Ageing dangerously; homing of senescent CD8 T cells in cutaneous Leishmaniasis.

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Summary

Both $CD8^+$ T cells and NK cells contribute to the immune response against the protozoan *Leishmania* parasite. Both are able to generate IFN-γ and both display cytotoxic features. These features may enable them to not only contribute to parasite clearance but also to cause immune-mediated pathology. This pathology is evident, for example, in the *Leismania*-induced skin lesions found in patients with cutaneous leismaniasis (CL). Here we highlight new data demonstrating that $CD8^+$ T cells and NK cells in CL display a highly cytotoxic senescent phenotype, and that the senescent T cells play a major role in mediating skin pathology. This is the first demonstration that senescent CD8 T cells contribute to immunopathology *in vivo*.

Article

Cutaneous Leishmaniasis (CL) is a serious tropical disease that can cause damage to the skin after infection with insect-borne protozoan parasites of the genus *Leishmania*. In the Americas the main causal agent is *Leishmania braziliensis*. The IFN-γ-driven Type 1 immune response to CL is both associated with a good prognosis, and also contributes significantly to immunopathology. This protective-but-damaging immune response in CL is known to be dominated by $CD4^+$ T cells and cytotoxic $CD8^+$ T cells, which display cytotoxic functions. It has also become apparent that other populations of cytotoxic cells, including Natural Killer (NK) cells may also contribute to pathogen clearance in CL. In order to develop improved strategies for vaccination or to develop strategies for therapeutic control post-infection, it is important to understand the contributions of immune cells to both pathogen clearance and to the infection-induced pathology.

Examination of the T cells in CL lesions has revealed that, as the condition progresses, the populations of infiltrating T cells shift. While in early lesions $CD4^+$ $CD25^+$ T cells (presumed to be regulatory) dominate, as lesions progress and grow larger they become dominated both by $CD4^+$ $CD69^+$ activated T cells, and by $CD8^+$ T cells displaying cytotoxicity-associated CD244. The contributions of NK cells to the response to *Leishmaniasis* in humans are less clear. It has been shown, for instance, that in *Leishmania major* infections NK-cell derived IFN-γ is important for activating the dendritic cells that mediate the T cell-dependent protection against the infection. While these NK cells may proliferate in response to Leishmania infection, and may be directly activated by *Leishmania*-associated molecular patterns, it is also possible that they are indirectly activated by IL-12 produced from antigen-presenting cells, as demonstrated in a mouse model of infection. Thus, NK cells may play a number of roles in the development of an effective T cell response against *Leishmania*.

Recently it has been observed that a proportion of the $CD8^+$ T cells that accumulate in people with CL both display a senescent phenotype, and express cutaneous lymphocyte associated antigen (CLA). These two factors may both be important for our understanding of the response to *Leishmania*. The senescent phenotype, often assessed by measuring expression of CD57 on T cells, is associated with chronic antigenic stimulation. While these heterogeneous senescent cells may display features associated with a reduced capacity to replicate, including shortened telomeres and an inability to respond to some *in vitro* stimuli, they also appear to be relatively persistent, and often display functional cytotoxic responses. In NK cells, as in T cells, the proportion that express CD57 increases with age. Similar to $CD57^+$ T cells, these $CD57^+$ NK cells are efficient producers of IFN-γ and are highly cytolytic. Even if they are not truly senescent, these $CD57^+$ NK cells are widely considered to be terminally differentiated. Cells expressing CLA are able to interact with its ligand E-selectin and home to the skin. This skin-homing property is thought to contribute to the accumulation of CLA-expressing $CD8^+$ T cells in CL lesions, and therefore to contribute to both pathology and protection.

In this issue of *Immunology* we report that the NK cells that expand in CL, like CL-associated $CD8^+$ T cells, display a senescent and highly cytotoxic phenotype. Unlike the CL $CD8^+$ T cells, however, the NK cells do not express CLA and do not therefore show the same level of skin-homing potential. Although the NK cells' presence in skin lesions correlates to some extent with the size of CL lesions, and therefore to the severity of the disease, these lesions are dominated by $CD8^+$ T cells. The authors therefore conclude that, although highly cytotoxic NK cells are found in the blood of CL patients, these NK cells' lack of CLA expression and are comparatively absent from CL lesions. Thus the NK cells may play only a minor role in lesional pathology. The senescent $CD8^+$ T cells therefore appear to be the most important cell populations mediating skin pathology in CL. This is an important first demonstration of an *in vivo* pathogenic role for senescent $CD8^+$ T cells.