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Analysis of the molecular mechanisms regulating FOXP3 gene and protein expression in TCR- and CD28-activated CD4⁺CD25⁺-T cells and their influence on regulatory functions

Summary

Despite the wide and highly qualified literature on the forkhead (FKH) box protein 3 (FOXP3) transcription factor, several questions remain regarding the mechanisms by which *FOXP3* gene is activated and the translated protein mediates suppressive function. We have recently demonstrated that CD28 signals independent from TCR and dependent on PI3K/NF- κ B pathways are sufficient to induce the transcription of FOXP3 and its recruitment to *CD25*, *Il-2* and *Ctla4* target promoters, and “anergic features” in CD28-activated CD4⁺CD25⁺FOXP3⁺ T cells. Taking advantage from these results, in this project we will analyse the following issues: 1) the characterization of the NF- κ B/Rel members recruited on *FOXP3* promoter after CD28 activation and their interaction with NFAT and AP1 transcription factors to constitute an enhanceosome regulating *FOXP3* promoter; 2) the determination whether, in CD28- but not in CD3-stimulated T cell, the region of *FOXP3* promoter is in an active chromatin conformation, and whether epigenetic changes occur in specific binding sites; 3) the ascertainment whether CD28- and TCR-mediated biochemical pathways function in independent or dependent manner in regulating FOXP3 protein expression in activated T cells and whether one or more of these pathways predominate in regulating the anergic or suppressive functions of T_{reg}. In conclusion, although this project certainly requires a considerable time length and might appear ambitious, we believe that by addressing investigations to all these unresolved problems, we can clarify the mechanisms that regulate FOXP3 expression and this could be the basis to identify therapeutic targets for the manipulation of T_{reg}.