Understanding and Exploiting the T - Cell Memory

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Abstract

Immunological memory is one of the lesser understood aspects of adaptive immunity which protects organisms from recurrent and persistent attack by pathogens. The central event in the generation of both humoral and cell mediated immune responses is the activation and clonal expansion of T cells. T cell activation is initiated by interaction of the TCR-CD3 complex with processed antigenic peptide bound to either a class I (CD8+cells) or class II (CD 4+cells) MHC molecule on the surface of antigen presenting cell (APC). On interaction of a naïve T cell with the processed antigen initiates a cascade of events which activates the resting T cell to enter the cell cycle, proliferating and developing into a clone of progeny cells, which differentiate into memory or effector T cells. Memory T cells are generated by antigen interaction and remain long but quiescent in nature, however responding with greater reactivity to a subsequent challenge with the same antigen, generating a secondary response. Memory cells, though in the G0 stage of the cell cycle require a lower level of activation than so naïve cells. A lot of work in this direction can yield a whole lot of interesting findings which will help us develop better vaccines for chronic animal diseases like Tuberculosis, Johne's disease using suitable animal models. A better understanding of these issues may lead to improvements in the design of vaccines which can be used to generate potent protective T cell memory against pathogens. In the present article various properties of memory T cells along with their implications to vaccine development have been reviewed.

Key words: Effector T cells; Memory T cells; CD4+ cells; CD8+ cells; T cell vaccines

Differentiation of Memory T Cells and Phases of response

CD 4+ and CD 8+ T cells leave the thymus and enter circulation as resting cells. There are about twice as many T cells as T cells in the periphery. Naïve T cells continually recirculate between the blood and lymph systems every 12-24 hours and 1 in 105 naïve T cells is specific for a given antigen , the recirculation makes sure that a naïve T cell will encounter the appropriate antigen. Upon primary exposure of an antigen, antigen specific T cells proliferate, generating a clone of progeny cells, which differentiate into memory or effector T cells. Effector cells migrate to peripheral tissues to fight pathogens secreting cytokines and other functions like B-cell help (CD4+TH cells) and cytotoxic killing activity (CD8+ CTLs). These effector cells, which are shortlived, may be derived from either naïve T cells or memory T cells after antigen activation. The cell membrane molecules expressed by effector and naïve populations are different. Some of these primed T cells developing into memory cells, which confer immediate protection as well as the capacity to mount a more rapid and effective secondary immune response are derived from both naïve T cells after they have encountered antigen and from effector cells after antigenic activation and differentiation. Even after the decline of effector cells these memory cells remain in an expanded population. Memory cells express high levels of various adhesion factors which equip them to a broad range of antigen-presenting cells (Kindt, et al., 2007). Memory T cells, in both human and murine systems, have been shown to proliferate more vigorously to antigen than naive cells (de Jong et al., 1991; Bruno et al., 1995).

The generation of memory cells involves three distinct phases as studied in inbred mice: expansion, contraction and differentiation into memory. When the TCR of a naïve T cell recognizes its cognate MHC-peptide complex processes by the APC the signals and action of costimulatory action bring about clonal expansion of the T cell population into effector cells which sectete cytokines and possess ex vivo killing potential. As the antigen is cleared, the response contracts about 10-20 folds and proceeds towards

differentiation into memory cells which lasts for a long time of a mouse (Ahmed and Gray, 1996; Banchereau, J and Steinman, R.M., 1998). The secondary response also involves all three phases except that the contraction is less severe (Grayson et al., 2002).

CD8+ Memory T Cells

Memory CD8+ T cells retain the expression of effector molecules such as intracellular perforin, Fas ligand and granzymes which account for their rapid cytolytic actions compared to naïve T cells (de Jong et al., 1991; Geisberg et al., 1992). Memory CD8 T cells have been shown to be heterogenous and to comprise at least three subsets, endowed with different migratory capacity and effector function. They have been classified on the basis of expression of CD45RA, a tyrosine phosphatase receptor, having a role in TCR-mediated signaling and CCR7, a chemokine receptor which supports trafficking through secondary lymphoid organs. Cells of the first subset, TM or effector memory cells generated in the primary response are CD45RA-CCR7- and express receptors for migration into inflamed non-lymphoid tissues. They have a high ex-vivo killing potential (perforin+) with poor proliferative capacity. Cells of the second subset, TCEM or central memory cells express L-selectin and CCR7 as naïve T cells and lack immediate effector function. These "central memory T cells" (TCM) have a low activation threshold and are CD45RA-CCR7+ which upon restimulation in lymphoid organs, proliferate and differentiate to effectors. They have a high proliferation potential but no ex-vivo cytotoxic potential (perforin-). The third subset of cells, TRAEM or CD45RA+CCR7- also called the 'terminal memory cells' traffic through non-lymphoid tissues with rapid ex-vivo cytotoxic potential (perforin++) but proliferate only in the presence of CD4, IL-2, IL-15 or IL-21(Sallusto et al., 1999; Appay et al., 2002; Ravkov et al., 2003).

The proportions of memory cells in each category reflect persistence of antigen. Cells are predominantly seen in infections on which antigen is cleared like influenza virus. Proportion of cells are more when high levels of antigen persist, such as in HIV and cells are more when low levels of antigens persist as in cytomegalovirus. (Appay et al., 2002; Champagne et al., 2001). Memory CD8 cells were the progeny of postcytolytic effector cells that had escaped Activation Induced Cell-Death, a regulatory mechanism to maintain cell numbers and homeostasis (Ashton-Rickardt and Opferman, 1999).

Memory T Cells and Vaccines

The success of T cell vaccines depends on both CD4 and CD8 T cells as CD4 cells provide growth factors and signals for generation and maintenance of CD8 cells which recognize and kill infected cells and secrete cytokines. The forte of T cell vaccines is to kill cells which are chronically infected by the contact with the CD8 cells which induces apoptotic death of the target cells but the CD8 cell is intact for additional killing. Activated CD8 cells also secrete cytokines and chemokines which prevent further replication of the microbe (Levy et al., 1996; Pal et al., 1997).

Historically most vaccines have worked by eliciting long-lived plasma cells. These vaccines induce antibody production which limits the disease by neutralizing the toxin or preventing the spread of the pathogen. But certain pathogens are not easily blocked by antibodies. To overcome this, researchers are looking at developing vaccines which elicit cellular immunity or 'T cell vaccines' which recognize and kill the infectious agent (Robinson and Amara, 2005). Vaccines against chronic pathogens that require cell-mediated immune responses to control, such as malaria, Mycobacterium tuberculosis (TB), human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are currently not available or are ineffective. Understanding the mechanisms by which long-lived cellular immune responses are generated following vaccination should facilitate the development of safe and effective vaccines against these emerging diseases (Esser et al., 2003) . BCG vaccine does not facilitate the generation of sufficient memory T cell responses to protect against long term infection. The key to which lies in affording the optimal protective efficacy to find the ideal balance of antigenic stimulation to generate effective memory T cell populations. The antigen dose dictates the fitness of these memory T cells. (Tricas and Nambiar, 2009).

Virus-specific memory T cell populations demonstrate plasticity in antigenic and functional phenotype, in recognition of antigen, and in their ability to accommodate new memory T cell populations. The adaptability of complex antigen-specific T cell repertoires allows the host to respond to a diverse array of pathogens and accommodate memory pools to many pathogens in a finite immune system. This is in part accounted for by cross-reactive memory T cells, which can be employed in immune responses and mediate protective immunity (Selin and Welsh, 2004).

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