BRUNO BUCHHOLZ

Fibroblast activation protein: an oncological target whose inhibition could also be beneficial in atherosclerosis

Stein S, Weber J, Nusser-Stein S, Pahla J, Zhang HE, Mohammed SA, Oppi S, et al. Deletion of Fibroblast Activation Protein Provides Atheroprotection. **Cardiovasc Res. 2020 May 13;cvaa142. doi: 10.1093/cvr/cvaa142**

Atherosclerotic plaque stability is a key determinant in the possibility of plaque rupture leading to a cardiovascular event. Structural plaque instability may produce acute clinical atherosclerotic manifestations as a consequence of thrombosis or emboli with vessel occlusion, as myocardial infarction or ischemic stroke. A plaque with a certain degree of progression consists of a lipid-rich nucleus with necrotic tissue surrounded by a fibrous capsule. Its stability will be conditioned by the extent and level of inflammation found in the nucleus and the capsule thickness. When the fibrous capsule is thick enough, there is less risk of rupture and it is also a barrier that separates the blood prothrombotic factors from the lipid nucleus, providing plaque stability. Both plaque components are not static elements; on the contrary, they have very active pathophysiological dynamics mainly subject to oxidative and inflammatory stress levels. Specifically, the plaque capsule is actively and permanently replacing its fibrous connective tissue components where extracellular matrix proteolytic enzymes play an important role. In this sense, collagenases as cathepsins and matrix metalloproteinases (MMPs) may produce exaggerated degradations that can reduce capsule thickness increasing plaque fragility. Recently, fibroblast activation protein (FAP), a soluble or membrane-bound serine protease with strong activity in collagen replacement, has been found to be significantly involved in the ventricular remodeling of hypertensive heart failure.

Based on a previous study showing high FAP expression in fibroatheromatous plaques, Stein et al. proposed as new objective to demonstrate the cause-effect relationship between FAP inhibition and atherogenesis progression using FAP deficient mice which, at the same time, can develop atherosclerosis by a lipid-rich diet and transgenicity [apolipoprotein E (Apoe-/-) and low-density lipoprotein receptor (Ldlr-/-)]. At the end of the protocol, atherosclerotic plaque histological and molecular studies of the abdominal aorta were performed. Interestingly, they observed a cause-effect relationship between FAP expression and atherosclerosis. Mice with FAP deletion decreased atherosclerotic progression independently of plasma lipid levels. Moreover, microscopic assessments revealed greater plaque stability, mainly higher fibrous capsule thickness due to reduced enzymatic collagen breakdown.

Fibroblast activation protein is a surface glycoprotein which is expressed in physiological conditions during embryonic development and to a lower degree in adult tissues. However, in adult life it is mostly expressed in fibroblasts in pathological conditions exhibiting great extracellular matrix remodeling, such as wound healing, tissue fibrosis associated with some autoimmune diseases and several malignant tumors. An increase in FAP expression has also been observed in remodeled hearts as a consequence of pressure overload. In this work, Stein et al. have shown for the first time that FAP plays an important role in atherosclerotic connective tissue remodeling and that its inhibition can delay fibro-lipid plaque evolution and increase its stability. It is worth mentioning that FAP depletion inhibits tumor cell growth, especially cancer cells, and that clinical trials are currently being conducted to evaluate the benefit of FAP inhibition in oncological treatment. As a whole, even though more studies are necessary, these results open an alternative door as a future therapeutic target for cardiovascular diseases with elevated extracellular matrix replacement, as atherosclerosis and cardiac remodeling.

Ethical approval

Not applicable.