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Protective role of regulatory B-cells in atherosclerosis

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B-cells with regulatory (Bregs) function have been recently discovered. There is emerging evidence that Bregs are protective in autoimmune and inflammatory disease, as well as in cancer. IL-10 production is considered to be one of the multiple mechanisms by which Bregs exert their protective effect. There exist many subsets of Bregs of multiple origins, each of which are defined by their differing cluster of differentiation phenotypes and cytokine production patterns.

In this project we studied spleen-derived T2 marginal zone Bregs with phenotype $CD21^{hi}CD23^{hi}CD24^{hi}$ concerning their capability of suppressing collar-induced carotid arterial neointima formation. Firstly, we expanded splenic $CD21^{hi}CD23^{hi}CD24^{hi}$ Bregs *in vitro*. We stimulated total splenic B-2 B-cells with agonistic αCD40, which resulted in enrichment of high levels of IL10 producing $CD21^{hi}CD23^{hi}CD24^{hi}$ B-cells. Secondly, we induced neointima formation in WT C57bl/6 mice by placing a tygon collar at the common carotid artery and subsequently performed adoptive transfer of αCD40 stimulated total B-2 B-cells. We showed that neointima formation was significantly decreased in the therapeutic treatment group. Furthermore, therapeutic adoptive transfer enriched Type1 regulatory T-cells (Tr1) in the suprailiac lymph nodes (SILN) of the recipients.

Previously, B-2 B-cells were believed to be pro-atherogenic and B-1 B-cells to be atheroprotective. However, in this project we revealed that B-2 B-cells have the potential to confer atheroprotection as well. We show a novel role of a distinct regulatory splenic T2 marginal-zone derived B-2 B-cell subset to promote atheroprotection in a model of collar-induced neointima formation. We show that donor IL-10 productive regulatory $CD21^{hi}CD23^{hi}CD24^{hi}$ B-cells within the total B-2 B-cell pool may contribute significantly to atheroprotection, as well as to Tr1-cell production in the spleen of the recipients upon adoptive transfer. However, further studies are strongly needed in order to unveil the very complex role of B-cells in the pathogenesis of atherosclerosis.

Taken together, the results of this project show for the first time that αCD40 stimulation expands a distinct subset of Bregs ($CD21^{hi}CD23^{hi}CD24^{hi}$ B-cells) with atheroprotective capacity *in vivo*. As such, the results published in this project contribute to current experimental research on cellular immunotherapy for the treatment of atherosclerosis in the future on a proof of principle basis.