PCSK9 IMPACTS DENDRITIC CELL MATURATION AND IMPAIRS ANTIGEN UPTAKE

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INTRODUCTION

- Previous work published by the lab of Dr. Chuan-Yuan Li at Duke University has shown that the lipid metabolism protein PCSK9 is secreted by tumors and can contribute to an immune excluded microenvironment in mouse tumor models
- B16 tumors with either PCSK9 knockout, or transplanted in host mice treated with anti-PCSK9 antibody evolocumab had reduced tumor growth, and substantially increased CD8 T cells in the tumor microenvironment
- Mechanistically, PCSK9 targets cell surface molecules and receptors leading to their endocytosis and degradation in the lysosome
- Dendritic cells are critical to priming the initial anti-tumor immune response by up take of tumor antigens and cross presentation to CD8 T cells
- We sought to evaluate whether PCSK9 impacts antigen uptake by dendritic cells, which requires cell surface phagocytosis receptors

METHODS

- We cultured monocyte derived dendritic cells from healthy donor PBMCs
- Dendritic cells were differentiated in the presence or absence of recombinant PCSK9
- Dendritic cells were incubated with labeled E. coli particles to evaluate antigen uptake
- Flow cytometry was performed to evaluate dendritic cell maturation

Figure 1: PCSK9 Inhibits Antigen Uptake by Dendritic Cells

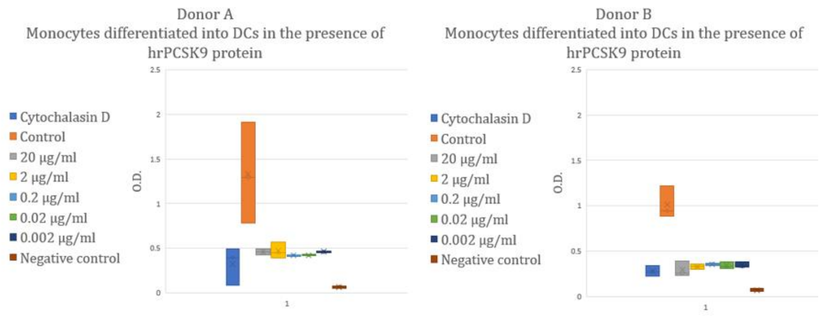
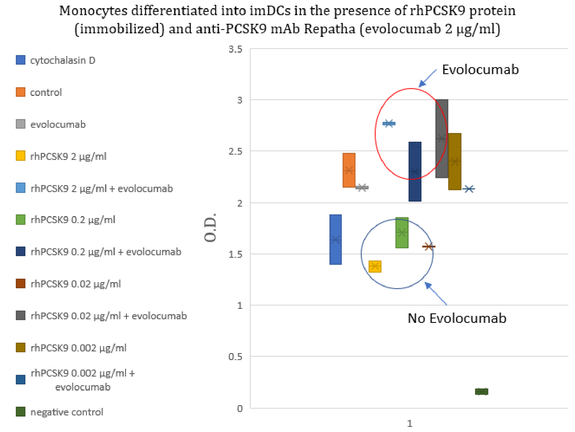
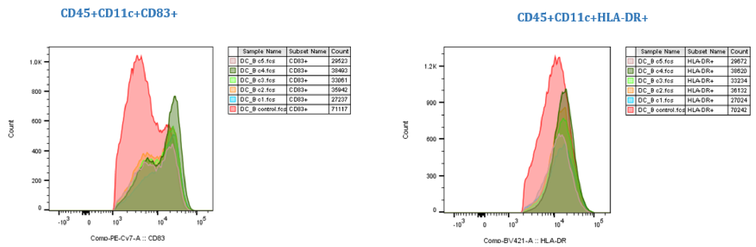


Figure 2: Addition of anti-PCSK9 antibody Evolocumab to DC differentiation culture restores antigen uptake



Inhibitor of phagocytosis: actin depolymarization agent cytochalasin D (imDCs are pretreated with cytochalasin D for 1h before co-incubation with bacteria). Bioparticles: Escherichia coli. The results are presented as optical density.

Figure 3: DC differentiated in the presence of PCSK9 are in more mature state



Human monocyte-derived dendritic cells (healthy donor B)
Control in Red

RESULTS

- Monocyte derived dendritic cells cultured/differentiated in the presence of recombinant PCSK9 have decreased antigen uptake capacity
- The addition of the anti-PCSK9 antibody Evolocumab restores antigen uptake capacity of dendritic cells cultured in the presence of recombinant PCSK9
- Surprisingly, dendritic cells cultured in the presence of recombinant PCSK9 are in a more mature state as evidenced by higher cell surface expression of CD83 and HLA-DR

CONCLUSIONS

- PCSK9 impairs antigen uptake by dendritic cells while also leading to dendritic cell maturation
- These preliminary findings require further validation in a tumor antigen specific model
- Our preliminary hypothesis is that PCSK9 interacts with dendritic cell phagocytosis receptors, leading to premature maturation of dendritic cells and impairment of antigen uptake
- Future studies will evaluate PCSK9 interaction with specific phagocytosis receptors, including CD91 or low-density lipoprotein receptor-related protein 1 (LRP1), a phagocytosis receptor expressed by dendritic cells
- Based on Dr. Li's original publication, clinical trials evaluating the combination of immune checkpoint inhibitors with anti-PCSK9 antibodies are planned