PCSK9 inhibition could ameliorate atherosclerosis and cardiovascular disease by immune mechanisms.

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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Minor ownership in Athera Biotechnologies and Annexin Pharmaceuticals, unrelated to PCSK9)
Declaration of Interest

• No conflict of interest
Background

- Atherosclerosis is the major cause of cardiovascular disease (CVD)
- Atherosclerosis is a vascular inflammation, where immune mechanisms are likely to play a key role.
- Lipids such as OxLDL are implicated as triggering pro-inflammatory factors
- Despite available lipid lowering drugs, there is a huge need for novel types of therapies, modulating immune system and acting anti-inflammatory
- Treatments are emerging! IL-1 inhibition is a promising candidate
- But are we already treating the inflammation?
- Yes, most likely: Statins!
- We here investigate immune modulatory effects of PCSK9 and inhibition of it.
Purpose and key points about methods

- Immunocompetent cells T cells, macrophages and dendritic cells (DC) are major components of human atherosclerotic plaques

- DC and T cell activation could play major role in promoting MI and stroke

- We study how human T cells from plaque interact with DC from the same individual

- Immune effects of PCSK9 and inhibition by silencing of the gene are studied in our ex vivo models
Should we ask the mouse about immunity and PCSK9 in atherosclerosis and CVD?

• CVD in animal models is not = CVD in humans.

• Lipids and immune reactions in human atherosclerosis are different from animal models!

• Ex vivo model of immune interactions
• Co-culture of human DC and T cells
• Source: Human plaques / peripheral blood
PCSK9 played an essential role in DC maturation, proinflammatory cytokine production and the subsequent T cell proliferation induced by oxLDL.
Results

• OxLDL but not LDL induced DC-mediated T cell activation and induced PCSK9 in DCs

• OxLDL promoted DC maturation into a pro-inflammatory phenotype

• T cells exposed to OxLDL-treated DCs proliferated and activated pro-inflammatory T cells

• Silencing of PCSK9 reversed the OxLDL effects and T regulatory cells

• OxLDL induced miRNA let-7c, miR-27a, miR-27b, miR-185. Silencing PCSK9 repressed miR-27a and to a lesser extent let-7c
Conclusions

• Inhibition of PCSK9 is anti-inflammatory and immune modulatory, *induction T regulatory cells upon* OxLDL-activation.

• PCSK9-inhibition may protect against atherosclerosis and CVD through immune mechanisms, independent of LDL-lowering.