Modulation of cholesterol avaibility though the LDLR affects $CD4^+$ T cells differentiation.

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AIM: Adaptive immune response has recently gained attention during atherosclerosis due to the correlation found between T effector memory cell (T_{EM}) expansion, reduced T naïve cells (T_N) and the progression of the disease. Whether this correlation is merely the consequence of increased levels of plasma cholesterol is debated. Here we aimed at investigating whether key players linking systemic and cellular lipid metabolism, such as the LDL-R, affect the differentiation and functionality of $CD4^+$ T cells in animal models and in humans.
METHODS: A detail characterization of $CD4^+$ T cells was performed in mice and humans by flow cytometry.
RESULTS: While under resting condition, differentiation of $CD4^+$ T cells in secondary lymphoid organs was similar in LDLR KO and WT, anti-CD3 and anti-CD28 stimulated $CD4^+$ T cells of LDLR KO, isolated from lymph nodes, proliferated more compared to WT. Following 16 weeks of western type diet, LDLR KO mice presented significantly reduced circulating levels of T_N (CD4+CD44-CD62L+) and increased T_{EM} (CD4+CD44+CD62L-) compared to WT, which were further correlated with the extension of atherosclerotic plaques in their aortic sinus. Similarly we observed that patients affected by familiar hypercholesterolemia (FH) (all heterozygote for LDL-R) presented significantly increased levels of circulating T_{EM} compared to age and sex matched controls, which was paralleled by increased proliferation of peripheral blood mononuclear cells (PBMC) *in vitro* after antigenic stimulation. Furthermore, circulating levels of Treg were significantly increased in FH patients compared to age and sex matched controls, suggesting that the expansion of T_{EM} might be the consequence of an impaired functionality of Treg.
CONCLUSIONS: Together our data propose a novel connection between cholesterol metabolism and immune response, showing that LDLR deficiency in $CD4^+$ T cells leads to an expansion of T_{EM} as a consequence of dysfunctional Treg cells thus supporting the increased immune response observed during atherosclerosis.