ABSTRACT

Abdominal aortic aneurysm (AAA) is a complex and multifactorial disease characterized by a focal pathological dilation of the abdominal aorta. The lack of effective treatment has led to an increase in the mortality rate due to the fatal consequence of the abdominal aorta rupture. As a consequence, this fact reveals the urgency of new insights into the molecular mechanisms that mediate the onset of this pathology and also the development of new drugs. Our group has been exploring and characterizing the underlying MFAP4-mediated mechanisms that lead the AAA formation.

In manuscript 1, we investigated the MFAP4 influence in the regulation of the inflammatory factors during the AAA development. For this stage of the work, double apolipoprotein E- and MFAP4-deficient (*ApoE*$^{-/-}$*Mfap4*$^{-/-}$) and control apolipoprotein E-deficient (*ApoE*$^{-/-}$) mice were infused subcutaneously with angiotensin II (Ang II) for 28 days. As results, we showed that MFAP4 was expressed in the tunica media in both normal aorta and AAA tissue from human and mouse. Also, we displayed that the blood pressure induction was independent of *Mfap4* while *ApoE*$^{-/-}$*Mfap4*$^{-/-}$ mice had lower AAA incidence and maximal diameter compared to *ApoE*$^{-/-}$. Following the *ApoE*$^{-/-}$ *Mfap4*$^{-/-}$ AAAs were further characterized by reduced macrophage infiltration, matrix metalloproteinase (MMP)-2 and MMP-9 activity, microvessel numbers, collagen content and elastic membrane disruption. Lastly, the MFAP4 stimulation significantly increased MMP-9 activity in monocytic THP-1 cells *in vitro*. Taken the results together, we suggest that MFAP4 induces inflammation, MMP activity and maladaptive remodeling of the ECM leading to an acceleration of AAA progression. Importantly, mechanistic in vitro studies demonstrate that MFAP4 is a critical biological component in the regulation of MMP-9 activity, acting as an essential aggravator of AAA development in mice.

To date, no study present in the literature, addressing inflammatory processes related to AAA development, were able to cease the degradation of elastic fibers. Supposedly, the triggering of the inflammatory process continues to occur in lesser intensity through alternative pathways, with the participation of other molecular components. Taking into account this fact and the results from the manuscript 1, we employed bioinformatics approaches to additionally explored an alternative pathway potential capable of ceasing the elastic fiber degradation. Thus, in the Manuscript 2,

we hypothesized a possible interaction between MFAP4 and the extracellular part of the neurogenic locus notch homolog 1 (NOTCH1) using information provided by the predicted protein-protein interaction (PPI) network. Also, we identified that the potential binding region of MFAP4 with NOTCH1 is localized between epidermal growth factor (EGF)-like 14 and EGF-like 15 domains. After a virtual screening of 2324 commercially available compounds, the natural product Morin was considered as a potential inhibitor for MFAP4-NOTCH1 interaction.

Considering the results from the manuscript 1 and 2, we may point out that MFAP4 as a potential target for modulating the inflammatory process in AAA and also for drug design.