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Original Article

5′-tiRNA-Cys-GCA regulates VSMC proliferation and phenotypic transition by targeting STAT4 in aortic dissection

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Accumulating evidence shows that tRNA-derived fragments are a novel class of functional small non-coding RNA; however, their roles in aortic dissection (AD) are still unknown. In this study, we found that 5′-tiRNA-Cys-GCA was significantly downregulated in human and mouse models of aortic dissection. The abnormal proliferation, migration, and phenotypic transition of vascular smooth muscle cells (VSMCs) played a crucial role in the initiation and progression of aortic dissection, with 5′-tiRNA-Cys-GCA as a potential phenotypic switching regulator, because its overexpression inhibited the proliferation and migration of VSMCs and increased the expression of contractile markers. In addition, we verified that signal transducer and activator of transcription 4 (STAT4) was a direct downstream target of 5′-tiRNA-Cys-GCA. We found that the STAT4 upregulation in oxidized low-density lipoprotein (ox-LDL)-treated VSMCs, which promoted cell proliferation, migration, and phenotypic transformation, was reversed by 5′-tiRNA-Cys-GCA. Furthermore, 5′-tiRNA-Cys-GCA treatment reduced the incidence and prevented the malignant process of angiotensin II- and β-aminopropionitrile-induced AD in mice. In conclusion, our findings reveal that 5′-tiRNA-Cys-GCA is a potential regulator of the AD pathological process via the STAT4 signaling pathway, providing a novel clinical target for the development of future treatment strategies for aortic dissection.

INTRODUCTION

The definition of aortic dissection (AD) is the rupture of the aortic intima due to various reasons, causing blood from the rupture orifice to enter the aortic wall, and forming the arterial wall separation..[1,2] Eighty percent of AD patients die of dissection rupture;[3] hence, once AD occurs, the patient should be immediately hospitalized and given surgical intervention. The vascular smooth muscle cells (VSMCs), an important constituent of arterial blood vessels, are believed to play a crucial role in the onset and progression of AD.[4] VSMCs have a prominent feature called phenotypic flexibility, which enables them to alternate between the contractile (differentiated) and synthetic (dedifferentiated) phenotypes.[5–8] Contractile VSMCs are characterized by the high expression of α-smooth muscle actin (α-SMA) and reduced proliferation and migration capabilities. In contrast, synthetic VSMCs contain low levels of differentiation markers and exhibit increased proliferation and migration.[9] VSMCs accelerate vascular remodeling through the occurrence of abnormal phenotypic alternations caused by various cell stimulants, such as oxidized low-density lipoprotein (ox-LDL) and platelet-derived growth factor BB (PDGF-BB).[10–12] Vascular remodeling involves the abnormal proliferation and apoptosis of VSMCs, subsequently damaging the state of vascular balance.[13,14] In addition to the abnormal proliferation and phenotypic transition of VSMCs, apoptosis is also an important link in AD progression.[15,16] Recent studies confirmed that compared with the control group, the apoptosis of VSMCs in human AD samples was more common.[17,18] Therefore, elucidation of the mechanisms involved in the phenotypic conversion and apoptosis of VSMCs during vascular remodeling under pathological conditions is essential for the development of new diagnosis and treatment strategies for AD.

The tRNA-derived stress-induced RNAs (tiRNAs) are a kind of newly discovered non-coding RNAs produced from mature tRNAs.[14,19–21] Under specific pathological conditions, mature tRNAs are cleaved by

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