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Short Communication

Dentistry Section

Pyroptosis- What We Know and the Road Ahead!

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ABSTRACT

Pyroptosis, a type of cell death, initiated by proinflammatory signals, is classically associated with inflammation. It was thought to occur mainly in macrophages and leukocytes during inflammatory conditions and involves the activation of caspase 1 {Interleukin-1beta (IL-1β)-converting enzyme} followed by the production of proinflammatory cytokines such as IL-1β. The process takes place within dendritic cells and macrophages, although there have been few reports of caspase-1 activity within other cells. Induction of pyroptosis involves the caspase-1 activity, however, how its downstream substrates bring about cell death is not well understood. And recently, there has been an addition to the gasdermin family, namely, Gasdermin-D (GSDMD) protein, which plays an important role during pyroptosis. Pyroptosis has been found to have a significant role in tumourigenesis, as it extrudes inflammatory mediators which are vital for tumour development. It is also well known that the activity of proto-oncogenes and antioncogenes, the microenvironment of the immune system, chronic inflammation, and oxidative stress, could determine tumourigenesis and hence the link to pyroptosis.

Keywords: Apoptosis, Caspase 1, Gasdermin, Inflammation

INTRODUCTION

Pyroptosis represents a type of cell death that is initiated by proinflammatory signals. It is classically associated with inflammation [1]. As we know, cell death is a normal biological occurrence, and as cells die, they need to be replaced by newer ones to carry out the functions of the cell. Scientific analyses have corroborated the theory that cell death is inextricably linked with the immune response against infection. Pyroptosis has been identified fairly recently, as a type of cell death which occurs following necrosis and apoptosis. While it is well known that apoptosis is a pattern of cell death seen most commonly in cells during embryonic development, and normal cell turnover and does not involve inflammatory processes, pyroptosis signifies cell death associated with inflammation [1]. Microbial infections are expunged from the body by pyroptosis, by eliminating the replication areas found intracellularly and improving the host's defence mechanism [2]. It was described first on macrophages infected with 'Shigella flexneri' in 1992. The term 'pyroptosis' was first attributed to Cookson and Brennan. Since these cells also undergo Deoxyribonucleic Acid (DNA) fragmentation and nuclear condensation, the process has also been described as 'inflammatory necrosis' [3].

MECHANISM OF PYROPTOSIS

The term pyroptosis is a conglomeration of two Greek root words 'pyro' and 'ptosis'. Pyro means fever, fire, or inflammation, and ptosis means falling. These words were strewn together cleverly to depict a new phenomenon of inflammatory Programmed Cell Death (PCD) [4]. Pyroptosis was previously purported to occur solely in macrophages and leukocytes during inflammatory conditions. The part played by pyroptosis to the body's defence mechanism, involves synergism between phagocytes. It is understood that the pathogens ingested by the macrophages are eradicated from the body by polymorphonuclear leukocytes. Pyroptosis involves the activation of caspase 1 (IL-1β-converting enzyme) followed by the production of proinflammatory cytokines such as IL-1β [5,6].

The process takes place to a large extent within defence cells such as dendritic cells and macrophages, although there have been few reports of caspase-1 activity within other cells, such as keratinocytes and intestinal epithelial cells [2,3]. We now know that the induction of pyroptosis involves the caspase-1 activity, however, how its downstream substrates bring about cell death is not well understood [6]. The quintessential features of pyroptosis involve the breakdown of the cell membrane and spillage of the cellular contents into the adjacent extracellular environment [6]. Although cleavage of the DNA and nuclear condensation are common attributes of pyroptosis and apoptosis, contrary to what occurs in apoptosis, the integrity of the nucleus is not compromised in pyroptosis. In pyroptosis, cell membranes are subjected to pore formation, rendering the cell permeable, in contrast with apoptosis, where the cell membranes are intact. Also, DNA damage and laddering is more prominent in apoptosis when compared to pyroptosis. The other major difference is the presence of nuclear condensation that takes place in pyroptosis, however it does not display any nuclear fragmentation as seen in apoptosis [Table/Fig-1] [2].

Characteristics	Apoptosis	Pyroptosis
Inflammatory	No	Yes
Pore formation	No	Yes
Membrane intact	Yes	No
Cell swelling	No	Yes
Chromatin condensation	Yes	Yes
DNA fragmentation	Yes	Yes
Nucleus intact	No	Yes
DNA laddering	No	Yes

[Table/Fig-1]: Difference between pyroptosis and apoptosis.

Although, it has been widely established that pyroptosis is a caspase-1-dependent process, the specific nuclease that causes the DNA cleavage during this cell death remains terra incognita. Caspase-1-dependent pyroptosis requires the initiation of the recognised inflammasomes. These inflammasomes are innate immune system multi-protein molecules of receptors and sensors which modulate the triggering of the caspase-1 and inflammation. This activation is in response to the host's presentation of infectious microbes and molecules. They have been shown in conjunction with numerous inflammatory disorders. The innate immunity immediately sets off-host responses to fight the offending antigen and as a result, the activation of the delayed adaptive immune responses takes place,

which controls the pathogen and triggers immunological memory to protect against future attacks. Host Pattern Recognition Receptors (PRRs) are a vital part of the innate immune system. Host recognises antigens by PRRs which differentiates them from the host's own by their molecular attributes and intracellular confinement. When PRRs are stimulated, direct recruitment of caspase-1 takes place through the Apoptosis-Associated Speck-like proteins (ASCs) to form a caspase-1-dependent inflammasome. ASCs are located within the nucleus of monocytes and macrophages and relocate themselves quickly to the cytoplasm during an antigenic attack and are known as key adaptor proteins in the activation of the inflammasomes [7-12].

Lately, however, there has been a brand-new addition to the gasdermin family, namely, Gasdermin-D (GSDMD) protein. It has been brought to light that this new member is a pivotal player in the occurrence of pyroptosis. Gasdermins belong to a family of pore-forming effector proteins that can permeate cell membranes and cause pyroptosis [7,8,12,13]. Gasdermins possess two domains: a cytotoxic N-terminal domain and a C-terminal repressor domain. A compliant linker connects these two domains. Gasdermins induce pyroptosis by proteolytic cleavage between the two domains. This cleavage facilitates the intramolecular inhibition on the cytotoxic domain, allowing it to ingratiate into cell membranes and create large oligomeric pores, which alters ion homeostasis and promotes cell death [7]. Once caspase cleavage is complete, the N-terminal fragment (GSDMD-cNT) gets unleashed from the GSDMD, which brings about the swelling of the cells till the point of their disintegration. It is now a widely held view that gasdermin-induced pyroptosis is conspicuously linked to a myriad of hereditary and inflammatory disorders, including cancer [7,8,12,13].

PYROPTOSIS IN ORAL CANCER

The phenomenon of pyroptosis assumes particular importance as recent extensive studies indicate that pyroptosis has particular significance during tumourigenesis, as it extrudes inflammatory mediators which are vital for tumour development [11-19]. It is a well-established fact that factors like the activity of proto- and anti-oncogenes, the microenvironment of the immune system, chronic inflammation, and oxidative stress, could determine tumourigenesis. Also, when tissues are exposed to an inflammatory environment on a long-term basis, the risk of the cancer formation is higher. When pyroptosis is activated, it induces the release of inflammatory mediators such as IL-1β and IL-18. These cytokines could promote tumourigenesis [14-17]. But since pyroptosis is also regulated cell death, it is also purported to prevent the formation and progression of neoplasms [18].

Various studies have been undertaken to further analyse the prognostic role of pyroptosis in cancer management and to formulate effective therapeutic strategies [15-21]. These studies had the express aim of increasing our understanding of the phenomenon of pyroptosis in various cancers, including cancers of the lung, breast, skin, and intestine. Some of these studies allude to the fact that in some cancers GSDMD-mediated pyroptosis can be triggered by the administration of certain drugs or molecules [19,20].

Studies have also been carried out to analyse the role of pyroptosis in oral cancers [14-19]. Results indicate that the application of anthocyanin can induce pyroptosis in Oral Squamous Cell Carcinoma (OSCC) with augmented NLRP3 (NLR family pyrin domain-containing three proteins expressed predominantly in macrophages), caspase-1, and IL-1β expression. Anthocyanin is a pigment, which occurs naturally in plants, and is water-soluble. Lately, an increasing number of studies have reported on the therapeutic effects of anthocyanins in cancers [19,20]. The possible inhibitory and basic molecular mechanisms of anthocyanin were studied by Yue E et al., on OSCC. They noted that there was a decreased rate of the OSCC cells when anthocyanin was administered. It was also reported that pyroptosis was induced, by the impediment of the migration and invasion of the OSCC cells, when anthocyanin was administered [19]. It was thus deduced that the increased expression of NLRP3, caspase-1, and IL-1β was interrelated to the activation of pyroptosis [20]. Many studies have been done on the molecular mechanisms of pyroptosis in the last two decades [6,8-10,13-16,19-21].

CONCLUSION(S)

To conclude, although the vital role of pyroptosis in cancer cannot be understated, the prevailing scientific data is insufficient to mount effective cancer therapy and management strategies. The mechanism of pyroptosis in different tumours needs to be explored, as well as the signalling proteins. This could lead to newer regimes for the treatment of related tumours. However, much information is still required in this regard and other proteins from the Gasdermin family should be scrupulously studied to scour for the possibilities of fresh treatment strategies. The connection between microbes and oral cancer further accentuates the role of pyroptosis in effectively grappling with oral cancer, by significantly improving our understanding of signaling pathways in oral cancer. In addition, there is an understandable justification in examining the effect of pyroptosis on oral potentially malignant disorders, as a significant number of these diverse lesions do undergo malignant transformation into OSCC. There is a pressing need to delve into and examine pyroptosis, to better understand its processes, which could have a critical impact on the design of more effective and efficient treatment regimes, when combating lifestyle crippling lesions and diseases.

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