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Survey

Inflammasome activation and metabolic disease progression

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ABSTRACT

Innate pattern recognition receptors NLRs are cytosolic sensors that detect endogenous metabolic stress and form a multiprotein complex called the inflammasome, that recruits and activates caspase enzymes mediating the activation of the cytokines IL-1β and IL-18. The innate immune system and metabolic system are evolutionarily conserved, intimately integrated, and functionally dependent. In recent decades, obesity-associated metabolic diseases have been become a worldwide epidemic. Here we review recent evidence that demonstrates the important roles of NLRs and inflammasomes in response to metabolic stress in different tissues.

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1. Introduction

The innate immune system is an evolutionarily conserved arm of the host immune system that forms the first line of defense against infectious agents [1]. The innate immune system relies on a repertoire of germline-encoded pattern recognition receptors (PRR) to sense pathogen-associated molecular patterns (PAMPs) derived from invading microbes and to detect endogenous stress signals through danger-associated molecular patterns (DAMPs). The major PRRs include Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-I-like receptors (RLRs), AIM2-like receptors (ALRs), and C-type lectin receptors (CLRs) [2]. PPRs are located on the cell membrane, or inside the cytosol to detect the presence of specific ligands in these respective compartments. Activation of PPRs triggers downstream signaling cascades, and leads to the activation of transcription factors and production of proinflammatory cytokines. The cytokines lead to a state of inflammation destined to remove the trigger of PRR activation and restore tissue homeostasis.

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Obesity has become a growing epidemic and affects more than 35% of the world's adult population. Obesity development is associated with multiple metabolic dysfunctions, such as insulin resistance, hyperglycemia, dyslipidemia, nonalcoholic fatty liver disease, and cardiovascular disease [3]. The metabolic system is closely associated with and functionally dependent on the innate immune system; thus understanding the chronic, low-grade inflammation in obesity is increasingly important to the development of therapeutic approaches.

As cytosolic PPRs of both PAMPs and DAMPs, the NLRs family has been recognized as a central player in the arena of metabolic function and disease progression. We will review the NLR family members, the inflammasomes and their activation, and their functions in metabolic disease progression.

2. NOD-like receptors

The Nucleotide Oligomerization Domain (NOD)-like receptors (NLRs) are a large family of intracellular pattern recognition receptors which are comprised of 22 members in human and 34 members in mice [4,5]. As an important player in the innate immune system, they are able to recognize a variety of PAMPs as well as DAMPs, and mediate immune responses to defend pathogen infection and endogenous damage.

Most members of this family share a similar domain structure consisting of a N-terminal caspase recruitment domain (CARD) or pyrin domain (PYD), an intermediate nucleotide-binding (NACHT) domain and a C-terminal leucine-rich repeat (LRR) domain. The CARD and PYD domains are responsible for protein–protein interactions, the NACHT domain is suggested to mediate ATP-dependent self-oligomerization, and the LRR domain is thought to be involved in ligand sensing and autoregulation [5,6]. NLRs are categorized in several subfamilies based on their N-terminal domains or phylogenetic similarities (Table 1).

The first NLRs discovered were the NOD subfamily members NOD1 and NOD2 that sense bacterial peptidoglycan (PGN). Specifically, Nod1 recognizes *meso*-diaminopimelic acid found predominantly in Gram-negative bacteria, whereas Nod2 detects muramyl dipeptide (MDP) present in all bacteria. Upon ligand binding, NOD1/2 can interact with the CARD-containing kinase RIP2 to activate the NF-κB pathway. NOD1/2 can also signal through the adaptor CARD9 to induce the activation of MAPKs (p39, ERK and JNK). Activation of NF-κB and MAPK induces transcriptional upregulation of proinflammatory cytokines [2,7]. NOD1/2 signaling is also involved in the induction of autophagy [8].

Aside from NOD1/2 and inflammasome-forming NLRs (see below), other NLR family members have also been described to have a variety of functions including regulation of NF-κB, RLR and inflammasome signaling as well as other cellular processes.

3. Inflammasomes

Different from NOD1/2, several NLR members including NLRP1, NLRP3 and NLRC4 and NLRP6 have been shown to assemble into large multiprotein complexes named inflammasomes to control caspase-1 and caspase-11 activity [5,9]. Inflammasome-dependent caspase-1 activation leads to the maturation and secretion of pro-inflammatory cytokines IL-1β and IL-18, and may also drive pyroptosis [10], mediate unconventional secretion of growth and inflammatory factors (such as IL-1α, FGF2, and HMGB1) [11], and regulate the activity of additional targets such as glycolytic enzymes [12], sterol-regulatory element binding proteins (SREBP) [13], and executioner caspase-7 [14]. Together, inflammasome pathways mediate diverse responses to defend against invading pathogens and tissue damage.

3.1. NLRP3 inflammasome

The most thoroughly characterized inflammasome is the NLRP3 inflammasome, which consists of the NLR family member NLRP3, the adaptor protein ASC and the effector protein caspase-1. Thus far, a broad range of exogenous and endogenous stimuli have been demonstrated to activate the NLRP3 inflammasome. These include infecting microorganisms such as Sendai virus, Influenza virus, adenovirus, the fungi *Saccharomyces cerevisiae* and *Candida albicans*, as well as several bacteria like *Staphylococcous aureus*, *Listeria monocytogenes* and *Shigella flexneri* [15–18]. In certain cases, the specific microbial components or products that trigger the NLRP3 inflammasome activation have been identified, such as bacterial RNA [19], hemozoin crystals produced by malaria-causing parasites [20,21] and a number of bacterial pore-forming

Table 1
Murine NOD-like receptor members and general functions.

Family	Members	Domain structures	Functions and mechanisms
NLRA	C II TA	CARD-AD-NACHT-LRR	MHC gene regulation
NLRB	NAIP	BIR-NACHT-LRR	Anti-apoptosis
NLRC	NOD1	CARD-NACHT-LRR	NF-κB pathway, autophagy
	NOD2	CARD-CARD-NACHT-LRR	NF-κB pathway, autophagy
	NLRC3	NACHT-LRR	Innate immune signaling regulation
	NLRC4	CARD-NACHT-LRR	Inflammasome
	NLRC5	NACHT-LRR	Inflammasome, MHC gene expression
NLRP	NLRP1	PYD-NACHT-LRR-F II ND-CARD	Inflammasome
	NLRP2	PYD-NACHT-LRR	Inhibition of NF-κB pathway
	NLRP3	PYD-NACHT-LRR	Inflammasome
	NLRP4	PYD-NACHT-LRR	Autophagy, NF-κB pathway
	NLRP5	PYD-NACHT-LRR	Reproduction and development
	NLRP6	PYD-NACHT-LRR	Inflammasome
	NLRP7	PYD-NACHT-LRR	Reproduction and development
	NLRP8	PYD-NACHT-LRR	Unknown
	NLRP9	PYD-NACHT-LRR	Unknown
	NLRP10	PYD-NACHT	Inflammasome
	NLRP11	PYD-NACHT-LRR	Unknown
	NLRP12	PYD-NACHT-LRR	Inhibition of NF-κB pathway
	NLRP13	PYD-NACHT-LRR	Unknown
	NLRP14	PYD-NACHT-LRR	Reproduction and development
Inflammasome components	ASC	PYD-CARD	Inflammasome adapter
	Caspase-1	CARD-p20/p10	Proinflammatory cytokines cleavage

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