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Review Article

IL-1 and EGF regulate expression of genes important in inflammation and cancer

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ABSTRACT

This review focuses on the mechanisms by which the expression of specific genes is regulated by two proteins that are important in inflammation and cancer, namely the pro-inflammatory cytokine interleukin (IL)-1β and epidermal growth factor (EGF). In the review the receptors that recognize factors that cause inflammation are described with main focus on the receptors associated with activation of IL-1β. The function of IL-1β and pathways leading to activation of transcription factors, particularly NFκB and Elk-1 are analyzed. Then the mechanisms of EGF action, with particular emphasis of the activation of Elk-1 are illustrated. The link between aberrant signaling of EGF receptor family members and cancer development is explained. The relationship between inflammation and tumorigenesis is discussed.

1. Pattern recognition receptors

Inflammation can be induced by two types of stimuli, microbial/viral infection and tissue damage. Conserved microbial and viral components such as cell wall proteoglycans, pathogen nucleic acids and toxins induce the immune response by activating several families of PRRs. These PRRs recognize molecular structures shared by many pathogens, known as pathogen-associated molecular patterns (PAMPs). In addition, several host PRR activators have been identified. Extracellular ATP, monosodium urate, cholesterol crystals, hyaluronan, or deposits of denaturated or modified proteins are classified as damage-associated molecular patterns (DAMPs). DAMPs can accumulate upon cellular harm caused by trauma or infection or as a result of metabolic disorders. Exogenous compounds such as asbestos, silica, turpentine oil, and alum adjuvant can also activate PRRs. PRRs include the Toll-like receptors (TLRs), the RIG-I like receptors (RLRs), the C-type lectin receptors (CLRs), and the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (Fig. 1) [1,2].

1.1. TLRs, RLRs and CLRs

TLRs were the first discovered class of PRRs and more than ten mammalian TLRs have been identified (ten in human). Each TLR detects distinct PAMPs derived from viruses, bacteria, mycobacteria, fungi and parasites. These include lipoproteins (recognized by TLR1, TLR2 and TLR6), double stranded RNA (recognized by TLR3), lipopolysaccharides (recognized by TLR4), flagellin (recognized by TLR5), single-stranded RNA (recognized by TLR7 and TLR8) and DNA (recognized by TLR9) The ligand for TLR10 is unknown. TLRs are present on the cell surface (TLRs 1, 2, 4, 5, 6 and 10) or are associated with intracellular vehicles (TLRs 3, 7, 8 and 9) [3,4]. The binding of PAMPs induces conformational changes in TLRs that allow formation of homodimers or heterodimers. Activation of TLRs leads to the activation of the transcription factors NFκB (by TLR1-TLR2, TLR2-TLR6, TLR4, TLR5, TLR7 and TLR9), IRF3 (by TLR3 and TLR4) or IRF7 (by TLR2, TLR7 and TLR9), which in turn leads to the secretion of inflammatory cytokines, type I interferons (IFNs), chemokines and antimicrobial peptides. The final activation of NFκB and IRF-3/7 is preceded by binding of adaptor molecules to TLRs. These adaptor molecules, such as MyD88 and TRIF, contain a TIR domain. With the exception of TLR3 that uses only the TRIF adaptor protein, all other TLRs can utilize the MyD88 adaptor either alone or in combination with other adaptors such as TIRAP/Mal, TRIF and TRAM. However, TLR4 can also function independently of MyD88 via TRAM and TRIF. TLR4 is the only TLR that activates two distinct pathways, the MyD88-dependent pathway and the TRIF-dependent pathway. MyD88 activates NFκB via IL-1 receptor-associated kinases and TRAF6. MyD88 also activates IRF7. TRIF activates IRF3 via TRAF3 [3–5].

Another PRR member, RLRs, includes two RNA helicases: retinoid acid-inducible gene I (RIG-I) and its homolog melanoma differentiation-associated gene 5 (MDA5). Both helicases contain a DExD/H box helicase domain responsible for recognition of dsRNA from various RNA viruses (genomic RNA or dsRNA generated as the replication intermediate of ssRNA viruses). RIG-I and MDA5 both possess two N-terminal caspase recruitment domains (CARDs)

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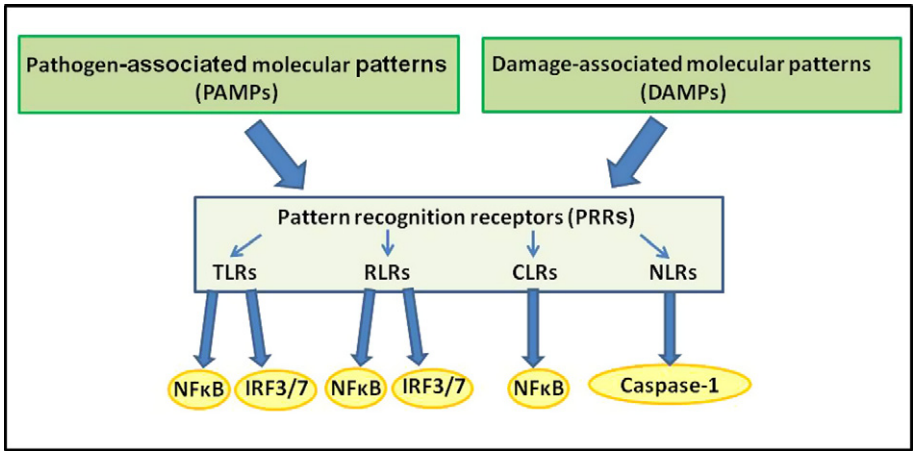

Fig. 1. Simplified scheme of activation of the transcription factors NFκB, IRF3 and IRF7, and caspase-1 after binding of PAMPs or DAMPs to receptors of the PRR family. *Abbreviations*: TLRs, Toll-like receptors; RLRs, RIG-I like receptors; CLRs, C-type lectin receptors; NLRs, nucleotide-binding oligomerization domain (NOD)-like receptors; IRF3/7, interferon regulatory factor 3/7; NFκB, nuclear factor κ B.

involved in initiating downstream signaling that leads to the activation of the transcription factors NFκB and IRF-3/7 [6,7].

Members of the CLR family, such as Dectin-1, Dectin-2 and Mincle, play key roles in antifungal immunity. The critical defining feature of CLRs is the presence of a carbohydrate recognition domain or a C-type lectin domain, which bind carbohydrate structures in a Ca^{2+}-dependent manner. However, not all CLRs bind carbohydrate structures or require Ca^{2+}. Dectin-1 is the major PRR involved in antifungal immunity. It recognizes β-1,3-glucans present in the cell walls of fungi, yeast, bacteria and plants and is Ca^{2+}-independent [8]. Dectin-2 recognizes complex carbohydrate structures in a Ca^{2+}-dependent manner. Mincle recognizes carbohydrate structures of pathogenic fungi [9]. These CLRs share signaling mechanisms; they are coupled to Syk kinase and thereby signal via CARD9, which leads to activation of NFκB and synthesis of inflammatory cytokines [10].

1.2. NLRs

Some pathogen-derived molecules may appear in the intracellular compartments of infected cells. Such agents are recognized not only by some TLRs and RLRs, but also by NLRs. Host-derived DAMPs and exogenous chemicals can also activate NLRs. NLRs possess three domains important for their function. The autoinhibition of NLRs in the resting state is mediated by the C-terminal region. This maintains NLRs in a conformational state that prevents downstream activation events until activation stimuli are detected. This C-terminal region of NLRs contains leucine-rich repeats (LRRs). Sensing of PAMPs or DAMPs by these LRR motifs triggers the oligomerization of NLRs through the central NOD. Finally, the N-terminal effector domain initiates specific downstream signaling cascades [11]. NLRs are divided into several subfamilies according to the structure of their N-terminal domain (NLRP, NLRC and NAIP). Members of the NLRP subfamily contain an N-terminal pyrin domain (PYD), NLRC proteins contain a CARD, and members of the NAIP subfamily contain a baculovirus inhibitory domain at their N-termini. NLRP1 differs from other NLRs proteins because it has two signal transduction domains, an N-terminal PYD and a C-terminal CARD. NLRs oligomerize after being activated and this facilitates recruitment of pro-caspase-1 through interaction between the CARD of pro-caspase-1 and the CARDs of NLRs [12]. With the exception of NLRP1, NLRPs lack CARDs and require the adaptor protein ASC to interact with pro-casapse-1. ASC has a PYD and a CARD. The PYD of ASC interacts with the PYD of NLR, and the CARD of ASC recruits pro-caspase-1 (Fig. 2). Recent studies indicate that NAIP proteins lacking both PYDs and CARDs recruit pro-caspase-1 by interacting with NLRC4 [13,14].

1.2.1. Inflammasomes and IL-1β activation

Oligomerization of NLRs and their interaction with pro-caspase-1 leads to the formation of large protein complexes called inflammasomes. In addition to NLRs, a member of the pyrin and HIN domain-containing protein (PYHIN) family, AIM2, is able to form an inflammasome through its recognition of cytosolic dsDNA from viruses, bacteria and the host itself. AIM2 has a PYD and interacts with pro-caspase-1 via ASC (Fig. 2). Inflammasomes are assembled and trigger caspase-1 autoactivation in response to danger signals. Caspase-1 in turn cleaves cytoplasmic pro-IL-1β and pro-IL-18 into mature bioactive cytokines. Thus the activation of inflammasomes by DAMPs leads to the activation of two pro-inflammatory cytokines of the IL-1 family, IL-1β and IL-18 (also known as interferon gamma inducing factor). Four inflammasomes with physiologic relevance have been identified. The names of the particular inflammasomes, NLRP1, NLRP3, NLRC4 and AIM2, are taken from the names of the PRRs that regulate their activities (Fig. 2). Two other inflammasomes, NLRP5 and NLRP6, have recently been suggested to promote IL-1β production, although an *in vivo* role for these molecules remains to be determined [15–19].

2. Biological role of IL-1α and IL-1 β

The biological activities of IL-1α and IL-1β are similar. An increased level of IL-1α/β induces production of GM-CSF, G-CSF, IL-6, IL-8, TNFα, IL-1Ra, soluble TNFα receptor, ACTH, cortisol and nitric oxide. Human systematic responses to IL-1α or IL-1β include fever, myalgias, joint pain, fatigue, headache, nausea, gastrointestinal discomfort, hypotension, neutrophilia, and thrombocytosis [20]. IL-1α and IL-1β are synthesized as precursor proteins. As described earlier, caspase-1 activates pro-IL-1β, whereas the Ca^{2+}-activated protease calpain cleaves pro-IL-1α into a mature form. In contrast to pro-IL-1β, the precursor form of IL-1α is fully active [21]. IL-1α is present in its precursor form in epithelial cells, keratinocytes and fibroblasts. It is highly mobile protein that translocates to the nucleus where it associates with chromatin and activates transcriptional machinery through IL-1R-independent activation of NFκB and AP-1 [21]. Passive release of IL-1α from cells is regulated differently during apoptosis and necrosis. In apoptotic cells, the mobility of the IL-1α precursor