ANTIBODIES FOR THE DIAGNOSIS AND/OR TREATMENT OF ATHEROSCLEROSIS

Summary:

Novel atherosclerosis biomarkers are in need to improve the strategies for diagnosis and prognosis of cardiovascular disease. CNIC and DKFZ researchers have discovered 18 novel antibodies that show reactivity against the atherosclerotic plaque, which can thus be potentially used for the diagnosis of this disease. Moreover, the use of one such antibody, A12, delays the progression of atherosclerosis and reduces the level of free circulating cholesterol and LDL.

Innovative aspects:

Atherosclerosis is a chronic inflammatory disease that underlies thrombosis and cardiovascular events, but it can remain asymptomatic for long periods of time. The presence of antibodies in the atherosclerotic plaque was described decades ago, and the connection between autoimmunity and atherosclerosis is well accepted. However, the immunogenic trigger and the impact of the antibody immune response during atherosclerosis are not well understood.

Atherosclerosis is triggered by the retention and oxidation of low-density lipoprotein (LDL) at the vessel sub-endothelium space, leading to an inflammatory immune response. In addition, B cells and the antibody immune response are known to be critical during atherosclerosis.

Antibodies can be used as diagnostic and therapeutic agents. CNIC and DKFZ researchers have performed a high-throughput single cell analysis of the antibody repertoire associated with atherosclerosis. They sequenced more than 1700 antibodies from LDLR-/- mice with high fat diet (HFD) and control mice, 18 of which showed reactivity against atherosclerotic plaques (AtherAbs). They found that one such antibody, A12, binds to atherosclerotic plaques in LDLR-/- HFD mouse model and in human carotid atherosclerosis lesions (Figure 1A).

Deep proteomics analysis showed that A12 antibody recognizes a self-protein, A12Ag1 whose distribution they found altered during atherosclerosis. The researchers also found that A12Ag1 is increased in the plasma of atherosclerotic mice and of humans with atherosclerosis (Figure 1B-C). In addition, they have shown that treatment of LDLR-/- HFD mice with infusions of A12 antibody delays atherosclerosis progression and reduces circulating free cholesterol and LDL. These findings open the way for A12 antibody as a very promising diagnostic and therapeutic tool in cardiovascular disease.

Competitive advantages:

- A12 and 17 additional identified AtherAbs have very specific reactivity patterns against the atherosclerotic plaque. These patterns differ from traditional markers of this disease, such as oxLDL.

- AtherAbs show specific reactivity against the atherosclerotic plaque from early stages of the disease, so they can potentially be used as diagnostic agents for the early detection of the disease, before the patients have symptoms. In addition, AtherAbs can be used to study the molecular physiology of atherosclerosis.

- AtherAbs were identified from LDLR-/- HFD atherogenic mice during the progression of the disease, thus, no toxicity is expected when used as a therapeutic agent.

- A12 AtherAb allows the detection of atherosclerotic plaque in vivo. Functional in vivo experiments showed that A12 infusion delays the progression of atheroma plaque in LDLR-/- HFD mice.

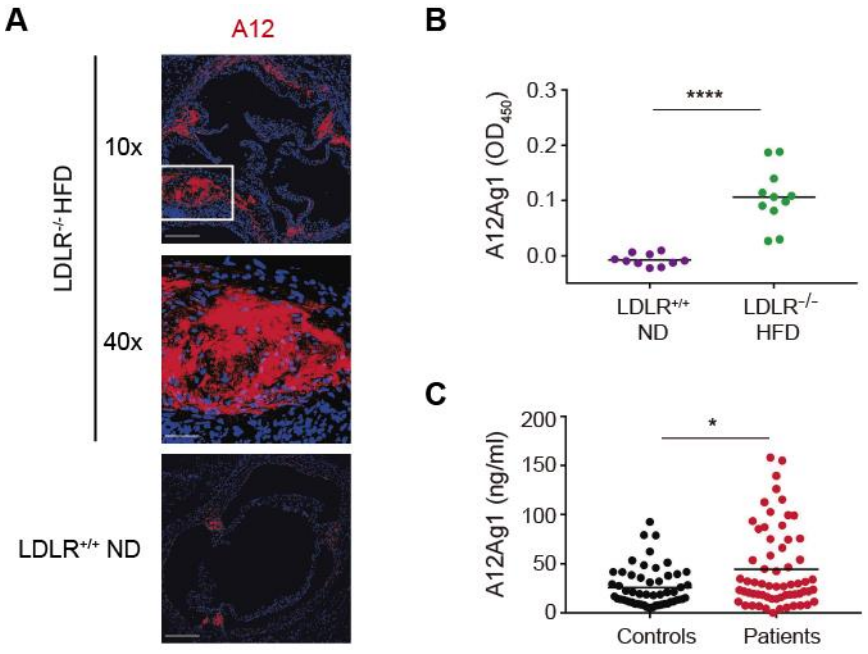

Figure 1. A12 antibody binds atheroma plaque and A12Ag1 as a novel atherosclerosis biomarker. (A) Immunofluorescence staining of aortic sinus sections from LDLR-/- HFD mice and control mice LDLR+/+ ND with A12 antibody (red) and Dapi (blue). **(B)** Quantification of A12Ag1 protein levels in plasma from LDLR-/- HFD and LDLR+/+ ND mice. **(C)** Quantification of A12Ag1 protein levels in plasma from human carotid atherosclerosis patients and control individuals.

Key words: Atherosclerosis, antibodies, A12 antibody, LDLR-/- HFD mice, atheroma plaque, cholesterol, LDL, B-cells, B-lymphocytes.

Technology type: atherosclerosis, diagnostic, therapy, antibodies.

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