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Review

Regulation, Activation, and Function of Caspase-11 in Inflammation

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ABSTRACT

Sepsis is the body's physiological response as a result of the passage of infectious bacteria into the bloodstream. In many areas of the body, inflammation damages organs and tissues even though it is essential for the healing of illnesses. Even while the amount of bacteria in the bloodstream plays a major role in determining the severity of sepsis, bacteria type and the pathways they can activate also play a role. In addition to being a protease enzyme, caspase-11 can be activated by a variety of molecular pathways. These pathways consist of a wide range of molecules and receptors including high-mobility group box 1 protein, toll-like receptor 4, receptor for advanced glycation end products-specific receptor, arachidonate 5-lipoxygenase, immunity-related GTPase family M protein, sphingosine-1-phosphate receptor 2, TIR-domain-containing adapter-inducing interferon-β, connexin-43, gasdermin D, NLR family pyrin domain containing 3. There are different paths that might be used in the treatment of septic outcomes caused by infection. In this review, we discussed the significance of the caspase-11, which is crucial to the inflammation brought on by sepsis even though all molecular routes are still poorly known.

Keywords: Caspase-11, high-mobility group box 1 protein, inflammasome, inflammation, sepsis, toll-like receptor 4

Inflammation can be described as the body's reaction to the beginning of healing after an injury.[1] It might exhibit various pathways in various pathogenesis. One of these is the inflammatory reaction brought on by sepsis. A clinical illness is known as sepsis results from the body's damaging reaction to infection.[2,3] The immune system recognizes microorganisms as they enter the body.[4] Our cellular and humoral immunities from birth allow for the development of semi-automatic systems for our reaction to these microorganisms.[4-6] Significant progress has been made in understanding the pathophysiology of sepsis and its underlying causes, as well as the interactions between bacteria carriers.[2] However, since it is still poorly understood, it cannot be ruled out as a clinical sign. Pyroptosis, which is mediated by caspases and is a manifestation of sepsis's inflammatory mechanism, occurs in the body. It is a type of caspase-1-dependent cell death, which sets it apart from other apoptotic pathways.[7] The connection between caspases and sepsis is based on this intrinsically inflammatory apoptotic form, which can be brought on in a variety of various ways. To understand the mechanism of sepsis and find a cure as a clinical illness, it is essential to comprehend the role of caspases in sepsis. Caspase-11 has a significant role in pyroptosis in sepsis. Caspases are protease enzymes involved in programmed cell death. In the caspase-1-mediated inflammatory response brought on by bacterial infection, caspase-11 is crucial for caspase-1 activation.[8]

HIGH-MOBILITY GROUP BOX 1 PROTEIN AND RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS

Cytokine inhibition in its early stages to reduce the effects of sepsis did not cause any significant changes.[9-11] This resulted in the study of late mediators, which leads us to high-mobility group box 1 protein (HMGB1).[9,12,13] All cell nuclei contain the protein HMGB1, which has a wide range of intracellular and extracellular functions.[14]

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Reviewing earlier researches reveals that liver cells as the primary source of HMGB1 in endotoxemia and sepsis.[9,15,16] The primary receptors of the HMGB1 protein are toll-like receptor 4 (TLR4) and receptor for advanced glycation end products [RAGE, also known as AGE-specific receptor (AGER)].[14]

As shown in Figure 1, during inflammation, HMGB1 binds to lipopolysaccharide (LPS) and enters the lysosomes of macrophages through its own receptor, RAGE. In addition to influencing how LPS enters the macrophage lysosome, HMGB1 also makes the double-layered phospholipid membrane of the lysosome more permeable after entering the lysosome. When LPS enters the cytosol, caspase-11 is activated.[15] It is important to consider the HMGB1-LPS-RAGE connection when trying to stop sepsis from leading to mortality. Despite the blockage of this pathway is still not completely understood, major advancements have been made in the studies conducted. It has been demonstrated in experiments that m2G7, recombinant box A, acetylcholine, and GTS-21 are effective in preventing the entry of HMGB1 into the cell in culture macrophages. In the investigations, it was found that the HMGB1 culture macrophages equally ingested reduced sulfonyl and disulfide into the cell. Despite that, it is not entirely clear whether the redox state of HMGB1 has an effect on RAGE-HMGB1 interactions.[17]

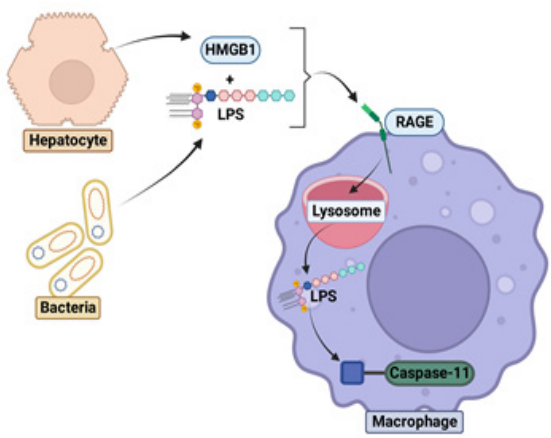

Figure 1. HMGB1/RAGE signaling pathway in caspase-11-driven inflammation.

Research findings on HMGB1-LPS binding, a different stage in the HMGB1-LPS-RAGE pathway, also produce impressive outcomes for a potential cure. Phenotypic screening devices utilizing recombinant HMGB1 were used to analyze mice peritoneal macrophages. It has been demonstrated that the 8-hydroxyquinoline derivative 7-[Phenyl(pyridin-2-ylamino)methyl]quinolin-8-ol specifically inhibits the HMGB1-dependent caspase-11 signaling pathway. It shows this effect by inhibiting HMGB1's LPS binding mechanism, resulting in stopping LPS from entering the cytosol. This inhibition prevented the caspase-11-dependent endotoxemia in mice from causing organ damage and death by drastically reducing the release of the interleukin (IL)-1 and IL-1ß.[18]

The issue of inhibiting this pathway via receptors has to be clarified and investigated further. Studies on the suppression of AGE-mediated caspase-11 inflammatory activation have demonstrated the possible use of arachidonate 5-lipoxygenase (ALOX5) in pharmacological treatments in this context. ALOX5 prevents AGE-mediated lipid peroxidation, which in turn prevents caspase-11-dependent pyroptosis in macrophages. Therefore, besides decreasing AGER receptors, exploiting AGER-ALOX5 interaction creates new opportunities to inhibit caspase-11-dependent inflammation and treat sepsis.[19,20]

CONNEXIN-43 AND TOLL-LIKE RECEPTOR 4

Gap junctions, which combine autocrine and paracrine functions, play a crucial role in facilitating cell-to-cell communication throughout tissues and organs. "connexins" are the proteins that make up these junction locations. A hemichannel called a "connexon" is created when the monomer of the six connexins joins.[21] The connexons of different varieties connect their cells to a nearby connexon and allow for cell-to-cell communication. By releasing adenosine triphosphate (ATP) from the cell in macrophages, the channel protein connexin-43 (Cx43) which is present in these channels, also contributes to the immune system. TLR-4, a member of the toll-like receptor (TLR) family, stimulates the Cx43.[22] Toll-like receptors function as a type of defense mechanism against outside substances that try to enter human tissue. The TLR-4 is associated with the activation of both Cx43 and caspase-11, according to research on models of inflammation and sepsis.[23,24, 25] Therefore, a separate analysis of TLR-4 and Cx43 might be beneficial.

As visualized in Figure 2, a model of peritonitis sepsis was created as a result of perforation of the cecum in a mouse study. TLR-4 receptors on the macrophage cells recognized the presence of bacteria in the sterile zone, which led to a rise in MyD88-mediated Cx43 release in the macrophages. By boosting the release of ATP from the cell, Cx43 has been found to activate the cell via an autocrine mechanism through

the P2Y1 receptor. Peritoneal macrophages start the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-6, IL-10, and IL-33 as a result of autocrine activation.[22] These findings imply that Cx43 inhibition or deletion might be a therapeutic possibility for peritonitis sufferers.

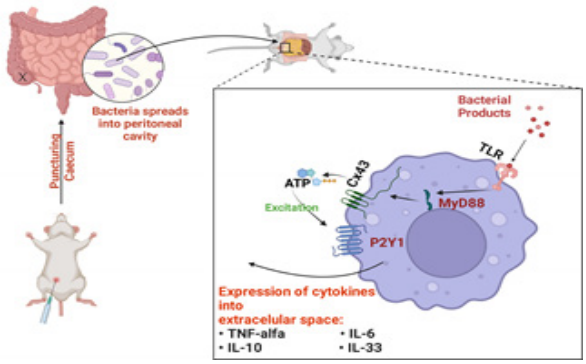

Figure 2. Caspase-11-mediated inflammation: Connexin-43 mechanism.

IMMUNITY-RELATED GTPASE FAMILY M PROTEIN/ GAMMA-AMINOBUTYRIC ACID (GABA)-A-RECEPTOR-ASSOCIATED PROTEIN

Immunity-related GTPase family M (IRGM) proteins are members of the immune system-related GTPase protein family. Although several variants exist in humans, only one IRGM protein is present and its activation requires IFN signaling.[26,27] Irgm1, Irgm2, and Irgm3 are the names of the three distinct forms of IRGM proteins found in mice.[26,28]

According to recent research, Irgm 2 and the autophagy effector gamma-aminobutyric acid (GABA)-A-receptor-associated protein (GATE-16) are involved in the inflammatory response to endotoxemia. The effects of Irgm2 and GATE-16 against the mechanism of Gram-negative bacteria-induced inflammation have been determined in experiments with culture macrophages and *in vivo* environments. Irgm2/Gate-16 inhibits the caspase-11-dependent inflammatory mechanism brought on by endotoxemia and pyroptosis in the organism. Guanylate-binding protein (GBP) dependent or independent caspase-11 inflammatory pathway is triggered in the deficiency or absence of Irgm2 and GATE-16.[26] Caspase-11 pathway activation of inflammation has been seen in cells lacking GBP, which is thought to be essential for inflammation even in the absence of Irgm2 alone.[29,30]

SPHINGOSINE-1-PHOSPHATE RECEPTOR 2

Sphingosine-1-phosphate (S1P), a modulator whose precursor is sphingosine, is implicated in a number of immunological systems, including the production of cytokines and the migration of lymphocyte cells. The actions of S1P are additionally aided by S1P carrier molecules such as serum albumin and high-density lipoproteins. It has been demonstrated that S1P carrier molecules decline during sepsis, similar to S1P. By increasing IL-1 production, sphingosine-1-phosphate receptor 2 (S1PR2) stimulation is assumed to trigger inflammation via caspase-11.[31] To comprehend the function of the S1PR2 signaling pathway, experiments based on *Escherichia coli* sepsis have been carried out using a variety of techniques. These studies revealed that S1PR2 activation leads to caspase-11-dependent pyroptosis. It has also been demonstrated that S1PR2 suppression or decreasing of S1PR2 levels greatly lowers pyroptosis in macrophages. Beside these findings have occurred, the S1PR2 signaling pathway needs caspase-11 to affect pyroptosis.[32]

TIR-DOMAIN-CONTAINING ADAPTER-INDUCING INTERFERON-B AND TOLL-LIKE RECEPTORS

A chemical known as toll/interleukin-1 receptor (TIR)-domain-containing adapter-inducing interferon-β (TRIF) serves as a bridge for the TLRs signaling pathway. The TRIF is required for the development of endotoxemia-induced inflammation driven by caspase-11 or vesicles of outer membranes.[33-35] We can observe that the TRIF molecule stimulates TLR3, and TLR4, and lead to the production of type 1 interferon (IFN-I) in inflammation, even if all of its functions are still unknown. The findings indicate that LPS leakage from the lysosome to the cytosol is not the only way to activate the caspase-11-mediated inflammatory pathway.[33] By allowing LPS into the cell, external membrane vesicles can also activate this process.[33,36] The TRIF molecule is also activated along the pathway that is induced by the aforementioned actions of the outer membrane vesicles.[33]

GASDERMIN D

The gasdermin D (GSDMD) gene produces the gasdermin D protein, which is essential for the caspase-11-dependent inflammatory response pathway. GSDMD is a substrate required for the release of gasdermin N (GSDMN) which has an activating role in the caspase-1 and caspase-4/5/11 dependent

inflammatory response mechanism. As a result of research using clustered regularly interspaced short palindromic repeats (CRISPR)-associated 9 (Cas9) genome editing system, it was discovered that GSDMD-deficient cells displayed resistance to the caspase-11/4/5, TLR4 pathway-based inflammatory response.[37]

In addition to the direct effects of GSDMD, it has been demonstrated that takes part together with caspase-11 in the HMGB1 release of hepatocytes.[9,15] The studies revealed that the transition of HMGB1 from the nucleus to the cytoplasm induced by extracellular LPS was mediated by GSDMD and caspase-11.[9]

NLR FAMILY PYRIN DOMAIN CONTAINING 3

Among the types of bacterial infections, the mechanisms activated in sepsis[38] with gram-negative bacteria have been thought to be even more specific. TRIF, TLR4, and Nod-like receptor family pyrin domain containing 3 (NLRP3)[39] contribute to inflammation induced by Gram-negative bacteria's endotoxins. NLRP3 is a protein secreted mainly by macrophages. It triggers an immune response by recognizing ATP and uric acid in the extracellular space as a result of cell damage or death. Although it is well known that inflammation starts with the detection of endotoxins by TLR4 receptor as a result of Gram-negative bacterial infection, the underlying mechanism has not been fully explored. However, TRIF activates caspase-11 via IFN-I in the pathway started by TLR4, according to research findings. Although caspase-11 does not play a role in NLRP3's detection of ATP and uric acid, it interacts with NLRP3 and causes caspase-1 activation. This mechanism is only seen against gram-negative bacteria, and these pathways have no function against gram-positive bacteria. To overlook TRIF's crucial function as a caspase-11 regulator in Gram-negative bacterial infections would be a mistake.[40,41]

In conclusion, macrophages are responsible for producing the inflammatory response brought on by bacterial endotoxins. In all pathways involved in the sepsis mechanism, caspase-11 is crucial in the development of the immune response. By attaching to the HMGB1 protein, which is mainly released into the extracellular space by liver cells in the HMGB1-mediated pathway, the bacterial endotoxin LPS triggers the inflammatory response. The inflammatory response is started when LPS seeps into the cytosol and activates caspase-11 since HMGB1 also makes the lysosome membrane more permeable. Arachidonate 5-lipoxygenase has also been demonstrated to have the ability to suppress RAGE receptor activity. With the interaction of RAGE and ALOX5 and the decrease in RAGE receptors, new therapeutic options are thus opened up. In addition, the transition of HMGB from the nucleus to the cytosol is aided by the GSDMD protein and caspase-11. However, this is not the only function of GSDMD in the inflammation mechanism. Another protein, GSDMN, which has an activating function in the caspase-4/5/11-dependent inflammatory response mechanism, also needs GSDMD as a substrate in order to be released. Although the exact cause is still unknown, the investigations have revealed that GSDMD deficiency ended up with resistance to the inflammatory response mediated by caspase-4/5/11 and TLR4. Sphingosine-1-phosphate is another modulator, the mechanism of which is currently unclear. Inflammation induced by caspase-11 is considered to be induced when the S1PR2, an S1P carrier protein, is stimulated. According to studies, sepsis-related pyroptosis is markedly diminished in macrophages lacking S1PR2 receptors. The mechanism that occurs through Cx43 enables LPS to trigger the inflammatory response without entering the cytoplasm. It activates Cx43 during sepsis via the TLR4 receptor MyD88, which recognizes bacteria in the sterile area. Outside the cell, ATP is released by Cx43. The same macrophage's P2Y1 receptor recognizes ATP in the extracellular environment, and an autocrine pathway stimulates the cell. Inflammatory cytokines such as TNF-α, IL-6, IL-10 and IL-33 are released by peritoneal macrophage cells in response to autocrine stimulation. Moreover, TLR4 functions in the NLRP3-directed route in addition to the Cx43 pathway. It has been demonstrated that TLR4 activates caspase-11 by releasing IFN-I through TRIF when it detects bacterial endotoxin. In order to activate caspase-1 and start the inflammatory response, the activated caspase-11 interacts with the NLRP3 protein. However, this NLRP3-interactive pathway is only seen against Gram-negative bacterial sepsis, not against gram-positive bacteria. There are many pathways that induce the caspase-11-mediated inflammatory response, but the cellular mechanisms that suppress it do not seem to be sufficient for now. It has been noted that the Irgm2/GATE-16 activation of the organism inhibits the process of caspase-11-dependent inflammation brought on by endotoxemia and pyroptosis. The inflammatory response seems to take place even in cells lacking Irgm2 on its own, despite the absence of GBP.

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