Published in final edited form as:

Nature. 2011 March 31; 471(7340): 581–582. doi:10.1038/471581a.

Cross-dressers turn on T cells

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Abstract

Memory T cells remember viruses from previous infections, providing immunity by facilitating the killing of infected cells. For this, they exploit cross-dressing, the transfer of antigens between antigen-presenting cells.

As their name suggests, antigen-presenting cells flag up the presence of foreign molecules (antigens) to killer T cells of the immune system, triggering the appropriate immune response. The cells generally acquire antigens in one of two ways: by direct presentation, in which the cell itself is infected with the antigen it presents; and by cross-presentation, in which the presenting cell engulfs components of an infected cell and then processes and presents the associated antigen. A third mechanism — cross-dressing — has also been postulated^{1–3}, in which an antigen-presenting cell acquires the requisite processed antigen directly from another infected antigen-presenting cell. On page 629 of this issue, Wakim and Bevan⁴ report the strongest evidence yet for the relevance of cross-dressing, showing in mice that this process is required for an effective antiviral response.

Humans possess some 100 billion versions of killer (cytotoxic) T cells, each of which carries a T-cell receptor on its cell membrane that recognizes a specific set of antigens. Antigenic peptides of 8–10 residues are presented to T cells as complexes with MHC class I molecules of the immune system. Unnecessary T-cell responses can gravely damage the host by triggering autoimmune effects, so safeguards are in place to prevent this. The most important safeguard is that naive T cells — those that have not previously been exposed to an antigen — must initially be activated by dendritic cells, a type of antigen-presenting cell. Dendritic cells are present in immune tissues such as the spleen and lymph nodes, and sample the blood and lymphatic system respectively for antigens. They are derived from the bone marrow and specialize in presenting viral and tumour antigens to T cells.

Once activated, T cells replicate at an astonishing speed (a 4–6-hour division time), leading to a 10,000-fold increase in effector-cell numbers within a few days. The effector cells live for weeks, but a subset called memory cells, which constitute only 1% of the cytotoxic T cells in the body, can live for decades. Having run the gauntlet of the activation safeguards as naive cells, memory cells' safeguards for preventing autoimmunity are relaxed, so they can respond more rapidly to an infection. Wakim and Bevan⁴ report that memory T cells can be activated through cross-dressing.

If viruses infect dendritic cells, the direct presentation of processed viral proteins can efficiently activate T cells (Fig. 1a). Many viruses, however, infect only one or a few cell types. They could therefore potentially avoid recognition by not infecting dendritic cells. To prevent this — and to be able to present tumour antigens — dendritic cells use cross-presentation, whereby they acquire antigens from extracellular fluids through the process of endocytosis, or from infected cells either by engulfing them or by the diffusion of antigenic peptides through 'gap junctions' formed between the cells (Fig. 1b). Cross-presentation seems to be essential for cytotoxic T-cell responses to many viruses⁵.

Cross-presentation can also occur by a process called trogocytosis — the transfer of cell-membrane patches or individual proteins between cells^{6,7} (Fig. 1c). This allows antigen presentation by acceptor dendritic cells to occur immediately, without any processing. Such cross-dressing has been demonstrated in proof-of-principle experiments^{2,3}, and Wakim and Bevan confirm that dendritic cells in culture transfer MHC class I–antigen peptide complexes by trogocytosis. Nonetheless, convincingly extending such findings to situations more like those encountered *in vivo* has remained notoriously difficult. Wakim and Bevan elegantly do just that using chimaeric mice that had received transplanted bone marrow.

To generate the chimaeric animals, the authors used γ -irradiation to destroy short-lived bone-marrow-derived cells — including the resident dendritic cells of the spleen and lymph nodes — in normal mice. They then transferred bone-marrow-derived stem cells to these animals from a variety of genetically manipulated mice. In this way, they could distinguish dendritic cells that generate MHC class I–peptide complexes from dendritic cells presenting the class I–peptide complexes to T cells. This revealed that cross-dressed dendritic cells (cells that had acquired the complexes) have a crucial role in activating memory, but not naive, T cells.

How can this selectivity be explained? One possibility is that memory T cells specifically interact with a subset of dendritic cells that are specialized for cross-dressing-based activation. Although Wakim and Bevan show that, in frozen sections of chimaeric spleens, memory and naive cells have a similar anatomical distribution, imaging the tissues of living animals might reveal differences in T-cell localization or behaviour relating to their immunological experience. However, the authors favour another explanation, which indeed seems more likely: that naive T cells, with their high activation threshold, disfavour cross-dressing, which involves the presentation of vanishingly small numbers of MHC class I–antigen complexes.

Whatever the explanation, it will be essential to characterize cross-dressed dendritic cells in more detail, particularly because they belong to a subset of immune cells ($CD8^-$) that are less adept at many types of cross-presentation than their cytotoxic ($CD8^+$) counterparts. What's more, cross-dressing may prove particularly important in cancer immunology, because the killing of infiltrating cross-presenting immune cells by T cells may be crucial for tumour eradication⁸.

Although these elegant experiments highlight the biological relevance of cross-dressing, it is likely that, under many circumstances, the standard direct-presentation and cross-presentation pathways are more prevalent. Nevertheless, Wakim and Bevan⁴ raise a noteworthy, yet largely neglected, issue: how the activation of memory and naive T cells differs for immune responses ranging from those to acute (sporadic) pathogens such as influenza virus and rotavirus, to persistent pathogens including HIV and hepatitis B and C viruses, and to tumours, where the rules are likely to differ altogether. More generally, their findings illustrate the astounding ability of the immune system to use minimal packets of information to control pathogens that seek to exploit the slightest chinks in our immune armour.

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Figure 1. Pathways to antigen presentation

a, Direct presentation occurs when an antigen-presenting cell such as a dendritic cell is infected, and displays processed antigenic peptides in complex with MHC class I molecules on its surface, thereby activating T cells. **b**, In cross-presentation, dendritic cells acquire antigens obtained by infected cells through endocytosis and phagocytosis, and — with or without some processing — load them onto class I molecules for presentation to T cells. **c**, In a third pathway, called cross-dressing, dendritic cells acquire preformed MHC class I molecules in complex with antigens from other cells by the process of trogocytosis or through gap junctions. Wakim and Bevan⁴ show that cross-dressing is used to activate memory T cells, but not naive T cells, in response to viral infection.