**Immune Reconstitution Inflammatory Syndrome (IRIS)**

Although the exact mechanism involved in the development of immune reconstitution inflammatory syndrome (IRIS) is not clearly understood, the explanation presented in this discussion is based on current theories.

As a background to understanding inflammatory responses, it is first important to appreciate that there are four defined CD4+ T cell subsets that provide a homeostatic balance between pro and anti inflammatory responses that occur in a healthy functioning immune system. **The four CD4+ T cell subsets** we will discuss are the Th1, Th17, Treg and the Th2 subset.

Initially, naive CD4+ T cells (termed Th0) encounter processed antigen by dendritic cells through the MHC class II and T cell receptor in the T cell zone of secondary lymphoid tissues, such as the lymph nodes. Depending on the type of cytokine released by the dendritic cell upon this interaction, the Th0 [is a receptor found on helper T cells and monocytes. The CD4 receptor on helper T cells binds to HLA is Human Leukocyte Antigen which is part of the Major Histocompatibility Complex (MHC) which are a set of genes that, in part, direct T cell mediated immunity. There are two classes of MHC that are involved with directing T cell immunity: class I present peptides to HLA class I and the interaction causes CD8 T cell activation. These cells are able to identify and kill cells infected primarily with viruses, but also many bacterial infections. CD8 T cells and class II present peptides to HLA class II and the interaction causes CD4 helper T cell activation. CD4+ T cells coordinate the immune response by releasing cytokines and signalling to other cells via cell-cell contact that enables others immune cells to perform their specialised functions (such as B cells). The number of CD4 cells in a sample of blood is an indicator of the health of the immune system. A normal CD4 count ranges from 500 to 1500. HIV infects and kills CD4 cells, leading to a weakened immune system and lower CD4 counts.] CD4+ T cells differentiate into either Th1, Th2, Th17 or Treg phenotypes.
Interleukin-12 released by the dendritic cells will cause the Th0 CD4 cells to differentiate into Th1 functional cells. These cells secrete IFN-γ which promotes pro-inflammatory responses and will mobilize the maturation of CD8+ cytotoxic T cells and stimulate NK cells.

When a combination of Transforming Growth Factor (TGF ?) and [simple_tooltip content='Interleukin-6 (IL-6) is involved in the acute phase response. It helps to promote B cell proliferation into plasma cells, it is involved in thrombopoiesis, and is synergistic with [simple_tooltip content='Interleukin 1(IL-1) has many functions on many different cells and is secreted by a number of cells including macrophages, monocytes and dendritic cells. It also helps to activate T helper cells by acting as a co-stimulator with the antigen presenting cell receptors and it helps promote the maturation and clonal expansion of B cells.']IL-1[/simple_tooltip] and TNF on T cells. This cytokine is found in increased levels in sites of inflammation']IL-6[/simple_tooltip] are released together by the dendritic cell, the Th0 CD4 cells differentiate into Th17 functional cells. These cells secrete IL-17, which also induces
pro-inflammatory cytokines and tips the balance towards inflammatory immune responses.

When the dendritic cells only release TGF-β, the Th0 CD4 cells differentiate into T regulatory (Treg) cells. These cells secrete IL-10 and TGF-β. IL-10 antagonises pro-inflammatory immune responses by suppressing Th1 and Th17 T cell development.

Th2 Subset

When the dendritic cells release IL-4 after Th0 binding, the cells differentiate into Th2 cells. These cells secrete IL-4 and IL-10 which antagonise pro-inflammatory responses by suppressing Th1 and Th17 T cell development. Th2 T cells also provide cytokine stimulation to promote the maturation of B cells to plasma cells and the production of antibodies.
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Homeostatic balance of pro- and anti-inflammatory immune responses.

In adaptive immune responses to pathogens, there is a critical balance between pro- and anti-inflammatory immune responses. Uncontrolled pro-inflammatory immune responses can result in damage to host tissues, whereas anti-inflammatory immune responses initiated prematurely can result in survival of the pathogen, which is deleterious for the host. Th1 and Th17 CD4+ T cell subsets result in pro-inflammatory responses and Treg and Th2 CD4+ T cell subsets result in anti-inflammatory responses. It is thought that in a natural healthy immune response, there is a homeostatic balance between these subsets, resulting in the elimination of the pathogen, but also reducing the risk of tissue damage in the process. Inability to clear pathogen, or an overload of antigen, is either a result of this balance or a cause of an imbalance.

Currently, it is thought that IRIS is a result of an imbalance towards pro-inflammatory immune responses during the immune reconstitution phase that occurs shortly after initiation of ARV therapy. There is a preferential differentiation of pro-inflammatory CD4+ T cell subsets.

If we break down the sequence of events: when a person becomes infected with HIV, the virus replicates preferentially in secondary lymphoid tissue.
This results in an accumulation of viral gp120, which interacts with CD4 receptors expressed on CD4+ T cells and promotes retention of CD4+ T cells in the lymph node by interference with lymph node homing and exit receptor regulation. When ARV therapy is initiated, the drugs act by inhibiting viral replication and allow the release of sequestered CD4+ T cells. Thus, the first phase of immune reconstitution following ARV therapy is the redistribution of sequestered CD4+ T cells from the lymph nodes to peripheral blood and tissues. It has been shown that the majority of these cells are Th1 and Th17 memory cells and the second phase is the resulting imbalance towards inflammatory responses due to these cells initiating uncontrolled pro-inflammation.

Click here to download combined PDF of CD4+ T cell subset graphics

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Link to the associated Case Study