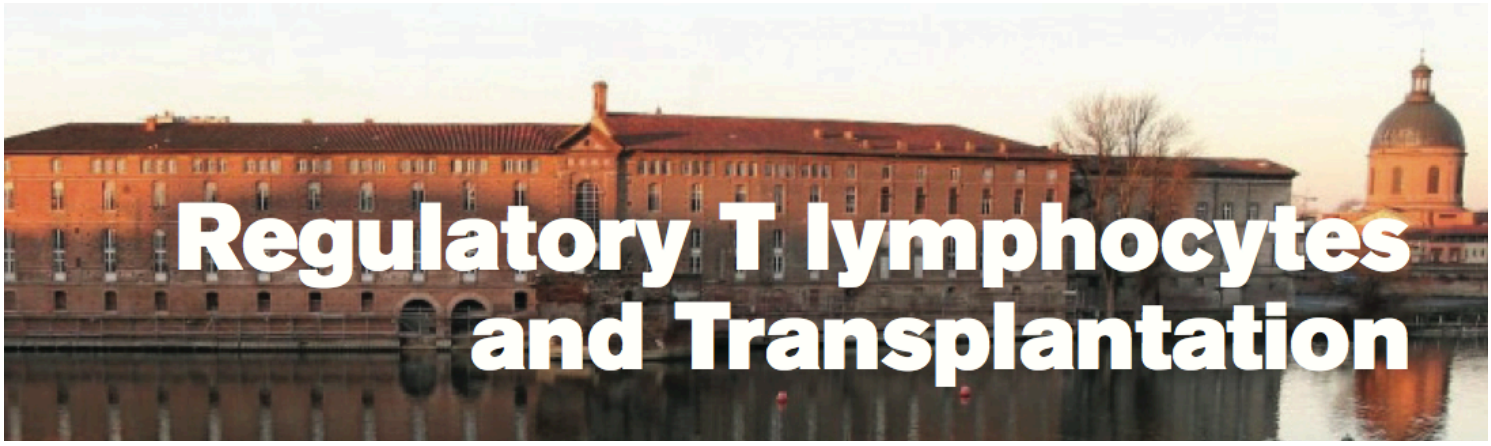

Nutrient sensing via mTOR in T cells

maintains a tolerogenic microenvironment

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We have used two different TCR transgenic mice strains specific for the male antigen DBY, both on a RAG-$1^{-/-}$ background, to show that tolerance to male skin grafts requires the peripheral induction of $Foxp3^{+}$ regulatory T cells (Treg). By introducing an hCD2-foxp3 knockin reporter that allows identification and in vivo depletion of $Foxp3^{+}$ Treg cells we have also shown that these Treg cells are required and sufficient to both induce and maintain tolerance, and that they actively suppress effector T cells locally, within the tolerated skin graft. We have proposed that tolerance is maintained by the induction, by Treg cells, of a tolerogenic microenvironment within tolerated tissues that inhibits effector cell activity but which supports the generation of further Treg cells by "infectious tolerance". Two important components of this tolerogenic microenvironment depend on metabolism and nutrient sensing. The first is the metabolism of extracellular ATP to adenosine by the ectoenzymes CD39 and CD73. These two enzymes are constitutively co-expressed on Treg cells, but can also be induced on a wide variety of cell types by TGFβ and the adenosine generated can be shown to be a potent inhibitor of T cell proliferation. The second mechanism is due to the up-regulation of multiple enzymes that consume essential amino acids (EAAs), which are sensed in naive T cells primarily via inhibition of the mTOR pathway, which in turn encourages their further differentiation into $foxp3^{+}$ Treg cells. We have found that the differentiation and stability of proliferating $Foxp3^{+}$ Treg cells (both nTreg and iTreg) are controlled by the symmetry of cell divisions, which are in turn controlled via nutrient sensing. mTOR activation, associated with graft rejection, allows the asymmetric inheritance of both mitochondria and the numb/notch signalling pathway in order to increase phenotypic diversity (or plasticity), while the mTOR inhibition associated with tolerance forces a symmetrical inheritance and exponential expansion of a stable Treg cell population.