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Commentary

Cell Death Pathways in Macrophages Infected by Mycobacterium leprae

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DESCRIPTION

Mycobacterium leprae (M. leprae), the causative agent of leprosy, exhibits a unique interaction with host macrophages. Macrophages are critical immune cells that play a dual role in the context of *M. leprae* infection. On one hand, they serve as the first line of defense, engulfing and attempting to kill the pathogen. On the other, they act as a niche for *M. leprae* survival and proliferation. The fate of macrophages during infection is pivotal in determining disease progression, and *M. leprae's* ability to manipulate different modalities of macrophage death is central to its pathogenicity.

Types of Macrophage Death in *M. leprae* Infection

Macrophages can undergo various forms of cell death, including apoptosis, necrosis, necroptosis, pyroptosis, and autophagic cell death. Each modality has distinct characteristics, mechanisms, and implications for the host-pathogen interaction.

Apoptosis: Apoptosis is a programmed form of cell death characterized by cellular shrinkage, chromatin condensation, DNA fragmentation, and the formation of apoptotic bodies. It is a non-inflammatory process that aids in pathogen containment. Apoptosis is considered a host defense mechanism against intracellular pathogens, including *M. leprae*. It limits bacterial replication and facilitates the presentation of antigens to T cells.Studies indicate that *M. leprae* infection can induce apoptosis in macrophages as an early immune response. However, the pathogen has evolved mechanisms to subvert or delay this process, promoting its survival. Efficient apoptotic pathways can reduce the bacterial load and stimulate an effective adaptive immune response. Dysregulation of apoptosis may contribute to disease progression and chronicity.

Necrosis: Necrosis is an unregulated form of cell death characterized by membrane rupture, cytoplasmic swelling, and the release of intracellular contents, leading to inflammation. *M. leprae* can induce necrosis in macrophages under specific conditions, particularly in cases of high bacterial load or oxidative stress. Necrosis benefits the pathogen by releasing nutrients and creating an inflammatory microenvironment conducive to bacterial survival. Necrotic cell death contributes to tissue damage and nerve destruction seen in advanced leprosy, exacerbating the disease's clinical manifestations.

Necroptosis: Necroptosis is a programmed form of necrosis mediated by receptor-interacting protein kinases (RIPK1 and RIPK3). It results in cell membrane rupture and inflammation. Emerging evidence suggests that *M. leprae* can trigger necroptosis in macrophages. This may represent a mechanism to balance host cell death and bacterial survival. The interplay between necroptosis and other forms of cell death in *M. leprae* infection remains an area of active research. Understanding the role of necroptosis could provide insights into therapeutic strategies to modulate macrophage death and control infection.

Pyroptosis: Pyroptosis is a form of inflammatory programmed cell death mediated by caspase-1 and gasdermin D. It is characterized by cell swelling, membrane pore formation, and the release of pro-inflammatory cytokines like IL-1β and IL-18. Pyroptosis is a double-edged sword in the context of *M. leprae* infection. While it can enhance inflammation and pathogen clearance, excessive pyroptosis may contribute to tissue damage and immune evasion by the pathogen. *M. leprae* may modulate pyroptotic pathways to favor its persistence within macrophages. Targeting pyroptosis pathways could be a potential therapeutic approach to mitigate inflammation and tissue destruction in leprosy.

Autophagic cell death: Autophagy is a cellular process that involves the degradation of damaged organelles and intracellular pathogens through lysosomal activity. Autophagic cell death occurs when autophagy is excessively activated, leading to cell demise. *M. leprae* can both induce and inhibit autophagy in macrophages. While autophagy can limit bacterial survival by degrading intracellular bacilli, *M. leprae* can manipulate autophagic pathways to evade host defenses. Autophagic cell death is less inflammatory compared to necrosis and may play a role in containing infection during early stages. Enhancing autophagy through pharmacological agents could represent a novel strategy for controlling *M. leprae* infection.

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CONCLUSION

The ability of *M. leprae* to exploit and modulate different modalities of macrophage death highlights its sophisticated strategies for survival and persistence. Each form of cell death apoptosis, necrosis, necroptosis, pyroptosis, and autophagic cell death plays a distinct role in the host-pathogen interaction, influencing the progression and clinical outcomes of leprosy. A deeper understanding of these processes may pave the way for targeted therapies to modulate macrophage death, enhance immune responses and reduce tissue damage in leprosy.