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Pathogen recognition receptors, cancer and inflammation in the gut

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Summary of recent advances

The pathogen recognition receptors (PRR) initiate immediate responses against infection and tissue damage to protect the host from microbial invasion. In response to mucosal damage, intestinal PRR signaling initiates damage repair processes. Recent advances appear to link PRR abnormalities and inflammatory as well as neoplastic intestinal disorders. Emerging evidence suggests a dual role of PRRs in which they may simultaneously induce tumorigenesis and anti-tumor immunity. PRR may induce tumor cell proliferation by activating cell survival signaling mainly via NF-κB, but this signal can activate dendritic cells to promote anti-tumor immunity. TLR signaling within the tumor cells may result in evasion of immune surveillance, propagation of metastatic growth, or rather, induction of tumor cell apoptosis depending on ligands. Epithelial cells induce endogenous PRR ligands when damaged or during neoplastic transformation. Targeted manipulation of PRR signaling may provide emerging opportunities for the development of new therapeutic strategies for many gastrointestinal diseases.

Introduction

Pathogen recognition receptors (PPR)s are a series of innate immune receptors that include membrane bound toll-like receptors (TLR)s, cytoplasmic Nod-like receptors (NLR)s and an RNA helicase family of receptors. PRRs recognize pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) and initiate immune responses against pathogens or repair responses in damaged tissues. Since the gastrointestinal mucosa is constantly exposed to diverse microorganisms and dietary antigens, the recognition and discrimination of pathogens from normal commensals or nutrients is one of the most important functions of the gastrointestinal tract, and homeostatic maintenance of PRR signaling is largely responsible for this function. Almost all of the TLRs, NLRs, and the RNA helicases (RIG-I and MDA5) are expressed by intestinal epithelial cells (IEC)s as well as in other types of cells in the intestine [1,2]. In the context of PRR-mediated intestinal mucosal homeostasis, TLRs balance inflammatory and anti-inflammatory responses against luminal antigens. Data have suggested that an additional balance of intestinal epithelial proliferation and apoptosis also involves TLR signaling [3,4]. Therefore, loss of these balances may induce dysregulated inflammation or abnormal epithelial regeneration. For instance, genetic studies have identified strong associations of PRR related gene mutations and development of idiopathic inflammatory bowel disease (IBD).

There are no conflicts of interest.

Recently, growing evidence has suggested involvement of PRRs, especially TLRs signaling, in tumor development [5–9]. Based on these reports, it seems that TLR signaling may both promote and prevent tumorigenesis. This paradox may be explained by the existence of different TLRs and different origins of tumor cells. For example, epithelial TLR4 signaling promotes tumorigenesis, but TLR4 signaling in dendritic cells (DCs) may help to promote anti-tumor immunity [5,10]. In fact, some TLR agonists have been tested for cancer immunotherapy and cancer vaccine adjuvant. The themes outlined in this paragraph will be covered in more detail later.

In this review, we discuss how PRR signaling maintains gastrointestinal homeostasis and how involvement of PRR signaling participates in inflammatory and neoplastic conditions of the gastrointestinal tract. We suggest opportunities for targeting of these pathways in inflammatory and neoplastic diseases.

Role of PRRs in the healthy gut

Our gastrointestinal tract is a unique organ that houses ~10^{14} microorganisms. The microbiota help to maintain our immune system and metabolic homeostasis as well as aid in digestion of nutrients. To maintain this coexistence, the gastrointestinal mucosa has to protect the host from pathogenic invasion while avoiding an excessive immune response against commensal bacteria. In order to avoid an excessive immune response and consequent deregulated inflammation, a variety of mechanisms regulate PRR signaling, especially in membrane bound TLRs.

Almost all TLRs, TLR1 through TLR9, are expressed not only on antigen presenting cells, but also on most cell types in the gastrointestinal mucosa [1,11,12]. IECs are the innermost lining of the mucosa, and TLR signaling is normally down regulated [13,14]. This down-regulation of signaling may be strictly controlled through decreased receptor expression on the epithelial cell surface and increased expression of inhibitors of TLR signaling [13,15,16]. DCs and macrophages in normal gastrointestinal mucosa have also been shown to be hyporesponsive or induce immune tolerance in response to TLR stimulation [17–19]. It has been suggested that the hyporesponsiveness of intestinal antigen presenting cells (APCs) may be due to epithelial or stromal derived factors such as thymic stromal lymphoprotein (TSLP) or TGF-β [19,20]. Therefore, epithelial or other stromal cells crosstalk with APCs to regulate their PRR response to maintain immune tolerance against commensals.

PRRs actively control commensal microbes by inducing antimicrobial peptides and secretory IgA. Defensins are antimicrobial peptides that are divided into two forms, α- and β-defensins. The α-defensins are constitutively expressed by Paneth cells or neutrophils and their expression is associated with NOD2 signaling. In contrast, β-defensins are inducible and mainly expressed by IECs. We have previously demonstrated that TLR4- and TLR2-dependent pathways can stimulate β-defensin-2 expression by human IECs [21]. Mucosal expression of another anti-microbial C-type lectin, Reg IIIγ, is regulated by MyD88-dependent signaling [22]. B cells can secrete non-specific IgA_2 to control the load of commensal bacteria in a T cell-independent manner. IECs and DCs have been shown to participate in the IgA_2 secretion through expression of the cytokines APRIL (A proliferation-inducing ligand), the BAFF (B cell-activation factor of the tumor necrosis factor family), or TSLP, which is responsible for local IgA class switching [23]. Most TLR ligands have been shown to induce expression of these cytokines, suggesting that PRR signaling culminates in increased IgA production in the intestinal mucosa.

Regulation of epithelial proliferation is an emerging role of PRRs in the gastrointestinal tract. We have shown that healing of injured intestinal epithelium requires the presence of intact TLR signaling [24]. Decreased epithelial proliferation is found in MyD88- and TLR4-deficient mice [24,25]. The defect in epithelial proliferation was attributed to lack of TLR4-mediated

regulation of cyclooxygenase-2 (Cox-2) expression and subsequent prostaglandin E_2 (PGE_2) synthesis [4]. MyD88-dependent signaling is suggested to be involved in redistribution of Cox-2 expressing stromal cells, which can modulate epithelial cell proliferation in response to mucosal injury [3]. In addition, TLR4 signaling activates epidermal growth factor receptor (EGFR) through induction of one of the EGFR ligands, amphiregulin [4]. Therefore, by recognizing commensals, PRRs not only maintain the intestinal epithelial lining in normal mucosa, but also initiate mucosal healing by activating other repair signaling in the case of mucosal damage.

PRRs in gastrointestinal inflammation

During epithelial injury or pathogenic infection, activated PRRs signal to induce local innate immune responses against mucosal microorganisms. The innate immune responses include local pro-inflammatory cytokine and chemokine expression and subsequently an acute inflammatory cell infiltrate to the site of infection or tissue damage. PRR signaling also presents local information to T and B cells to generate antigen specific adaptive immunity and activate regulatory T cells at the same time in the lymphoid tissue. In addition, innate PRR signaling has to initiate a repair process to restore a damaged mucosal barrier so that the host can avoid further exposure to the luminal pathogens or commensals [3]. Therefore, PRR signaling in gastrointestinal mucosa works to clear a dangerous situation in the most efficient way. The initiation of regulatory immune functions is important to diminish unnecessary tissue damage induced by secreted pro-inflammatory substances. Emerging evidence demonstrates the requirement of direct TLR signaling in full activation of regulatory T cells [26,27]. Failure of any of these steps may result in prolonged or uncontrolled gastrointestinal inflammation.

Discovery of disease associated gene mutations has significantly improved our understanding of the pathogenesis of IBD. IBD, ulcerative colitis and Crohn's disease, are idiopathic conditions of sustained and uncontrolled inflammation in the gastrointestinal tract [28]. Ulcerative colitis only affects the large intestine while Crohn's disease may affect any part of the gastrointestinal tract. Based on findings in the inflamed mucosa, it had been thought that IBD results from aberrant adaptive immunity in the intestine. However, the first gene discovered associated with disease susceptibility in Crohn's disease encoded NOD2 [29,30]. Further studies have demonstrated several polymorphisms in PRRs as candidate genes in IBD (Table 1). Importantly, most of these PRR-associated polymorphisms in IBD are loss-of-function mutations. Animal studies have provided detailed roles of individual PRRs in intestinal inflammation. Targeted gene knockout mice represent how the loss of function of a particular PRR influences intestinal inflammation. The gastrointestinal phenotype of PRR knockout mice are listed in Table 2. Most of the PRR-knockout mice are susceptible to dextran sodium sulfate (DSS)-induced colitis. [24,25] [25] [31] Subsets of patients with Crohn's disease express serum antibodies reactive against flagellins derived from commensal bacteria, and truncating mutations in TLR5 prevent the development of these antibodies [32,33]. [34] [35] [36].

Since PRR signaling may induce both pro- and anti-inflammatory cytokines, the balance of the cytokine induction is important to determine the course of mucosal inflammation. Roles of PRR signaling in cytokine production may differ between epithelial cells and other cell types in the intestinal mucosa. Mucosal DCs from patients with IBD have been shown to express more IL-12 and IL-6 but a similar amount of IL-10 compared to DCs from control subjects [37]. In contrast, IECs have been shown to play a central role for induction of intestinal immune tolerance by producing IL-10 and TGF-β in response to TLR stimulation [38]. TLR2 signaling is known to induce IL-10, and TLR4 can induce IL-10 and TGF-β, cytokines important for induction of regulatory T cells (Tregs). In the clinical setting, patients homozygous for the 3020insC frameshift mutation in the NOD2 gene demonstrate defective release of IL-10 from

peripheral blood mononuclear cells after stimulation with TLR2 ligands [39]. Monocytes from patients with the Asp299Gly polymorphism of TLR4 demonstrate defective expression of anti-inflammatory cytokines rather than pro-inflammatory cytokines in response to TLR4 stimulation [40]. Therefore, PRR signaling in intestinal inflammation may act as a double-edged sword: in the early phases of colitis PRR signaling may increase inflammation but it is also responsible for stopping inflammation and repairing the epithelium.

PRRs and gastrointestinal carcinogenesis

Recognition of bacterial and/or viral products by PRRs may induce an injury repair response, which is associated with tumor promotion. Activated PRR signaling may support tumor growth through complex effects on the microenvironment. We have shown using a bone marrow chimera model that induction of chemokines (KC and CCL2) by intestinal epithelial TLR4 signaling is required to create a tumor promoting microenvironment in the setting of chronic colitis [41]. A recent finding demonstrates extracellular matrix proteoglycan produced by primary cancer cells activates TLR2 on macrophages, which facilitates metastatic tumor growth by establishing a microenvironment [42]. Huang et al, have shown that *Listeria monocytogenes* when present in the microenvironment of tumors accelerate tumor growth via TLR2 signaling in a mouse model of colon cancer xenografts into a BALB/c mouse [43]. In addition, TLR4 expression by colorectal tumor cells may facilitate evasion from immune surveillance perhaps through iNOS-mediated immune modulation [44]. Contrary to the above findings, lack of MyD88 or TLR5 enhanced tumor growth and inhibited tumor necrosis in a mouse model of colon cancer xenografts into a nude mouse [45]. This result was confirmed by tumor regression by stimulating TLR5 with a peritumoral flagellin treatment. An important difference is that the latter experiment is performed in the nude mouse which lacks adaptive immunity. Therefore, different PRRs may work differently in intestinal tumorigenesis.

Emerging evidence has suggested that genetic polymorphisms in PRRs are associated with gastrointestinal cancer. Table 3. These results indicate that abnormal PRR signaling may, at least in part, increase the risk in development of gastrointestinal cancer.

It has long been thought that cancers represent a “wound that does not heal” and a final stage of an abnormal and uncontrolled tissue repair process [46]. The wound healing process shares some aspects of tumorigenesis. We have found that TLR4 or MyD88-deficient mice have defective intestinal mucosal repair in response to chemically induced mucosal damage due to impaired response of Cox-2 and PGE_2 production [4]. This impaired PGE_2 production results in reduced transactivation of epidermal growth factor receptor (EGFR) [4]. In IECs, TLR4-deficent mice also have defective expression and secretion of amphiregulin, one of the EGFR ligands [5]. These data indicate that MyD88-dependent TLR4 signaling is largely responsible for intestinal mucosal wound healing. As a result, we have found that TLR4-deficient mice are protected against a murine model of colitis-associated tumor [5]. An animal study has demonstrated involvement of MyD88-dependent signaling in gastrointestinal tumor growth by using the $Apc^{Min/+}$ mouse model [47]. The $Apc^{Min/+}$ mice carry a germline mutation in the tumor suppressor *Apc* gene, which is responsible for familial adenomatous poliposis coli and also frequently mutated in sporadic colorectal cancer. In this study, MyD88-deficiency in $Apc^{Min/+}$ mice resulted in a significant decrease in visible tumors in the small and large intestine [47]. Importantly, MyD88-deficiency did not influence the overall incidence of tumor development in this model.

Epidemiological studies have suggested that chronic inflammation plays a significant role in the development of gastrointestinal malignancies. A variety of chronic inflammatory conditions, e.g. Barrett’s esophagus, long-standing IBD, and *H. pylori* -associated chronic gastritis, markedly elevate the risk of developing gastrointestinal malignancies. A great deal of work has been done to identify bacterial factors important in *H. pylori* pathogenesis. Of

these, expression of the CagA protein is thought to confer the greatest oncogenic risk. On the host side, TLR signaling may be quite important in *H. pylori* -associated gastric cancer. Chronic infection with *H. pylori* increases TLR4 and MD-2 expression in gastric epithelial cells, and recognition of *H. pylori* LPS augments NF-κB activation [48,49]. Furthermore, TLR4 is strongly expressed by tumor cells of *H. pylori* -associated gastric carcinoma [49].

We have reported that tumor cells in human and a mouse model of colitis-associated cancer have increased expression of TLR4 [5]. To assess whether this up-regulation of TLR4 in tumor cells is functionally involved in the pathogenesis of colitis-associated tumor, we challenged TLR4-defficient mice to a mouse model of colitis-associated cancer. We found in this study that TLR4-deficient mice exhibit a significantly decreased incidence and size of colorectal tumors compared to WT mice [5]. More recently, the importance of TLR signaling in colitis-associated tumorigenesis has also been shown in IL-10 knockout mice [50]. In this report, azoxymethane (AOM)-treated IL-10 knockout mice demonstrated development of multiple colorectal tumors including invasive cancer, but tumor development is completely abolished both under germ-free conditions and in the absence of MyD88 (IL-10−/− x MyD88−/− double knockout mice). These results indicate that chronic inflammation up-regulates TLRs, especially TLR4, which signaling through MyD88 promotes tumorigenesis in the gastrointestinal tract.

Several other studies however have demonstrated a protective role of TLR4 signaling against development of neoplastic lesions [8,51]. These conflicting results are observed outside of the gastrointestinal tract, such as lung and skin. It is possible but not yet clear that depending on the organ, TLR signaling plays diverse roles in tumorigenesis. At least the role of TLR signaling in tumor development may differ between the tumor cell and the environment, because the immune environment can either promote or impede tumor growth.

PRRs in anti-tumor immunity

Tumor immunosurveillance, a mechanism to protect hosts against the emergence of a tumor, is established by the interplay between antigen presenting cells (mostly DCs) and natural killer (NK) cells that recognize the transformed cells, followed by the subsequent development of tumor-specific cytotoxic T cell (CTL) responses. In this process, DCs are indispensable in cross-presenting tumor-associated antigens to CTLs, and TLR signaling may contribute to the phagosome maturation that enhances the antigen presentation [52]. However, DCs are not only efficient at generating CTLs, but can also generate tumor-specific regulatory T cells. This generation of tumor-specific Tregs is an obstacle to tumor immunity.

A recent study suggests that TLR4 and MyD88 play an important role in anti-cancer immune responses following chemotherapy and irradiation [53]. TLR4-deficient mice have significantly larger tumors than wild-type mice after doxorubicin and oxalplatin treatment or irradiation, yet displayed similar growth rates of a skin-transplanted colon cancer and thymoma cells in the absence of treatment [53]. Recently, a direct role of PRRs in the induction of anti-tumor immunity has been postulated. PRRs, in particular TLR4, detect endogenous ligands termed DAMPs that are released from injured and inflamed tissues. A wide range of DAMPs including high mobility group B1 (HMGB1), hyaluronan, S100 proteins, heat shock proteins, and fibronectin may activate TLRs to induce danger signaling [54–56]. In the tumor environment, damaged or necrotic tumor cells secrete these DAMPs, which subsequently trigger TLR4 activation in DCs and enhance antigen presentation to promote anti-tumor responses. In fact, TLR4 polymorphisms, manifested by TLR4 loss-of-function allele, lose this antigen cross-presentation process resulting in early tumor relapse and an increase in the frequency of metastasis in patients with breast cancer [53,57]. Therefore, impaired PRR function of TLR4 may attenuate the ability of anti-tumor immunity, thus acting in a tumorigenic manner.

PRRs as new therapeutic targets in gastrointestinal inflammation and cancer

TLR agonists are being developed for the treatment of cancer, allergies and viral infections, and as adjuvants for vaccines to prevent or treat cancer and infectious diseases. Several reports have demonstrated the efficacy of TLR and NOD2 agonists for prevention of murine IBD [58–61]. Notably, most of the inhibitory effects of these agonists are observed when administered prior to induction of intestinal inflammation. A subset of patients with Crohn's disease showed decreased expression of mucosal TLR3 [62]. Crohn's disease-associated NOD2 mutations are considered to be loss-of-function mutations [63]. Therefore, stimulation of TLR3 or NOD2 signaling in the mucosa can be a strategy for patients with Crohn's disease with decreased expression of TLR3 or carrying NOD2 mutations, respectively. On the other hand, blocking TLR signaling is expected to be another strategy for IBD treatment, because TLR2 and TLR4 are up-regulated in IBD [62,64]. TLR4 antagonists are currently being developed [65]. However, when we studied a blocking antibody to TLR4 in acute and chronic murine models of colitis, acute inflammation was dampened and recovery delayed [66]. One aspect of TLR signaling that has not been well appreciated is that they can generate suppressive as well as inflammatory responses in innate immune cells and can promote the induction of regulatory as well as effector T cells. Therefore, to obtain more effective strategies, agonists or antagonists of a targeted function of PRR signaling need to be taken into account for future treatment.

Modulation of TLR signaling as anti-cancer therapy has been more successful than the above-mentioned strategies against inflammatory diseases. Generation of effective immunotherapy or therapeutic anti-cancer vaccines requires breaking the immunological tolerance and generating effector T cell responses specific for the "self" tumor antigens. In addition, we need to overcome the form of immune evasion and subversion by the tumor, which in many ways resembles those evolved by pathogens to circumvent protective immune responses of the host. The potential of TLR ligands to enhance and improve the efficacy of tumor vaccines has been shown. TLR3, TLR4, TLR7 and TLR9 ligands potently activate CD8+ CTLs with increased IFN-γ production and form an immunostimulatory microenvironment [67]. Synthetic ligands for TLR7, TLR4 and TLR9 have been through preclinical evaluation and clinical trials against cancer [68,69]. TLR4 activation by the organic compounds OK-432 or OK-PSA induces strong anti-cancer immunity [10,70]. Studies have shown enhanced chemosensitivity upon TLR stimulation. For example, TLR7 ligation results in sensitization of the chronic lymphocytic leukemia B cells to chemotherapeutic agents (vincristine) *in vitro*, presumably by enhancing vincristine-induced JNK signaling [71]. Another anti-tumor strategy is induction of apoptosis by TLR signaling. It has been observed that cells stimulated with TLR ligands undergo programmed cell death by Fas-associated death domain protein and subsequent caspase recruitment [72,73]. Studies have shown increased apoptosis of cancer cells by stimulating with the TLR3 agonist, suggesting that the TLR3 agonist may be another option for anti-cancer immunotherapy [74,75]. A recent report has shown a breakthrough in anti-cancer immunotherapy by taking advantage of RIG-I mediated immune response. Poeck et al., designed a small interfering RNA (siRNA), acting as an anti-tumor agent not only to silence the anti-apoptotic Bcl2 but also to activate RIG-I to stimulate anti-tumor immunity [76]. In this study, RIG-I signaling synergized with siRNA-mediated Bcl2 silencing to provoke massive apoptosis of tumor cells in lung metastasis *in vivo*.

Conclusions

The roles of PRRs in gastrointestinal inflammation and tumorigenesis are currently being elucidated. Extensive studies into the role of PRR signaling in gastrointestinal homeostasis have increased our understanding of the complicated and delicate balance of the PRR functions in the gastrointestinal mucosa. Very interestingly, defects in any part of PRR signaling in the

gastrointestinal mucosa results in either inflammation or tumor development. In particular, epithelial TLR4 signaling via MyD88 may play a pivotal role in the development of cancer in the gastrointestinal tract. A better understanding of this complicated receptor family will provide clues for a future generation of effective strategies to treat many gastrointestinal diseases.

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Abbreviations

PAMP	pathogen-associated molecular pattern
DAMP	danger-associated molecular pattern
RIG-I	retinoic acid inducible gene I
MDA5	melanoma differentiation-associated gene 5

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Table 1

PRR polymorphisms associated with IBD

Polymorphisms/Mutations	Disease Association
NOD2 (R702W, G908R, 3020insC)	Chrohn's Disease [29,30]
NOD1 (intronic region)	Age of IBD onset [77]
TLR2 (R753Q)	Ulcerative Colitis [78]
TLR4 (Asp299Gly)	Ulcerative Colitis and Chrohn's Disease [79–81]
TLR9 (−1237C)	Chrohn's Disease [82]

Table 2

Gastrointestinal phenotype of PRR KO mice

Gene Deficiency	Phenotype
TLR2	Increased susceptibility to DSS colitis [25]
TLR4	Increased susceptibility to DSS colitis [24] Bacterial translocation [25]
TLR5	25% of mice develop spontaneous colitis [31]
TLR9	Increased susceptibility to DSS colitis [83,84]
MyD88	Increased susceptibility to DSS colitis [25] Decreased heat-shock protein (hsp25 and hsp72) in colonic epithelium; Increased susceptibility to radiation injury [25]
NOD2	Increased susceptibility to oral infection of Listeria monocytogenes [34] Decreased expression of paneth cell α-defensins (Defcr4 and Defcr-rs10) [34]
$NOD2^{2939ic}$	Increased susceptibility to DSS colitis [35]
RIG-I	Spontaneous colitis, susceptible to DSS [36]

Table 3

PRR polymorphisms associated with Gastrointestinal Cancer

Polymorphisms/Mutations	Cancer
TLR2 (−196 to −174del/del)	Non-cardiac gastric cancer in Japanese population [85]
TLR4 (Thr135Ala)	Poorly differentiated gastric adenocarcinomas [86] Gastric cancer [87]
(Asp299Gly)	Gastric cancer [87]
(Thr399Ile)	Pre-malignant lesions [88]
NOD2 (3020insC)	Colorectal cancer in older Polish patients [89]
NOD2 (R702W, G908R, 3020insC)	Colorectal cancer in Greek population [90] Not associated with gastric cancer in Caucasian population [91] Not associated with colorectal cancer in Hungarian subjects [92]
TLR2 (microsatellite GT)	Colorectal cancer in Croatian patients [93]
TLR4 (Asp299Gly)	