Commentary for the article: MicroRNA-1246 regulates proliferation, invasion and differentiation in human vascular smooth muscle cell by targeting cystic fibrosis transmembrane conductance regulator (CFTR)

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Received: 29 December 2020 / Revised: 29 December 2020 / Accepted: 4 January 2021 / Published online: 16 January 2021
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In this issue of Pflügers Archiv European Journal of Physiology, Pan et al. demonstrate the effects of miR-1246 in the regulation of proliferation, migration, and differentiation of vascular smooth muscle cells (VSMCs) [6]. By using human VSMC cell lines and molecular, cellular and functional approaches, the authors demonstrated that miR-1246 actions on VSMCs are exert through downregulation of cystic fibrosis transmembrane conductance regulator (CFTR) protein. Atherosclerosis is a chronic low-grade inflammatory process that involves large and medium-caliber arteries and is one of the leading causes of morbidity and mortality worldwide. Therefore, it is essential to advance in the knowledge of the cellular and molecular mechanisms that lead to its development and complication given its high impact on health [1, 4]. VSMCs dysfunction represent a key step in the pathophysiology of atherosclerotic lesion [9], turning the comprehension of the mechanisms that lead to VSMCs dysfunction an area of great interest since they can offer an alternative for the development of new therapeutic strategies.

Recent findings support the fact that miRNAs are involved in different pathological process of VSMCs by stimulating a high rate of proliferation, migratory capacity, apoptosis, calcification, aging, and switch their contractile differentiation to

a secretory phenotype, which leads to formation of a neointima with excessive extracellular matrix deposition and inflammation that contributes to progressive damage during atherosclerosis (Fig. 1) [1, 2, 4, 9]. Furthermore, Sun et al. [8] have shown in an atherosclerosis model of Apo E ^{-/-} mice fed with a western diet for 16 weeks, that miR-146b-5p protects against atherosclerosis by inhibiting VSMCs proliferation and migration. In this regard, it should be noted that some drugs like olmesartan (an Ang II AT1 receptor antagonist) are also capable of regulating miRNAs, such as miR-665, improving VSMC dysfunction [10].

The molecular targets of miRNAs involve downstream elements such as transcription factors and intracellular signaling cascades that control basic cellular processes in VSMCs. Thus, the proliferative and migratory phenotypes have been described to be induced when some miRNAs are increased, such as miR-24, miR-26a, miR-146a, miR-221, miR-222, or when other miRNAs are decreased like miR-1, miR-31, miR-125b, miR-133, and miR-143 [1, 2, 4, 9]. Some of the intracellular targets of miRNA can affect VSMCs proliferation by regulating cell cycle molecules and apoptosis pathway such as kinase-dependent cyclins. Additionally, the synthetic and secretory phenotypes can be stimulated by increasing the expression of miR-21, miR-26a, and miR-34a or by decreasing the expression of miR-29b, miR-31, miR-145, and miR-205 [1, 2, 4, 9]. The present study of Pan et al. now adds a new player, miR-1246, to the list of miRNAs involved in VSMC dysfunction [6]. Recently, miRNA-1246 has gained relevance as a genomic regulator that promotes proliferation and invasion in tumorigenesis [7]. The authors also demonstrate the association of the chloride channel CFTR transporter as the molecular target of miR-1246. The CFTR transporter acts as a chloride channel (cAMP dependent) and it has been reported to be involved in the regulation of pH, cell volume, and proliferation and migration [5]. Previous studies have shown that

This article is a commentary to the original article <https://doi.org/10.1007/s00424-020-02498-8>

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Fig. 1 The multiple roles of miRNAs in VSMCs in the pathogenesis of atherosclerosis. Solid arrow indicates stimulation and T-line indicates inhibition

the CFTR channel is not only involved in the vascular remodeling of cerebral arteries, but it also protects against vascular inflammation and atherogenesis in apo E deficient mice, by decreasing NF κ B levels and MAPK activity [9, 10]. The activation of this CFTR channel, not only inhibits oxidative stress, but also prevents the development of arterial hypertension by facilitating VSMCs relaxation [3, 11].

Together, all this evidence highlights the importance of miRNAs as key regulators of vascular function, thus exposing an intricate network of subcellular interaction typical of a complex pathological process as atherosclerosis. Meanwhile, further investigations will be required to elucidate a possible pharmacological modulation of miRNAs as a promising candidate for a new therapeutic strategy for atherosclerosis.

Compliance with ethical standards

Conflict of interest The authors declare he has no conflict of interest.

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