Mycobacterial Diseases
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Perspective

Role of Mycolactone in Buruli Ulcer

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DESCRIPTION

Mycobacterium ulcerans causes Buruli Ulcer (BU), a persistent severe skin disease. It is an acid-fast *Bacillus* that is related to the organisms that cause tuberculosis and leprosy. Although the disease is known to be connected to contaminated water, the mode of transmission of *Mycobacterium ulcerans* is not entirely understood. Buruli ulcer disease is caused due to unhygienic conditions like stagnant or sluggish moving water. *Mycobacterium ulcerans* secretes mycolactone, a lipid toxin that acts as an immunological suppressor, necrotizing agent, and promoter of cellular death in mammalian tissues.

Buruli Ulcer (BU) epidemiology, transmission, and clinical management

Buruli Ulcer (BU) is a necrotizing skin disease caused by *Mycobacterium ulcerans* infection, and it is the third most common mycobacterial illness after tuberculosis and leprosy. Epidemiological and genetic research has showed that *Mycobacterium ulcerans* is connected with lentic settings, implying that the bacteria do not transmit from person to human, but rather by reservoir displacements that have yet to be uncovered. The transmission of ulcerans from reservoirs to humans is now thought to be the result of a combination of skin contamination and insect bites or puncture injuries. Buruli Ulcer (BU) usually begins as a painless subcutaneous nodule, edema, or plaque that grows larger over time. After several weeks to months, the overlying epidermis peels back to reveal inactive, necrotic lesions of the cutaneous and subcutaneous tissues. Osteomyelitis can emerge as a result of hematogenous bacteria seeding from distant foci of infection.

Mycolactone genetics, chemistry, and biodistribution

Mycobacterium ulcerans is unique among human infections in that it may create a diffusible toxin known as mycolactone. Mycolactone production is enabled by large polyketide synthases, the genes for which are carried by a megaplasmid. Mycobacterium variants of a conventional mycolactone structure, corresponding to a 12-membered lactone ring replaced with two polyketide-derived chains, are produced by ulcerans strains from diverse geographical origins or genetically related mycobacteria. Mycolactone plays an important role in the aetiology of Buruli Ulcer (BU). Its synthesis is needed for bacterial pathogenicity, and injecting pure mycolactone into the dermis in animal models induces Buruli Ulcer (BU)-like lesions. Whereas mycobacterium while ulcerans bacteria rarely spread beyond the epidermis, mycolactone is found throughout the body. Its unique mass spectrometric signature was found in the peripheral blood cells, spleen, liver, and kidneys of mice infected with *Mycobacterium ulcerans*. Mycolactone that was structurally intact was found in ulcer exudates, healthy skin around ulcers, and serum in individuals with progressing illness. Notably, mycolactone was discovered in perilesional skin several weeks after antibiotic therapy was completed, indicating a sluggish clearance rate. Several immunological studies of Buruli Ulcer (BU) patients have also found changes in the systemic production of IFN-g that disappear after surgical removal of the lesions.

Role of mycolactone associated with Buruli Ulcer (BU) illness

Mycolactone's role in each manifestation of Buruli ulcer (BU) illness, including cutaneous necrosis linked with a relative lack of inflammatory infiltrates and pain, as well as faulty cellular responses at the systemic level, has been the topic of extensive investigation over the last decades. The section that follows provides an overview of the main findings. The biological mechanism(s) of mycolactone-induced skin ulceration were first explored by observing mycolactone's cytopathic effects on cultured keratinocytes, fibroblasts, epithelial and endothelial cells. Fluorescently labelled mycolactones penetrated cultured fibroblasts in a non-saturable and non-competitive manner, allowing them to localise in the cytosol *via* passive diffusion across the plasma membrane. According to recent studies using computer simulations or lipid monolayers, the passage of mycolactone across cellular membranes may still alter their dynamic properties and cause mechanical and physical perturbations. For example, exposure to mycolactone induced rapid alterations in the actin cytoskeleton of HeLa cells, coinciding with a defective capacity of the cells to establish

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adhesive contacts and migrate directionally in wound-healing assays in *vitro.* Longer treatments (>48 h) produced cell retraction, separation, and apoptosis in all skin cells tested, albeit with small variability in time-to-death across cell types. Mycolactone depleted the blood coagulation regulator thrombomodulin from the cell surface in human dermal microvascular endothelial cells. When mycolactone was injected intradermally into mouse ears, it generated significant changes in the epidermal architecture. These findings suggested that mycolactone causes Buruli ulcer (BU) formation through a combination of cell death in the dermis and subcutaneous tissues, epidermal remodelling, loss of healing potential, and coagulation control.

CONCLUSION

We have made considerable progress in our understanding of the molecular pathways behind mycolactone biology, and thus Buruli Ulcer (BU) pathogenesis, in recent years. The substrate selectivity of mycolactone inhibition uncovers clear gaps in our understanding of membrane protein integration, in addition to showing the vital relevance of Sec61 functioning for immune cell function, migration, and communication. Furthermore, experiments with mycolactone have revealed a unique immune modulatory pathway developed by *Mycobacterium ulcerans*, and it is hoped that this can be used therapeutically to minimise inflammatory conditions. As a result, systemically given mycolactone proved efficient in minimising skin inflammation and inflammatory discomfort in animal models of human illnesses.