Molecular basis of the interaction of *Mycobacterium leprae* with peripheral nerve: implications for therapeutic strategies

A. RAMBUKKANA
Laboratory of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York, USA

Invasion of the Schwann cell of the peripheral nervous system by *Mycobacterium leprae* represents a crucial, early step leading to nerve damage in leprosy patients.[1,2] Currently, more than one-quarter of all reported leprosy patients worldwide have disabilities, and nearly half among them are severely disabled.[3] Although patients can be cured of infection by multidrug therapy, nerve damage and the resulting deformities of leprosy can continue during and even after antimicrobial therapy. Most workers believe that the best strategy for preventing such long-term consequences of leprosy as disabilities lies in detecting and preventing the disease at an early stage. Therefore, the early molecular events of the interaction of *M. leprae* with peripheral nerve are important, as an aid to the development of novel strategies designed to prevent the early interaction of *M. leprae* with peripheral nerve.

Identification of the G-domain of laminin-2 in the basal lamina of the Schwann cell and the laminin receptor, α-dystroglycan, as neural targets of *M. leprae*[4,5] has opened up a new area of scientific inquiry relevant to the pathogenesis of nerve damage in leprosy. In addition to these host factors, specific bacterial components are responsible for the neural tropism of *M. leprae*. Our preliminary studies suggest that *M. leprae* is equipped with multiple surface molecules, both specific to *M. leprae* and common to the cell wall of other mycobacterial species, which interact with laminin-2 in the basal lamina of Schwann cell-axon units.[6,7]

We are currently investigating the interactions of these surface-components of *M. leprae* with the laminin-2G domain at both the molecular and the cellular levels. We are also attempting to solve the three-dimensional structures of these interactions, using the known crystal structures of individual modules of the laminin-2G domain. These studies may have significant implications for developing novel drugs and vaccines capable of blocking the attachment of the organisms to the Schwann cell-axon units, thereby preventing the neurological damage before immune-mediated injury aggravates the disease. A major research program is also focused on the molecular basis of nerve degeneration in early *M. leprae* infection. Identification of the principal factors responsible for the nerve damage at an early stage will facilitate development of therapeutic strategies to prevent the neurological injury. These studies will also provide clues to the unexplainable nerve damage that continues in patients who are 'cured' of leprosy. Obviously, alternative approaches, other than multidrug therapy, are necessary for the management of nerve damage in leprosy patients. In addition, from the neurobiological point of view, uncovering the mechanisms by which *M. leprae* manipulate the targeted neural cell molecules and their associated functions will

generate important tools for dissecting the complex mechanisms of nerve function, which may have implications beyond leprosy.

References

[1] Stoner GL. Importance of the neural predilection of *Mycobacterium leprae* in leprosy. *Lancet*, 1979; **10**: 994–996.
[2] Job CK. Nerve damage in leprosy. *Int J Lepr*, 1989; **57**: 532–539.
[3] World Health Organization. *Weekly Epidemiol Rec*, 1998; **76** (Suppl. 2): 133–134.
[4] Shimoji Y, Ng V, Matsumura K, Fischetti VA, Rambukkana A. A 21-kDa surface protein of *Mycobacterium leprae* binds peripheral nerve laminin-2 and mediates Schwann cell invasion. *Proc Natl Acad Sci USA*, 1999; **96**: 9857–9862.
[5] Rambukkana A, Salzer JL, Yurchenco PD, Tuomanen EI. Neural targeting of *Mycobacterium leprae* mediated by the G domain of the laminin-alpha2 chain. *Cell*, 1997; **88**: 811–821.
[6] Rambukkana A, Yamada H, Zanazzi G *et al*. Role of alpha-dystroglycan as a Schwann cell receptor for *Mycobacterium leprae*. *Science*, 1998; **282**: 2076–2079.
[7] Rambukkana A. How does *Mycobacterium leprae* target the peripheral nervous system? *Trends Microbiol*, 2000; **8**: 23–28.

DISCUSSION

Dr Kaplan: How selective is the binding of PGL-I to Schwann cells? What other cells have you studied?

Dr Rambukkana: The Schwann cell alone does not secrete laminin, but only after it has ensheathed an axon. The laminin molecule is composed of three chains, and assembly occurs within the Schwann cell. Only then is laminin secreted so that it can interact with collagen and produce the basal lamina. Muscle cells secrete the same laminin, and we find slight binding of PGL-I to muscle cells.

Dr Colston: I remember some work by Dr Job that showed *M. leprae* within muscle cells. It may be that the mechanism of entry of *M. leprae* into the cell is not entirely specific to Schwann cells.

Dr Lockwood: What is the source of your Schwann cells?

Dr Rambukkana: We work with cells from the rat. However, the laminin is structurally similar to that of human Schwann cells. Unfortunately, we can't work with human Schwann cells in our system.

Dr Sengupta: How specific is the binding of PGL-I to laminin?

Dr Rambukkana: The PGL-I derived from BCG does not bind.

Dr van Brakel: You suggested that the immune system may not play a role early in neuropathy. Do you believe that the neuropathy results directly from perturbation of the Schwann cells?

Dr Rambukkana: We have some preliminary evidence that simply the attachment of the organism to the basal lamina strongly activates Schwann cells, which lie directly on the myelin sheaths.

Dr Kaplan: If you infect Schwann cell cultures *in vitro*, the *M. leprae* do not enter the cells, nor do they enter cells which are coated with laminin. Is is possible that the organisms must somehow breach the outer layers before encountering a specific receptor that mediates phagocytosis?

Dr Rambukkana: There may exist other mechanisms. We have some evidence that bacterial components are capable of degrading laminin.