

# Dottorato di ricerca in Medicina traslazionale dello sviluppo e dell'invecchiamento attivo - XXIX ciclo



## Curriculum: Medicina traslazionale e clinica

### "Metabolic control of FoxP3 expression in human regulatory T cells"

#### Abstract

Regulatory CD4<sup>+</sup>CD25<sup>+</sup> T (Treg) cells play a central role in the maintenance of immune self-tolerance and homeostasis. Although Treg cells operate through multiple mechanisms, it appears that the expression of the transcription factor Forkhead-box-P3 (FoxP3) is crucial for their function. Here we describe human peripheral Treg (pTreg) cells that develop from CD4<sup>+</sup>CD25<sup>-</sup> T (Tconv) cells following suboptimal stimulation *via* the T cell antigen receptor (TCR). This population of pTreg cells, which we call inducible Treg (iTreg) cells, is characterized by high FoxP3 expression, strong suppressive capacity and an active proliferative and metabolic state. The development of iTreg cells tightly depends on glycolysis, which controls FoxP3 splicing variants containing exon 2 (FoxP3-E2), through the glycolytic enzyme enolase-1. Remarkably, iTreg cells suppressive activity is impaired in autoimmune diseases such as relapsing remitting multiple sclerosis (RR-MS), and associates with the reduction of FoxP3-E2 expression, secondarily to impaired glycolysis and IL-2/IL-2R/STAT-5 signalling. These results suggest a novel mechanism that links glucose metabolism to the induction of specific FoxP3 splicing variants, *via* enolase-1, that directly impact on human Treg cell function, in health and in autoimmunity.