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Research Article

ROLE OF CASPASES IN INFLAMMATORY RESPONSES

Jinny Tomar

Amity Institute of Biotechnology, Amity University Gurugram, Haryana

A R T I C L E I N F O

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A B S T R A C T

The role of inflammasomes has been very crucial in the process of survival both in terms of stress and infection for a cell. Inflammatory responses have been found to be dependent on the activation of inflammatory caspases, with the release of certain cell specific cytokines at different stages of infection. This review paper has tried to illustrate the role of caspases in inflammation, be it in the inflammasomal complex or the choice of inflammatory pathway adapted for a specific kind of stress induced in a cell due to infection, injury, auto immune disorders. Being a major part of pyroptosis, Inflammatory caspases have been identified as one of the potential target for therapeutic in case of a number of infections and cell immune related issues.

INTRODUCTION

Inflammation and inflammatory responses are crucial for our existence, due to their role in the defence mechanism of an organism. Inflammation as we are aware of is the immune system response to pathogens, injuries, chemicals or radiation exposure or due to certain medical conditions. A lot has been said about the mechanism of inflammation, which in itself represents a series of responses both at cellular level as well as at tissue level. These responses have been governed by different pathways (Abdulkhaleq *et al*., 2018)

During inflammation, body releases substances known as inflammatory mediators, or regulatory molecules responsible for generating and maintaining an inflammatory response at a specific site of infection (Informedhealth.org). These could be explained in terms of pathogens associated molecular patterns-PAMPs or Molecules associated with damaged or dying cells, thereby known as danger associated molecular patterns-DAMPs. Such specific patterns are recognized by highly specialized pattern recognition receptors-PRRs in different cells of the human body (Purves and Hughes, 2016). A number of PRRs have been identified, which play significant role in immune response, with the help of interleukins and tumor necrosis factor receptors during infection

Corresponding author:* **Jinny Tomar
Amity Institute of Biotechnology, Amity University Gurugram, Haryana

Inflammasomes

The inflammasomes are defined as multi protein complexes, which activate certain caspases leading to release of specific cytokines. Inflammasomes get activated due to a number of signals generated by cells under attack of various pathogens. This complex comprises of caspase1, apoptosis associated speck like protein (ASC) and toll like receptors (TLR)/ C-type lectin receptors (CLR)/ nucleotide oligomerization domain (NOD) like receptors (NLRs)/ retinoic acid inducible gene like receptors (RLR) or absent in melanoma (AIM) like receptors (ALR) (Verma *et al*., 2016). It has been found that in humans, the NLRP3 inflammasome complex can be activated with the help of caspase4 and caspase5, which directly binds to other bacteria. This process involves two major steps- Priming and activation, followed by changes in the cell-production of ROS, potassium efflux and so on (Purves and Hughes, 2016, Ali *et al*., 2016). This leads to translocationof NLRP3, followed by its oligomerization. Formation of ASC protein, triggers activation of caspase-1, which leads to cleavage of Gasdermin D. Gasdermin D protein family has two major domains at N and C-terminal and a polypeptide chain, it is the N-terminal which is found responsible for the process of pyroptosis, causing inflammation (Shi *et al*., 2017, Huang *et al*., 2019).

Pyroptosis is a highly conserved mechanism in vertebrates which provides resistance against pathogens and also supports the immune system. This happens with the release of cytokines such as interleukin-1b and interleukin-18. In order to execute this process two possible pathways have been suggested: one which is dependent on Caspase-1 i.e., canonical

pathway and the other non-canonical pathway which is dependent on caspase-11 (Yuan *et al*., 2018).

A number of factors acts as stimulants for the activation of these pathways: the canonical inflammatory pathway is triggered by the presence of microbial infections, while in case of non-canonical inflammatory pathways, infections due to gram negative bacteria leading to release of lipopolysaccharide causes stimulation of series of signalling for the pathway activation (Crowley *et al*., 2017).

Inflammatory caspases

The role of caspases in inflammation and cell death has been studied since decades, to be precise it was first studied as inflammatory form of programmed cell death based on caspase-1. This process was named as pyroptosis (pyro-related to fire/fever and ptosis meaning a falling), as the origin was a microbial infection leading to release of certain toxins and other particles like silica crystals, monosodium urate etc along with release of danger signals (Cookson and Brennan 2001).

The role of different caspases has been shown in a specific division of caspases; those involved in the process of inflammation are referred as inflammatory caspases which includes caspase-1, caspase-4 and caspase-5 in humans. These inflammatory caspases have been studied from the past many decades. There's one more member in this family but it has been found to expressed in mouse: murine caspase-11. It has been observed that both caspase-1 and caspase-11 have larger domains to interact with other proteins, prominently the death domains (Scott and Saleh 2007, Lamkanfi and Dixit 2014)

It is the inflammatory caspases which have been found to play critical role in inflammation due to infectious state in a being. The activation and release of pro-inflammatory caspases has been seen to mediate the process of inflammation (Boliver *et al*., 2020). Inflammatory caspases-1, 4, 5, 11 and 12 have a caspase recruitment domain (CARD) at their N terminal region. It has been shown that bacterial lipopolysaccharide tends to activate them causing bacterial shock, specifically due to gram negative bacteria.

The fate of cell directing whether the cell will follow towards the process of necrosis/apoptosis/ inflammation is also dependent on caspase-8. As it has been observed that cells lacking caspase 8 in macrophages show defects in the resistance to infections, its significance in inflammation has only strengthened (Delenay *et al*., 2019).) Caspase-12 role (functional in a specific group of African origin population) have also been suggested to have an important role in anti-inflammatory responses (Scott and Saleh 2007).

Inflammatory Response Pathways

Inflammatory response of a specific cell, tissue is a coordinated event of signals, which further guides the inflammatory mediators to show specific response in a cell. The mechanism of inflammatory response not only consider certain pathogens invasion, or induced stress, or auto immune disorders but also includes certain chronic ailments like cardiovascular diseases, kidney disorders, diabetes, cancer, lungs infection, Alzheimer's disease, Kawasaki disease, autoimmune lympho-proliferative syndrome and so on.

Every illness is associated with a specific pattern of events, which could be repeated over expression of certain genes as well as associated proteins, which play a significant role in the understanding of the disorder. In the same manner in case of inflammation, some important point to remember while studying inflammatory responses could be summarised as: certain patterns are released in the cell under attack of pathogens or even auto immune disorders, inflammatory pathways need to be activated, as caspases are present as zymogens, and on the basis of the caspases involved, certain mediators are released (Chen *et al*., 2018). A better understanding of the inflammatory responses could be studied by understanding the different pathways involved in inflammatory responses. The two main Pathways leading to the activation of inflammatory caspases involves Canonical and Non-Canonical Inflammatory pathways as shown in figure.

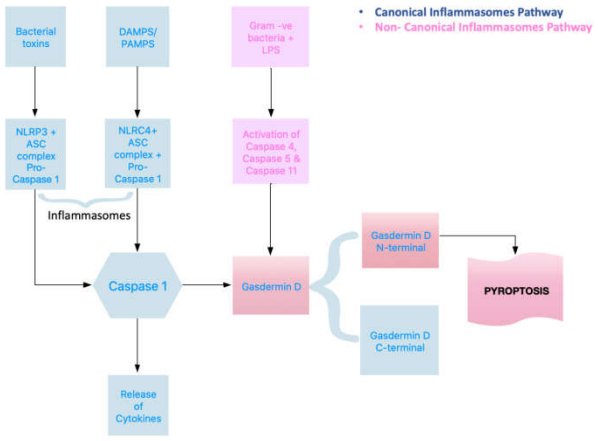

Figure: The diagrammatic representation of Canonical Inflammasome Pathway (shown in blue color) and the Non-Canonical Pathway (shown in pink color). In canonical pathway both i) activation of caspase1, via inflammasome complex of NLRP3 and ASC due to bacterial toxins release and ii) DAMPs/ Pamps being the cause of NLRC4-ASC-Pro-caspase-1 complex, leads to activation of Gasdermin D by removing the Gasdermin D C-terminus and proceeding for pyroptosis. Non Canonical pathway on the other hand is not dependent on Caspase-1 activation.

The canonical pathway shows activation of caspase-1, through two different modes: i) Due to presence of bacterial toxins in the cell, leading to formation of a multi-protein complex of nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome with Apoptosis-associated speck like protein containing a caspase recruitment domain (ASC) and pro-caspase-1, which gets activated and results into release of certain cytokines like interleukins. ii) due to the presence of danger associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs), formation of another inflammasomal complex occurs which involves, neuronal apoptosis inhibitory protein (NAIP)/NLR family caspase activation and recruitment domain–containing protein 4 (NLRC4) inflammasome, ASC and pro caspase-1, this further converts the zymogen into active caspase-1 (Jo *et al*., 2016, Lim *et al*., 2019, Tenthorey *et al*., 2020).

Non- Canonical pathway shows that the infection due to gram negative bacteria may result in bacterial lipopolysaccharide, which in turn activates caspase-4, pro-caspase-5 and in case of mouse pro-caspase-11, which then tends to activate the process of inflammatory response of pyroptosis through Gasdermin D. The two inflammasomes pathway with or without the

involvement of caspase-1, leading to pyroptosis have been explained in this figure (Abe and Morell 2016, Gao *et al*., 2018). This pathway suggests that there is still a long way to go to fully understand the activation as well as involvement of the inflammatory caspases in response to specific situations in the body.

This pathway clearly indicates the role of inflammatory caspases in inflammatory responses. It has been well established that viral, bacterial, fungal infections i.e., pathogens based infections, along with auto immune disorders, neuro degenerative disorders, intestinal disorders, stress related depression and even cancer (Wong *et al*., 2016.

Future Directions

An important factor which need to be carefully monitored and determined is the mode of action of different microbial infections i.e., to study the factors which determine whether canonical or non-canonical inflammatory pathway will be preferred.

More understanding of the immune responses of inflammasomes, may further help in making improved prediction of therapeutic approaches in terms of better target molecule to get desired medical response in the treatment of immune system based illness/disorders. In this age of personalized medicine, role of certain genes expression causing caspase 12 to express in certain group of African population indicates not to ignore this fact. So, what could be suggested for future is to perform translational studies, implementing the knowledge of targeted genes and structural and biochemical information of inflammasomes.

Further exploring the territories of the functionality, mode of action of different caspases can significantly increase the chances of enhanced efficacy of targeted drugs along with better diagnosis for effective treatment. Answering these questions will greatly improve our understanding of the inflammatory caspases, and may shed light on novel therapeutic targets.

Conflict of Interest

I declare that this work does not have any competing financial interests.

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