

Steroid Resistant Lymphocyte Subpopulations in Ulcerative Colitis
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Background: Ulcerative colitis (UC) is an inflammatory condition affecting the bowel that usually responds to treatment with steroids. However, approximately one third of patients with UC do not respond adequately to steroid therapy, and may require surgical removal of the whole of the large bowel (colectomy). Current therapies for steroid resistant UC, such as ciclosporin, have significant side effects and which can occasionally be very serious. In the human body, immune responses depend on a population of white cells called lymphocytes. These cells provide lifelong immunity that can follow after exposure to disease or vaccination. One type of lymphocyte, a T cell, is involved in responses to infection and inflammation. Steroids act by suppressing lymphocytes and thus reducing inflammation and immune responses. It is possible to measure the steroid sensitivity of an individual's lymphocytes in the laboratory. Our group has previously shown that the outcome of steroid treatment for an acute flare of UC is predicted by laboratory measures of lymphocyte steroid sensitivity, no matter how severe the disease. In addition, we have shown that 20-30% of the general population are steroid resistant and that this characteristic is stable over time and not reliant on the presence of disease. Most recently, we have made the observation that this resistance to suppression by steroids is not a property of all lymphocytes, but resides in a group of peripheral blood T cells expressing markers on their surface called CD4 and intermediary levels of CD25 at rest (CD4+CD25^{int} cells). CD25 is a cell surface receptor for a chemical (interleukin-2 (IL-2)) which plays a key role in inflammatory responses in the body. Basiliximab a drug that blocks IL-2, has been shown in a pilot study to improve steroid sensitivity in steroid resistant patients with UC. We believe that variation in numbers of CD4+CD25^{int} cells could explain the failure of some individuals to respond adequately to steroids. Greater understanding of these mechanisms may enable us to develop new treatments for the treatment of UC and other inflammatory diseases.

Purpose: In this project we propose to: 1) Develop a greater understanding of the molecular mechanisms of steroid resistance in the CD4+CD25^{int} subgroup of resistant T cells. 2) Compare the properties of these cells in steroid resistant versus steroid sensitive individuals with UC. 3) Search for new genetic cell markers for this cell population to enable early identification of steroid resistant patients in the future. The results of this study may lead to new treatments that will reduce the number of patients with UC needing colectomy, and allow us to tailor treatment regimes depending on an individual's ability to respond to steroids.

Plan of Investigation: Development of assays to explore the molecular mechanisms of steroid resistance: A novel assay is now available that has proven to be a highly sensitive means of examining the interaction between steroid receptors and the activity of chemical messengers inside the cell. We propose to establish similar assays in steroid sensitive and steroid resistant cell populations to monitor cell pathways to identify why cells are steroid resistant. We will compare these results to our current, well-established, assays of steroid sensitivity. Exploring the role of CD4+CD25^{int} cells in steroid resistant patients: In this study two different T-cell populations will be isolated from healthy volunteers – CD4+CD25^{int} steroid resistant cells and CD4CD25 negative cells which are steroid sensitive. The pathways that make these cells steroid sensitive or steroid resistant will be compared. Identification of novel markers of the steroid resistant T-cell: Gene array techniques have enormous potential to identify a panel of genes expressed in steroid resistant cells. We will use this new technique to identify new surface markers of steroid resistant cells so that these cells can be identified and their growth followed during steroid therapy.