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Mycobacterial Diseases

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Short Communication

Zebrafish Models for Nontuberculous Mycobacterial Infections

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DESCRIPTION

Nontuberculous Mycobacteria (NTM) are a diverse group of opportunistic pathogens that are capable of causing a wide range of infections in humans, particularly in immunocompromised individuals and those with chronic lung diseases [1]. These infections can be challenging to treat due to the slow-growing nature of the bacteria, their inherent resistance to many antibiotics, and the ability to form biofilms. NTM species, such as *Mycobacterium avium*, *Mycobacterium abscessus*, and *Mycobacterium marinum*, are increasingly recognized as important human pathogens. Animal models are essential for studying the mechanisms of NTM infection and testing potential therapeutic interventions [2]. The zebrafish (*Danio rerio)* has emerged as a valuable model for studying NTM infections due to its genetic tractability, optical transparency, and physiological similarity to humans.

Advantages of zebrafish as a model organism

Zebrafish share significant genetic homology with humans, making them a relevant model for studying human diseases. Their immune system consists of both innate and adaptive components, closely resembling the human immune response to mycobacterial infections [3]. Zebrafish embryos and larvae are optically transparent, allowing real-time imaging of bacterial infections and immune responses. This transparency enables the direct observation of bacterial colonization, host-pathogen interactions, and immune cell recruitment [4]. Zebrafish can be easily genetically manipulated using techniques such as CRISPR-Cas9, allowing researchers to study the role of specific genes in host immunity or bacterial virulence. This makes the zebrafish model an ideal system for studying the genetic basis of NTM infection and the host's immune response [5]. Zebrafish embryos develop rapidly, and hundreds of embryos can be generated from a single pair of adults. This high fecundity makes zebrafish suitable for large-scale genetic and chemical screens to identify potential drug candidates or genetic factors that influence NTM infection.

Granuloma formation

Zebrafish have been used to model infections caused by several NTM species, most notably *Mycobacterium marinum*, a close relative of *Mycobacterium tuberculosis* and a pathogen that causes skin infections in fish and humans [6]. *Mycobacterium marinum* naturally infects zebrafish and causes granuloma formation, a hallmark of mycobacterial infections, making it an ideal system for studying the pathogenesis of NTM. One of the key features of NTM infections is the formation of granulomas-organized structures of immune cells that attempt to contain the mycobacteria [7]. Granulomas are important to understanding mycobacterial diseases because they represent both the host's attempt to control the infection and a protective niche for the bacteria. In zebrafish infected with *M. marinum*, granulomas can be visualized in real-time using fluorescently labelled bacteria and immune cells. This allows researchers to observe the dynamics of granuloma formation, bacterial growth, and immune cell recruitment and to study the factors that influence these processes.

Immune response and host-pathogen interactions

The zebrafish model also allows for the study of the innate and adaptive immune responses to NTM infection. The zebrafish innate immune system, which includes macrophages and neutrophils, is particularly relevant in early stages of mycobacterial infection, where the bacteria are engulfed and may persist inside host cells [8]. These innate immune cells are involved in both controlling bacterial growth and contributing to granuloma formation. The adaptive immune system, including T and B cells, also plays a role in controlling chronic mycobacterial infections, and zebrafish provide a system for studying how adaptive immunity responds to NTM. Zebrafish are useful for studying the interactions between host immune cells and NTM [9]. Using fluorescent markers, researchers can visualize how macrophages and neutrophils interact with mycobacteria in real-time. This has led to the discovery of important insights into bacterial survival strategies, such as the ability of mycobacteria to

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persist within host cells or to evade immune responses. The zebrafish model has also revealed the importance of specific cytokines and chemokines in orchestrating the immune response to NTM infections.

Drug screening and therapeutic development

Zebrafish are increasingly used in drug screening for NTM infections due to their small size and the ease with which large numbers of larvae can be used in high-throughput assays. Chemical screens using zebrafish larvae infected with fluorescently labelled NTM can identify compounds that reduce bacterial burden, disrupt granuloma formation, or modulate the immune response [10]. The use of zebrafish in drug screening is particularly valuable given the increasing antibiotic resistance seen in NTM species, such as *M. abscessus*, which is notoriously difficult to treat with conventional antibiotics. Several potential therapeutic agents have been tested in zebrafish models of NTM infection, including new antibiotics, immune-modulating drugs, and inhibitors of quorum sensing, a bacterial communication system linked to virulence and resistance. The zebrafish model allows for rapid evaluation of these compounds' efficacy and toxicity, providing a bridge between in vitro studies and more complex mammalian models.

CONCLUSION

The zebrafish model has become an indispensable tool for studying nontuberculous mycobacterial infections. Its unique advantages, including optical transparency, genetic tractability, and suitability for high-throughput drug screening, make it an ideal system for studying the complex host-pathogen interactions that characterize NTM infections. By using zebrafish, researchers have gained valuable insights into granuloma formation, immune responses, and bacterial virulence strategies, and the model continues to contribute to the development of novel therapeutic strategies for combating these challenging infections.

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