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Caspase Work Model During Pathogen Infection*

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Abstract: Caspases are an evolutionarily conserved family of aspartate-specific cystein-dependent proteases with essential functions in apoptosis and normally exist in cells as inactive proenzymes. In addition to the inflammatory caspases, the initiator and effector caspases have been shown to have an important role in regulating the immune response, but are involved in different ways. We give a brief introduction on the benefit of apoptosis on the clearance of invasive pathogens, and the caspase functions involved in the immune response. Then we construct a working model of caspases during pathogen invasion. A detailed description of the three modes is given in the discussion. These three modes are regulated by different inhibitors, and there may be a novel way to treat intracellular pathogen and autoimmune diseases based on the specific inhibitors.

Key words: Caspases; Immune Response; Pathogen Infection

Caspases are an evolutionarily conserved family of aspartate-specific cystein-dependent proteases with essential functions in apoptosis and normally exist in cells as inactive proenzymes. The caspases are divided into three groups[23]: I, the inflammatory caspases (caspase-1, -4, -5, -11, -12, -14); II, the initiator caspases (caspase-2, -8, -9, -10); III, the effector caspases (caspase-3, -6, -7). Certain caspases have large domains that contain related homotypic oligomerization motifs such as the caspase recruitment domain (CARD, caspase-1, -2, -4, -5, -9, -11, -12) and the death effector domain (DED, caspase-8 and -10). When receiving specific signals, the caspases with large prodomains can be auto-activated in large multimeric complexes, such as the apoptosome, the death inducing signaling complex (DISC), the p53-induced protein with a death domain (PIDDsome) and the inflammasome[38]. The short prodomain caspases (caspase-3,-6,-7,-14) are activated by proteolyesis with maturation caspases or other proteases. The signals triggering the activation of inflammatory caspases are from the nuclear oligomerization domain (NOD) signalling pathway while the initiator caspases are recruited to a large multimeric complex through DED or the CARD to

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become proteolytically active with the apoptosis signal and cleave executioner caspases. Executioner or effector caspase-3, -6 or -7 act on cell substrates, such as: protein kinase δ (PKCδ), actin and lamin A, to induce apoptosis[21]. All caspases express a conserved cysteine in the active site and interact with aspartate containing tetrapeptides in their substrates.

However, not only do the inflammatory caspases have the ability to affect the immune response during pathogen invasion, but the initiator caspases and effector caspases show an indispensable role in regulating the immune response (as follows). Until now, specific caspase roles have been identified independently. However, a systemic view of the caspases' functions in immune responses suggests some form of cooperation takes place to clear the invading pathogen. The cooperation referred to here differs from that occuring in apoptosis. Here we discuss the benefits of pathogen-induced apoptosis which is mostly caspases-based and a provide a brief review of the role or caspases in the immune system. Then, based on findings to date, we suggest and discuss a functional model of caspases in responding to introduction of pathogens.

CASPASES FUNCTIONS INVOLVED IN THE IMMUNE RESPONSE

Apoptosis and Immune

To fully understand the relation between caspases and immune response, we must first understand pathogen-induced apoptosis produced by caspases operating in cascade. Apoptosis is an evolutionarily conserved mechanism essential for normal development and defense against pathogens. Three major signal pathways can independently lead to the activation of a caspase cascade and apoptosis: the extrinsic or death receptor pathway, the intrinsic or mitochondrial pathway, and the cytotoxic mechanism induced by perforin and granzymes[4]. Pathogens inhibit the apoptosis of the host cell and induce chronic infection by a variety of strategies. During infections by pathogenic viruses, bacteria and protozoans, lymphocyte cells will proliferate and differentiate into effector immune cells to clear the invasions by killing the pathogen or infected cells or undergoing apoptosis.

Research on infection in protozoan parasites show that a complete protozoan infection can be divided into four stages: (1) invasion and multiplying within host cells, inhibiting the host cell apoptosis; (2) apoptosis occurring with the release of perforin- and GrB-containing granules in CD8 T cells, and expression of Fas Ligand (FasL) in CD4 T cells, (3) activation of CD4 and CD8 T cells to express Fas and FasL and (4) activation-induced cell death, which results in defective immune responses leading to tissue lesions caused by the dysfunction of the tissue or the organ[8]. However, Protozoan parasites which cannot be completely eliminated by the immune system cause chronic infections and varying degrees of pathogenesis. Obviously, the first stage of the pathogen infection is to inhibit the apoptosis of the host cells and involves proliferation to the point where sufficient pathogen is present to pass the immune barrier and reach the susceptible tissue. This puts a heavy load on the effector immune cells to clear the pathogens. Some intracellular bacteria and virus also ensure their proliferation in a similar manner to the protozoan parasites, by blocking the apoptosis of the host cells during early infection[7,28]. When inhibiting

apoptosis, they commonly block activation of a caspase, although their target caspases differ.

Macrophage surveillance is an essential factor in the initial host reaction to infection by initiating an inflammatory response. The activation of macrophages is triggered by the recognition of self and non-self stimuli mediated through a myriad of specialized membrane and intracellular receptors[23]. The macrophage can also use apoptosis to alert the immune system to the harmful pathogen invasion. Macrophages are probably exposed to a wide variety of harmless bacteria in the intestinal lymphoid follicles, the vast majority of which can be killed efficiently within the phagosome of the macrophage. However, when a macrophage encounters a potentially harmful microbe, including some proteins produced by pathogenic bacteria (e.g. haemolysins, adenylate cyclase toxins, inhibitors of Nuclear Factor of the κ-Enhancer (NF-κB) activation and protein translation) it would choose to kill itself by inhibiting various pathways (protein synthesis, mitogen-activated protein kinases (MAPK), NF-κB activation), alterating cAMP levels or disrupting membrane integrity[22]. By inducing apoptosis, the macrophage can indicate the presence of a potentially harmful pathogen. Cytokines[27] are quickly released to neighbors which will enhance the engulfing ability of the monocytes and macrophages and promote the lymphocytes to maturate effector cells. Although the macrophage is no longer a vehicle for transmitting pathogens to other cells it may be exposed to more potent bactericidal cells and the humoral immune system. This may be a plausible reason for the ability of macrophage apoptosis to help control infections by *Mycobacterium tuberculosis*[13]. Some pathogens have successfully acquired the ability to evade the destruction of the phagosome and even grow in macrophage vacuoles while inhibiting the death of macrophage to benefit their infection and proliferation. Due to its mobility in the circulatory system, a macrophage with live intracellular pathogens can transmit the pathogens to a susceptible tissue or organ, leading to massive proliferation and the dysfunction of the organ. The peripheral blood mononuclear cells, neutrophils, and eosinophils can also be target cells in which a pathogen can survive.

The apoptosis of the host cell, the phagocytes and the active killing of the infection cell by CTL in acquired immunodeficiency with Granzyme B and perforin all involve caspases. These contribute to the effective and complete clearance of harmful pathogens by leading to the cell death of infected cells and the secretion of the cytokines in phagocytes by apoptosis, but do not act directly.

Caspase-1 Contributes to Inflammation by Two Distinct Pathways

IL-1β and IL-18, produced predominantly by monocytes/macrophages, are able to activate neutrophils and macrophages for the clearance and control of the invasions. IL-1β and IL-18 play a prominent role in polarizing T helper responses. IL-18 is important in inducing the response of Th1 characterized by the production of IFN-γ. IL-1β is important in the early differentiation of Th17 responses, and can also enhance Th17 responses with the help of IL-23[16]. Usually, IL-1β and IL-18 exist in the cytosol as the inactive precursors (pro-IL-1β and pro-IL-18) which require cleavage into the bioactive cytokines by an enzymatic process. Caspase-1, a central component of the inflammasome, is one of the

most important enzymes responsible for processing pro-IL-1β and pro-IL-18 to their mature active forms, IL-1β and IL-18[16, 32]. The transcription of pro-IL-1β and pro-IL-18 mainly results from the stimuli by bacteria, viruses, fungi, and protozoans.

The activation of Caspase-1 in macrophages is dependent on the signal from NOD-like receptors (NLRs)[5] and apoptosis-associated speck-like protein (ASC)[35]. TLRs and NLRs act together during the secretion of mature IL-1β and IL-18. The signal from the TLRs leads to the transcription of pro-IL-1β and pro-IL-18 while the signal from the NLRs leads to the activation of caspase-1 which processes the pro-IL-1β and pro-IL-18 to their mature type. In addition to cleaving the pro-inflammatory cytokines, caspase-1 plays an important role in the induction of macrophage death during the infection. Pyroptosome-dependent caspase-1 activity can result in a highly inflammatory form of cell death known as pyroptosis, most frequently as a consequence of infection with intracellular pathogens, and is likely to form part of the antimicrobial response in myeloid cells. Pyroptosis is caspase-1 dependent by definition and occurs independently of pro-apoptotic caspases[3]. The pyroptosis is proven[3] to be mediated by a unique pyroptosome largely composed of oligomerized ASC dimers, which is distinct from the inflammasome. Caspase-1 activation can also lead to the activation of caspase-7 downstream of the Nlrc4 inflammasome and presentation of a role for caspase-7 in host defense against an intracellular bacterium[1].

A function of caspase-1 as an activator of NF-κB is based on the B-cell. In contrast to pro-IL-1 maturation, caspase-1-induced NF-κB activation is not inhibited by the virus-derived caspase-1 inhibitor cytokine response modifier A and is as effectively induced by the enzymatically inactive caspase-1 C285A mutant. Caspase-1 interacts with receptor interacting protein (RIP) 2[20]; dominant-negative forms of RIP2 and IκB kinase complex-β can inhibit caspase-1-mediated NF-κB activation. Structure-function analysis shows that the CARD of caspase-1 mediates the activation of NF-κB[15]. These results show that caspase-1 contributes to inflammation by two distinct pathways: proteolytic of pro-IL-1β and pro-IL-18 or RIP2-dependent activation of NF-κB in the B-cell.

Caspse-11 and Cytokine Secretion, Cell Migration

Similar to caspase-1-deficient mice, caspase-11-deficient mice fail to produce IL-1β in response to LPS and are resistant to LPS-induced septic shock[11]. Caspase-11 does not process pro-IL-1β directly, but its expression is essential for the activation of caspase-1. Caspase-11 is not normally expressed in most cell types, but its expression can be induced by different inflammatory stimuli. An increase in caspase-11 was seen in macrophages, lymphocytes, and hepatocytes with LPS or IFN-γ *in vitro*[24]. Likewise, the expression of caspase-11 is undetectable in healthy mice but readily induced by injection of LPS[24]. Unlike most caspases, transcriptional control of the expression level appears to be more important in the case of caspase-11, but not in the proteolytic processing step during their activation. Although a role for other proteases or activators cannot be excluded, increased expression of caspase-11 most likely leads to its auto-activation. Both LPS and IFN-γ conditions that are known to induce caspase-11 expression in macrophages could activate the promoter sequences.

Under pro-inflammatory stimulus, the expression of

Caspase-11 is also upregulated to promote cell migration by promoting actin interacting protein 1(Aip1)–Cofilin-mediated actin depolymerization, distinct from the receptor mediated Rho–Rac–Cdc42 pathway[19]. As actin dynamics are involved in regulating multiple cellular events (including cell migration, cell division and secretion)[9], the ability of caspase-11 to regulate actin depolymerization may contribute to phagocytosis.

Caspase-12 and Immunosuppressant Function

Caspase-12 deficiency shows resistance to sepsis and its presence exerts a direct suppressive effect on caspase-1, resulting in enhanced vulnerability to bacterial infection and septic shock[25]. In addition to the caspase-1-dependent pathway, a caspase-1-independent pathway was shown to play a role in dampening mucosal immunity to bacterial infection[17]. Caspase-12 deficiency enhances production of antimicrobial peptides, cytokines, and chemokines to entric pathogens, an effect dependent on bacterial type III secretion and the NOD pathway. Normally, caspase-12 binds to RIP2, displaces TNF receptor-associated factor (Traf)6 from the signaling complex, inhibits its ubiquitin ligase activity, and blunts NF-κB activation. NOD activation and resulting antimicrobial peptide production constitute an early innate defense mechanism, and caspase-12 inhibits this mucosal antimicrobial response[17].

Caspase-8 and T-cell proliferation

Caspase-8 deficiency in the T-cell lineage results in a marked depletion of peripheral T-cells and a profound impairment of the *in vivo* immune response to viral infection, resulting in a defective response to antigens and mitogens[30]. Full-length caspase-8 is required for the catalytic activity necessary for rapid T-cell proliferation in response to TCR ligation, but processing of the caspase is only necessary to promote apoptosis. Caspase-8 catalytic induction in proliferating T cells occurs independently of extrinsic and intrinsic apoptotic-signaling cascades[18]. The location of active caspase-8 may profoundly influence its functional capacity as a regulator of either cell cycling or cell death[14].

NF-κB is the generic name of a family of transcription factors that act as dimers and regulate genes involved in the inflammatory and immune responses as well as in some aspects of cell proliferation, survival, differentiation and cell death[10]. NF-κB is sequestered in the cytoplasm by interacting with IκBs. Normally, the activation of NF-κB can be divided into two phases. The first phase involves cytoplasmic events which lead to the activation of a kinase complex composed of three subunits: IκB kinase(IKK)α, IKKβ and NEMO/IKKγ. Following these events, a second phase occurs primarily in the nucleus to execute its fundamental function as a transcription factor. This two-step mechanism of NF-κB activation is common to all cell types and stimuli[29]. However, TCR-mediated activation of NF-κB is characterized by the signaling process in spatially segregated domains. The differences occur mainly upstream of the IKK complex. Several genetic studies have identified signaling components involved in the TCR to NF-κB pathway: ZAP-70, SLP-76, PLCγ1, SAP, Fyn, PKCθ, Vav1, Bcl-10, Carma1, MALT1/paracaspase and RIP-2. Carma1, Bcl10 and MALT1 (CBM), associated with each other, play an important and previously unforeseen role in antigen receptor-induced NF-κB activation downstream of PKC[35].

The CBM are coprecipitated with active caspase-8 in proliferating murine effector T cells[14]. In cells lacking caspase-8, Bcl-110 still binds to MALT1, but this complex no longer recruits IKK in response to signals. These suggest that Caspase-8 may work upstream of CBM to facilitate the oligomerization and activation of CBM, thus promoting the recruitment of IKK. Alternatively, caspase-8 could bridge CBM and IKK, facilitating binding between these two complexes[33].

Caspase and its Viral Infection

Host defense against viral infection depends on the detection of viral components by Retinoic acid-inducible gene I (RIG-I)-like helicases receptors (RLPs) and the subsequent production of type I IFN (IFN-α and IFN-β)[31]. Transcription of IFN-β is regulated by cooperative activation of transcription factors such as NF-κB, activating transcription factor-2/c-Jun, IFN regulatory factor (IRF)-3, and IRF-7. Upon viral infection, the IRFs in the cytoplasm are phosphorylated by TANK-binding kinase 1 (TBK1) and IKKε and translocated into the nucleus to regulate gene expression[29]. In addition to TLR3, TLR7, and TLR9, dsRNA can also be recognized by the RLPs: retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene (Mda) 5 with two CARDs that mediate the activation of NF-κB, IRF3, and IRF7[39].

Caspase-8 and caspase-10 are involved in RLPs-mediated signaling, particularly inflammatory responses. It has been suggested that the CARD-containing IFN-β promoter stimulator (IPS) 1 serves as an adapter for these helicases, and interacts with FADD and RIP1 which have been shown to be involved in antiviral responses[2]. However, in spite of structure-based analyses, the interactions among IPS-1, FADD, and caspase-8/10 are still unclear[12]. There is also an important role for caspase-12 in controlling the infection of West Nile virus via the pattern-recognition receptor RIG-I[34]. However, evidence also shows the activation of some caspases may help the virus infection. A determinant of virus pathogenicity was found to be related to caspase cleavage motifs identified in proteins of numerous viruses. For example, the virulence of avian influenza virus mutants possessing alterations in the N-terminal NP and C-terminal M2 caspase motifs for chickens was significantly diminished[40]. This may open a new avenue for the design of live vaccines. The activation of Caspase-3 shows a significant influence on the propagation of influenza virus[37]. This may indicate that the caspase-3 activation during the onset of apoptosis is a crucial event for efficient influenza virus propagation.

CASPASES MODEL IN IMMUNE RESPONSE

To illustrate when and how the caspase works, based on the summary above we can propose a working model of the caspases during pathogen invasion. When the phagocytes first encounter the bacteria, the TLRs detect the existence of bacteria, viruses, fungi, protozoans, and then initiate the transcription of pro-IL-1β, pro-IL-18 and other cytokines. Almost at the same time, the NLRs and ASC detect the existence of intracellular components and trigger the activation of caspase-1 in the inflammasome. In this period, the activation of caspase-11 is essential for the cleavage of the pro-caspase-1 while caspase-12, with a “negative” domain, inhibits the activation of caspase-1.

Caspase-1 in the inflammasome processes the pro-IL-1β and pro-IL-18 to mature forms which in turn will provide several functions in the immune cells. For the intracellular bacterium, caspase-1 activation can lead to the activation of caspase-7 downstream of the Nlrc4 inflammasome and provide a role for caspase-7 in host defense. The active caspase-11 can also enhance cell migration of phagocytosis by promoting actin interacting protein 1(Aip1)–Cofilin-mediated actin depolymerization. In some cases, the caspase-1 in pyroptosome will be activated and lead to the pyroptosis of macrophages which results in a massive secretion of cytokines and the unprocessed pathogens. In the phagocytes, the pathogen components are processed, then through the antigen presenting cells (APCs) the antigen signals are transmitted to the TCR on the specific T-cell. The antigen stimuli on the BCR lead to signal transmission within the B-cell. Along with RIP2, the caspase-1 activates the IKKs, which leads to the activation of NF-κB. With the antigen from APCs, caspase-8 in T-cells with CBM takes part in the activation of NF-κB by acting on the IKKs. The activation of NF-κB in B-cells leads to the activation, proliferation and inflammation of the cells, while promoting the activation, transcription and differentiation of T-cells. During the virus infection, acting at TBK1 and IKKi, Caspase-8 and caspase-10 are involved in RIG-I- and Mda5-mediated IRF3/ IRF7 activation which is important for the transcription of IFN, an important antiviral cytokine. Pathogens may escape from the early clearance by the immune system and infect susceptible cells, leading to a massive proliferation. To expose the pathogen to more potent bactericidal cells, the cell death of the host cell is induced with the participation of caspases, and this allows the phagocytes, antibodies and other molecules neeeded to clear the invading pathogens.

DISSCUSSION

Phage caspases act in cascade within the proteolytic process. They assist but do not directly mediate bactericidal activity of the immune cell or participate in the killing of invasion pathogen. The caspase-1, -11 in phagocytes, and caspase-12, caspase-7 show they can regulate innate immune response by affecting the phagocytes' mobility and the maturing and secretion of cytokines. Caspase-1 is mainly responsible for the pyroptosis and processing of the pro-IL-1β and pro-IL-18 in macrophages. In addition to activating the pro-caspase-1 in macrophage by its proteolytic, caspse-11 can also promote actin depolymerization which contributes to the phagocytosis. Caspase-12 is an immunosuppressant with a direct effect on caspase-1 and a caspase-1-independent pathway for dampening mucosal immunity. Caspase-7, downstream of the Nlrc4 inflammasome, has a role in the host defense against an intracellular bacterium. Moreover, caspase-1 in B-cells, caspase-8 in T-cells and caspase-8, -10 involved in antiviral processes regulate the acquired immune response and the transcription of IFN by mediating the activation of transcription key factors. Caspase-1 in B-cells and caspase-8 in T-cells mediate the activation of NF-κB, while caspase-8, and -10 involved in RIG-I- and Mda5-mediated signaling together mediate the activation of IRF3/ IRF7 to influence the transcription of IFN. It is apparent that the same caspase has different functions in different situations. It is also possible that the different caspases or even the same caspase role in the immune response

can be controlled by different inhibitors. Here, we highlight the essential role of caspases in the immune response during the pathogen infection and a possible ideal treatment for a specific disease based on a specific caspase activity.

It is possible to regulate the activation of a specific caspase in a particular function with less effect on other caspases or the same caspase in other role by using an appropriate inhibitor. For example, for caspase-1, there is an inhibitor on hand, caspase-12 which is thought to be detrimental to *in vivo* handling of systemic bacterial infections and predisposes to sepsis but is a potential inhibitor for the caspase-1 when it regulates innate immune response.

Based on the results from studies outlined above, it can be seen that caspases can be targets for the treatment of different kinds of diseases. Some chronic diseases caused by the prolonged existence of intracellular pathogens can be attacked by promoting the apoptosis of the host cells, so a drug which promotes the activity of caspase-1 may have great potential.

Caspases may also be effective for autoimmune diseases, such as MAS and Lymphoma. Macrophage activation syndrome (MAS), a life-threatening complication of rheumatic disease, is thought to be caused by the activation and uncontrolled proliferation of T lymphocytes and well-differentiated macrophages, leading to widespread hemophagocytosis and cytokine overproduction. For this case, caspase-1 in the macrophage would be a possible target. Caspase-12 could control the activity of caspase-1 in a macrophage to control cytokine overproduction and release.

Lymphoma is a cancer of the lymphatic cells of the immune system. Typically, lymphomas present as a solid tumor of lymphoid cells and the treatment might involve chemotherapy, radiotherapy or bone marrow transplantation. However, we can suggest a specific treatment for T-Cell Lymphomas and B-Cell Lymphomas. Uncontrolled proliferation of T lymphocytes in MAS, T-Cell Lymphomas, might be treated by a caspase-8 inhibitor in T-cell and B-Cell Lymphomas by a caspase-1 inhibitor in B-cells.

However, at present there is little research on inhibitors targeting different functions of the caspase. For their specific targetting without side effects on other caspases, the development of the specific inhibitors for different functions of the caspase should be investigated further. To do this in an effective manner, we need more information on the mechanism by which caspases affect both the immune response and other pathways in which they participate.

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