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Extended Abstract
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Asia Pharma 2016 : Targeted inhibition of transcription factor STAT3 for the prevention and treatment of cancer - Gautam sethi - National University of Singapore

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Cardiovascular and cerebrovascular diseases, especially heart attack and stroke, significantly contribute to worldwide mortality , causing approximately 17 million deaths per year. Moreover, atherosclerosis is recognized as the original cause of most cardiovascular and cerebrovascular diseases 3-5. As a chronic progressive inflammatory arterial wall disease, atherosclerosis is characterized by the accumulation of lipids in the intima, thickening of the arterial wall, and narrowing of the vascular cavity. The major drivers leading to atherosclerosis include hyperlipidemia, hyperglycemia, insulin resistance, hypertension, and other factors such as genetics, age, cigarette smoking, and mental status 6. Thus, various atherosclerosis treatments have emerged that directly target the above risk factors, such as lipid-lowering medications and antiplatelet aggregation therapies. However, these treatments are not entirely effective due to incomplete knowledge of the mechanisms of and effective target sites for atherosclerosis. Therefore, the mechanism of atherosclerosis has been a popular focus of research, from which scholars hope to find novel breakthroughs, develop feasible intervention measures, and improve the overall prevention and treatment strategies for atherosclerosis. Emerging studies reveal that the signal transducer and activator of transcription 3 (STAT3) may play a critical role in all these factors, which indicates that STAT3 might become a new target of atherosclerosis therapies. STATs, consisting of seven members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6), have dual functions in signal transduction and transcriptional regulation. STAT3, one of the seven STAT members, was initially identified by two individual groups in 1994 and has increasingly gained focused attention due to its significant roles in diverse biological processes, including cell proliferation, cell differentiation, cell survival, inflammation, immunity, and angiogenesis . Since the gene Stat3 was first described as an oncogene in 1999 , STAT3 has become the research focus for several disease areas as a potential anticancer target. Previous studies have verified that STAT3 plays an essential role in various diseases, including cancers , myocardial ischemic injury, stroke, and obesity . Recently, with the study of cardiovascular and cerebrovascular diseases becoming increasingly popular, STAT3 has been demonstrated to play roles in several cardiovascular diseases, including arteriosclerosis, cardiac hypertrophy, and heart failure. Although atherosclerosis is considered the critical pathological basis of most cardiovascular and cerebrovascular diseases, no specific reviews are aimed at the emerging roles of STAT3 in atherosclerosis. Thus, the present review aims to fill this gap.

In this review, by summarizing the current literature, we highlight the essential roles of STAT3 in atherosclerosis and present STAT3 inhibitors that may become potential treatment agents for atherosclerosis. First, we describe the general background of STAT3, including its structure, function, and regulation. Subsequently, we discuss the pathological roles of STAT3 in atherosclerosis from three independent but related biological processes, endothelial cell dysfunction, macrophage polarization, inflammation, and immunity. Moreover, we summarize the current inhibitors of STAT3 and explore their implications in atherosclerosis treatments. Finally, we highlight some potential issues and propose some solutions to these issues. In conclusion, this review may contribute to the application of STAT3 as a novel target of atherosclerosis therapies. Endothelial cell dysfunction causes the accumulation of lipids, inflammatory cells, and coagulation materials as well as vascular smooth muscle cell (VSMC) proliferation, thus promoting atherosclerotic plaque formation . Numerous clinical studies have shown that vascular endothelial cell dysfunction is the initiator of and key link to ensuing atherosclerosis. Furthermore, endothelial cell dysfunction is closely related to injuries induced by various types of hazards (smoking, hyperlipidemia, oxygen free radicals, etc.) Atherosclerosis is closely correlated with inflammation and exhibits diverse inflammatory behaviors at different stages. In the early stage of atherosclerosis, inflammation is mainly associated with mononuclear macrophage infiltration and increased secretion of proinflammatory cytokines, including IL-6, TNF-□ and IL-1□, while in the progressive stage of atherosclerosis, it mainly manifests as massive VSMC proliferation . Additionally, studies have found that p-STAT3 mainly localizes in the endothelial nucleus of the inflammatory response region of atherosclerotic plaques but not in the noninflammatory response region, which strongly indicates that STAT3 activation is involved in the atherosclerotic inflammation. After the discovery of Th17 cells, several groups addressed their potential contribution to atherogenesis. Moreover, elevated numbers of Th17 cells, which produce the proinflammatory molecule IL-17A, are associated with autoimmune diseases and have been observed in atherosclerotic lesions. Recently, Th17 cell processes were verified to be closely related to the occurrence and development of atherosclerosis, and STAT3 is the key regulator of Th17 cell differentiation through IL-6 induction In addition to its well-established roles in the nucleus during the progression of atherosclerosis, STAT3 is also present in mitochondria and contributes to the regulation of the electron transport chain (ETC) activity. As a major source of cellular ROS, mitochondrial-derived reactive oxygen species (mtROS) are natural byproducts of the ETC. STAT1 and STAT2, also play essential roles in atherosclerosis. STAT1 has been identified as a regulator of foam cell formation and atherosclerotic lesion development in an intraperitoneal inflamemation model and an atherosclerosis-susceptible bone marrow transplantation mouse model. Since the substitution of valine with phenylalanine at amino acid (V617F) within the JH2 'kinase-like' domain of JAK2 was demonstrated

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to result in an overactivation of JAK2, inhibitors targeting JAK2 specifically have become the focus of studies. Over the years, numerous JAK2 inhibitors have been designed, including ruxolitinib, tofacitinib, AG490, AZD1480, SB1578, and WP1066. These inhibitors inhibit the JAK2/STAT3 signaling pathway in a similar way, which indicates that they may function by suppressing immune and inflammatory responses during the development of atherosclerosis. Inhibitors approved by the FDA, including ruxolitinib and tofacitinib, suggest that STAT3-inhibiting strategies may offer promising developments in clinical fields 237-241. Recently, Johnson et al. provided the first evidence that inhibitors of STAT3 activation protect against Ang-II-induced oxidative stress, endothelial dysfunction, and hypertension in mice.

Previously, substantial evidence has provided support for the hypothesis that STAT3 is a prominent regulator of various cancers, ischemic injury, and obesity. However, the role of STAT3 in the regulation of atherosclerosis has not been clearly illustrated, and atherosclerosis is still a threat to humans. In this review, we provided a basic overview of STAT3 and showed its pathological roles in atherosclerosis. After summarizing previous studies, we illustrated how aberrant STAT3 activation contributes to endothelial cell dysfunction, macrophage polarization, inflammation, and immunity and may thus become an essential modulator during atherosclerosis.

Biography :

After completion of his postdoctoral training at University of Texas MD Anderson Cancer Center, Prof. Gautam Sethi joined Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore in 2008 as an Assistant Professor and was promoted to Associate Professor in 2015. The focus of his research over the past few years has been to elucidate the mechanism (s) of activation of oncogenic transcription factors such as NF-kB/STAT3 by carcinogens and inflammatory agents and the identification of novel inhibitors of these proteins for prevention of and therapy for cancer. From traditional Chinese and Indian medicinal plants, his group has identified numerous small molecules that can suppress various pro-tumorigenic signaling cascades involved in cancer initiation and promotion.

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