阻斷穀氨醯胺的代謝路徑可抑制移植後之排斥現象

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Targeting Glutamine Metabolism Prevents Allograft Rejection

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Purpose:

Upon antigen recognition and costimulation, T cells up-regulate the metabolic machinery necessary to sustain effector function and proliferation. A hallmark of this response is a switch to an increased necessity for glutamine. We hypothesize that inhibition glutamine metabolism might prevent graft rejection.

Materials and Methods:

OVA antigen-specific CD4+ or CD8+ Thy1.1+ cells were isolated from OT-I or OT-II transgenic mice and adoptively transferred into C57BL/6 Thy1.2+ host, which were then infected with OVA-expressing Vaccinia to stimulate and expand the antigen-specific cells. The mice were treated with 6-Diazo-5-oxo-L-norleucine (DON, an inhibitor of glutamine metabolism) for 3-5 days. Host splenocytes were harvested for analyzing the number and population of donor cells by flow cytometry and their capacity of cytokine production by ELISA. From these experiments we determined the effect of this inhibitors and then applied them to a BALB/c to C57BL/6 full thickness skin graft model.

Results:

For CD8+ T cells responses to vaccinia we found the treatment with DON resulted in a greater than 80% decrease in effector cells and IFN-g production. For CD4+ T cells we observed this decrease along with an increase in Foxp3+ regulatory T cells. When we applied this regimen to the mismatched skin graft model we were able to have an increase in graft median survival time, compared to those that received no treatment (22 vs 11 days, p=0.0019).

Conclusion:

Targeting glutamine metabolism represents a novel means of inhibiting T cell effector function while preserving mechanisms of immune regulation. Such a regimen can inhibit acute rejection and promote graft survival.