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Progress in research on immunological mechanism of leprosy

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ABSTRACT

Leprosy is a chronic infection acquired after getting exposed to *Mycobacterium leprae (M.Leprae)*, especially via contact or through nasal secretions of the affected hosts. Ninety five percent of the entire population is naturally immune to leprosy due to the inherent natural immunity against the pathogen. The components of *M.leprae* include the lipoarabinomannam, the mycolyl-arabinogalactan-peptidoglycan complex, the protein-peptidoglycan complex, and muramyl dipeptide which are potent inducers of inflammatory mediators, especially TNF-α. Immunologically and clinically leprosy is classified into the Tuberculoid pole, Borderline tuberculoid, Mid borderline, Borderline lepromatous and lepromatous pole. In the Tuberculoid pole, the naive CD 4 lymphocytes differentiate into either T_h1 or T_h17 cells. Th1 secretes IL-2, TNF-α, IFN-γ, and Th17 secretes IL-17, IL- 21 and TNF-α. In the Lepromatous pole, the naive CD 4 lymphocytes differentiate into Th2 cells, which secrete IL-1β, IL-4, and IL-6 that promotes antibody formation. Knowing about the immune cells, mechanisms of their interaction and substances responsible in leprosy reactions can provide a potential way of enhancing the immune response to *M.leprae* especially in the Lepromatous pole or ways of preventing the nerve damage and skin lesions in leprosy.

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INTRODUCTION

Leprosy is a chronic infection acquired by being exposed to *M. leprae*, an acid fast bacillus. *M.leprae* is a slow growing organism with a longer incubation period. Initially it could not be cultured in vitro[1,2] because of its genetic composition which allows it to depend on the host energy metabolism for survival. Genetic studies reveal that it has less than 50 % coding capacity and a lot of pseudogenes with the rest being responsible for its in vivo survival and pathogenesis in the host.[3] The identification of the nine banded armadillos and *M.leprae* being able to infect the species has enabled the identification of the immune cells involved in the leprosy reactions with the development of appropriate drug combinations to improve on the health outcome. Since the introduction of the Multidrug Therapy (MDT) for leprosy, it's prevalence in the endemic regions has been reduced to less than 1000 cases per 10,000 population. Lepra reactions have been shown to occur before, during and after the MDT course for leprosy, worsening the nerve and skin lesions. Given that *M. leprae* has a predilection to the peripheral nerve Schwann cells, this leads to the severe nerve lesions, with consequent motor and sensory loss, muscle atrophy, and deformities, especially in Lepromatous leprosy cases. This occurs due to the exaggerated immune response to the Mycobacterium leprae. There is diverse immune responses towards *M.leprae* both the cell mediated and humoral mediated, with the cells involved being CD 4^+ T cells and antibodies respectively. The antibody response leads to more severe nerve and skin lesions with systemic manifestations. The histopathology of tissues appears multibacillary which makes these cases very contagious either through the skin contact or nasal secretions. This indicates the T_h2 mediated immune reaction is not effective in combating *M.leprae*. Finding ways to shift the immune response from a T_h2 to T_h1 mediated will reduce the bacillary load in Lepromatous cases and prevent the systemic involvement of leprosy. The T_h17

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response appears to enhance the type 1 reaction. It offers a potential target into either enhancing the immune response in case of lepromatous pole or regulating the exaggerated response in some cases.

MYCOBACTERIUM LEPRAE

The components of the *M.leprae* includes: the lipoarabinomannan (a lipopolysaccharide-like component), the mycolyl-arabinogalactan-peptidoglycan complex, the protein-peptidoglycan complex, and muramyl dipeptide all of which are potent inducers of the inflammatory mediators, especially the TNF-α.[4]

Due to its lipid content on the cell wall, M.leprae can leave persistent antigens on the nerves and skin which will continuously stimulate the host immune reactions, even after the completion of multiple drug therapy.[5]

GENETIC DETERMINANTS: SUSCEPTIBILITY TO LEPROSY

Ninety five percent of the entire population is naturally immune to leprosy,[6] which is due to the inherent natural immunity against the *M.leprae*. Various genes regulating both innate and adaptive immune response influence the disease outcome. The TLRs, NOD2 & MRC1 (mannone receptor type 1) are responsible for pattern recognition receptors and mycobacterial uptake, promoting autophagy, and the LTA4H regulates lipoxin A4 levels. The stimulation of these pathways regulates the cellular metabolism upon infection, and activates cytokine production through the NF-κB and the vitamin D- vitamin D receptor pathways. The PARK2 gene regulates the host cells apoptosis. The TNF, LTA & IFNG genes triggers and maintain the formation of granulomas. The HLA gene in chromosome 6, IL-10 and the TNF/LTA axis, the IFNG/IL-12 axis induces the differentiation of naive CD 4 lymphocytes. Single nucleotide polymorphism in these genes influences the immune response and subsequent susceptibility to *M.leprae* and its antigens.[7-11]

MODES OF TRANSMISSION

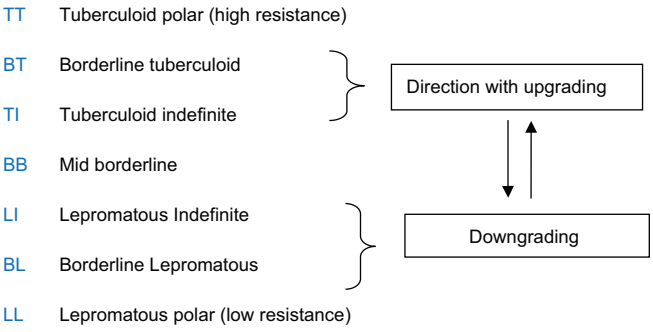
Leprosy is a communicable disease and can be transmitted from person to person via the respiratory droplets and skin contact with the infected people. *M.leprae* has been shown to be found in the nasal mucosa and skin, and this can be shed off and acquired by close contacts.[12-17] However the Tuberculoid pole of leprosy is the least communicable of all the communicable diseases and the Lepromatous pole is the most contagious. Avoiding contact can lessen the chance of acquisition especially hosts with lepromatous leprosy.

RIDLEY & JOPLING CLASSIFICATION OF LEPROSY

Mycobacterium leprae has been shown to be able to stimulate a wide range of host innate and adaptive immunity, both cell-mediated and humoral mediated response, with the predominance of the $CD4^+$ lymphocytes and antibodies respectively.[18]

This has led to an immunological classification of leprosy into five forms: tuberculoid polar leprosy (TT), borderline tuberculoid (BT), midborderline (BB), borderline lepromatous (BL), and lepromatous pole (LL)[19-21] as shown in table below. Due to the difference in immune response at the two poles, biopsy samples shows the tuberculoid pole is paucibacillary and the lepromatous pole is multibacillary, fewer bacilli and more bacilli respectively. The skin lesions in the multibacillary form are less, usually localized and in the paucibacillary forms they are multiple and widespread. The leprosy reactions in the two poles occur regardless of viability of M.leprae.[22]

MODIFIED RIDLEY & JOPLING'S CLASSIFICATION



IMMUNOLOGY: LEPRAE REACTIONS

The tuberculoid pole of leprosy has a $CD\ 4^+$ lymphocyte mediated, delayed type hypersensitivity.[17, 23-26] The naive CD 4 T lymphocytes upon stimulation differentiate into either T_h1 or T_h17 T lymphocytes depending on the cytokine environment.[27]

Type I reaction (reversal reaction)

T_h1 secretes IL- 2 that leads to more differentiation of the naive CD 4 cells into T_h1 cells and the IFN-γ, TNF-β which signals for macrophage activation from the monocytes.[25,26] T_h17 has been implicated in the type I reaction to *M.leprae*. The Foxp3 staining has been observed,

which is a transcription factor regulating the differentiation of T regulatory cell (CD 4^+ CD 25^+).[28]

T regulatory cells are involved in down regulating the immune response to avoid exaggerated response including the T_h17 mediated response which seems to play a role in the type I reaction to M.leprae.[29-32] T_h17 is stimulated from the naive CD 4 cells by IL-6, IL-21 and TGF-β.[33-43]

The mature T_h17 then secretes IL-17, which is a pro-inflammatory cytokine. Also it secretes IL-21, showing that this cytokine has an autocrine function on T_h17.[44] IL-23 are necessary for the expansion of the already differentiated T_h17 cells and in maintaining IL-17 secretion. It achieves this by binding to the IL-23R on the surface of the T_h17 cells.[38,44-47] IL-6, IL-21 stimulates the expression of IL-23R.[48] The IL-17, IL-21 then mediates inflammatory response against the pathogen.[49] Mature T_h17 cells have the ability to secrete TNF-α, and also it can stimulate other immune cells to secrete the cytokine.[50,51] T regulatory cells have been reported that they can be genetically reprogrammed. Inducible T regulatory cells, in presence of TNF-α, IL-6 can be reprogrammed to T_h17 phenotype. Naturally occurring T regulatory cells can be stimulated to secrete IL-17 and to down regulate their Foxp3 expression in the presence of IL-6, IL- 23 and IL-1.[52-55] This can serve as a potential therapeutic target into enhancing the immune response to *M.leprae*, or suppressing the exaggerated leprosy reactions. Appropriate reprogramming factors should be sought for. The monocytes then cross the endothelium, become macrophages with a capacity to carry out phagocytosis. The phagocytosis by macrophages is mediated by complement receptors CR 1 (CD 35), CR 3 (CD 11b/CD 18), and CR 4(CD 11c/CD 18) and is regulated by protein kinases.[56,57] This leads to granuloma formation, with differentiated macrophages, epithelioid and giant cells with a reduction in the bacillary load (paucibacillary).

The T_h1, T_h17 mediated response is effective against *M.leprae*. It's an upgrading immune response that leads to the tuberculoid pole. Due to the predilection of *M.leprae* to the extreme cool ends and in the nerve Schwann cells, the type I reaction leads to severe nerve damage, characterized by nerve thickening with lose of motor and/or sensory activity in the affected regions, edema and erythematous skin lesions. Systemic involvements are rare.

Type II reaction (Erythema nodosumLeprosum)

The type II reaction, erythema nodosumleprosum occurs in the lepromatous pole. It's a T_h2 mediated response with the involvement of the antibodies.[5,58] Some studies have shown a ratio of 1: 2 for CD 4^+: CD 8^+ T lymphocytes.[58] The cytokines involved include IL-1β, IL-4, IL-6,and TNF-α.[25,59-62] They signal for the synthesis of specific antibodies from the B lymphocytes which are specific to the epitopes on the *M.leprae*. Immune complexes are formed which are eliminated by the complement activation.[63] The large amount of TNF-α observed has been linked to the chemotaxis of neutrophils into the inflammatory sites.[64] The expression of the E-selectin leads to the attachment of the polymorphonuclear cells to the endothelial cells leading to diapedesis, and their infiltration into the infected tissue. The infiltration by neutrophils also leads to tissue damage due to the lysosomal enzymes that they secrete. The damage is especially in the peripheral nerves and the extremities, with loss of motor activities and/or sensation and multiple skin lesions characterized by erythema, edema with systemic manifestations of fever, arthralgia, weight loss, lymphadenopathy, anorexia, and edema. The type II reaction is not effective against *M.leprae* as biopsy samples of individuals with the lepromatous leprosy shows cells with multiple acid-fast bacilli implying they have a specific energy to *M.leprae*.

The leprosy reactions occur before, during and after completion of multidrug therapy.[5] It's the main reason for the neuropathy and the skin deformation that befalls on the leprosy infected individuals. Intake of corticosteroids, emotional/physical stress, and pregnancy predisposes to these reactions.[65] Individuals with HIV/AIDS have not shown a higher susceptibility to leprosy, even with the reduced CD 4^+ T cell count to100 cells/μL. However some studies have shown that leprosy reactions can occur in individuals co-infected with HIV after antiretroviral therapy.

CONCLUSION

The T_h17 lymphocytes offer a new therapeutic potential into enhancing the immune response in the Lepromatous pole cases. The T_h1 and T_h17 response is more effective and this reduces on the nerve, skin lesions and the systemic effects of *M.leprae* infection. Upgrading the response will improve on the management of leprosy.

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YL - Concept and design of the study, critical revision of the manuscript; **KKB -** Reviewed the literature and manuscript preparation.

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