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Commentary

Inflammatory Illnesses of Dental Fibroblasts and Prevention of Non-canonical Pyroptosis

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ABOUT THE STUDY

Inflammatory caspases trigger the lytic cell death process known as pyroptosis. Both canonical and noncanonical pyroptosis exist, depending on the stimuli and caspases involved. The NOD-, LRR-, and Pyrin domain-containing 3 (NLRP3) inflammasome or the Absent in Melanoma 2 (AIM2) inflammasome are two examples of the multimeric protein complex known as the canonical inflammasome that is generated during canonical pyroptosis. The canonical inflammasome triggers pro-autoproteolytic caspase-1's processing, which ultimately results in pyroptosis. Cytoplasmic Lipopolysaccharide (LPS), a particular kind of inflammasome known as the "noncanonical inflammasome". Formation of the noncanonical inflammasome results in the activation of human caspase-4/5 or murine caspase-11 and promotes pyroptosis rather than activating caspase-1. Both canonical and noncanonical pyroptosis have the same executioners, which are members of the gasdermin protein family, but having different activation pathways. Gasdermin D (GSDMD), a member of the gasdermin protein family, has undergone the most extensive research and is frequently linked to inflammatory illnesses. Activated caspases cleave GSDMD during pyroptosis. GSDMD releases an N-terminal fragment with pore-forming activity after the autoinhibitory C-terminus is cut off. In the plasma membrane, this fragment oligomerizes and creates holes.

The two inflammatory illnesses that are most frequently diagnosed in dentistry offices are pulpitis and periodontitis. Humans experience significant suffering as a result of the spontaneous pain brought on by pulpitis and the unchecked inflammation in the periodontal tissues, which may ultimately lead to tooth loss. Immune cells are crucial to the emergence of these illnesses. Dental fibroblasts, including PDLFs and DPCs, are the main kind of cell in dental pulp and periodontium, and they are also a part of innate immunity. Previous research suggested that pyroptosis might mediate the development of oral inflammation, and it was discovered that different pathogens can simulate pyroptosis in dental fibroblasts. However, prior research on pyroptosis in dental fibroblasts has been surprisingly scarce given our increased understanding of the phenomenon, particularly after the gasdermin protein family was shown to be the executioners of pyroptosis. The expression of NLRP3, AIM2, and caspase-4 is also elevated in tissues taken from individuals with oral inflammatory illnesses, suggesting that these inflammasomes may play a role in the development of the illness. Therefore, the purpose of this work was to examine how dental fibroblasts reacted when the NLRP3 inflammasome, AIM2 inflammasome, and noncanonical inflammasome were stimulated.

The inflammatory state may be influenced by cellular metabolites, according to earlier investigations. Itaconate and -ketoglutarate are examples of tricarboxylic acid cycle intermediates that have an impact on immunological responses by blocking specific enzymes or causing covalent changes to proteins. DMF, a cell-permeable fumarate derivative, is used to treat Multiple Sclerosis (MS). It's interesting to note that a recent study found that exogenous DMF application and endogenous fumarate accumulation both prevented pyroptotic cell death and GSDMD-NT production in macrophages, suggesting that DMF can prevent pyroptosis in immune cells by specifically targeting GSDMD. This finding showed that DMF might be a potential treatment drug for several pyroptosis-related disorders as cleavage of GSDMD is the last step in pyroptosis. Dental fibroblasts have a significant impact on the development of illnesses, but they are not completely responsible for oral inflammatory diseases. It is unknown how DMF will affect dental fibroblasts when they are exposed to pyroptotic stimuli.

Here, we employed LPS priming+nigericin stimulation, LPS transfection, and poly(dA:dT) transfection to cause pyroptosis in dental fibroblasts. Dental fibroblasts were found to be more vulnerable to cytoplasmic LPS-induced noncanonical pyroptosis than to canonical pyroptosis. Additionally, by blocking the cleavage of GSDMD and the subsequent localization of GSDMD NT on the plasma membrane, pretreatment with DMF inhibited the cytoplasmic LPS-induced pyroptotic cell death in dental fibroblasts.

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