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Autoimmune disease & immunological tolerance

Autoimmune disease occurs when the immune system is directed against the body's own tissues, resulting in destruction or disruption. Autoimmune diseases are a major public health problem in industrialized nations. For some autoimmune diseases the symptoms can be treated, but for the most part specific therapies that can cure the underlying immunological disease are unavailable. Defining the events and mechanisms that lead to the initiation of autoimmune diseases will lead to an understanding of the processes of immunological tolerance and the development of new predictive, preventative and therapeutic strategies.

a. Intracellular cell signalling in dendritic cells

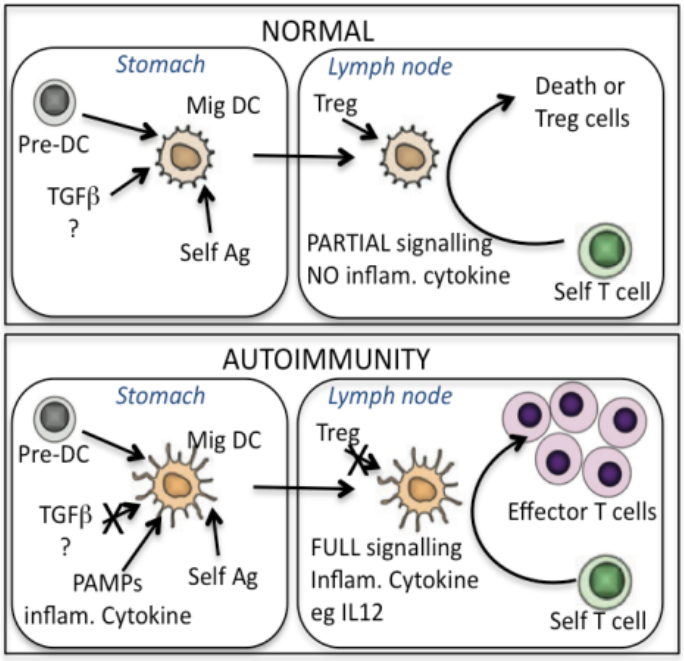

Fig 1. *Hypothesis to explain role of migDC in autoimmunity*.

Dendritic cells (DC) present self-antigens to T cells and unarguably contribute to extrathymic immune tolerance. However it is not clear how the different subsets of DC contribute to this process, or what changes occur in DC during autoimmune disease. We wish to extend our findings that only a specialised DC subtype called migratory DC from the gastric mucosa present stomach autoantigens to T cells in normal mice and mouse models of autoimmune disease. The current project is designed to reveal the intracellular signalling events of migDC and provide an explanation of how they participate in immune tolerance or the initiation and propagation of autoimmune disease.

b. The use of regulatory T cells to cure autoimmune disease

Treg cells are specialised T cells that suppress immune responses. Treg cells show potential in the treatment of inflammatory diseases such as autoimmune disease. We have developed methods for the generation of Treg cells *in vitro* and demonstrated that they can be used to reverse advanced autoimmune disease. Our aims are now to optimize the therapeutic potential of Treg cells and discover how Treg cells reverse the disease process.

Immune responses to pathogenic bacteria

The WHO estimates that bacterial infectious diseases account for ~10 x 10^6 deaths annually. This area of our research is directed toward maximizing the chances of developing more effective vaccines and antimicrobial drugs throuh a better understanding of how the immune system combats bacterial infections.

a. The role of plasmacytoid dendritic cells in combating bacterial pathogens

Though poorly understood, plasmacytoid dendritic cells (pDC) are known to be the primary source of type I interferons (IFNs) produced in response to many viral infections. We have discovered that pDC play a central role in the response to the bacteria that causes Legionnaire's disease, the first demonstration that pDCs are involved in combating bacteria. Surprisingly, unlike the pDC response to viral invasion, the ability of the cells to combat bacterial infection was independent of type I IFN production.

Our results show a role for pDC in combating bacterial infections by mechanisms not previously described for this cell type. We aim to define the role of pDC in combating a range of pathogenic bacteria and the mechanisms they use. We hypothesize that pDC recognise bacterial products by toll-like receptors (TLR) and that the consequent activation of signalling pathways results in the secretion of cytokines or chemokines in addition to type I IFN. The cytokines and chemokines attract and activate effector cells, such as macrophages, neutrophils, and NK cells, that secrete cytokines or dispose of the pathogens directly.

Recent publications

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