Buruli Ulcer: What are the Future Perspectives in Dealing with the extensive Necrotizing Skin Disease

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Abstract: Buruli ulcer (BU) is a necrotizing skin disease cause by mycolactone-producing *Mycobacteria ulcerans.* The disease leaves permanent disabilities, stigmatization, a clinical challenge linked to morbidity and treatment with negative socioeconomic impact. The current effective treatment remains antibiotics combination therapies of rifampicin and streptomycin with 2-10% of the patients developing worse extensive ulcers after the treatment and there is no vaccine. In the case of extensive ulceration, the treatment option remains surgical resection and skin grafting which is very challenging and even when successful leaves scars and disability.

This review focuses on the recent understanding of mechanisms upon which mycolactone-producing *Mycobacteria ulcerans* induces extensive skin ulcers and suggest areas within the pathological pathways which can be targeted for the future management and treatment of the disease. The mycolactone binds to Sec 61 translocon subunit and inhibits the binding immunoglobulin protein (BiP). A point mutations R66I, R66G, and S82P in the Sec61α subunit has been shown to prevent mycolactone binding to the Sec61 lumen. The mycolactone also compromised the cytoskeleton and dysregulated immunity through the activation of the AT2R receptor. Thus, targeting the mycolactone binding site either by inducing mutation or competitive inhibition compounds, blocking the AT2R receptor and the uncontrol activation ARP2/3 could revolutionize the management of extensive ulceration in BU patients.

Keyword: Buruli ulcer, mycolactone, *Mycobacteria ulcerans,* dermatological disease, subcutaneous necrosis, bacteriophage therapy.

INTRODUCTION

Buruli ulcer (BU) is a dermatological disease of skin papules which advance to subcutaneous necrosis and ulceration [1, 2]. BU is environmentally favoured disease that affected immunocompetent individuals of all ages but frequently seen in children and young adolescents, especially in West Africa [3, 4]. The global prevalence of BU from 2010-2017 stands at 23,206 cases with 40% of the cases occurring in the under 15 years [5, 6]. It is of public health importance due to its negative socioeconomic impact, clinical challenges & treatment, permanent disability, and stigmatization [7, 8]. BU is the third major human disease caused by *Mycobacterium*, but it remains neglected [9].

The causative organism, *Mycobacteria ulcerans* produces mycolactone, a cytotoxic and immunosuppressive substance that induces the ulceration which frequently results in permanent disability [10-12]. A necrotizing skin disease induced by macrolide toxin with two polyketides derived side chains (mycolactone) produce by nontuberculous mycobacteria, *Mycobacterium ulcerans* [13, 14]. The necrotic disease starts as a painless papule or nodule and gradually leads to permanent ulceration [15,16]. The extensive and irreversible deformation of skin lesions are characterized by yellow-whitish necrotic cells surrounded oedema [9]. The mycolactone stimulates nerve degeneration in the perineural and endoneurial cells leading to loss of pain sensation in the necrotic ulceration in Buruli ulcer cases [17, 18]. The mycolactone suppress the cellular immunity through inhibit of secretion of chemokines such as macrophage inflammatory protein (MIP)-1a, monocyte chemoattractant protein 1, T cell expressed and secreted and interferon-gamma inducible protein 10 [19-22].

To prevent necrotizing skin disease requires the resolution of the systemic abnormalities induced by *M. ulcerans*. The current understanding of the underlying factors involved in wound healing such as cytoskeletal function which play an important role in immunity and maintenance of the skin integrity is well known. Although it is equally important to remove the causative organism or source by eliminating *M. ulcerans*, the already secreted mycolactone compromised the cytoskeleton, dysregulated immunity and the extensive ulceration among BU patients may not be resolved. Therefore, it is important to review the current literature

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on the underlying factors responsible for the permanent and the ulceration of BU and identify the areas of interest for future research and management of this skin disease.

M. ulcerans Mycolactone and how it Induces Painless but Fetal Ulcers

Mycolactone inhibits pain signalling by triggering neuronal hyperpolarization [23-27]. The Mycolactone involves in the entire cellular pathways by stimulating AT2R receptors which leads to the opening of TRAAK potassium channels [25, 28-30]. The cellular pathways activated by mycolactone involves phospholipase A2 (PLA2), cyclooxygenases and prostaglandins (PGE2) [25, 30, 31].

Phospholipases A2 releasing lysophospholipids and free fatty acids, including arachidonic and oleic acids [32-34]. These products are precursors for several biological signalling processes [35, 36]. Arachidonic acid is converted to eicosanoids (prostaglandins and leukotrienes) which regulate sleep, immune responses, inflammation, pain, neuropathic pain, neuropsychiatric disorders [37-39]. PLA2 also inhibit pain by "silent" nociceptors making it unresponsive to noxious intensities of the mechanical stimulus [40-42]. The nociceptors are pseudo-unipolar neurons in the peripheral ganglia are bifurcate nerves which send stimulus through the peripheral axon to the skin, or the organs, and an axon to the central nerve system (CNS) to the spinal cord where the information proceeds to the brainstem and reaches the cerebral cortex for the perception of pain [43, 44]. The noxious stimuli activate transient receptor potential (TRP) and purinergic channels, which potentiate sodium channels activation leading to hyperalgesia [45-49]. The cells in the injured area release neuropeptides (substance P, CGRP), bradykinin, cytokines, chemokines, neurotrophins, nitric oxide, proteases, protons, and reactive aldehydes (extracellular PLA2-derived lipid mediators) which excites prostaglandins, prostacyclins, thromboxanes, and leukotrienes, and inflammatory substances which results in peripheral sensitization [50-53].

The sustained activation of nociceptors provokes transcriptional and post-translational modifications that upregulation of Na+ channels and activation of protein kinase A and C which lead to Ca2+ and Na+ channels sensitization [54-57]. The pre-synaptic neurotransmitters (glutamate, calcitonin gene-related peptide, substance P) and released ATP potentiating the activation postsynaptic plasticity [58-60]. The transient receptor potential cation channel subfamily V member 1 (TRPV1) expressed in a subpopulation of neurotransmitters has established a role in the development of hyperalgesia [61-63]. Similarly, vesicular glutamate transporter 2 (*Vglut2*), substance P (SP) or calcitonin gene-related peptide (CGRP) signalling mediates hyperalgesia in persistent inflammation [62, 64, 65]. These signalling mechanisms result in nerve degeneration, an

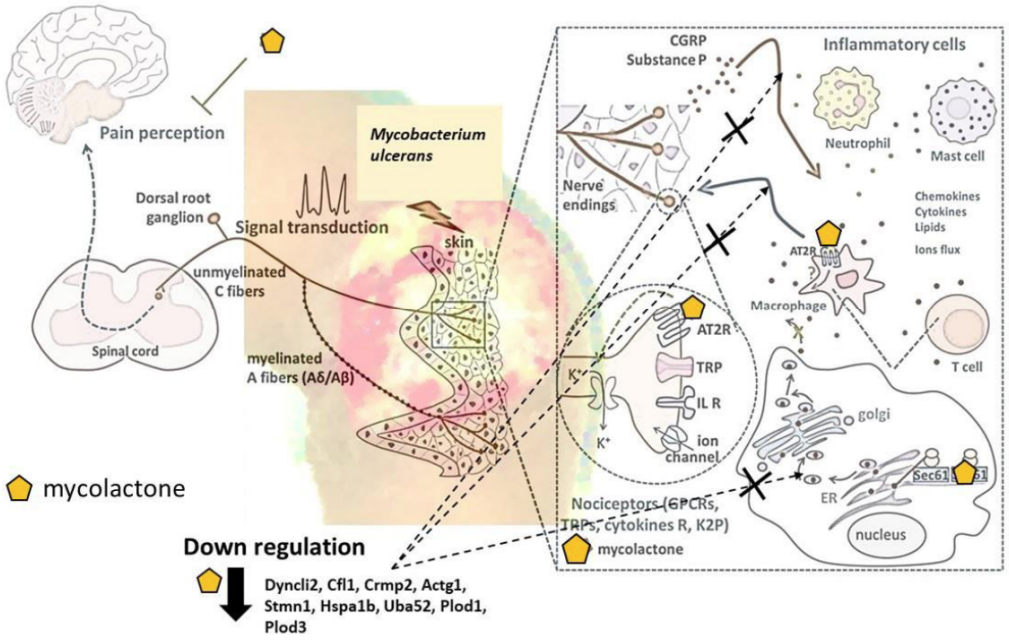

Figure 1: Mechanisms underlying the host cytopathogenesis caused by *Mycobacterium ulcerans* toxin mycolactone.

underlying analgesic factor in the progressive necrotic lesions and wounds observed in Buruli ulcer patients [66, 67] (Figure **1**).

M. ulcerans Mycolactone and Immune Cells in Extensive Necrotic Lesions / Open Wound in Buruli Ulcer Patients

M. ulcerans infects macrophage, a major phagocytic immune cell, by the uptake of mycobacteria into its cells where the bacilli undergo proliferation and cause apoptosis of the macrophage [68, 69]. This results in the release of the bacilli and immunosuppressive substance, mycolactone [70]. The mixed of the bacilli and the mycolactone result in poor inflammatory reaction, cell cycle arrest, the necrosis of adipocytes and fibroblasts [71-73]. Mycolactone has been reported to inhibit IL-2, IL-10, TNF-α [74]. It also inhibits maturation of dendritic cells, cytokines and chemokines production, a response induced by LPS and polyinosinic-polycytidylic acid [75]. It has been shown that activation and production of TNF, IL-1β, IL-6, IL-10, and IFN-α-inducible protein-10, IL-8 are inhibited by mycolactone in a dose-dependent manner [76, 77, 78]. This is an indication of mycolactone blocking pro-inflammatory cytokines and thwarts activation of oxidative species produced by monocytes or macrophages [79, 80, 81]. T cells are also immune-regulated through NF-κB and T cell receptor by represses TNF-α activity resulting in the blockage of IL-2 production, a T cell proliferation factor [82, 83]. These immunomodulatory activities triggered by mycolactone from *M. ulcerans* suggest dysregulation of cell-mediated immunity (CMI) in infected individuals [84, 85] (Figure **1**).

Destruction of Skeletal Muscles by Mycolactone in Extensive Ulceration in Buluri Ulcer Disease

Biological processes such as endocytosis, immune synapse formation, signalling, adhesion, and migration and maintenance of skin integrity are controlled by cytoskeleton through actin polymerization and dynamism [86, 87, 88]. In the presence of mycolactone, the epidermis becomes necrotized which characterized the extensive wounds in Buruli ulcers [89-94]. The mycolactone induces cytoskeletal rearrangements and detachment by seizing the actin-nucleating factors, the Wiskott-Aldrich syndrome protein (WASP) family [95-97]. The mycolactone activates N-WASP mimicking the Rho GTPase activation of WASP dependent actin polymerization [7, 97, 98]. This activation results in an uncontrolled activation and concentration of ARP2/3 in the perinuclear region which subsequently cause a defect in cell adhesion and migration due to abnormal assembly of actin in the cytoplasm [99-102] (Figure **2**).

Additionally, proteomic studies have shown that mycolactone affects cytoskeleton and collagen biosynthesis by altering the expression of Cytoplasmic dynein 1 intermediate chain 2 (Dync1i2), Cofilin 1 (Cfl1), Collapsin response mediator protein 2 (Crmp2), stathmin (Stmn1), Procollagen-Lysine,2-Oxoglutarate 5-Dioxygenase 1 & 3 (Plod1, Plod3), and Prolyl 4-Hydroxylase Subunit Alpha 1 (P4ha1) [97, 103]. The downregulation of Dync1i2, Cfl1, Crmp2 and Stmn1 modifies the function of microtubule-associated molecular motor dynein, a regulator of actin dynamics, and microfilament assembly or disassembly [97, 98, 103]. These compromise the transport elements involved in the Golgi apparatus, endosomes, lysosomes, microtubule assembly through the binding alpha/beta-tubulin heterodimers and microtubule-destabilizing oncoprotein [104]. These observations indicate that extensive wounds or ulcers in BU patients are partly due to cytoskeletal dysfunction [104-108].

The Future Perspective of Tackling Extensive Necrosis in Buruli Ulcer Cases

The current anti-mycobacterial antibiotics combination therapies have shown to be efficient against *M. ulcerans*, the causative organism of Buruli ulcer disease, however, 2-10% of the patients develop extensive ulcers after effective antibiotic treatment [109-111]. The matrix metalloproteinase-3 (MMP-3) and vascular endothelial growth factor (VEGF) remain down-regulated and inhibit wound healing [112-116]. These observations require new treatment options for the management of the destruction of cutaneous and subcutaneous tissues by *M. ulcerans.*

Targeting the Sec61 Translocon in the Buruli Ulcer Patients

It has been shown that mycolactone provokes a conformational change in the Sec 61 translocon by similarly binding to Sec61α subunit as cotransin (CT8) [67,117]. The binding interaction impedes the secreted and integral membrane proteins and prevents the process involved in binding immunoglobulin protein (BiP) [118-120]. The point mutations of R66I, R66G, and S82P in the Sec61α subunit prevent mycolactone bindings to the lumen, that is conferring resistance to mycolactone-mediated blockade of protein secretion [121, 122]. These single point mutations in the Sec61

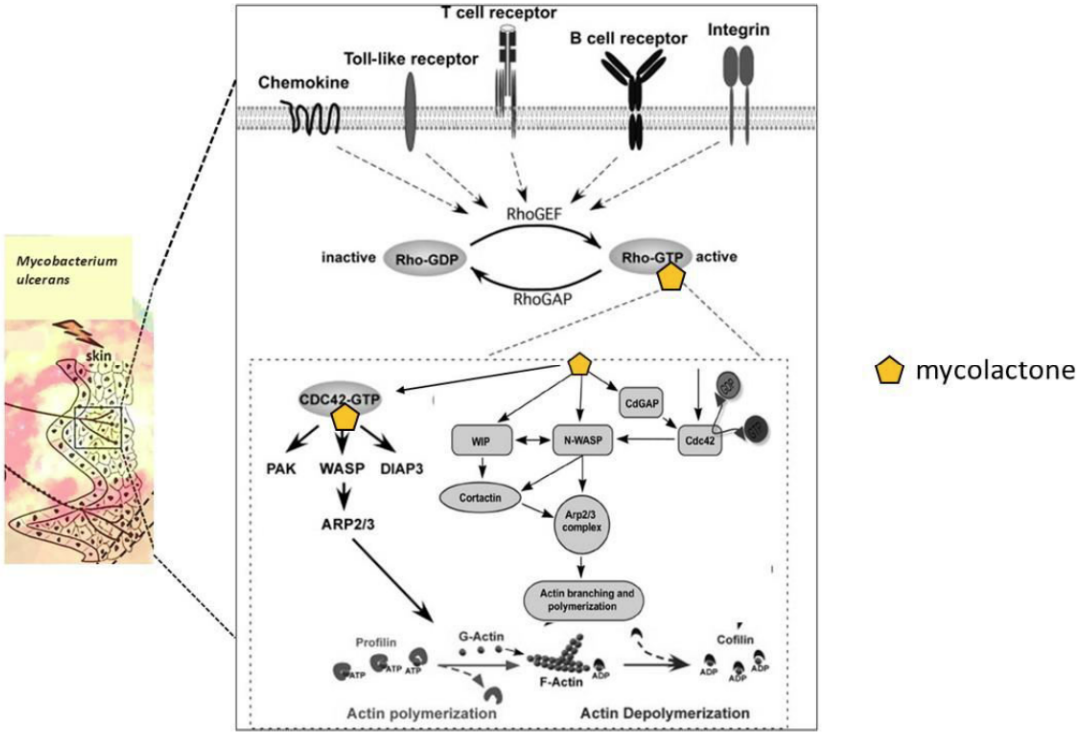

Figure 2: The mycolactone mimicking the Rho GTPase to activate N-WASP in the Wiskott-Aldrich syndrome protein (WASP) dependent actin polymerization pathway and induces cytoskeletal rearrangements and detachment by seizing the actin-nucleating factors, the WASP family in extensive necrosis in Buruli ulcer patients.

channel has shown to not affect the channel function [123-125]. Impressively, mycolactone failed to stimulate defect in the production of IFN-γ in cells expressing R66G-Sec61α, as both T cells and macrophages were able to establish their bactericidal capacity through the production of iNOS by LPS + IFN-γ–driven [122]. This finding has great implications for the future treatment and prevention of extensive ulceration in Buluri ulcer patients as establishing single point mutation in the Sec61 channel can restore the immune competence in BU patients.

Inhibiting Cytoskeletal Destruction by Mycolactone in Buluri Ulcer Patients

The current study has shown that coadministration of mycolactone and wiskostatin suppressed the degradation of the junctional organization, stratification of keratinocytes, epidermal thinning and epithelial cells rupturing [7, 126]. This finding provides us with future therapeutic potential to inhibit the extensive ulcers underling *M. ulcerans* infections [28, 127]. The design of mycolactone analogues that can competitively bind to N-WASP and displace mycolactone from the active site of N-WASP would be an ideal treatment option for Buruli ulcer patients.

Adaptation of Phage Therapy for the Treatment of *M. ulcerans and* Buluri Ulcer Disease

The control and prevention of the progressive and extensive ulceration caused by *M. ulcerans* should be the main target for future treatment in Buluri ulcer disease [128]. A lytic bacteria virus, phage D29 has been demonstrated to reduce *M. ulcerans* after a single inoculation on subcutaneous of experimental animal models [129-131]. The topical administration of phage is shown to offer an improved treatment option for ulcerative lesions [132-135]. The phage D29 has a broad virus particle adsorption rate as it can be detected in several organs including blood and spleen just a few hours after inoculating subcutaneously and persist in the draining lymph nodes for longer periods [136, 137]. It has been shown to induce cellular infiltration of macrophages and lymphocytes which increase the secretion of TNF, IFN-γ, and IL-10 to maintain the local mononuclear inflammatory response to *M. ulcerans* [138-140]. This observation could provide the best option for the treatment of mycolactone induce ulceration and BU.

Discussion

The current treatment of Buruli ulcer (BU) remains administered daily for 8 weeks of antibiotic therapy with

rifampin and streptomycin combination [141]. This kills *M. ulcerans* bacilli and promotes wound healing or reduces early lesions which can be resolved by surgery and skin grafting [142]. However, both treatments have challenges such as drug resistance, the ineffectiveness of surgery and skin grafting among patients with extensive ulceration and about 2-10% of the patients with early lesions results into extensive ulceration after antibiotic treatment [110]. To address the deficiencies in the treatment of extensive ulceration in BU disease requires a critical understanding of the mechanisms underlying its pathology.

The AT2R receptor blocking is a grey area that is yet to be exploited for the treatment of BU disease. The entire cellular pathway in the pathology of BU is mediated by AT2R receptor and its activation by mycolactone. Macrophage and monocyte infiltration are a cardinal feature for the control of infections which is characterized by elevated pro-inflammatory cytokines and chemokines [143]. However, the persistent existence of these factors is associated with tissues and organ damage in a chronic phase of infections [144]. Microphages which play a significant role in inflammation also express all the major components of the renin-angiotensin system (RAS), or renin-angiotensin-aldosterone system (RAAS), a hormonal mechanism involved blood pressure regulatory system [145]. The Angiotensin II receptors, the AT1 receptor and AT2 receptor play a role in the inflammatory response and its regulation during infections [146]. The macrophages produce pro-inflammatory cytokine through Toll-like receptor-4 (TLR4) activation signalling via lipopolysaccharide (LPS) [147]. The AT1 receptor upregulates TLR4, thus aggravating pro-inflammatory cytokine production by macrophages. On the other hand, the AT2 receptor attenuates pro-inflammatory cytokines by inducing IL-10 production in LPS-activated macrophages [148]. The AT2 receptor actives a persistent increase in phosphorylation of extracellular signal-regulated kinase (ERK-1/2) which boost IL-10 production in macrophages [149]. The mycolactone-producing *M. ulcerans* exploits the ERK-1/2 activation pathways amassed pro-inflammatory cytokines resulting in the tissue damage and extensive ulcers in BU patients. Currently, not many studies have been done in this area to harness a potential treatment for extensive ulceration in BU patients.

Another important area which has not yet been exploited for the management of extensive ulcers in BU patients is actin polymerization signalling pathways. The uncontrol activation ARP2/3 through the mimicking the Rho GTPase by mycolactone play an important role in the pathogenesis of ulcer in BU. The actin cytoskeleton is essential for the maintenance of cell morphology and motility, therefore breaching its integrity is a problem in wound healing in extensive ulcers in BU disease [150]. Future studies into the mechanisms for the uncontrol activation ARP2/3 and inhibiting some of the upstream signalling components could serve as Achilles heel for stabilizing and inducing autoinhibited conformation of N-WASP in the BU disease.

CONCLUSION

To date, the treatment of extensive ulceration in Buluri ulcer disease is still very challenging. As the treatment option remains surgical resection and skin grafting which leaves scars and disability. There is no vaccine for BU disease, although, Bacille Calmette-Guérin (BCG) vaccination has shown to temporary protect against BU disease. The current drug treatment remains a combination therapy of rifampicin and streptomycin. Although this combination therapy decreases relapse rate, it is not without drawbacks such as inability to resolve disability, rapid drug resistance, administration and compliance challenges. The review exploited the current knowledge of the mechanism underlying the extensive ulcerations or lesions caused by mycolactone-producing *M. ulcerans* to suggest possible areas of interest for the future treatment of BU disease. The future studies on blocking the AT2R receptor and the uncontrolled activation ARP2/3 could serve as an important area for treatment and management of extensive ulceration in BU disease.

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