Joint Meeting
SFI & DGfI
26-29 SEPTEMBER 2023
Palais de la Musique et des Congrès STRASBOURG

P111

SMAD4 TGF-?-independent function dictates naive CD8+ T cell fate and prevents gut inflammation

IGALOUZENE R. [1], HERNANDEZ-VARGAS H. [1], GUYENNON A. [1], BENECH N. [1], BAUCHD. [1], BARRACHINA C. [1], DUBOIS E. [1], MARIE J. [1], SOUDJA S. [1]

[1] Centre de Recherche en cancologie de Lyon, Lyon, France

Characterizing naïve T cells as being completely "naïve" may not accurately reflect their true nature and functionality. SMAD4, a key mediator of TGF-? signaling, plays a crucial role in T cells preventing chronic intestinal inflammation. In spite of this, the mechanisms underlying this control remain obscure. Using different genetic and epigenetic approaches, we reveal that SMAD4 in naïve CD8 T cells prevents microbiota-mediated chronic intestinal inflammation in a TGF-?-independent manner by preconditioning their fate prior to their activation. Mechanistically, SMAD4 acts as a basal repressor of TGF-?-target genes by histone deacetylations in naïve CD8 T cells. Inversely to TGF-? signaling, SMAD4 endows naïve CD8 T cells with a robust effector program and limits their potential differentiation into gut intraepithelial lymphocytes. In addition, in a feedforward mechanism, SMAD4 inhibits the expression of TGF-?-signaling-repressors, predisposing CD8 T cells to an efficient TGF-? mediated immunosuppression. Hence, in a TGF-?-independent manner, SMAD4 both blocks the TGF-? signature in naïve CD8 T cells and restrains their future epithelial localization and intestinal pathology. Our findings unveil SMAD4 as a critical regulator of CD8 T cell differentiation, programming the fate of CD8 T cells during their naive stage, ultimately shaping their behavior and function in subsequent immune responses. These insights provide an original avenue for modulating future immune responses.