

Role of skin homing T cells in acute dengue infection

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Dengue viral infections are one of the most important emerging vector borne diseases, infecting an estimated 390 million individuals annually, resulting in 96 million clinically apparent infections (1). A total of 70% of the burden of dengue infection is seen in resource poor countries in Asia, where it is a significant public health problem. Although a recently concluded phase 3 trial of a dengue vaccine in Asia, showed that the vaccine was safe and highly immunogenic, its overall efficacy was 56.5% (2).

The dengue virus (DENV) is introduced to individuals by an infected *Aedes* mosquito, which passes the virus into the skin. Cells such as Langerhans cells and CD14⁺ and CD1c⁺ dendritic cells (DCs), which are present in large numbers in the skin have shown to be readily infected by the virus (3). As DCs are known to be potent activators of T cells, infected DCs are likely to prime T cells and imprint with the capacity to home back to the skin. The paper entitled 'Virus-specific T lymphocytes home to the skin during natural dengue infection' published by the research group led by Rivino *et al.* shows that cutaneous lymphocyte associated antigen (CLA)⁺ DENV specific T cells are highly expanded in acute dengue and are involved in surveillance (4). Initially using a pentamer specific for a HLA-A*11 NS3 peptide, they have phenotyped T cells in patients with acute dengue and shown that approximately 60-80% of pentamer positive cells expressed CLA. By using pentamers specific for different peptides, they have further confirmed that expression of CLA was not specific to HLA-A*11 restricted NS3 peptide alone. The CLA expressing cells were of the highly differentiated effector or memory cells of the T effector memory (TEM) or TEMRA re-expressing subsets (TEMRA) and were highly expanded in the acute phase. The frequency of pentamer

positive CLA expressing cells diminished during the post febrile phase to levels found in the convalescent phase. Since the majority of the patients in their cohort had a secondary dengue infection, a high frequency of CLA⁺ highly differentiated effector memory T cells may be partly due to an expansion of cross-reactive DENV-specific T cells of the previous infecting serotype. Previous studies too have shown that DENV HLA-A*24 and HLA-A*11 specific T cells are highly expanded in acute dengue and are suboptimal in eliminating the infecting DENV serotype (5). Therefore, in order to further confirm the protective role of CLA⁺ T cells in acute dengue, it would be important to characterize if the frequency of these cells associate with clinical disease severity and early resolution of viraemia.

Many studies have shown that T cells are highly activated in dengue and some have suggested that bystander activation of T cells specific to other viruses such as cytomegalovirus (HCMV) may occur. However, the investigators have shown that although HCMV-specific T cells are also highly activated, that they did not express CLA, demonstrating that CLA expression on DENV-specific T cells are likely to be due to priming of such T cells by skin DCs infected by the DENV. Indeed since the skin is the primary site of infection by the DENV, it appears rational that DENV-specific effector memory T cells should home to the skin, surveilling for possible entry of the DENV. Therefore, in order to further confirm the role of CLA expressing DENV specific T cells in acute dengue, the investigators have shown that CLA expressing DENV-specific T cells are enriched in patients with acute infection and are able to mount an anti-viral response. The authors then undertook elegant skin sampling using suction blisters, which obviate the need for skin biopsy processing

with disperse and collagenase, or prolonged culture, before analyzing *ex vivo* T cell responses. Using this approach they demonstrate enrichment of DENV-specific T cells in the skin compared to the blood of acutely infected patients.

In summary, Rivino and colleagues have highlighted the importance of DEN-specific skin cell homing T cells in acute dengue infection, further confirming the role of T cells in protection against dengue. Although cross reactive T cells were implicated in causing severe disease, several recent studies have shown that DENV-specific memory T cells are likely to be important in protection in dengue (6-9). DENV-specific T cells which were multifunctional and directed against protective HLA-alleles were detected in individuals who were naturally infected with dengue suggesting that DENV-specific polyfunctional T cell responses of higher magnitude associate with protection (7). Another study showed that similar frequencies of DENV-specific cross reactive T cell responses were present in those with varying severity of past infection and that DENV-specific memory T cells of those with clinically non-apparent infection were more likely to produce only granzyme B (8). It was also shown that DENV specific cytotoxic CD4⁺ T cells expressing granzyme B and perforin, which were directed against HLA alleles that associate with milder infection were detected at a high frequency than those following natural infection (6). Collectively, all these studies suggest that both CD4⁺ and CD8⁺ cytotoxic DENV-specific T cells that predominantly produce granzyme and perforin and express CLA are likely to associate with protection.

Dengue continues to be a global health problem and vector controlling measures to curb infection rates have not so far been successful. Therefore, there is an urgent need for an effective dengue vaccine. An ideal vaccine should provide protection against all four DENV serotypes and should not enhance subsequent clinical disease. Given the emerging data on the importance of DENV-specific T cells in protection against dengue, it would be important to develop a vaccine that induces DENV-specific T cell immunity. Although some candidate dengue vaccine do induce T cell immunity, the correlates of protective T cell or antibody responses are currently not known. Therefore, along with the development of safe and effective dengue vaccines, it would be crucial to continue to explore the correlates of protective immunity to dengue.

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Footnote

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