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Modulation of immunity by dendritic cells

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Abstract

Several approaches have been taken to enhance immunity against chronic viral infections or tumors in humans. A relatively new and alternative approach involves the use of dendritic cells as adjuvants to prime or boost T-cell immunity. DCs constitute a system of antigen presenting cells (APCs) that are initiators and modulators of the immune response against microbial, tumor and self-antigens. Recent clinical studies in humans from several laboratories indicate they have the potential to elicit durable memory T-cell responses and regression of disease in the cancer setting. We will discuss some of the special antigen presenting features that make them such potent APCs and adaptable for use in the clinic.

DCs are highly specialized to present antigens in small amounts to T cells. This is reflected by their ability to process non replicating viruses to T cells and their capacity to "cross-present" antigens from dead cells. We have shown that DCs phagocytose apoptotic or necrotic cells into endosomal compartments and process antigens for presentation onto both class I and II molecules. The antigens can be derived from virus infected cells or tumor cells and the efficiency of presentation is high with 1 dead cell being sufficient to charge the equivalent of 100 DCs with antigen. Cross-presentation is optimal when DCs phagocytose apoptotic cells in their immature state and then undergo maturation. CD4 helper cells, maturation stimuli e.g. CD40L, LPS or inflammatory cytokines can enhance cross-presentation up to 100 fold. The mechanism of apoptotic cell uptake by DCs involves at least one set of receptors, the alphavbeta5 integrin and CD36. Today cross-presentation is considered to be essential for generating immunity to organisms that otherwise fail to infect APCs directly (e.g. EBV) or to tumors that by themselves are poor APCs. How antigens access MHC class I molecules from exogenous cell associated antigens is still poorly understood and current studies from my laboratory about this process will be discussed.

Methods now exist to generate large numbers of DCs from monocytes or CD34+ stem cells for clinical use. We have studied the immunogenicity of antigen pulsed DC injections in healthy volunteers and have demonstrated that small numbers of DCs can prime and boost CD4 and CD8 T-cell responses. The responses are durable and dependent upon mature vs. immature DCs, which induce regulatory cells instead. Clinical trials have been initiated to test the immunogenicity of peptide pulsed DCs to induce immunity in patients infected with HIV-1 or with stage III melanoma. Preliminary data from these studies will be presented.

DC based immunotherapy is at a promising but early stage. Evidence that DC based vaccines offer advantages over currently used adjuvants is essential to validate their use. DC vaccination is likely to be of most benefit when applied in prophylactic or adjuvant settings and in combination with other treatment modalities. The improvement of this approach for modulating immunity in the clinic will come from future studies.

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