Apolipoprotein E modulates adaptive immune response by promoting cellular cholesterol metabolism

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Background: Adaptive immune response has recently gained attention during atherosclerosis due to the correlation found between T effector memory cell (TEM) expansion, T naïve cells (TN) contraction and the progression of the disease. Whether this correlation is merely the consequence of increased plasma cholesterol levels or the consequence of altered intracellular lipid metabolism is debated.

Aim: to investigate how key players linking systemic and cellular lipid metabolism as apolipoprotein E (ApoE) affect adaptive immune response in mouse models and humans.

Methods: Phenotypical, in vitro and in vivo functional characterization of immune cells was performed through flow cytometry in ApoE KO and WT littermates. Immunophenotyping of circulating immune cells and in vitro culture of monocyte-derived dendritic cells (MDCs) was carried out in human carriers of different ApoE isoforms.

Results: ApoE deficiency resulted in increased TEM and decreased TN levels in the circulation and secondary lymphoid organs ($p<0,05$), an increased proliferation of CD4Tcells ($p<0,01$) and a faster rejection following skin graft allotransplantation (SGA,$p<0,01$). This phenotype was the consequence of myeloid-derived ApoE as WT recipients transplanted with ApoEKO bone marrow presented a reduced graft survival after SGA compared to ApoEKO transplanted with WT BM($p<0.05$), which was independent of plasma cholesterol levels. Among myeloid-derived cells, ApoE deficiency was associated with an enhanced ability of dendritic cells (DCs) to trigger allogenic Tcell proliferation compared to WT DCs ($p<0,01$) but no difference was observed in Tcells proliferation induced by allogenic DCs (p=n.s.). DCs were significantly increased in the spleen of ApoE KO mice and associated with a more antigen-presenting phenotype ($p<0,01$), which was associated with an accumulation of cholesterol and oxysterols.

In humans, carriers of ApoE4 isoform (ε4/3,ε4/4) showed increased TEM and decreased TN levels compared to ApoE2 (ε2/2,2/3) and ApoE3 (ε3/3) carriers ($p<0,01$ and $p<0,05$ respectively). This phenotype was the consequence of an enhanced ability of ApoE4 MDCs to induce Tcell polarization toward TEM compared to ApoE2 and ApoE3 carriers following mixed lymphocyte reaction. As ApoE3 and ApoE2 isoforms have similar affinity for the anti-atherogenic HDL while ApoE4 interacts preferentially to the pro-atherogenic VLDL, we tested that serum from ApoE3 but not ApoE4 carriers dampened the activated phenotype of ApoE4 MDCs and was associated with a reduction of cellular cholesterol.

Conclusion: our data suggest that DCs-derived ApoE orchestrates the activation of DCs-Tcell axis via the control of cholesterol and oxysterol availability in DCs thus suggesting the use of players of

intracellular cholesterol metabolism as a treatment to dampen the over-activation of the immune response frequently associated with cardiovascular diseases.