgrowth[62]. The repair of axons, spinal cord or brain tissue that has been damaged as a result of crush injury is also coordinated by TLRs[63–65]. In the large intestine, even in the absence of overt infection or injury, TLR activation mediates proper epithelial barrier function by strengthening tight junctions and inducing cytoprotective factors[66–68]. TLR signalling also mediates the repair of damaged tissue secondary to multiple types of colonic injury, including damage as a result of infection or exposure to chemicals or radiation[66,69–72]. This leads to the repositioning of tissue-resident prostaglandin-secreting stromal cells, which then trigger colonic epithelial progenitors to proliferate at crypt bases[60]. In the lung, basal inhibition of apoptosis through signalling of TLR2 and TLR4 maintains epithelial homeostasis[24] and also protects from bleomycin- and hyperoxia-induced lung injury[24,73]. TLR signalling is also necessary for liver regeneration after partial

hepatectomy[74,75] and full thickness wound healing in the skin[76]. TLRs have been shown to regulate the compensatory proliferation of parenchymal cells after injury in the liver, colon and central nervous system[66,70,74,75,77].

What ligands activate TLRs to induce tissue repair and to maintain tissue homeostasis? At sites colonized by the indigenous microflora, such as the colon, microbe-derived ligands stimulate TLR-dependent tissue homeostasis during the steady state and following injury[66,70]. Ligands derived from the indigenous flora may also be important in the liver owing to the presence of microbial ligands for TLRs in entero-hepatic circulation[78]. In sterile sites, TLRs are likely to be activated by endogenous ligands that are derived from necrotic cells, such as HMGB1 (REFS 79,80) or extracellular matrix components that are generated as a result of tissue injury[81].

TLRs and cancer

TLRs as negative regulators of cancer. In the 18th century Deidier observed a positive correlation between infection and the remission of malignant disease, making the first inference that microbes could have anticancer properties[82]. At the end of the 19th century, William Coley observed that repeated injections of a mixture of bacterial toxins from the Gram-positive bacterium *Streptococcus pneumoniae* and the Gram-negative bacterium *Serratia marcescens* served as efficient anti-tumour therapeutic agents, providing evidence that microbial products, rather than infection itself, may mediate an anti-tumour effect[83]. It was later discovered by Shear and Turner that LPS was the "haemorrhage producing fraction" of Coley's toxin that accounted for its anti-tumour effect[82]. As LPS stimulates TLR4, these results suggest that the anti-tumour effect of Coley's toxin was a result of TLR activation.

Other microbe-derived therapeutics with anti-tumour activity can be linked to their ability to activate TLR. OK-432, a lyophilized preparation of group A streptococcus[84] that is used in the treatment of cervical, gastric and oral squamous cell carcinoma[85–87] was recently shown to stimulate TLR4 (REFS 88,89). *Mycobacterium bovis* bacillus Calmette–Guérin (BCG; a potent activator of TLR2- and TLR4-dependent signalling)[90,91] has been used for 30 years as an effective treatment of bladder cancer through the intravesicular injection of these mycobacteria[92].

Potent anticancer effects against established tumours in both mice and humans after the administration of purified ligands for TLRs have been demonstrated[82,93] as a result of local (at the site of the tumour) and systemic delivery[93]. Administration of LPS has been used in Phase II clinical trials for the treatment of colorectal and lung cancer[94] and leads to tumour regression when directly injected into adoptively transferred tumours[95]. This effect has also been shown on injection of flagellin[96]. Locally, application of synthetic ligands for TLR7 and TLR8, such as imiquimod, are under investigation for the treatment of skin cancer and chronic lymphocytic leukaemia[97–99] as is the TLR9 ligand, CpG, for the treatment of brain, skin and renal cancer and lymphoma[93,100].

TLR agonists might mediate their anti-tumour activity through a multitude of mechanisms. High doses of TLR agonists, especially those such as poly(IC) that stimulate TLR3, can lead to apoptosis and have been shown to directly kill both tumour cells and ancillary cells of the tumour microenvironment, such as the vascular endothelium[101–104]. TLR activation may also cause tumours to regress by increasing vascular permeability[82] and by directly or indirectly recruiting leukocytes, resulting in tumour lysis by NK and cytotoxic T-cells.

One of the most appreciated functions of TLRs in cancer therapy is stimulation of the adaptive immune system. In these studies, tolerance to tumour self-antigens is broken, presumably by TLR-mediated upregulation of co-stimulatory signals to the adaptive immune response, a property known as adjuvanticity. This has been used in cancer vaccines, as targets of gene therapy and in raising anti-tumour antigen-specific T cells *in vitro* for adoptive transfer[93].

Does activation of TLRs have a physiological (not only an iatrogenic) role in inhibiting tumorigenesis? In the majority of studies, exogenous TLR agonists have been used to induce anticancer T-cell responses. The responses are often not achieved under physiological circumstances. However, two recent studies have suggested a more physiological role of TLRs in inducing anti-tumour T-cell responses[79]. In one study, the ability of numerous chemotherapeutic agents to kill established, adoptively transferred tumours was decreased in TLR4- and MYD88-deficient mice[79]. The authors demonstrate that HMGB1 binds to TLR4 and that HMGB1, which is released by chemotherapy-induced cell death, can activate TLR4 and induce anti-tumour T-cell immunity[79]. In a second report, C3H/HeJ mice with a loss-of-function mutation in TLR4 that were treated with DMBA to induce skin tumours developed more tumours than wild-type mice, perhaps owing to decreased activation of interferon-γ-dependent anti-tumour T-cell responses[105].

The major physiological role that TLRs have in cancer may be preventing infection by microbial pathogens that are associated with its development. TLRs are important in the recognition of microbial pathogens such as Epstein–Barr virus[106], hepatitis B and C viruses[107–110], human papilloma virus[111] and *Helicobacter pylori*[112,113], all of which are important aetiological agents of human cancer.

Classically, the ability of TLR signalling to activate the adaptive immune system has led to attempts to harness this response against cancer cells through the use exogenous administration of TLR ligands. More research is needed to determine the role of microbial and endogenous TLR ligands in inhibiting tumorigenesis in both infectious and non-infectious situations.

TLR stimulation drives tumorigenesis. The original idea that stimulation of TLRs has a positive role in tumorigenesis came from reports demonstrating that TLR ligands augment the growth of adoptively transferred tumours[96,114–117]. For example, systemic LPS administration increased migration, invasion and angiogenesis at secondary sites of an intravenously injected metastatic mammary adenocarcinoma cell line[115]. Similarly, increased rates of proliferation and decreased rates of apoptosis were evident in metastatic tumours that were formed after the adoptive transfer of a colonic adenocarcinoma cell line followed 9 days later by an intraperitoneal injection of LPS[116]. Indeed, TLR stimulation in a variety of tumour cell lines leads to increased survival and proliferation *in vitro*. Isolated plasma cells from patients with multiple myeloma were shown to express an increased repertoire of TLR compared with plasma cells from healthy donors[118,119]. Stimulation of these cells with various TLR ligands led to increased proliferation in part owing to autocrine secretion of IL-6 (REFS 118,119). By decreasing endogenous expression of TLRs in tumour cell lines it was demonstrated that TLR4 was required for the optimal growth of adoptively transferred tumour cells lines (even in the absence of exogenous LPS administration) and that intratumoral administration of *Listeria monocytogenes* induced TLR2 signalling in tumour cells and promoted their growth[117,120].

TLR ligand administration might also act on host cells to enhance the growth of adoptively transferred tumour cells. In a model in which systemic administration of LPS enhanced the growth of adoptively transferred cells, it was shown that TLR4 signalling in the recipient was required for

LPS-induced tumour growth. The suggested mechanism involved a host-dependent increase in circulating levels of TNF that led to the upregulation of NF-κB-regulated anti-apoptotic factors, such as BCL-X_L, cIAP1 and cIAP2, in the tumour cells[116].

The studies cited above have demonstrated a role of TLRs in promoting tumour survival and growth using adoptive transfer methods. Recently, however, data have indicated that TLRs (and IL-1–IL-18R signalling) have a crucial role in the development of tumours as they arise in their natural microenvironment, thus revealing a previously unknown aspect of tumorigenesis. Mice injected with the mutagen diethylnitrosamine develop liver carcinomas that are dependent on both mutagen-induced cell death and compensatory proliferation. It has been suggested that the response of stromal cells such as tissue-resident macrophages to the death of hepatocytes is crucial to the proliferation and expansion of pre-cancerous cells and tumour promotion[121]. This promotion is the result of the NF-κB-dependent production of inflammatory mediators such as IL-6 following recognition of necrotic hepatocytes by tumour stroma[121,122]. Recently, it was shown that MYD88 is crucial for the promotion of diethylnitrosamine-induced hepatocellular tumours[122]. In response to hepatocyte cell death, MYD88 signalling was responsible for the activation of NF-κB and for the production of factors such as IL-6 (REF. 122).

MYD88 has also recently been shown to be crucial for tumour promotion in models of spontaneous ($Apc^{Min/+}$) and carcinogen-induced (azoxymethane) intestinal tumorigenesis[123]. $Apc^{Min/+}$ mice are heterozygous for a mutant allele of the tumour suppressor adenomatous polyposis coli (APC)[124]. After loss of heterozygosity (LOH) at the *APC* locus, small foci of initiated intestinal epithelial cells form macroscopic tumours. This process is dependent on factors derived from epithelial cells, such as matrix metalloproteinase 7 (MMP7), and the tumour stroma, such as COX2 (REFS 125–127). $Apc^{Min/+}$ mice that are deficient in MYD88 have both a decreased incidence and size of tumours compared with $Apc^{Min/+}$ wild-type mice[123]. The effect of MyD88-dependent signalling was independent of initiation as the frequency of microademomas (a proxy for LOH) was similar between MYD88-deficient and MYD88-sufficient $Apc^{Min/+}$ mice within a litter. Insight into the mechanism by which MYD88 regulated tumorigenesis came from analysis of positive regulators of tumorigenesis, which demonstrated that MYD88 regulated the expression of COX2, MMP7 and cytosolic phospholipase A2 (REF. 123), which are important in many aspects of tumour growth[125–128].

A recent report demonstrated that, in addition to its action in the liver and intestinal tract, MYD88 is a crucial positive regulator of chemically induced tumours of both skin and connective tissue[129]. MYD88-deficient mice formed fewer tumours upon administration of DMBA and TPA or 3′-methylcholanthrene (MCA), which led to the development of skin papillomas and sarcomas, respectively[129].

These recent studies indicate that TLR signalling contributes to the growth of tumours in numerous organs and thus may represent a general principle of tumorigenesis. As MYD88 is also activated by IL-1–IL-18R activity, it is possible that this pathway also contributes to tumorigenesis in these models.

Whether TLRs are involved in tumour initiation is not yet clear. The data from the $Apc^{Min/+}$ mice indicate that they are not. However, the $Il10^{-/-}$ mouse model of colitis-associated carcinoma shows that colitis in this context is dependent on TLR recognition of the intestinal microflora. Thus, as tumour initiation is secondary to colitis, a role for TLRs seems likely[130]. A formal role of TLRs in initiation with concatenate inflammation is yet to be determined; however, one can envision several possible roles for TLRs in initiation. Chronic and unregulated stimulation of TLRs could lead to damage and mutation of DNA and aberrant chromosomal translocation by inducing free radicals or activation-induced deaminase, respectively[112,113,131,132]. Furthermore, induction of factors such as macrophage migration inhibiting factor (MIF) and BCL-6 by TLRs may impair the DNA damage response through inhibition of p53-mediated growth arrest and apoptosis[133,134], thereby driving tumour initiation.

Importantly, the experiments discussed above indicate a link between tissue repair and tumorigenesis at the level of molecular recognition of tissue injury. It remains to be determined whether the TLR-mediated homeostatic response to tissue injury that is associated with tumorigenesis orchestrates processes such as angiogenesis that are ancillary to tumour promotion. TLR activation is known to stimulate angiogenesis *in vitro*[135] through the expression of pro-angiogenic factors such as IL-8, vascular endothelial growth factor and MMPs, and there is *in vivo* evidence that TLRs might regulate the angiogenic switch[76]. Futhermore, TLR signalling in tumour cells, the vascular endothelium or other cells may aid various stages of progression and metastasis. In addition to regulating angiogenesis, TLR signalling has been shown to augment tumour cell adhesion and invasion and increase vascular permeability[136], although a role for TLRs in the natural events of metastasis has yet to be determined.

PRRs and tumorigenesis

Over the past decade we have learned that there are a limited number of conserved modules by which metazoans recognize and orchestrate a response to different classes of microbes[137]. It is likely that there will also be a limited number of modules by which organisms respond to and repair different types of injured tissues. For example, we know that there are hypoxia-dependent and hypoxia-independent homeostatic pathways of tumour-associated neoangiogenesis[138]. Are TLRs a special family of PRRs that are involved in homeostatic aspects of tumorigenesis because they have endogenous ligands, have an ancient role in development and are crucial to adult mammalian tissue repair? Or will other families of PRRs involved in microbial and tissue injury recognition systems act similarly to TLRs during certain types of tumorigenesis? The host response to parasites is often associated with tissue remodelling and results in certain classes of inflammatory responses such as the recruitment of mast cells[137], which can be important for tumour growth and survival[139,140]. Could a common pattern recognition module couple mast cell recruitment in these physiological and pathophysiological host responses? Are there type I and type II classes of tumour-associated inflammation driven by instructions from different types of pattern recognition molecules? If pattern recognition responses are required for tumorigenesis and these are homeostatic responses, then perhaps we can learn how many of these types of responses there are for a given tissue or tumour and therefore determine how robust these processes are to inhibition[141]. If there are a restricted number of ways for a tissue to induce the inflammatory and repair response, than perhaps there are a limited number of ways for a tumour to develop.

Concluding remarks

It has been known for some time now that tumorigenesis (especially in the case of solid tumours) bears the stamp of inflammation and tissue repair. Tumour promotion and progression are associated with the production of numerous inflammatory mediators, including cytokines and chemokines, the recruitment and activation of leukocytes,

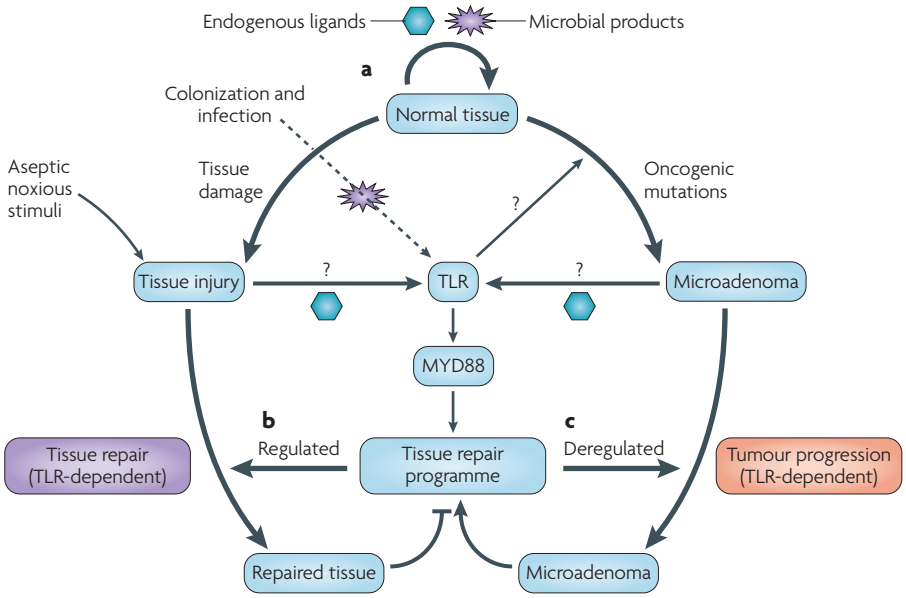

Figure 2 | **Toll-like receptors (TLRs) in tissue repair and tumorigenesis.** In organs such as the lung, brain and colon, activation of TLR signalling at the steady state maintains tissue architecture (**a**). In the face of tissue injury due either to infection or aseptic noxious stimuli, signalling of TLRs is instrumental in inducing tissue repair. This signalling can be caused by the colonizing microflora, infectious microbes or endogenous ligands such as extracellular matrix or intracellularly derived molecules. The eradication of the noxious stimulus and/or repair of the tissue negatively feeds back on this circuit to suppress the tissue repair programme (**b**). However in the presence of deregulated infection, inflammation and/or tissue injury as occurs during various stages of tumorigenesis, the unregulated TLR-regulated tissue repair response can drive tumour growth and progression in a positive feedback of unregulated tissue injury and repair (**c**).

particularly mast cells, macrophages and neutrophils, and the orchestration of ancillary processes such as neoangiogenesis and tissue remodelling.

Why is the inflammatory response so tightly coupled with tumorigenesis? As noted above, there are likely to be several unrelated reasons that underlie this connection. In this regard, it is important to distinguish between inflammation-induced cancers and cancer-induced inflammation. Thus, infection- or injury-induced inflammation can promote tumorigenesis owing to chronic tissue damage with subsequent induction of tissue repair. On the other hand, tumour growth can mimic tissue damage (in the case of solid tumours) and this can trigger TLR-dependent inflammatory responses (FIG. 2). Likewise, tumour growth — even without overt tissue damage — is sensed (in some cases by TLRs) as an abnormal occurrence and thus triggers inflammation by mechanisms that are still poorly defined.

As sensors of cell death and tissue remodelling, TLRs may have a universal role in cancer. Cell death, tissue injury and remodelling may be unavoidable consequences of tumour development and are also associated with a plethora of environmental risk factors for cancer, such as the effects of chemicals and physical trauma. Thus, cancer-induced inflammation is not a stochastically acquired and selected property. Rather, cancer-induced inflammation may be a normal response of the host to the tissue injury and malfunction that is caused by tumour growth. This cancer-associated tissue injury does not resolve itself but may actually be perpetuated by the homeostatic inflammatory and tissue repair response[142] (FIG. 2).

Our understanding of the role of TLRs (and other PRRs) in cancer is primitive. Yet, it is clear from the results of animal studies that TLRs have an important part in cancer development. This conjecture is supported by the association of numerous polymorphisms in TLRs with human cancer in a variety of organs including the nasopharynx, stomach, prostate, breast, blood and colon[143–159]. Future studies will be necessary to delineate the mechanisms by which gain- or loss-of-function polymorphisms in TLRs correlate with risk or protection from cancer.

Harnessing TLRs for cancer immunotherapy and vaccines is promising. However, in a variety of circumstances the activation of TLRs may aid the development of tumours, so targeting the TLRs will not be a straightforward process. Further understanding the role of TLRs and other PRRs in tumorigenesis should provide interesting insights into cancer development. A major challenge for the future will be to dissect the key parameters that determine the outcome of TLR stimulation on tumour initiation and progression.

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DATABASES

National Cancer Institute Drug Dictionary: http://www.cancer.gov/drugdictionary/
BCG | bleomycin | imiquimod

Pathway Interaction Database: http://pid.nci.nih.gov/PI3K_Akt_signalling

UniProtKB: http://www.uniprot.org
α-crystallin A chain | APC | BCL2A1 | BCL-6 | BCL-X_L | caspase 8 | CD14 | CD36 | CD80 | CD86 | cIAP1 | cIAP2 | COX2 | endoplasmin | FADD | fibronectin | HMGB1 | HSP60 | HSP70 | HSPB8 | ICAM1 | IL-15 | IL-18R | IL-6 | IL-8 | IRF3 | IRF5 | IRF7 | LY96 | MIF | MMP7 | MYD88 | NF-κB | p53 | TICAM1 | TICAM2 | TIRAP | TLR1 | TLR2 | TLR3 | TLR4 | TLR5 | TLR6 | TLR7 | TLR8 | TLR9 | XIAP

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