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INFLAMMATORY PROTEIN CASPASE-1 PLAYS A CRUCIAL ROLE IN THE IMMUNE RESPONSE DURING MICROBIAL INFECTIONS

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ABSTRACT

Caspase-1 is a proteolytic enzyme that mediates the immune response in physiological and pathological states, including infections. Activation of caspase-1 is linked to the production of cytokines. Caspase-1 induces pyroptosis by cleaving the protein Gasdermin D (GSDMD), a pore-forming protein that perforates the plasma membrane. Caspase-1 limits the replication of microorganisms by activating the innate immune response. Microorganisms activate inflammasomes that participate in the exacerbation of cytokine production, causing a worsening of the infectious state. Caspase-1 is derived from the inactive molecule pro-caspase-1 and is activated by the inflammasome complex which in turn is activated by both exogenous and endogenous danger signals to the cell, activating NOD-like receptor family, pyrin domain containing 3 (NLRP3). Caspase-1 mediates the formation of IL-1β which, by binding to its receptor IL-1R, activates the cascade that leads to the formation of NF-kB, with generation of inflammatory cytokines and adhesion molecules such as ICAM-1.

KEYWORDS: *Caspase-1, enzyme, infection, inflammasome, virus, bacteria*

INTRODUCTION

Caspase-1 is an important protein in the immune response to infections. This enzyme belongs to the family of cysteine protease caspases that are activated during inflammation (1). Caspase-1 is involved in the activation of inflammatory cytokines mainly derived from innate immune cells. Inflammatory caspase-1 is a proteolytic enzyme that processes precursors of pro-inflammatory cytokines such as pro-IL-1β and pro-IL-18 (2). Furthermore, caspase-1 induces pyroptosis, or cell death, by cleaving the protein Gasdermin D (GSDMD), a pore-forming protein that perforates the plasma membrane during pyroptosis (3).

During infections caused by viruses or bacteria, caspase-1 is activated by an intracellular NOD-like receptor family, pyrin domain containing 3 (NLRP3) complex which belongs to the inflammasome family (4). The task of caspase-1 is to convert pro-IL-1β and pro-IL-18 into their mature active forms that are highly inflammatory cytokines (5). In addition to mediating inflammation, IL-18 also mediates fever, and induces the recall of immune cells to the inflamed site after an infection (6).

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Caspase-1 activates the immune response to limit the replication of microorganisms (7). This activation is important for the containment of the infecting microbes. However, the activation of caspase-1 can also harm the host, depending on the degree of enzyme activation. Normal physiological activation induces an immune response useful to the patient, while exaggerated activation causes inflammation (8). Therefore, the effect of caspase-1 must be balanced; if it is too mild it leads to an ineffective immune response, while, if it is too strong, it can cause serious inflammatory damage.

DISCUSSION

Both bacterial and viral microorganisms activate caspase-1 (1). Some microorganisms activate certain inflammasomes, such as *Salmonella typhi*, and others, such as viruses, activate other inflammasomes (9). Inflammasomes participate in the exacerbation of cytokine production, contributing to the worsening of infection (10). Both caspase-1 and IL-1β play a crucial role in the innate inflammatory response (11).

Caspase-1 is synthesized as an inactive zymogen (pro-caspase-1) and is activated within multiprotein complexes called inflammasomes (12). Activation of the inflammasome at the molecular level occurs through exogenous danger signals such as lipopolysaccharide (LPS) and pathogen-associated molecular patterns (PAMPs), or endogenous signals such as damage-associated molecular patterns (DAMPs) and extracellular ATP that activate inflammatory receptors, including NLRP3 (13).

IL-1β is a key cytokine in inflammation and requires two signals to be activated (14). The first is LPS, which induces the transcription of pro-IL-1β via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (15). The second is ATP, which activates the inflammasome that in turn activates caspase-1, a reaction that leads to the cleavage of pro-IL-1β into mature IL-1β (16). Once activated, IL-1β binds to its receptor (IL-1R) on target cells and activates the signaling cascade via MyD88, IRAK, and NF-κB (17). This induces the expression of other pro-inflammatory cytokines including IL-6 and tumor necrosis factor (TNF), and some adhesion molecules (e.g. ICAM-1), causing fever and systemic inflammatory responses (18).

Infected macrophages and monocytes activate NLRP3, although it is still unclear how microorganisms can trigger the activation of this multiprotein complex that forms in response to intracellular danger signals (19). NLRP3 activation has been demonstrated in virus-infected macrophages and monocytes in *in vitro* mouse models. These studies suggest that the virus triggers non-canonical caspase 4/11-mediated NLRP3 activation (20). NLRP3 is a cellular sensor that recognizes both DAMP and PAMP signals (Fig.1).

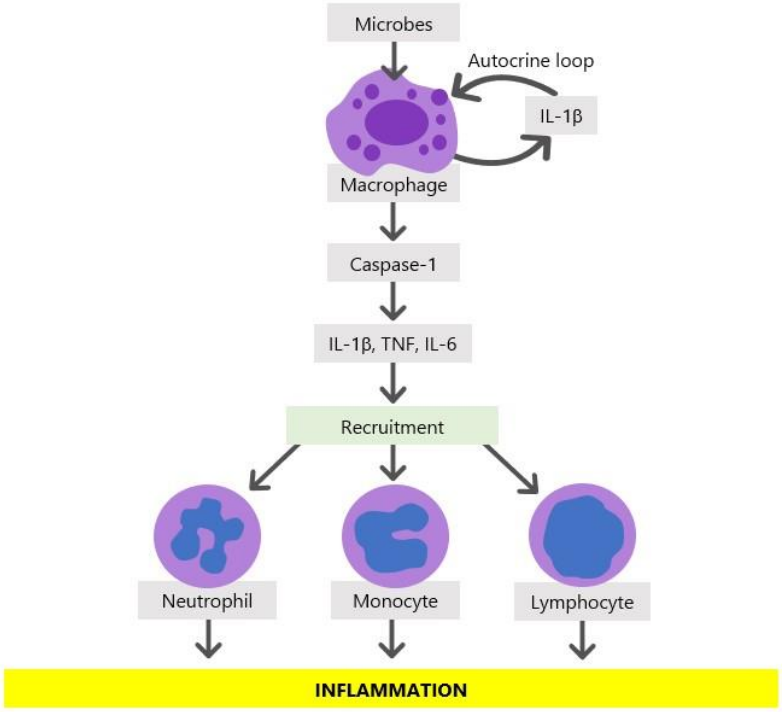

Fig. 1. *Macrophages are activated by IL-1 to release inflammatory cytokines and recruit neutrophils, monocytes, and lymphocytes to the site of inflammation.*

The caspase activation and recruitment domain (CARD) that connects NLRP3 to caspase-1 is not directly present on NLRP3 (21). This job is performed by the adapter protein ASC, also known as PYCARD (22). NLRP3 has an N-terminal pyrin domain (PYD) and PYCARD has two domains: an N-terminal PYD and a C-terminal CARD (23). Upon stimulation, NLRP3 oligomerizes and interacts via PYD-PYD with apoptosis-associated speck-like protein containing a CARD (ASC), creating an inflammasomal "speck" (24). These reactions allow the recruitment and activation of procaspase-1 into active caspase-1.

Transcription of pro-IL-1β, NLRP3, and other pro-inflammatory proteins is induced by signals such as Toll-like receptors (TLRs) that activate NF-kB (25). Other secondary activating stimuli include extracellular ATP, reactive oxygen species (ROS), urate crystals, bacterial toxins, and others that cause NLRP3 oligomerization and the formation of the inflammasome complex (26). The complex activates caspase-1, which matures IL-1β and IL-18, induces pyroptosis (via GSDMD) (27). Thus, caspase-1 induces a rapid response to infections, with control of tissue repair and immune response (28).

Excessive activation causes chronic inflammatory diseases such as gout (caused by monosodium urate), atherosclerosis, autoimmune diseases (such as lupus and rheumatoid arthritis), metabolic diseases (type 2 diabetes), neurodegenerative diseases (Alzheimer's and Parkinson's), amongst others (29).

The NLRP3 complex is an important alarm signal that activates caspase-1, triggering the inflammatory response mediated by cytokine activation that promotes pyroptosis (30). Inhibition of caspase-1, and hence of IL-1β, could be helpful in the therapy of chronic infectious diseases (31).

CONCLUSIONS

Caspase-1 is an inflammatory caspase that plays a critical role in innate immunity and activates pro-inflammatory cytokines such as IL-1β and IL-18 by cleaving their precursors. Caspase-1 is a proteolytic enzyme derived from pro-caspase-1 (inactive) that is activated in infectious processes where an inflammatory state mediated by IL-1β is generated. Caspase-1 limits the replication of microorganisms by activating the innate immune response, but its overproduction increases the levels of IL-1β that activates the recruitment of immune cells with the formation of other pro-inflammatory cytokines. Inhibiting caspase-1, and therefore, IL-1β, could have therapeutic value for some chronic infectious diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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