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Mini-review

The innate immune signaling in cancer and cardiometabolic diseases: Friends or foes?

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ABSTRACT

The innate immune system is responsible for sensing pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) by several types of germline-encoded pattern-recognition receptors (PRRs). It has the capacity to help the human body maintain homeostasis under normal conditions. However, in pathological conditions, PAMPs or DAMPs trigger aberrant innate immune and inflammatory responses and thus negatively or positively influence the progression of cancer and cardiometabolic diseases. Interestingly, we found that some elements of innate immune signaling are involved in these diseases partially *via* immune-independent manners, indicating a deeper understanding of the function of innate immune signaling in these diseases is urgent. In this review, we summarize the primary innate immune signaling pathways and their association with cancer and cardiometabolic diseases, with the aim of providing effective therapies for these diseases.

Abbreviations: AIM2, absent in melanoma 2; ALRs, AIM2-like receptors; AMPK, AMP-activated protein kinase; ASC, apoptosis-associated speck-like protein containing CARD; ASK, apoptotic signal-regulating kinase; ATF, activating transcription factor; BCR, B cell receptor; CAC, colitis-associated cancer; CARD9/Bcl-10/Malt1, caspase recruitment domain family member 9/B cell leukemia/lymphoma 10/mucosa associated lymphoid tissue lymphoma translocation gene 1; CDK, cyclin-dependent kinase; cIAPs, cellular inhibitor of apoptosis proteins; CLRs, C-type lectin receptors; CREB, cAMP response element binding protein; CTL, cytotoxic lymphocyte; DAI, DNA-dependent activator of interferon-regulatory factors; DAMP, danger-associated molecular patterns; DCBLD2, discoidin, CUB and LCCL domain containing 2; DDX41, DEAD-box helicase 41; DLK, delta like non-canonical Notch ligand; DNA-PK, DNA-dependent protein kinase; DSS/AOM, azoxymethane/dextran sulfate sodium; DUOX, dual oxidase; EGFR, endothelial growth factor receptor; ER, endoplasmic reticulum; ERBIN, Erbb2 interacting protein; ERK, extracellular signal-regulated kinase; FADD, FAS-associated protein with death domain; FOXO1, forkhead box protein O1; FRMPD, FERM and PDZ domain-containing protein; G6PD, glucose-6-phosphate dehydrogenase; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HFD, high-fat diet; HMGB, high-mobility group box; iE-DAP, γ-D-Glu-mDAP; IFN, interferon; IKK, IκB kinase; IL, interleukin; IPS, interferon-β promoter-stimulator; IRAK, IL-1 receptor-associated kinase; IRF, IFN regulatory factor; ISGF, interferon-stimulated gene factor; JNK, c-Jun N-terminal kinase; KRAS, Kirsten rat sarcoma viral oncogene; LGP, laboratory of genetics and physiology; LRR, leucine-rich repeat; LUBAC, linear ubiquitin complex; Mal, MyD88 adaptor-like; MAP3K, mitogen-activated protein kinase kinase kinase; MAPK, mitogen-activated protein kinase; MAVS, mitochondrial antiviral signaling protein; MCD, methionine choline deficient; MDA, melanoma differentiation-associated factor gene; DC, dendritic cell; MEK, MAPK/ERK kinase; MHC, major histocompatibility complex; MRE11, double-strand break repair protein MRE11; mTORC1, mammalian target of rapamycin complex; MyD88, myeloid differentiation factor 88; NACHT, NAIP (neuronal apoptosis inhibitor protein), CIITA (MHC class 2 transcription activator), HET-E (incompatibility locus protein from *Podospora anserina*) and TP1 (telomerase-associated protein); NADPH, nicotinamide adenine dinucleotide phosphate; NAIP, neuronal apoptosis inhibitor protein; NALP, NLR family, pyrin domain containing; NBD, nucleotide-binding domain; NEMO, nuclear factor (NF)-κB essential modulator; NIH, NF-κB-inducing kinase; NOD, nucleotide-binding oligomerization domain; NOS, nitric oxide synthase; NLRA, acidic-containing NLR; NLRC, CARD-containing NLR; NLRP, PYRIN-containing NLR; NLRs, NOD-like receptors; NLRX1, NLR family member X1; PAMP, pathogen-associated molecular patterns; PD-1, programmed death 1; PPARγ, peroxisome proliferator-activated receptor gamma; PRR, pattern-recognition receptors; RalB, v-ral simian leukemia viral oncogene homolog B; RIG-I, retinoic acid-inducible gene I; RIP2, receptor-interacting protein 2; RLRs, RIG-I-like receptors; STAT1, signal transducer and activator of transcription 1; STING, stimulator of interferon genes PYHIN; SOD1, superoxide dismutase 1; Syk, spleen tyrosine kinase; TAB2, TGF-β-activated kinase 1/MAP3K7-binding protein 2; TAK1, TGF-β-activated kinase 1; TANK, TRAF family member-associated NF-κB activator; TBK, TRAF family member-associated NF-κB activator-binding kinase; T2DM, type 2 diabetes mellitus; TGF, transforming growth factor; TIR, Toll/IL-1 receptor; TIRAP, TIR domain-containing adaptor protein; TLRs, Toll-like receptors; TNF, tumor necrosis factor; TRADD, TNFR-associated death domain; TRAF, TNF receptor-associated factor; TRAM, TRIF-related adaptor molecule; VSMC, vascular smooth muscle cells; xIAP, X-linked inhibitor of apoptosis protein; Y750, tyrosine 750.

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Introduction

It is clear that obesity is a risk factor for cardiometabolic diseases. In addition, epidemiological studies have also revealed that various types of cancers (including hepatocellular carcinoma, pancreatic cancer, and breast cancer) are strongly associated with obesity [1]. Thus, with the high prevalence of overweight and obesity, the incidences of cancer and cardiometabolic diseases are continuously increasing, and these two disorders gradually constitute the heaviest health and economic burden worldwide [2]. Therefore, to determine the latent pathogenesis of these diseases and to take early prevention steps will be the key points to solve these social problems.

Accumulating evidence indicates that chronic inflammation is one of the pivotal triggers for carcinogenesis, which has been well demonstrated by animal studies and clinical investigations during the past 150 years [3–5]. Hepatocellular carcinoma with HBV or HCV infection, gastric cancer with *Helicobacter pylori* infection, colorectal cancer with a history of inflammatory bowel disease, and pancreatic cancer in patients with chronic pancreatitis are classic examples [6]. Similar to carcinogenesis, a growing body of evidence for the vital role of chronic low-grade inflammation in various cardiometabolic dysfunctions has recently been demonstrated [7,8]. Inflammation has been shown to play a critical role in the development of obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD), resulting in severe cardiovascular disorders [9]. These data indicate that inappropriate inflammation, as a pathogenic factor or a regulator, contributes to the pathogenesis of these diseases.

The innate immune signaling, activated by pattern-recognition receptors (PRRs) after sensing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), is proved to be responsible for triggering inflammatory response [10]. In the past fifteen years, our group and others have ascertained the roles of innate immune signaling underlying the development of cancer and cardiometabolic diseases [11,12]. Of note, our findings demonstrate that some elements of innate immune signaling pathways influence the initiation and progression of these diseases in an immune-independent manner [13]. Therefore, understanding the mechanism linking innate immune signaling and those disorders is essential. In this review, we summarize the current knowledge of innate immune signaling pathways and their roles in cancer and cardiometabolic diseases, with the aim of providing pharmacologic targets for the prevention and effective therapeutics of these diseases.

Pattern-recognition receptors (PRRs) and innate immune signaling

The PRRs activated by PAMPs or DAMPs bind to different adaptors and activate various downstream kinases which in turn activate transcription factors, ultimately leading to the production of type I interferons (IFNs), inflammatory factors and chemotactic factors during innate immune responses (Table 1). PRRs are classified into two groups on the basis of their locations: membrane receptors and intracellular receptors. Membrane receptors include Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) that are expressed either on cell surfaces or membrane of endosome [20]. They are responsible for detecting extracellular microbial ligands or those within endosomes. The latter group consists of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and absent in melanoma 2 (AIM2)-like receptors (ALRs), which are free in the cytoplasm [20], where they detect the presence of intracellular pathogens. These PRR-mediated innate immune responses allow the host to fight against infection and maintain homeostasis.

Table 1
Pattern-recognition receptors and their adaptors in innate immune signaling.

Signaling	Receptors	Adaptors	References
TLR	1–10 in humans, 1–9 and 11–13 in mice	MyD88, TRIF	[14,15]
CLR	Dectin-1, Dectin-2, DCIR, MICL . . .	FcRγ	[16,17]
NLR	NOD1, NOD2, inflammasomes forming NLRs . . .	RIP2, ASC	[18,19]
RLR	RIG-I, MDA5, LGP2	IPS-1 (MAVS)	[20,21]
ALR	AIM2, IFI16	ASC, STING	[22–24]

Toll-like receptors (TLRs) and TLR signaling

Toll-like receptors (TLRs) are grouped into two classes on the basis of their localization and PAMPs. Cell surface located TLRs (TLRs 1, 2, 4, 5, 6 and 10) recognize microbial membrane components, while endosomal TLRs (TLRs 3, 7, 8 and 9) recognize microbial nucleic acids; importantly, TLR4 can also located in endosome [14]. TLRs contain a transmembrane region, a variable number of LRR motifs that recognize and bind to PAMPs, and a Toll/interleukin (IL)-1 receptor (TIR) domain that acts as the docking site for TIR-containing cytoplasmic adaptor proteins [25]. Ligand recognition by TLRs results in the recruitment of multiple TIR domain-containing adaptors, including myeloid differentiation factor 88 (MyD88), TIR domain-containing adaptor protein (TIRAP)/MyD88 adaptor-like (Mal), TIR domain-containing adaptor inducing IFN-β (TRIF), and TRIF-related adaptor molecule (TRAM) [15]. All TLRs, excluding TLR3, recruit MyD88 as a signaling adaptor. In addition, TLRs 1, 2, 4, and 6 recruit TIRAP as a bridge between the TIR domain of the TLRs and MyD88. In endosomes, TLRs 3 and 4 recruit the TRIF adaptor, and TLR4, but not TLR3, recruits TRIF through TRAM [15]. Following PAMPs or DAMPs binding, MyD88 recruits the IL-1 receptor-associated kinase (IRAK1-4) complex [26]. The activated IRAK complex subsequently triggers an interaction with tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6). Then, TRAF6, in conjunction with the dimeric E2 ubiquitin-conjugating enzymes Ubc13 and Uev1A [27], catalyzes the formation of a Lys63 (K63)-linked polyubiquitin chain on TRAF6 itself [15], transforming growth factor [TGF]-β-activated kinase 1/mitogen-activated protein kinase kinase kinase 7 [MAP3K7]-binding protein 2 (TAB2), and nuclear factor (NF)-κB essential modulator (NEMO). The polyubiquitin chains play an important role in recruiting TGF-β-activated kinase 1 (TAK1) *via* TAB2/3. A complex formed by TAK1 and IKK provides the appropriate conditions for TAK1 to phosphorylate IKKs [28]. Phosphorylated IKKα/β subsequently promotes the degradation of the inhibitory IκB protein, which interacts with and inactivates NF-κB [29] (Fig. 1). In addition to the MyD88-dependent pathway, TLR3 and TLR4 utilize the TRIF-dependent pathway to activate both IFN regulatory factor 3 (IRF3) and NF-κB in endosomes [30]. TRIF catalyzes IRF3 phosphorylation and induces its nuclear translocation by recruiting a signaling complex that includes the non-canonical IKKs, TRAF family member-associated NF-κB activator-binding kinase 1 (TBK1) and inducible IKK (IKKi) *via* TRAF3 [31] (Fig. 1). The final results of TLR activation are to activate transcription factors, such as IRFs, NF-κB, AP-1, and to induce antiviral type I IFNs and various other cytokines.

C-type lectin receptors (CLRs) and CLR signaling

C-type lectin receptors (CLRs) are also the cell surface receptors with a similar location but different pathways from certain TLRs. The CLR family consists of approximately 1000 members with a variety of functions, and its primary role is antifungal immunity [32]. According to their signaling motifs and signaling potential, CLRs are grouped into Syk-coupled CLRs with immunoreceptor tyrosine-based activation motif (ITAM) domains, CLRs with immunoreceptor