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Short Communication

Kruppel Like Factor and Endothelial Dysfunctions

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Abstract

Atherosclerosis is a chronic progressive disease caused by vascular injury, and is induced by the interaction of various inflammatory cells and mediators. The Kruppel-like factor 4 (KLF4) is an important transcription factor that has a role in cell growth, differentiation, proliferation, and regulation of cardiovascular disease. It is gained interest of scientist as KLF4, in particular, plays an important role in the pathogenesis of atherosclerosis.KLF4 may be an important "molecular switch" and is being used as biomarker and therapeutic targetin atherosclerosis and vascular disease.

Keywords: Kruppel Like Factor; KLF4; Atherosclerosis; Cardiovascular Disease

Introduction

Kruppel-Like Factors (KLFs) are a family of transcription factors that regulate a wide range of biological processes, including development, differentiation, and metabolism. In recent years, evidence has emerged linking KLFs to the development and progression of atherosclerosis, a chronic inflammatory disease that underlies most cases of cardiovascular disease. Atherosclerosis is characterized by the accumulation of lipids and other molecules within the arterial wall, leading to the formation of plaques that narrow the lumen and impair blood flow [1]. Although the precise etiology of atherosclerosis is not fully understood, it is believed to involve a complex interplay of genetic, environmental, and lifestyle factors.

Role of KLF-4

Recent studies have shown that KLF4, in particular, plays an important role in the pathogenesis of atherosclerosis. KLF4 is expressed in a wide range of cell types, including endothelial cells, smooth muscle cells, and macrophages, all of which play important roles in the development and progression of the disease [2].

- In endothelial cells, KLF4 regulates the expression of genes involved in inflammation, oxidative stress, and endothelial dysfunction, all of which are hallmarks of atherosclerosis. Studies have shown that KLF4 can activate the expression of pro-inflammatory cytokines such as IL-6 and IL-8, and can also upregulate the expression of adhesion molecules such as ICAM-1 and VCAM-1, which play a critical role in the recruitment of monocytes and other inflammatory cells to the site of plaque formation.
- In smooth muscle cells, KLF4 modulates the expression of genes involved in cell proliferation, migration, and extracellular matrix synthesis, all of which are important for the development and progression of atherosclerotic plaques. In particular, KLF4 can induce the expression of smooth muscle cell markers such as smooth muscle alpha-actin and calponin, and can also activate the expression of matrix metalloproteinases, which are involved in the degradation of the extracellular matrix.
- In macrophages, KLF4 regulates the expression of genes involved in lipid metabolism, foam cell formation, and inflammatory signalling. Studies have shown that KLF4 can activate the expression of scavenger receptors such as CD36 and SR-A, which facilitate the uptake of oxidized LDL by macrophages and the formation of foam cells within the arterial wall [3,4].

Overall, these findings suggest that KLF4 plays a critical role in the pathogenesis of atherosclerosis by modulating the expression of genes involved in inflammation, oxidative stress, endothelial dysfunction, smooth muscle cell proliferation and migration, and macrophage foam cell formation [1,5]. Targeting KLF4 and other KLF family members may therefore represent a promising therapeutic strategy for the prevention and treatment of atherosclerosis and its associated cardio metabolic complications.

KLF4 and endothelial dysfunction

Endothelial dysfunction is an early initiator of atherosclerosis and is characterized by the impaired ability of the endothelium to

regulate vascular tone and homeostasis. KLF4 expression is up-regulated in response to pro-inflammatory stimuli such as TNF-α, IL-1β, and oxidized LDL, which are known to contribute to endothelial dysfunction. KLF4 mediates its effects on endothelial cells by regulating the expression of genes involved in inflammation and oxidative stress [6].

One of the key genes regulated by KLF4 in endothelial cells is endothelin-1, a potent vasoconstrictor that contributes to endothelial dysfunction. KLF4 has been shown to upregulate the expression of endothelin-1 in response to pro-inflammatory stimuli, leading to vasoconstriction and impaired vascular function. In addition to endothelin-1, KLF4 also regulates the expression of other genes involved in the regulation of vascular tone and homeostasis, including eNOS, caveolin-1, and thrombomodulin.

KLF4 and smooth muscle cell proliferation and migration

Smooth muscle cells play a critical role in the pathogenesis of atherosclerosis by contributing to the formation and progression of atherosclerotic plaques. In response to pro-inflammatory stimuli, smooth muscle cells become activated and proliferate, migrate, and synthesize extracellular matrix components, ultimately leading to the formation of atherosclerotic plaques.KLF4 has been shown to regulate the expression of genes involved in smooth muscle cell proliferation and migration, including smooth muscle alpha-actin, calponin, and matrix metalloproteinases. In addition, KLF4 has been shown to interact with myocardia, a key regulator of smooth muscle cell differentiation, to modulate gene expression and smooth muscle cell phenotype [7].

KLF4 and macrophage foam cell formation

Macrophage foam cells are a hallmark of atherosclerotic plaques and are formed when macrophages take up oxidized LDL and become engorged with lipids. KLF4 has been shown to regulate the expression of genes involved in lipid metabolism and foam cell formation, including scavenger receptors CD36 and SR-A. In addition to its effects on foam cell formation, KLF4 also regulates the inflammatory response of macrophages. KLF4 has been shown to activate the expression of pro-inflammatory cytokines such as IL-1β and TNF-α, as well as the chemokine MCP-1, which contributes to the recruitment of monocytes and other inflammatory cells to the site of plaque formation.

Targeting KLF4 for the prevention and treatment of atherosclerosis

Given the central role of KLF4 in the development and progression of atherosclerosis, targeting this transcription factor has emerged as a promising therapeutic strategy for the prevention and treatment of the disease. Several approaches have been explored for targeting KLF4, including small molecule inhibitors, RNA interference, and gene editing.

- One approach for targeting KLF4 involves the use of small molecule inhibitors that can disrupt KLF4 function. Several compounds have been identified that can bind to KLF4 and inhibit its activity, including the naturally occurring compound resveratrol and synthetic compounds such as ML264 and GSK-J4. These compounds have been shown to reduce inflammation and endothelial dysfunction *in vitro* and *in vivo*, and may have potential for the treatment of atherosclerosis.
- Another approach for targeting KLF4 involves the use of RNA interference to knock down KLF4 expression. Several studies have shown that siRNA-mediated knockdown of KLF4 can reduce inflammation, foam cell formation, and atherosclerotic plaque formation in animal models of the disease. However, the use of RNA interference for therapeutic purposes is challenging due to issues related to delivery and specificity.
- Gene editing approaches such as CRISPR/Cas9 have been explored for the targeted disruption of KLF4 expression or function. However, gene editing strategies for the treatment of atherosclerosis are still in the early stages of development and face significant challenges related to specificity and safety [7,8].

Conclusion

KLF4 plays a critical role in the pathogenesis of atherosclerosis by modulating the expression of genes involved in inflammation, oxidative stress, endothelial dysfunction, smooth muscle cell proliferation and migration, and macrophage foam cell formation. Targeting KLF4 and other KLF family members may represent a promising therapeutic strategy for the prevention and treatment of atherosclerosis and its associated cardio metabolic complications. However, further research is needed to fully understand the role of KLFs in atherosclerosis and to develop safe and effective therapeutic approaches.

Bibliography

1. Yoshida T and M Hayashi. "Role of Krüppel-Like Factor 4 and its Binding Proteins in Vascular Disease". *Journal of Atherosclerosis and Thrombosis* 21.5 (2014): 402-413.

2. Zheng X., *et al*. "Key role of microRNA-15a in the KLF4 suppressions of proliferation and angiogenesis in endothelial and vascular smooth muscle cells". *Biochemical and Biophysical Research Communications* 437.4 (2013): 625-631.

3. Hansson GK. "Inflammation, atherosclerosis, and coronary artery disease". *The New England Journal of Medicine* 352.16 (2005): 1685-1695.

4. N S., *et al*. "Myeloid Krüppel-like factor 4 deficiency augments atherogenesis in ApoE-/- mice--brief report". *Arteriosclerosis, Thrombosis, and Vascular Biology* 32.12 (2012): 2836-2838.

5. Lavigne MC., *et al*. "Growth and phenotypic characterization of porcine coronary artery smooth muscle cells". *In Vitro Cellular and Developmental Biology – Animal* 35.3 (1999): 136-143.

6. Goikuria H., *et al*. "Characterization of Carotid Smooth Muscle Cells during Phenotypic Transition". *Cells* 7.3 (2018).

7. Wang TM., *et al*. "microRNA let-7g suppresses PDGF-induced conversion of vascular smooth muscle cell into the synthetic phenotype". *Journal of Cellular and Molecular Medicine* 21.12 (2017): 3592-3601.

8. Zheng B., *et al*. "Role of Kruppel-like factor 4 in phenotypic switching and proliferation of vascular smooth muscle cells". *IUBMB Life* 62.2 (2010): 132-139.