Pathogenesis of Leprosy

5

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Leprosy pathogenesis has not been definitively understood. However, three points are indisputable: the etiological agent is *Mycobacterium leprae* (*M. leprae*), the disease develops in susceptible individuals, and in endemic countries the environment (low socioeconomic status and overcrowding) plays a role in the transmission of the infection.

Leprosy disease and clinical manifestations are the result of a dynamic interactive process between *M. leprae* and the cell-mediated immunity (CMI) of genetically predisposed subjects. The vast majority (95%) of the exposed population is not susceptible to the disease; of the remaining 5%, the larger part successfully eliminates *M. leprae* through an efficacious immune response, while only a relatively small percentage (1%) develops leprosy [1–3].

M. leprae has some peculiarities (Chap. 2): it is the only bacterium with neurotropism that is more appropriate for peripheral nerves, and it is not cultivable in any known artificial media. There are no suitable animal models for experimental studies. Leprosy patients are the only reservoir of significance, despite the fact that leprosy-like infection has been reported in a few wild armadillos in the south of Texas and Louisiana. Although the exact mode of transmission is not known, untreated multibacillary patients are the main source of infection as they can discharge up to 10^7 bacilli/day by droplets from the nose, from the mouth, or from ulcerated nodules (portal of exit). Protected from ultraviolet radiation and in a hot wet climate, *M. leprae* can also survive for 6 weeks in soil [4–6].

Overcrowding and poor socioeconomic conditions favor leprosy transmission. The portal of entry of organisms into the body is still debated. The mucosa of the

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upper airways is considered the main route of entry. Published reports of initial leprosy lesion developing locally following accidental inoculation, tattooing, vaccination, and dog bites in humans suggest that *M. leprae* can enter through the skin. The exact incubation time is unknown and can vary from a few months until 20 years or more [1–3]. The portal of entry of the bacillus is one of the factors that influence the position of the patient in the leprosy spectrum. Transcutaneous inoculation is correlated to the indeterminate form (I) and to the hyperergic forms (TT, BT) with a shorter incubation period. Entry of the bacillus via the mucosa of the upper respiratory tract is correlated to hypoergic disseminated forms (BB, BL, LL) with longer incubation periods [7].

Once *M. leprae* is inside the subject, it enters lymph and blood vessels to reach its target: the Schwann cells. *M. leprae* enters Schwann cells by binding the G domain of the a2 chain of laminin 2, a component of their basal lamina. This form of laminin is restricted to peripheral nerves, which explains the specific tropism of *M. leprae*. The Schwann cells engulf *M. leprae* within their phagosomes, but cannot destroy *M. leprae* because Schwann cells lack lysosomal enzymes. Schwann cells are sanctuaries where the bacilli are protected from macrophages and can replicate slowly over years. *M. leprae* seems to have abandoned genes normally required for replication ex vivo and assumed a unique ecological niche with a very limited host range and the need for growth within cells. Only genes essential for the formation of a mycobacterial cell wall have been retained. The leprosy bacillus might therefore be dependent on host metabolic products, which could explain its long generation time and inability to grow in culture [1, 6].

Host genetic factors influence the CMI and have a partial effect on both the development of leprosy and the pattern of disease (Chap. 3). The nature of the adaptive T cell response is determined in part also by the instruction of the innate immune response (Chap. 4). Moreover, besides typical TH1/TH2 responses, also natural killer T cells (NKT), FOXP3+ regulatory T (Treg) cells, and T helper 17 cells (TH17) and even B cells might be implicated in leprosy pathogenesis (Chap. 4) [8, 9].

The CMI determines either the elimination of the bacillus or the development of the disease. In fact, at some stage, infected Schwann cells process and present antigenic determinants of *M. leprae* to antigen-specific T lymphocytes that initiate a chronic inflammatory granulomatous reaction (Chap. 4). *M. leprae* may migrate outside the nerves to endothelial cells or may be phagocyted by macrophages that act as antigen-presenting cells [10]. At this exact point, the CMI plays a pivotal role. Subjects with a predominant Th1 immune response will develop a high degree of CMI with epithelioid granuloma formation that will destroy all the bacilli with either healing or development of localized disease (tuberculoid leprosy, TT) [11]. In TT M1 macrophages produce tumor necrosis factor-alpha (TNF-a) and interferon-gamma (IFN-γ) and generate free radicals that destroy *M. leprae*. LL shows a predominance of two populations of macrophages: M2 macrophages that induce the production of interleukin (IL)-10, transforming growth factor (TGF)-ß, and fibroblast growth factor (FGF)-ß, which contribute to the immunosuppressive response as well as tissue repair. M4 macrophages produce IL-6, TNF-a, MRP8, matrix

metalloproteinase (MMP)7, and MMP12; this subpopulation is less effective in the elimination of *M. leprae*, and M4 macrophages can induce the establishment of a regenerative environment and remodeling of the extracellular matrix, which are important for the pathogen–host interaction during infection by *M. leprae* [12, 13].

TT has a short incubation time (2–3 years) and remains circumscribed to the skin and nerves of a limited area of the body. In fact, macrophages of TT patients are able to annihilate bacilli, to completely process the mycobacterial antigens, and to obtain normal complete antigenic information and CMI immune response. On the contrary, individuals with a predominant Th2 response will develop a weak CMI without forming an efficacious granulomatous response and an increased humoral immunity: bacilli will survive and replicate, developing systemic disease (lepromatous leprosy, LL) [2]. Macrophages of LL patients engulf bacilli but are only able to partially destroy *M. leprae*, probably because of a deficit of lysosomal phospholipases, resulting in incomplete antigenic information and accumulation of mycobacterial phospholipids as cytoplasmic droplets (lepra cells, described by Virchow in 1863) [14]. Bacilli age and replicate over the years (incubation time 10–20 years) outside the nerves (in the dermis around the superficial vascular plexus) in the cooler areas of the skin and disseminate through the blood to the lymph nodes, liver, and spleen. Skin lesions derive from progressive accumulation of *M. leprae* and macrophages in the skin. In contrast to patients who present a vigorous CMI response, patients with anergy against *M. leprae* can be infected also after short contact with an infected subject [1, 3].

As seen, the CMI determines the clinical form of the disease, which varies along a spectrum (Chap. 6) that starts with a tuberculoid pole, goes through borderline cases, and ends with a lepromatous pole (Chap. 6). The spectral manifestations of leprosy are continuous, and there is a gradation in the clinical manifestations of the disease (Chap. 10). Patients with tuberculoid leprosy (TT) have a high degree of CMI, having one or two skin lesions with monolateral asymmetrical distribution, with no or few bacilli and epithelioid granuloma on histopathology (Chap. 12). Moving in the spectrum toward the lepromatous pole, the CMI decreases progressively; borderline tuberculoid (BT) patients have few lesions, asymmetrically distributed, with no or few bacilli and epithelioid granulomas on histopathology. In mid-borderline (BB) patients, the lesions become symmetric, there is a discrete number of bacilli, and granulomas show both epithelioid and macrophage features. CMI progressively decreases, so that borderline lepromatous (BL) and lepromatous leprosy (LL) patients show many symmetrically distributed lesions with many bacilli and macrophage granuloma on histopathology. BL and LL have a low CMI and increased humoral immunity. In each of the five forms, the clinicobacteriological and histopathological parameters have to agree with each other (Chaps. 10 and 26) [15–17]. Different sophisticated immunological studies on lymphocytes, cytokines, and molecular receptors in patients have confirmed that the immune response determines the clinical and histological manifestations of leprosy in all its different forms (Chap. 4) [6].

In short, the spectrum is determined by the balance between CMI and bacilli: high CMI response means low number of bacilli (paucibacillary leprosy: TT and

part of BT); low CMI response means high number of bacilli (multibacillary leprosy: BB, BL, LL, and part of BT). In the Ridley–Jopling spectrum, clinical, bacteriological, and histopathological parameters always have to correlate [2].

Patients of the two poles (TT and LL) have immunologically stable disease, while borderline patients (BT, BB, and BL) can shift from one form to another in the presence of trigger factors (immunosuppressive drugs, concomitant diseases, stress, and pregnancy) and can frequently manifest acute nerve damage related to type 1 reaction. Nerve damage during type 1 reaction is associated with an abrupt increase in CMI against *M. leprae* antigenic determinants released by Schwann cells. The nerve is damaged as an innocent bystander during the immune response [2].

Indeterminate leprosy represents an early stage of the disease in which the degree of CMI is still not clear. Patients with indeterminate leprosy can either heal or might develop leprosy and move on the spectrum (Chap. 6) [2, 18].

M. tuberculosis infection and bacillus Calmette–Guérin (BCG) vaccination protect against leprosy [1–3, 6].

References

1. Ridley DS. Pathogenesis of leprosy and related diseases. London: Wright; 1988.
2. Ridley DS. Histological classification and the immunological spectrum of leprosy. Bull WHO. 1974;51:451.
3. Job CK, Robert C. Hastings “Leprosy”. 2nd ed. Edinburgh: Churchill Livingstone; 1994.
4. Scollard DM, Adams LB, Gillis TP. The continuing challenges of leprosy. Clin Microbiol Rev. 2006;19:338–81.
5. Goulart LR, Goulart IM. Leprosy pathogenetic background: a review and lessons from other mycobacterial diseases. Arch Dermatol Res. 2009;301:123–37.
6. Britton WJ, Lockwood DN. Leprosy. Lancet. 2004;363:1209–19.
7. Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into foot-pad of mice. J Exp Med. 1960;112:445–54.
8. Fabel A, Giovanna Brunasso AM, Schettini AP, Cota C, Puntoni M, Nunzi E, Biondo G, Cerroni L, Massone C. Pathogenesis of leprosy: an insight into B lymphocytes and plasma cells. Am J Dermatopathol. 2019;41:422–7.
9. Modlin RL. The innate immune response in leprosy. Curr Opin Immunol. 2010;22:48–54.
10. Scollard DM. The biology of nerve injury in leprosy. Lepr Rev. 2008;79:242–53.
11. Massone C, Nunzi E, Ribeiro-Rodrigues R. T regulatory cells and plasmacytoid dendritic cells in Hansen disease: a new insight into pathogenesis? Am J Dermatopathol. 2010;32:251–6.
12. de Sousa JR, Lucena Neto FD, Sotto MN, Quaresma JAS. Immunohistochemical characterization of the M4 macrophage population in leprosy skin lesions. BMC Infect Dis. 2018;15(18):576.
13. Röltgen K, Pluschke G, Spencer JS, Brennan PJ, Avanzi C. The immunology of other mycobacteria: M. ulcerans, M. leprae. Semin Immunopathol. 2020;42(3):333–53.
14. Abulafia J, Vignale RA. Leprosy: pathogenesis updated. Int J Dermatol. 1999;38:321–34.
15. Nunzi E, Fiallo P. La lebbra per immagini. Florence: Technological Research Srl; 1997.
16. Nunzi E, Fiallo P. La lebbra. In: Giannetti A, editor. Trattato di dermatologia. 2nd ed. Padova: Piccin; 2001.
17. Moschella SL. An update on the diagnosis and treatment of leprosy. J Am Acad Dermatol. 2004;51:417–26.
18. Alemu Belachew W, Naafs B. Position statement: leprosy: diagnosis, treatment and follow-up. J Eur Acad Dermatol Venereol. 2019;33(7):1205–13.