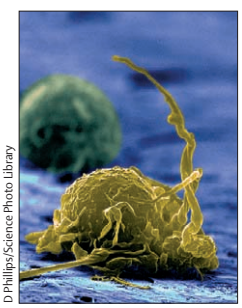
Mycobacterium-associated immune reconstitution disease: macrophages running wild?



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In an insightful review, Stephen Lawn and colleagues[1] describe the immunological mechanisms, diagnosis, manifestations, and possible treatment of mycobacterium-associated immune reconstitution disease (IRD) in HIV patients receiving antiretroviral therapy. Like most authors, Lawn and colleagues focus on the functional reconstitution of the CD4 T lymphocyte as a driving factor in IRD. Although this is certainly a promising research strategy, we believe that much may be gained by broadening the focus of IRD research and taking a closer look at, for example, macrophages (and monocytes as their less differentiated counterparts) as possible driving cells behind mycobacterium-associated IRD.

The essential role of macrophages during mycobacterial infections—and most notably during infections with *Mycobacterium tuberculosis*—has been described previously, and was reviewed extensively by Kaufmann.[2] Essentially, macrophages (most commonly alveolar macrophages) are the most important target cells for *M tuberculosis* infection. The bacteria survive inside the macrophage in maturation-arrested phagosomes; mycobacterium-specific CD4 and CD8 T lymphocytes are recruited, resulting in inflammation and granuloma formation, both of which constitute the basis of the various clinical presentations described.[2]

Microarray-based research has shown that *M tuberculosis* induces profound changes in the expression pattern of many macrophage-associated genes in infected macrophages. In this fashion, Wang and co-workers[3] showed that *M tuberculosis* induces cytokines such as interleukin 8, chemokines such as MIP1α and RANTES, the interferon-response gene *Stat1*, and perhaps surprisingly 22 unique ribosomal proteins—such data can be an interesting first step in the search for molecular markers for certain disease states. In general, markers of both immune suppression and immune activation are seen during active pulmonary tuberculosis, leading to the paradoxical situation of a concomitant failing immune control and a pathological state of inflammation.[4]

In the case of HIV infection, macrophages are among the first cells to be infected during sexual transmission, and they constitute an important tissue reservoir in various organs—including the lungs and the central nervous system—during the chronic state of the disease. Through the CD4 receptor and the CCR5 co-receptor, the virus gains access to the cell; however, by contrast with CD4 T lymphocytes, infected macrophages do not die as a result of infection, but instead develop several severe dysfunctions. Examples of such dysfunctions are their reduced efficacy of response against certain pathogens,[5] their function as a persisting reservoir for the virus during antiretroviral therapy,[6] their involvement in the infection and killing of CD4 T lymphocytes,[7] and their driving role in the development of HIV-associated dementia.[8]

Tentative microarray-based experiments indicate that HIV modifies the expression pattern of a large number of monocyte/macrophage-associated genes. In-vitro HIV infection of monocyte-derived macrophages appears to induce many genes of the interferon system,[9] while monocytes from HIV-infected patients display a gene expression pattern associated with a chronic inflammatory invasive phenotype.[10]

It has been shown by Freedman and colleagues[11] that productive infection of macrophages by HIV is not needed to induce dysfunctional behaviour: triggering the CCR5 and CXCR4 co-receptor by HIV gp120 seems to be sufficient to modulate macrophage activation. This observation is supported by Cicala and colleagues,[12] who showed that in-vitro gp120 stimulation of monocyte-derived macrophages is sufficient to induce profound changes in macrophage gene expression patterns. Additionally, HIV-induced dysfunction and aberrant gene expression profiles in the monocyte population in the peripheral blood are also described,[10,13] despite the fact that only a small fraction of the monocyte population is actually infected, again indicating that receptor triggering by viral antigens (and not necessarily direct infection) is sufficient to induce differential monocyte/macrophage activation.

Considering their crucial role during the pathogenesis of both HIV and mycobacterial infections, we find it probable that macrophages have

an essential role in mycobacterium-associated IRD. This hypothesis is supported by the observation, as Lawn and colleagues indicate, that macrophages were implicated in paradoxical reactions to tuberculosis treatment in HIV-seronegative patients with pulmonary tuberculosis in South Africa.[14] Furthermore, it is described by Lawn and colleagues that IRD often occurs within the first weeks after the initiation of antiretroviral therapy and before a substantial increase in CD4 T lymphocyte count is witnessed. Additionally, a large retrospective cohort study by Shelburne and co-workers[15] shows that a rapid initial fall in viral load is a much better predictor of IRD than a rapid increase in CD4 count, indicating that a (partly) reconstituted CD4 T lymphocyte population is possibly not the most important causative agent of IRD.

Instead, we suggest that monocytes and macrophages from HIV patients in advanced stages of the disease, and especially from patients coinfected with mycobacteria, display dysfunctional/immunosuppressed behaviour. These dysfunctions are the result of a combination of immunoregulatory effects mediated by mycobacteria[4] and HIV, and are reversed during antiretroviral/antimycobacterial therapy. This functional recovery could result in an excessive activation of the macrophage in the presence of mycobacterial antigens, leading to the various manifestations of IRD described in detail by Lawn and colleagues.[1]

The drop in both viral load and amount of free viral antigens during the first days and weeks of antiretroviral therapy could be a possible mechanism for the swift recovery of the macrophage function. As the monocyte/macrophage encounters less triggers for the different receptors, the aberrant genetic expression profile and general dysfunction/suppression of the monocyte/macrophage is abolished.

In conclusion, we can state that current studies on IRD, focusing on reconstitution of T lymphocyte number and function, are an interesting and exciting field of research. However, we feel that other cell types besides the T lymphocyte should not be discounted in attempts to further analyse and characterise IRD. An interesting tool to verify the putative monocyte/macrophage contribution to IRD, and indeed to identify possible diagnostic or even prognostic molecular markers for IRD could be microarray-based analysis of monocytes/macrophages from HIV-infected patients experiencing IRD.

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