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SIGIRR, a negative regulator of colon tumorigenesis

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Abstract

Inappropriate activation of the Toll-IL-1R (TL-IL-1) signaling by commensal bacteria contributes to the pathogenesis of inflammatory bowel diseases and colitis-associated cancer. Recent studies have identified SIGIRR as a negative regulator of TL-IL-1 signaling. It dampens intestinal inflammation and tumorigenesis in the colon. In this review, we will discuss the role of SIGIRR in different cell types and the mechanisms underlying its tumor suppressor function.

Introduction

The intestinal tract is inhabited by trillions of microbes collectively referred to as commensal microflora. The host has developed a mutualism with commensal bacteria where they are beneficial to each other [1]. An important aspect of this relationship is the “microbial tolerance” installed by host immune system. A group of membrane proteins, named Toll-like Receptors (TLRs) can recognize molecules derived intestinal-resident and pathogenic bacteria and initiate inflammatory response, mounting the defense attack. [2]Inappropriate activation of these receptors is implicated in the pathogenesis of inflammatory bowel disease (IBD). Patients with ulcerative colitis (UC), a type of inflammatory bowel disease, stand a higher risk of developing colon cancer, indicating an association of inflammation and tumorigenesis [2]. The chronic inflammation process is commonly believed to be the cause of neoplastic transformation of the intestinal epithelium [3]. Therefore, the “microbial tolerance” of the intestinal epithelial layer is not only important for controlling local inflammation but also for preventing tumorigenesis in the colon.

Many mechanisms have been proposed to explain how the host immune system selectively ignores resident bacteria but retains its ability to fight pathogenic invasion. A popular model suggests that the temporally and spatially regulated expression of TLRs can restrict their exposure to pathogen associated pattern molecules (PAMPs), which are the cognate ligands derived from bacterial components in order to avoid rampant activation of inflammatory responses. However, the dilemma of this model is that the TLRs expressed in the intestine

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Conflict of Interest

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are not completely blind to the commensal flora. In fact, signaling through TLRs provides gut epithelium with tonic signals critical for the survival for intestinal epithelial cells (IECs) and tissue repair after injury [4]. Another mechanism known to contribute to the tolerance relies on negative regulators of TLR signaling, among which the Single Immunoglobulin IL-1 Receptor Related molecule (SIGIRR or *Tir8*) is an important member.

SIGIRR, a negative regulator of TLR-IL-1R signaling

The Toll-IL-1 receptor (TL-IL-1R) superfamily is defined by the presence of an intracellular Toll/IL-1 receptor (TIR) domain. These receptors play crucial roles in the immune response and can be divided into two main subgroups based on their sequence feature. The Leucine Rich Repeat motif (LRR)-containing subgroup consists of at least ten Toll-like receptors (TLRs). These receptors have received intense attention as different TLRs can be activated by specific pathogen products [5]. The immunoglobulin domain-containing subgroup includes the IL-18R, ST2 and IL-1R, whose ligands are major inflammatory mediators. While IL-18 signaling is important for Th1 immunity, IL-33 has been identified as the ligand for ST2 and plays a critical role in Th2 immunity [6, 7]. Importantly, IL-1 has recently been shown to play an essential role in Th17 cell differentiation [8].

The TLR-IL-1Rs can induce TAK1 (TGF β -activated kinase 1)- and MEKK3 (MAP kinase kinase kinase 3)-dependent pathways, involving cascades of kinases organized by multiple adapter molecules into parallel and sequential signaling complexes, leading to the activation of transcription factor NF κ B, which plays a critical role in cell survival [9, 10]. TLR-IL-1Rs also mediate mRNA stabilization and translation control of cytokines/chemokines and cell cycle regulators, which is essential for effective inflammatory response and tissue repair. TLR-IL-1Rs-mediated TAK1-dependent NF κ B activation is coupled with posttranscriptional regulation through receptor proximal signaling events to induce the robust production of cytokines and chemokines in bone-marrow-derived macrophages [11, 12]. Differentially, the TLR-IL-1Rs-mediated MEKK3-dependent pathway is uncoupled from posttranscriptional regulation and only induces expression of genes that are not regulated at posttranscriptional levels. These genes include inhibitory molecules A20 and I κ B α , which exert an overall inhibitory effect on inflammatory gene expression. [9] SIGIRR is a negative regulator of the TLR-IL-1R signaling. SIGIRR deficiency sensitizes mice to LPS induced septic shock [13, 14]. It also leads to excessive inflammation during *Mycobacterium tuberculosis* infection [15]. The expression of SIGIRR is strategically positioned in epithelial cells but not in macrophages, which suggests differential pathway activation in different cell types [10]. While the TAK1 dependent pathway may serve for inflammatory response, the MEKK3 dependent pathway may be responsible for controlled tonic activation of NF κ B, which is essential for cell survival and tissue repair.

SIGIRR is a transmembrane protein with a single immunoglobulin domain (Ig) and a cytoplasmic portion that shares highly conserved motifs with Toll-IL1 Receptor (TIR) domain. TIR domain of SIGIRR protein is divergent from that of the IL-1 receptor in two amino acid residues that are crucial for signaling transduction, rendering it defective in mediating downstream events. [16] Nevertheless, it retains the ability to mediate homotypic interaction with other TIR domain-containing proteins [14]. SIGIRR inhibits IL-1R and TLR signaling pathways through differential mechanisms. SIGIRR interferes with the heterodimerization of Ig domains of the receptor subunits of the IL-1R, whereas the intracellular TIR domain inhibits both IL-1R and TLR signaling by attenuating the recruitment of receptor proximal signaling components to the receptor [17]. (Figure 1)

SIGIRR negatively regulates signal transduction of several receptors of the TLR-IL-1R superfamily. Overexpression of SIGIRR can inhibit NF κ B-dependent luciferase expression

mediated by IL-18R, IL-1R, ST2, TLR4 and TLR9. SIGIRR-deficient kidney epithelial cells showed increased NF κ B and JNK activation in response to IL-1 β , LPS and CpG DNA. Similarly, in bone marrow derived dendritic cells, SIGIRR deficiency increased IL-12 production in response to imiquimod treatment, indicating that SIGIRR plays a similar role in the TLR7 mediated signaling. In one of our previous studies, we reported that SIGIRR overexpression could not inhibit NF κ B activation through TLR5 and TLR3. Moreover in SIGIRR-deficient kidney epithelial cells there was no significant difference in response to flagellin or poly I:C [7, 14, 17, 18]. In contrast to this study, Zhang and colleagues observed that overexpression of SIGIRR in human airway epithelial cells could attenuate the production of cytokines induced by flagellin [19]. (Table 1) These studies suggest that a more detailed investigation is needed to define the spectrum of receptors inhibited by SIGIRR and how this corresponds to cell-type.

TLR-IL-1R superfamily and Colon tumorigenesis

As mentioned earlier, TLR-IL-1R signaling plays a critical role in the active cross talk between the commensal microflora and the host. Mice deficient in MyD88, TLR2 or TLR4 failed to launch the tissue repair program after DSS insult, rendering them susceptible to DSS induced colitis [20]. Initiation of the tissue repair program requires the engagement of TLRs with their cognate ligands, which are derived from the commensal bacteria. Thus, the TLR-IL-1R and gut microflora have a beneficial impact on the homeostasis of the intestinal epithelium. Unfortunately, the beneficial role played by the same signaling can also be an omen for cancer. Microbial infection, injury, inflammation and tissue repair are all associated with the development of colon tumorigenesis. For example, ulcerative colitis-associated cancer involves the inflammation of the submucosa, which is induced by direct contact with the intestinal microflora [3]. The tumorigenic processes resulting from tissue injury and inflammation is also mediated by TLR-IL-1R signaling.

Studies using MyD88 deficient mice have demonstrated a protective effect of MyD88 deficiency against tumorigenesis in APC^{Min/+} mice, a murine model of spontaneous tumorigenesis in the intestinal tract [4]. Similar results were obtained from studies with the TLR4 knockout mice, which were resistant to AOM/DSS induced colorectal cancer [21]. Thus, the signaling through MyD88, especially the ones mediated by TLR4, seems to be required for carcinogenesis. However, MyD88 deficiency became a tumor-promoting factor in the AOM/DSS model, in which dextran sodium sulphate (DSS) was used to enhance the genetic lesion induced by pro-carcinogen azoxymethane (AOM). IL-18 knockout mice share the similar phenotypes with MyD88 deficient mice in the AOM/DSS induced colon cancer model, displaying increased tumor formation and growth [22]. Consistent with this finding, deficiency in components of inflammasome, the machinery producing IL-1 β and IL-18, renders mice susceptible to AOM/DSS induced colon carcinogenesis [23, 24]. The complexity of phenotypes manifested by these knockout mice indicates that the TLR-IL-1R signaling plays multiple roles in the process. The knockout mice used in previous studies mostly were defective in either the signaling pathway or the production of cytokine, which has largely limited our scope since compensating mechanism may take over in the absence of TLR-IL-1R signaling and complicate the scenario.

This problem was resolved with the advent of SIGIRR knockout mice. Because SIGIRR negatively regulates the signaling, its deficiency does not debilitate the pathway. Rather, it exaggerates the intensity of the original signal, providing a model of excessive TLR-IL-1R signaling and enabling us to look at the same problem from another side. SIGIRR knockout mice exhibit deregulated homeostasis with increased proliferation and decreased apoptosis of the IECs. Constitutive phosphorylation of I κ B and JNK was observed in crypt cells isolated from SIGIRR deficient mice, which was accompanied by increased production of

proinflammatory mediator in physiological state [25]. SIGIRR deficiency increases the susceptibility to DSS induced colitis [13] [25]. NF κ B target genes, Bcl-xL and CyclinD1, are highly induced in SIGIRR deficient colon, contributing to the increased cell survival and proliferation. In the AOM/DSS model, SIGIRR-deficient mice showed increased tumor incidence, total tumor number as well as tumor size. Indicating that SIGIRR is a negative regulator of tumor promotion and progression [25, 26]. In addition, increased expression of classic tumor promoters including IL-6 and Cox-2 was found in the knockout mice. Moreover, SIGIRR was demonstrated to decrease tumor initiation in the *Apc^{Min/+}* model, where it also suppressed tumor growth. Interestingly, in both models the effect of SIGIRR deficiency depends on the presence of commensal microflora, suggesting the TLRs mediated signaling is the initiator of the aggravated inflammation and tumorigenesis [27].

The tumor-suppressing function of SIGIRR in colon carcinogenesis was demonstrated in three separate studies. But the mechanism underlying its function remains to be elucidated because the previous studies have used the complete SIGIRR-knockout mice in which SIGIRR expression is absent in all cell types. However, the colon consists of multiple cellular compartments. Underlying the epithelium is a layer of mucosal tissue called lamina propria which houses a variety of immune cells including T cells and dendritic cells. The effect of SIGIRR deficiency may be an intrinsic defect of the IECs. It is also possible that the lamina propria provides an input to the IECs through cytokines produced by T cells and dendritic cells (DCs) where SIGIRR is also abundantly expressed. In the following review we will discuss the function of SIGIRR in each cell type and how it could impact the tumorigenesis.

SIGIRR in intestinal epithelial cells

SIGIRR is highly expressed in the colon epithelium, which undergoes continuous and rapid renewal. TLR-mediated NF κ B activation in gut epithelial cells has been suggested to provide the survival signal, termed tonic signal. In absence of SIGIRR, the tonic signal was exaggerated, resulting in increased expression of genes important for cell survival and proliferation, including Cyclin D1, c-Myc and Bcl-xL. Adoptive transfer experiments revealed that TLR4 expressed by IECs is important for recruiting Cox-2 expressing macrophages that amplify the size and number of dysplastic lesion [28]. Corroboratively, intestinal-epithelial-specific expression of SIGIRR in SIGIRR knockout mice largely rescued the deregulated homeostasis and decreased tumorigenesis, suggesting that epithelial-derived SIGIRR is a primary effector in suppressing colon tumorigenesis. SIGIRR dampens the excessive secretion of chemokines to reduce the recruitment of immune cells to the colon, decreasing the intensity and duration of the inflammation, which results in better resolution of colitis and tumor formation [25, 27].

NF κ B has long been a suspected mediator between tumorigenesis and inflammation. Intestinal epithelial specific knockout of IKK β , an upstream kinase crucial for NF κ B activation, decreased tumor multiplicity but not tumor size in an AOM/DSS model, suggesting that activation of NF κ B contributed to tumor initiation and tumor promotion [29]. Hyper activation of NF κ B can increase the production of IL-6, which can then act on IECs to activate STAT3. The IL-6-STAT3 axis has been shown to be important for early stages of colon tumorigenesis [30]. In addition, the level of phosphorylated STAT3, the active form of the transcription factor, is elevated in colorectal carcinomas from human patients [31]. Moreover, activation of STAT3 has also been shown to enhance tumor growth in xenograft models[32].

Activation of NF κ B, JNK and mTOR pathway were also enhanced in SIGIRR deficient IECs. JNK can cross talk with Wnt signaling, which controls the proliferation and

differentiation of intestinal epithelial stem cells. A positive feedback connects the two pathways through c-Jun, the substrate of JNK and TCF4, a component of TCF4/ β -catenin complex. Enhanced activation of JNK can accelerate colitis-induced tumorigenesis [33]. mTOR pathway has been shown to promote the cell cycle progression by enhancing the translation of cell cycle regulators. It has also been shown to influence Wnt- β -catenin pathway by phosphorylating GSK3 β , which controls the stability of β -catenin. Importantly, the increased anaphase bridge index (ABI) that contributed to tumor initiation can be explained by the hyper-activation of mTOR activity. ABI is an indicator of chromosome instability. mTOR hyper-activation was reported to result in G1-S phase acceleration and eventually chromosome instability [34].

Another relevant signaling pathway that might have contributed is the activation of ERK in Apc^{Min/+} model. One study suggests that the protective effect conferred by MyD88 deficiency in Apc^{Min/+} mice is a result of inactivation of ERKXXREFXX. ERK stabilizes the oncoprotein MYC and prevents its degradation. SIGIRR deficiency can exaggerate the activation of ERK in the IECs by commensal bacteria, which can explain the increased c-Myc level reported in SIGIRR deficient Apc^{Min/+} colonocytes [35].

SIGIRR in adaptive immune cells

Induction of adaptive immune surveillance is an important part of the intestinal immune system to guard against commensal and pathogenic microbes, involving professional antigen presenting cells and lymphocytes that reside in the organized lymphoid structures of the intestinal immune system. In response to commensal or pathogenic microbes, the professional antigen presenting cells (DCs) are able to produce cytokines to regulate the differentiation of CD4⁺ Th cells. T helper cells differentiate into functionally distinct effector subsets. Th1 cells produce IFN- γ and regulate cellular immunity, whereas Th2 cells produce IL-4, IL-5, IL-13 and regulate humoral immunity. While Th1 cell activation is associated with Crohn's disease, Th2 cytokines are often detected in patients with ulcerative colitis, the latter of which is associated with increased risk of developing colon cancer [36]. Th17 cell subset has also recently been shown to regulate tissue inflammatory responses. While Th17 cells have been implicated in the generation of protective immunity to extracellular bacterial infection, exaggerated activation probably leads to abrogation of mucosal T cell homeostasis, leading to intestinal inflammation [37].

SIGIRR expression was highly induced in polarized Th2 and Th17 cells, but its expression remains low in naïve T cells and Th1 cells. A novel cytokine IL-33, an IL-1 family member, signals via ST2 receptor and promotes T helper type 2 (Th2) responses. SIGIRR can form a complex with ST2 upon IL-33 stimulation and specifically inhibit IL-33/ST2-mediated signaling. Its expression is highly induced during Th2 cell polarization and upon restimulation. Importantly, SIGIRR-deficient Th2 cells produce higher levels of "Th2 cytokines", including IL-4, IL-5 and IL-13 than that in wild-type cells. IL-33-induced Th2 response was enhanced in SIGIRR-deficient mice compared to that in wild-type control mice, suggesting a negative regulatory role of SIGIRR in Th2 response via IL-33/ST2 signaling in vivo [7]. The response type may be important in that Th1-cell mediated response is likely to generate macrophages that has antitumor activity, whereas Th2-cell mediated response tends to polarize macrophages to a tumor-promoting phenotype. Thus, SIGIRR deficiency could lead to hyper activity of Th2 cells, which can exacerbate the intestinal inflammation and nurture a microenvironment for tumorigenesis [38].

Recent studies have also shown that IL-1-mediated signaling in T cells is essential for Th17 differentiation/maintenance and autoimmune disease. While SIGIRR expression was induced during Th17 differentiation, SIGIRR deficiency leads to enhanced expansion of

Th17 cells and increased induction of Th17 associated cytokines (IL-17, IL-17F, IL-21 and IL-22). Importantly, IL-1 stimulation results in increased Th17 cell expansion in differentiated SIGIRR-deficient Th17 cells, suggesting that the impact of SIGIRR on Th17 effector function is probably through its modulation on IL-1 signaling in differentiated Th17 cells [39]. Consistent with these findings, it has been shown that SIGIRR deficiency exacerbated Th17 cell responses in fungal infection and increased severity of systemic autoimmune diseases [40, 41]. In DSS-induced colitis model, SIGIRR-deficient colon tissues produced more IL-13, IL-17 as well as IFN- γ compared to that in wild-type mice, indicating the potential contribution of T-cell-derived SIGIRR in the modulation of Th17 cell activation and function during intestinal inflammation. Th17 cells and IL-17 have been implicated in colon tumorigenesis. In a mouse model of enterotoxigenic *Bacteroid fragilis* (ETBF), a predominant Th17-mediated colitis was observed, which eventually resulted in tumorigenesis. Blockade of IL-17A alone was enough to inhibit the infection-associated carcinogenesis [42]. The strong association between Th17 cells and colitis suggests a scenario in which excessive inflammation resulting from unhampered expansion of SIGIRR-deficient Th17 cells enhances the tumorigenic environment.

Despite a modest expression level in the dendritic cells, SIGIRR has been shown to play an important role in regulating dendritic cell function. M. Lech and colleagues have reported a protective effect of SIGIRR in both hydrocarbon oil-induced and homozygous Lpr mouse model of systemic lupus erythematosus (SLE). In the former study the authors showed that SIGIRR suppressed TLR-7 mediated activation of dendritic cell, protecting the mouse from hydrocarbon oil-induced lupus [18]. In the latter work, they demonstrated that lack of SIGIRR led to enhanced activation of dendritic cells upon lupus autoantigen exposure, increasing its expression of proinflammatory and antiapoptotic mediators [41]. Dendritic cell derived SIGIRR is also a crucial regulator of antidonor reactivity of kidney grafts. Being an important population in the lamina propria, dendritic cell might be the primary source of tumor-promoting cytokines including IL-6 and TNF α [43].

Discussion

TLR-IL-1R signaling plays a crucial role in the mutualism between host and commensal microbes residing in the intestinal tract. The commensal bacteria trigger different TLRs to maintain the tonic signal that is essential for epithelial homeostasis and tissue repair. However, the same signal can also lead to chronic inflammation that promotes the tumorigenesis in the colon. The delicate balance is maintained by SIGIRR through inhibition of the TLR-IL-1R signaling. SIGIRR deficiency resulted in severe colitis and associated carcinogenesis in both chemical induced model as well as spontaneous model of colon cancer. The mechanism underlying the effect of SIGIRR deficiency could be epithelial intrinsic as well as a result of the input from hyperactive T cells and dendritic cells. (Figure 2) Due to the different function of SIGIRR in different cell types, the precise contribution to colitis-associated tumorigenesis from different cellular compartments is not yet known. Despite the complexity resulting from the multiple roles of SIGIRR, SIGIRR deficiency has provided a precious tool for probing the function of TLR-IL-1R signaling.

The expression pattern of SIGIRR is highly conserved among vertebrates, with high expression found in the intestinal tract, which suggests a conserved function of SIGIRR in the intestine [44]. Existing evidence suggests that SIGIRR also modulates innate immune response in differentiated human intestinal epithelial cells [45]. Moreover, in ulcerative colitis patients, SIGIRR expression is lower in disease active tissue compared to normal tissue [46]. Given its unique role in controlling inflammation and tumorigenesis, SIGIRR holds the potential of being a valuable biomarker in related diseases.

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Figure 1. SIGIRR negatively regulates IL-1R and TLR signaling through differential mechanisms

SIGIRR inhibit both IL-1R and TLR4 signaling by attenuating the recruitment of MyD88 to the TIR domain of the receptor, thereby interfering with the formation of receptor-proximal signaling components. In addition, SIGIRR also disrupt the heterodimerization of the extracellular domain of IL-1R with its accessory protein, decreasing the intensity of the signal.

Figure 2. Mechanism of SIGIRR mediated anti-inflammation and tumor suppression in colon SIGIRR expression suppresses the TLR activation by commensal bacteria. Loss of SIGIRR in intestinal epithelial cells increases NFkB activation as well as mTOR signaling, contributing to increased cell survival. After DSS injury, the exaggerated TLR signaling enhances the inflammatory response, leading to increased expression of chemokines and cytokines. Excessive chemokine and cytokine production leads to increased recruitment of immune cells, contributing to the aggravated inflammation. The impact from cytokines and exaggerated TLR signaling can promote cell proliferation, which results in increased tumorigenesis in the AOM/DSS model. Meanwhile, hyper-activated T helper cells can contribute to the inflammation by secreting proinflammatory cytokines.

Table 1

Summary of evidence for receptors inhibited by SIGIRR

Receptor	Ligand	Experimental Model	Readout	Reference
IL-1R	IL-1 β	SIGIRR overexpression	NF κ B-dependent luciferase assay	14,17
		SIGIRR-deficient and wildtype kidney epithelial cells and splenocytes	NF κ B activation (EMSA [*])	
		Cytokine injection into mice	JNK phosphorylation	
IL-18R	IL-18	SIGIRR overexpression	NF κ B-dependent luciferase assay	14
ST2	IL-33	SIGIRR overexpression	NF κ B-dependent luciferase assay	7
		SIGIRR-deficient and wildtype Th2 cells	Th2 cytokine production	
TLR4	LPS	Endotoxin Challenge	Survival rate	14,17
		SIGIRR-deficient and wildtype kidney epithelial cells	NF κ B activation (EMSA)	
		SIGIRR-deficient and wildtype splenocytes	JNK phosphorylation	
TLR5	flagellin	Overexpression in human airway epithelial cells	NF κ B activation (EMSA)	19
			JNK phosphorylation	
TLR7	imiquimod	Production of IL-6 and TNF α	Ligand induced proliferation	18
		SIGIRR-deficient and wildtype primary dendritic cells	IL-12 expression	
TLR9	CpG DNA	SIGIRR overexpression	NF κ B-dependent luciferase assay	14,17
		SIGIRR-deficient and wildtype splenocytes	Ligand induced proliferation	

* EMSA Electrophoretic Mobility Shift Assay