Marató TV3 2011 (DT): Systems Biology Analysis of Immune Tolerance in Organ Transplantation

Description

Life-long immunosuppression is typically regarded as obligatory for solid-organ recipients to avoid the risk of rejection and graft loss. Evidence that not all patients require perpetual immunosuppression is found in a subset of patients who successfully discontinue immunosuppression and yet maintain normal graft function. In liver transplantation recent data indicate that this phenomenon of spontaneous operational tolerance is more prevalent than previously appreciated. Thus, among liver recipients 15 to 40% or more can successfully discontinue immunosuppression, depending on recipient age and how remote from transplant they are. A delineation of the mechanisms responsible for the establishment of tolerance is however required in order to be able to intentionally induce tolerance in recipients not predisposed to spontaneously develop it. Recent clinical studies identified a liver tissue derived gene expression signature indicative of tolerance. The most informative gene expression markers were involved in the regulation of iron metabolism, suggesting that iron homeostasis, previously implicated in the regulation of inflammatory responses, might also influence the maintenance of immune tolerance. These results correlated with a circulating T cell immunophenotype biased towards an antigen experienced, exhausted phenotype.

On the basis of these results, the goal of the current project is to use a systems biology approach to investigate in tolerant liver recipients the interplay between intra-graft gene expression, gut microbiota and circulating T cell receptor repertoire. Our results will expand our understanding of the pathogenesis of tolerance in human transplant recipients by providing critical information on the pathways regulating the immunogenicity of liver allografts.

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