IL1RAP – a future target to reduce vascular inflammation and adhesion?

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Aim

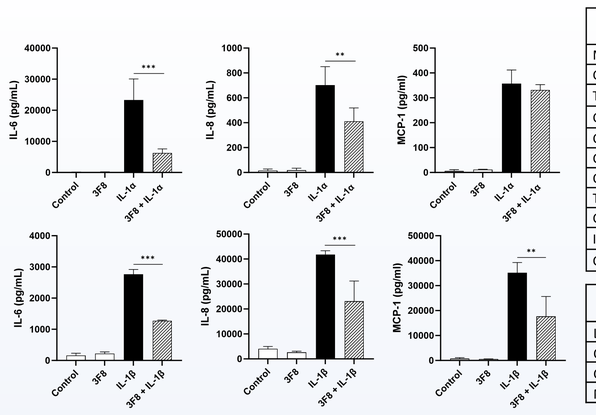
To evaluate the role of inhibition of the coreceptor IL1RAP with a novel antibody, developed by the Swedish Biotech company Cantargia AB, in vascular cells.

Conclusion

IL1RAP targeting antibodies can reduce the expression of IL-1α and IL-1β induced inflammation and adhesion in endothelial cells.

Results

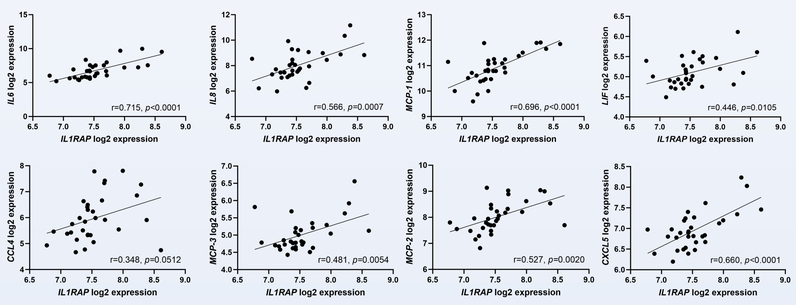
Blocking effect of IL1RAP antibody 3F8 on IL-1β and IL-1α induced release of inflammatory proteins in endothelial cells



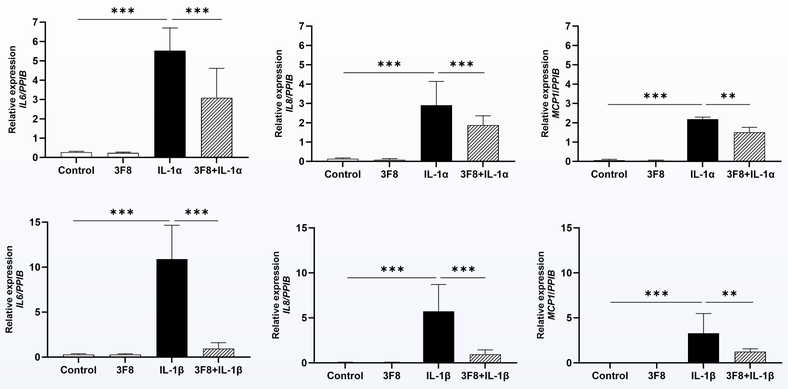
OLINK	Protein expr. (NPX) FC by 3F8 + IL-1α
MCP-2	-3,46393
CCL3	-3,28153
TNF	-2,47800
CXCL5	-1,99089
CX3CL1	-1,88434
CCL4	-1,82499
OPG	-1,25702
TNFRSF9	-1,09005
CSF-1	-1,02851
IL-18R1	-0,62336
CCL11	-0,61413

OLINK	Protein expr. (NPX) FC by 3F8 + IL-1β
LIF	-4,74689
OPG	-2,29076
CCL4	-2,28000
MCP-3	-1,29192

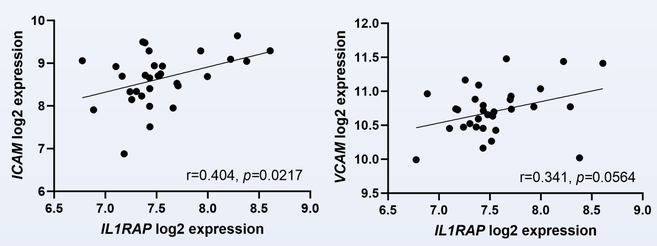
IL1RAP expression correlates to markers of inflammation in human atherosclerotic plaques



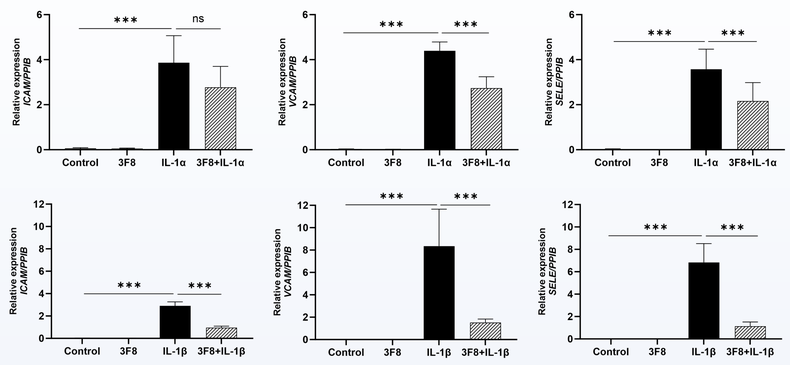
The IL1RAP blocking antibody 3F8 inhibit gene expression of inflammatory cytokines in endothelial cells



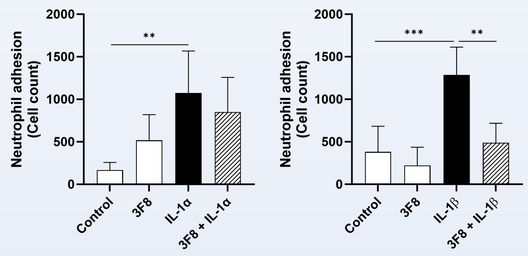
IL1RAP expression correlates to ICAM expression in human atherosclerotic plaques



The IL-1α and IL-1β induced expression of adhesion markers affected by the IL1RAP blocking antibody 3F8 in endothelial cells

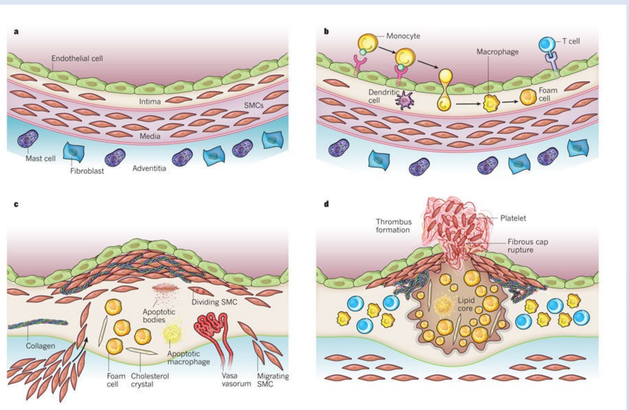


The IL-1α and IL-1β induced neutrophil adhesion to endothelial cells affected by the IL1RAP blocking antibody 3F8

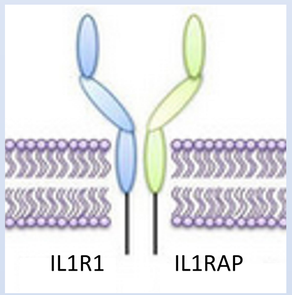


Introduction

Cardiovascular diseases (CVDs) are the leading cause of death and inflammation is central in atherosclerosis. The atherosclerotic process starts with endothelial activation and expression of adhesion molecules followed by migration of leukocytes and smooth muscle cells, progression and ultimately stenosis or thrombosis.



Stages in the development of atherosclerosis (from Libby et al Nature 473: 317-25, 2011)



The IL1R1 and the coreceptor IL1RAP. (Right figure, modified from Murray et al Front Cellular Neurosci 9: 1-17, 2015)

The IL-1 family of cytokines is central and expression of IL-1α and IL-1β is expressed in atherosclerotic lesions [1]. Genetic or pharmacological inhibition of IL-1α or IL-1β ameliorated atherosclerosis in mice [2-4]. Previously, the CANTOS study showed reduced CRP levels and reduced additional events after administration of canakinumab in patients with previous infarction [5].

References

[1] Moyer CF, et al. Am J Pathol. 1991;138:951-60.
[2] Kirii H, et al. Arterioscler Thromb Vasc Biol. 2003;23:656-60.
[3] Bhaskar V, et al. Atherosclerosis. 2011;216:313-20.
[4] Kamari Y, et al. Atherosclerosis. 2007;195:31-8.
[5] Ridker PM, et al. N Engl J Med. 2017;377:1119-1131.

Methods

Endothelial cells +/- LPS in presence or absence of IL1RAP binding antibodies

- ELISA
- Real time PCR
- Olink® proteomics
- Neutrophil adhesion assay

GSE43292 dataset of atherosclerotic lesions

- Correlation analysis

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