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The sterol element binding protein 1c (SREBP1c) preserves cellular metabolism and immunosuppressive function of regulatory t cells

F. Bonacina[1], C. Procaccini[2], S. Pedretti[1], G. Stucchi[1], A. Moregola[1], J. Bogie[3], G. Matarese[2], N. Mitro[1], and G. D. Norata[1]

[1]University of Milan, Department of Pharmacological and Biomolecular sciences, Milan, Italy
[2]Federico II, Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Naples, Italy
[3]Hasselt University - transnational University Limburg, Campus Diepenbeek, Agoralaan Gebouw D, Diepenbeek, Belgium

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Aim: Balance of cellular metabolism is increasingly recognized as a hallmark of physiologic cellular functions; this also extends to cells of the immune system. Here, we aimed at investigating the role of SREBP1c, a key protein regulating intracellular fatty acid (FA) metabolism, on the metabolism and function of Treg, that play a key role in immune tolerance maintenance.

Material and Methods: A detailed immunophenotyping through flow cytometry and metabolic profiling (metabolomics and seahorse analysis) of isolated Tregulatory (CD4+CD25+, nTreg) and in vitro induced Treg (iTreg) cells were performed together with in vitro and in vivo assays of Treg function from SREBP1c KO and WT littermates. RNAseq and lipidomics was performed on iTreg.

Results: Srebp1c deficiency reduced suppressive (-21%,p<0,01) and increased migratory function (+40%,p<0,05) of nTreg and iTreg, tested by in vitro assays. In vivo, Srebp1c KO mice presented reduced circulating and tissues' level of Treg compared to WT mice (-66%,p<0,01) and nTreg from Srebp1c KO mice worsened Experimental Autoimmune Encephalomyelitis progression compared to WT nTreg. We addressed impaired Treg function to metabolic alteration due to Srebp1c deficiency: KO iTreg showed an increased glycolytic potential with preserved mitochondrial function coupled to accumulation of glycolytic metabolites and lactate (+20%,p<0,01) and reduced energy charge (-40%,p<0.01). We associated the switch to anaerobic glycolysis in KO Treg to an impaired lipid metabolism, as suggested by impaired abundance of lipid species (TG, LPC and PC); this was confirmed by RNAseq showing a downregulation of lipid metabolism's pathways and upregulation of glycolysis. In parallel, tolerogenic response was impaired, a phenotype associated to a reduced transcription and activation of Foxp3, the master regulator of Treg function.

Conclusion: By restrain glycolysis and preserving lipid metabolism, our data have identified SREBP1c as a checkpoint crucial for the immunometabolic suppressive response of Tregs.