CFID Summer Student Research Project Proposal

Can sCD127 secretion in response to IL-7 be predicted by a single nucleotide polymorphism?

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Background:

IL-7 is a key cytokine in T-cell development and proliferation. IL-7 mediates the immune response through the binding to its specific receptor expressed on the surface of target cells. This receptor is composed of two subunits, the common gamma chain and the specific □ chain, CD127. In addition to membrane-bound CD127 (mCD127), a soluble form of this protein as been detected and is thought to play a role in regulating the immune responses. In infectious diseases such as tuberculosis, levels of sCD127 in the plasma have been correlated with disease progression. In septic shock patients, elevated sCD127 in plasma is associated with increased mortality. Soluble CD127 also appears to have a role in HIV pathogenesis.

Two distinct processes contribute the extent of sCD127 expression. First, IL-7 induces the production of sCD127. In one study in SIV infection, the degree to which IL-7 induced sCD127 predicted the outcome from IL-7 therapy. Second, a single nucleotide polymorphism (SNP) in the CD127 gene, dictates the relative expression of the sCD127. An example of its clinical relevance is that a specific SNP (r6897932), which results in a decrease in sCD127, is associated with an increased risk of development and progress of multiple sclerosis. Whether or not these two phenomena (IL-7 induced sCD127 and SNP associated levels of sCD127) are linked is unknown.

IL-7 has been studied as a therapeutic agent in a number of diseases, including HIV infection, as it expected to increase T cell number and enhance immune function. While results to date have been mixed, it appears that there are individuals who respond well to IL-7 therapy and others that don't. It is possible that those individuals that respond well to IL-7, release greater amounts of sCD127. And further, it is possible that the presence of a SNP in the CD127 gene dictates which individuals produce more sCD127 in response to IL-7.

Hypothesis:

A SNP in the CD127 gene predicts the ability of CD8 cells to produce sCD127 in response to IL-7 and may be a valuable tool in determining who is likely to experience the beneficial effects of IL-7 therapy. We therefore hypothesize that the nature of the SNP predicts the ability of lymphocytes to produce sCD127 in response to IL-7.

Objectives:

1) To determine the presence or absence of the T-allele r6897932 SNP in a cohort of 24 health donors.
2) To determine the ability of CD8+ T cells from the genotyped donors to produce sCD127 in response to IL-7.

Experimental Plan:

Peripheral blood mononuclear cells (PBMC) from 24 health donors will be isolated. DNA will be isolated and r6897932 SNP genotype will be analysed using a commercially available assay. Individuals with the T/T or C/T genotype express lower levels of sCD127 than those with the C/C variant with the distribution being T/T 5-7%, C/T 27-40% and C/C
55/75% of the population. Given this distribution, studying 24 individuals should provide an adequate number of T and non-T genotypes to determine if there is an association with sCD127 expression.

CD8+ T cells will also be isolated from PBMC by negative selection and incubated for 24 hours in the presence of IL-7 (10 ng/ml). The amount of sCD127 in the supernatant will then be measured using ELISA.

The relationship between sCD127 expression in response to IL-7 and presence or absence of the T allele r6897932 SNP will be determined by Mann-Whitney U test.

Significance and Implication:

A correlation between the presence of a SNP in the CD127 gene and the ability of cells to produce sCD127 in response to IL-7 may be a valuable tool to determine which patients are likely to experience the beneficial effects of IL-7 therapy, whether this be in the setting of HIV, TB, sepsis, or in any other disease in which IL-7 therapy may be of benefit.