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Review

Dual character of Toll-like receptor signaling: Pro-tumorigenic effects and anti-tumor functions

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ABSTRACT

As a major class of pattern-recognition receptors, Toll-like receptors (TLRs) play a critical role in defense against invading pathogens. Increasing evidence demonstrates that, in addition to infection, TLRs are involved in other important pathological processes, such as tumorigenesis. Activation of TLRs results in opposing outcomes, pro-tumorigenic effects and anti-tumor functions. TLR signaling can inhibit apoptosis and promote chronic inflammation-induced tumorigenesis. TLR activation in tumor cells and immune cells can induce production of cytokines, increase tumor cell proliferation and apoptosis resistance, promote invasion and metastasis, and inhibit immune cell activity resulting in tumor immune escape. In contrast, the engagement of other TLRs directly induces growth inhibition and apoptosis of tumor cells and triggers activation of immune cells enhancing anti-tumor immune responses. Thus, the interpretation of the precise function of each TLR in tumors is very important for targeting TLRs and using TLR agonists in tumor therapy. We review the role of TLR signaling in tumors and discuss the factors that affect outcomes of TLR activation.

Contents

Abbreviations: AOM, Azoxymethane; BaP, Polycyclic aromatic hydrocarbons benzo[a]pyrene; BMDCs, Bone marrow-derived dendritic cells; CAC, Colitis-associated colorectal cancer; CCL5, Chemokine ligand 5; Cox-2, Cyclooxygenase-2; CpG-ODNs, CpG oligodeoxynucleotides; CYP1A1, Cytochrome P450 subclass 1A1; DC, Dendritic cell; DEN, Diethylnitrosamine; DSS, Dextran sodium sulfate; EGFR, Epidermal growth factor receptor; HCC, Hepatocellular carcinomas; HMGB1, High mobility group box-1 protein; HNSCC, Head and neck squamous cell carcinoma; HSPs, Heat shock proteins; IRF, IFN regulatory factor; IFNAR1, IFNα receptor 1; LLC, Lewis lung cancer; LPS, Lipopolysaccharide; MDA5, Melanoma differentiation-associated protein-5; mDCs, Myeloid dendritic cells; MM, Multiple myeloma; MyD88, Myeloid differentiation factor 88; NB, Neuroblastoma; PAMPs, Pathogen-associated molecular patterns; PBMC, Peripheral blood mononuclear cells; PGE_2, Prostaglandin E_2; PI3K, Phosphatidylinositol-3′-kinase; Poly(A:U), Polyadenylic-polyuridylic acid; Poly(I:C), Polyinosinic-polycytidylic acid; PRRs, Pattern-recognition receptors; PSK, Polysaccharide krestin; IRAK, Interleukin-1 receptor-associated kinase; SAA, Serum amyloid A; TAMs, Tumor associated macrophages; TIRAP, TIR domain-containing protein; TLRs, Toll-like receptors; TRAM, TRIF-related adaptor molecule; Treg, Regulatory T cells; TRIF, TIR domain-containing adaptor inducing interferon-β; WT, Wild type

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1. Introduction

Toll was first discovered as a receptor involved in recognition of fungi and embryo dorsoventral polarity determination in *Drosophila* [1,2]. Toll-like receptors (TLRs), similar to *Drosophila* Toll, are a major class of pattern-recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and trigger signals responsible for the activation of innate and adaptive immune responses. TLR4 was first demonstrated in 1998 to be the receptor for lipopolysaccharides (LPS) of Gram-negative bacteria in mice [3]. Thus far, 11 mammalian TLRs have been identified. Both humans and mice express TLR1-TLR9, recognizing and responding to molecules related to a broad class of microorganisms (Table 1). TLR engagement with ligands induces homo- or heterodimerization and conformational change of the TLRs. TLRs are homodimeric with the exception of TLR1/TLR2 and TLR2/TLR6, which sense triacyl lipopeptides and diacyl lipopeptides, respectively. TLR5 recognizes flagellin, the structural protein subunit of the bacterial flagellum. TLRs 3, 7, 8, and 9 are nucleic acid receptors residing predominantly within the endosomes. TLR3 recognizes double-stranded RNA and synthetic double-stranded RNA molecules such as polyinosinic-polycytidylic acid [poly(I:C)], whereas TLR7 and TLR8 recognize single-stranded RNA and synthetic mimicking ligands such as Imiquimod. TLR9 recognizes unmethylated CpG sequences in microbial DNA molecules as well as CpG oligodeoxynucleotides (CpG-ODNs), short, single-stranded synthetic DNA molecules. In addition to bacterial and viral structures, TLRs recognize the host-derived molecules released from injured tissue, triggering a non-infectious inflammatory response [4,5]. For example, high mobility group box-1 protein (HMGB1) can activate TLR2 and TLR4.

Two main TLR signaling pathways, myeloid differentiation factor 88 (MyD88)-dependent or independent, have been identified (Fig. 1). In the MyD88-dependent pathway, MyD88 and TIR domain-containing protein (TIRAP) are required to recruit the interleukin-1 receptor-associated kinase 4 and 1 (IRAK4, 1) for the activation of TRAF6 and TAK1, leading to early activation of NF-κB and MAPK and transcriptions of a range of genes, including pro-inflammatory cytokines, chemokines, cytosolic enzymes and other protein factors (for review [6,7]). The MyD88-independent pathway, through TIR domain-containing adaptor inducing interferon-β (TRIF) and TRIF-related adaptor molecule (TRAM), results in the activation of the late phase NF-κB and the IFN regulatory factor (IRF) that controls the gene expression of type I IFNs [7].

Chronic infection by bacteria and viruses is recognized as a risk factor for tumorigenesis. *Helicobacter pylori* infection causes chronic gastritis and peptic ulceration and is the strongest known risk factor for the development of gastric cancer [8]. It is well established that chronic infections with hepatitis B and C viruses can result in chronic hepatitis and liver cirrhosis, and represent major risk factors for development of hepatocellular carcinoma (HCC) [9]. Human papillomavirus persistent infection is an essential factor for the invasive cervical cancer, the second most common malignancy in women worldwide [10]. Epstein–Barr virus infection is linked to endemic Burkitt's lymphoma in Central Africa and nasopharyngeal carcinoma in Southeast Asia [9]. The underlying mechanism which infection increases cancer risk has been ascribed to infection-induced inflammation [9,11]. TLRs sense the microbial invasion and trigger an inflammatory response against invading pathogens. There is increasing evidence that TLR signaling plays a critical role in tumorigenesis and tumor regression. Genetic disruption of several TLRs and adaptor molecules of the TLR pathway is associated with tumor development and progression in mice [12–15]. Activation of TLRs in immune or tumor cells regulates anti-tumor immunity of the host [16] or induces tumor immune evasion [17,18]. Microbial components (exogenous TLR ligands) as well as host-derived molecules (endogenous TLR ligands) are involved in

Table 1
Natural and synthetic ligands of Toll-like receptors [5].

TLRs	Microbial ligands	Host-derived ligands	Synthetic ligands
TLR1	Triacyl lipopeptides		Pam3CSK4 for TLR1/TLR2
TLR2	Peptidoglycan, lipoteichoic acid, lipoarabinomannan, lipopeptide, zymosan, glucuronoxylomannan, phospholipomannan, porins, and LPS	Biglycan, carboxyalkylpyrrole, endoplasmin, HMGB1, HSP60, HSP70, human cardiac myosin, hyaluronan, monosodium urate crystals, pancreatic adenocarcinoma upregulated factor (PAUF), and versican	Pam3CSK4 for TLR1/TLR2
TLR3	Double strand RNA	mRNA	Poly(I:C) and poly(A:U)
TLR4	LPS, mannan, viral envelope proteins, and glycoinositolphospholipids	Biglycan, CD138, α-crystallin A chain, β-defensin 2, endoplasmin, fibrinogen, fibronectin, heparan sulphate, HMGB1, HSP22, HSP60, HSP70, HSP72, hyaluronan, monosodium urate crystals, oxidized phospholipids, PAUF, peroxiredoxin 1, resistin, S100 proteins, SAA3, surfactant protein A, and tenascin-C	Taxol/paclitaxel, lipid A, and MPL
TLR5	Flagellin		
TLR6	Diacyl lipopeptides, peptidoglycan, and zymosan	Versican	Pam2CSK4 and FSL-1 for TLR2/TLR6
TLR7	Single strand RNA	RNA and small interfering RNA (siRNA)	Resiquimod (R-848), loxoribine, bropirimine, and imiquimod (R-837)
TLR8	Single stranded RNA	Human cardiac myosin and siRNA	R-848, bropirimine, and R-837
TLR9	Hemozoin and unmethylated CpG DNA	DNA and HMGB1	CpG-ODNs