
Seminar

Exploring the limiting nature of the signaling subunit of the common gamma chain family of cytokine receptors

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The common gamma chain family of cytokine receptors consists of receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokines that pair up with the signaling subunit, the gamma chain. We asked the question, how is the gamma chain shared among the receptors of this family? Individuals lacking expression of the gamma chain suffer from severe combined immunodeficiency.

Treatment includes gene therapy of patient stem cells reconstituted with the gamma chain. In such treatments, there is no control over the amount of gamma chain reconstituted and studies show that excess expression can cause tumors. Using quantitative approaches, we found that under normal circumstances, the amount of gamma chain at the surface of T cells is limiting in absolute numbers. Signaling via these receptors, however, is very sensitive and does not require more than a few receptors occupied by cytokines. Under conditions where cells are exposed to multiple cytokines, we found that IL-7 has the unique ability to cross-inhibit IL-4 and IL-21 responses. This occurs as a result of the limited number of gamma chain molecules at the cell surface, because over-expressing the gamma chain relieves the cross-inhibition. We used computational modeling and experimental approaches to test several hypotheses to explain the cross inhibition phenomenon. Our results are consistent with a model in which IL-7 causes the clustering of IL-7 receptor and gamma chain, thereby sequestering it away from other gamma chain cytokine receptors. Our work represents an example of the use of multi-disciplinary and quantitative approaches to address complex problems in immunology.

Friday, Apr 18th 2014

2:00 PM (Tea/Coffee at 1:45 PM)

Seminar Hall, TCIS