Fibronectin is a crucial extracellular matrix (ECM) protein regulating ECM-dependent cell adhesion, migration, and differentiation. Besides being deposited as insoluble fibrils in tissues, it is also produced as soluble dimers by the liver and released in plasma. The presence of fibronectin in atherosclerotic plaques was described more than 20 years ago and plasma fibronectin has been shown to act as modulator of plaque development and phenotype (1).

Despite encoded by a single gene, several different variants of fibronectin are produced by alternative splicing. In particular, the exon encoding for the extra-domain A (EDA) is scarcely represented in adult tissues, but its expression is increased in several diseases. Although the evidence that experimental exclusion of EDA reduces atherosclerosis in mice (2), its role in atherosclerosis progression is far from being fully elucidated.

In this issue, Pulakazhi Venu et al. (3) provide new insight into the topic by studying two different transgenic animal models constitutively excluding (EDA−/−) or including (EDA+/+) EDA in fibronectin. Albeit the constitutive inclusion of EDA resulted in an increase in atherosclerotic burden as compared with EDA−/− mice, atherosclerotic plaques of EDA+/+ mice showed typical features of stability (i.e. increase in collagen and differentiated vascular smooth muscle cells content, reduced proteinases expression and macrophages infiltration). These results were confirmed in vitro and were independent of total fibronectin levels. Furthermore, by using a liver-specific conditional EDA knock-out, the authors found that the effects on atherosclerosis were mainly due to locally produced EDA instead of the one in plasma fibronectin.

Of note, the previously described association between higher EDA levels and stable phenotype in human carotid atherosclerotic plaques (4) clearly suggests a translational perspective for these observations. Indeed, although the complete comprehension of the molecular mechanisms will probably require further investigations, the current study (3) provides an exciting starting point and perspective for investigating EDA as a novel potential molecular target for atherosclerotic plaque stabilisation, which may significantly add to the currently available therapeutic options (5).

**Conflicts of interests**
None declared.

**References**