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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.

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Histone glycoxidation and its role in cancer autoimmunity

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The emerging correlation of AGE-RAGE axis with cancers has led researchers to study the role of sugars and their byproducts as potential relevant mediators. Where, some workers have established the association between hyperglycemia and cancer by investigating AGEs in blood circulation, our group has observed a strong autoimmune response against neo-epitopes generated upon histone proteins due to glycoxidation induced structural perturbations. In this study, we report the methylglyoxal induced conformational changes in histone H1 and H2A leading to modifications in the aromatic residues, changed tyrosine microenvironment, intermolecular cross linking and generation of AGEs, masking of hydrophobic patches and a hypsochromic shift in the in ANS specific fluorescence, amorphous aggregation, thermal stability and the formation of Nε-(carboxyethyl) lysine. Modified histones induced high titer antibodies in rabbits and the IgG isolated form sera of rabbits immunized with modified histones exhibited specific binding with their immunogens in Western Blot analysis. IgG isolated from the sera of patients with different types of cancers showed better recognition for neo-epitopes on the modified histones in ELISA and gel retardation assay, reflecting the presence of circulating auto-antibodies in cancer against glycoxidatively modified histones in cancer patients. Keeping in view the role of protein post translational modifications in stimulating cellular and humoral immune responses, methylglyoxal modified histones may also be considered as potential antigenic candidates for eliciting autoimmune response in cancer patients.

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