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Transforming growth factor-β programs central-memory differentiation in *ex vivo* stimulated human T cells by modulating ID3 expression

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Adoptive immunotherapy (AI) has emerged as a potentially curative therapy for advanced cancer and infections. Recent findings suggest that the transfer of T-cells with "early" memory features may improve the therapeutic potential of AI. TGF-β is a pleiotropic cytokine that controls a large spectrum of biological and pathological processes. In T-cell biology, TGF-β is mostly known for its immunoregulatory properties, but recent evidence has revealed a novel role of TGF-β in T-cell memory differentiation and maintenance. Thus, we investigated whether TGF-β could promote features of memory in *ex vivo* stimulated human T-cells to further improve the efficacy of clinical protocols for AI. Here we show that agonistic TGF-β stimulation leads to the expression of central memory markers without significantly altering T-cell expansion or polyfunctional cytokine secretion following stimulation. Furthermore, TGF-β exposure decreased expression of transcription factors responsible for effector differentiation (T-BET, GATA3 and BLIMP1) and increased those associated with memory differentiation, notably ID3. The knock-down of ID3 by specific siRNA revealed that TGF-β-driven T-cell memory differentiation largely depends on ID3. Moreover, TGF-β-exposed T-cells showed enhanced persistence, expansion and alloreactivity after adoptive transfer into NSG mice. Finally, using clinically relevant culture methods to generate T-cell lines against viral and tumor antigens, we found that TGF-β programmed the expression of early memory markers without significantly curtailing T-cell expansion or antigen-specificity. This finding provides a rationale for clinical use of TGF-β to optimize memory phenotype of *ex vivo* pathogen/antigen-specific T-cells expanded for AI.

Biography

Amina Dahmani is currently a PhD candidate in Microbiology-Immunology at Université de Montréal, Canada. She has completed her Master degree in Immunology at Univérsité Laval, Canada, in Cellular Therapy Lab directed by Dr Jacques P Tremblay, where she studied the development of immunological tolerance to allogeneic myoblasts transplantation as potential therapy for Duchenne Muscular Dystrophy. Later she has joined Dr Jean-Sébastien Delisle team's, dedicated to cancer and viral adoptive immunotherapy to complete her PhD. She is currently working to improve adoptive immunotherapy protocols.

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