

FAK Family Kinases: A Potential Therapeutic Target for Atherosclerosis

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Abstract: Atherosclerosis (AS) is a chronic progressive inflammatory disease of the vascular wall and the primary pathological basis of cardiovascular and cerebrovascular disease. Focal adhesion kinase (FAK) and proline-rich tyrosine kinase 2 (Pyk2), two highly homologous members of the FAK family kinases, play critical roles in integrin signaling. They also serve as scaffolding proteins that contribute to the assembly of cellular signaling complexes that regulate cell survival, cell cycle progression, and cell motility. Research indicates that the FAK family kinases is involved in the gene regulation of vascular cells and that aberrant expression of this family is associated with pathological changes in vascular disease. These findings establish the FAK family kinases as a critical signaling mediator in atherosclerotic lesions and inhibition of its activity has the potential to attenuate the pathological progression of AS. This review highlights the indispensable role of the FAK family kinases in abnormal vascular smooth muscle cell proliferation, endothelial cell dysfunction, inflammation, and lipid metabolism associated with AS. We also summarize therapeutic targets against the FAK family kinases, providing valuable insights into therapeutic strategies for AS.

Keywords: FAK family kinases, atherosclerosis, inhibitors, cellular signaling

Introduction

Cardiovascular disease (CVD) has a significant impact on mortality and morbidity worldwide, with atherosclerosis (AS) being the primary pathological basis of CVD.¹ Atherosclerosis involves the development of fibrofatty lesions within the arterial wall and is characterized by arterial wall thickening, intimal lipid deposition, and luminal narrowing.² The risk factors contributing to the development of AS include hypertension, smoking, diabetes mellitus, hyperlipidemia, inflammation, aging, and genetic predisposition.³ Advances in cellular and molecular biology have greatly contributed to our understanding of AS and offer new perspectives for clinical management. Endothelial cells (EC), inflammatory cells, and vascular smooth muscle cells (VSMC) play pivotal roles in AS progression, with pathogenesis revolving around endothelial dysfunction, abnormal lipid metabolism, inflammatory response, oxidative stress, and macrophage polarization.⁴ Recent research has indicated that the focal adhesion kinase (FAK) family kinases and its signaling pathways play critical roles in these pathogenic mechanisms, suggesting that the FAK family kinases is a potential target for AS therapy. This review presents the primary advances in the last 20 years, starting with the discovery of FAK family kinases and ending with the idea of using FAK family kinases as a potential therapeutic target for AS (Table 1).

FAK and proline-rich tyrosine kinase 2 (Pyk2) are members of the FAK family kinases and are key protein tyrosine kinases involved in integrin signaling. FAK was discovered in 1992 and named after its prominent localization in focal adhesions.^{5,16,17} FAK has been implicated in various biological processes, including embryonic development, and several diseases, including CVD and cancer, through its regulation of cell migration. In 1992, Pyk2 was independently isolated as a focal adhesion protein similar to FAK, which is typically distributed throughout the cytoplasm but is enriched in the perinuclear region.¹⁸ Pyk2 regulates downstream signaling through protein phosphorylation and plays a role in cell survival, migration, epithelial-mesenchymal transition, and carcinogenesis.¹⁹ Currently, there is no comprehensive review explaining the specific roles of the FAK family kinases in AS progression. This review aims to address this gap.

Table 1 Advances in Understanding the Mechanism of FAK Family Kinases-Mediated Atherosclerosis

Study	Results	Ref.
Hanks et al, 1992	Chicken and mouse FAK(PTK2) cDNA is cloned.	[5]
Whitney et al, 1993	Human FAK cDNA is cloned.	[6]
Schaller et al, 1994	Y397 autophosphorylation site of FAK binds to SH2 domain of Src.	[7]
Rocic et al, 2001	PYK2 regulates VSMC protein synthesis.	[8]
Nowakowski et al, 2002	The structures of kinase domains for FAK are the first determined.	[9]
Ceccarelli et al, 2006	Two crystal structures of an NH ₂ -terminal fragment of FAK containing the FERM domain.	[10]
Sayers et al, 2008	FRNK expression promotes SMCs maturation during vascular development and following vascular injury.	[11]
Son et al, 2014	Petunidin directly suppresses FAK activity attenuate aortic SMCs migration.	[12]
Yurdagul et al, 2016	Macrophage recruitment and VCAM-1 expression were decreased in FAK-KD (Cre ⁺) mice.	[13]
Jeong et al, 2019	VS-4718 induced loss of FAK activity and increased nuclear FAK blocks neointimal hyperplasia.	[14]
Velatooru et al, 2021	FAK K152 SUMOylation plays a key role in endothelial activation and senescence.	[15]

This review summarizes the existing literature on the important role of the FAK family kinases in AS. Here, we review the structure, function, and activation pathways of the FAK family kinases. We then discuss the pathological involvement of the FAK family kinases in AS, focusing on four interrelated processes: VSMC proliferation, EC dysfunction, foam cell formation, and the development of inflammatory responses. In addition, we provide an overview of drugs that inhibit the FAK family of kinases.

Overview of the FAK Family Kinases

Structure of the FAK Family Kinases

FAK (gene symbol: PTK2) and Pyk2 (gene symbol: PTK2B) exhibit a similar structural composition, comprising three primary elements: a central kinase domain, an N-terminal FERM domain, and a C-terminal fragment domain that contains an adhesion-targeting sequence (Figure 1). The FERM domain comprises three distinct substructures (F1, F2, and F3).¹⁹ The nuclear localization sequence within the F2 lobe of the FERM structural domain and the nuclear export sequence in the kinase structural domain play crucial roles in facilitating the shuttling of FAK and Pyk2 between the nucleus and cytoplasm of the cell.²⁰ The proline-rich FAT structural domain targets FAK to the adhesion complex, where both FAK and Pyk2 localize to integrin-containing sites by binding paxillin and talin, resulting in focal adhesion formation.²¹ However, Pyk2 exhibits reduced adhesion localization because of its inability to bind talin. Further, the FAT region contains the tyrosine phosphorylation sites Y861 and Y925 that are phosphorylated by Src kinase. FAK and Pyk2 possess three proline-rich regions: one situated between the FERM and central kinase structural domains, and the other two located between the central kinase and FAT structural domains.

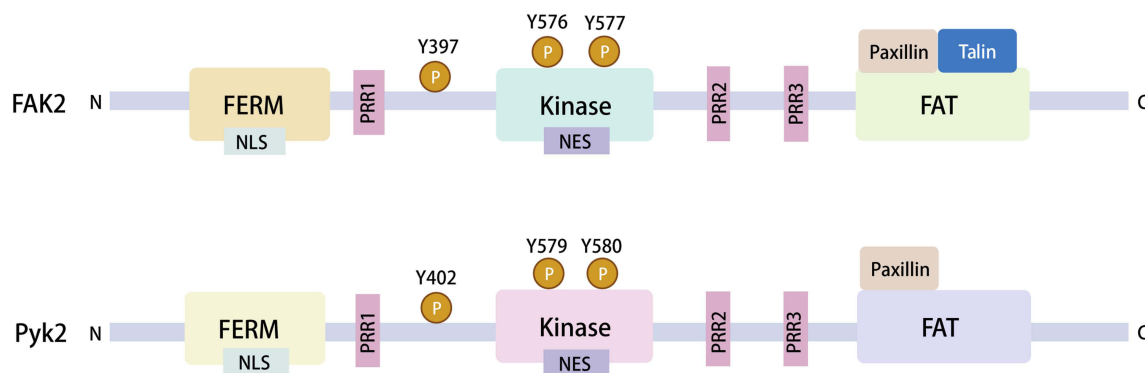


Figure 1 The structure of the FAK Kinase Family. FAK and Pyk2 consist of three structural domains: the central kinase structural domain, the N-terminal FERM structural domain, and a C-terminal structural domain containing an adhesion targeting sequence. The central kinase structural domain is flanked by three proline-rich regions. The nuclear localization sequence (NLS) of the FERM structural domain and the nuclear export sequence (NES) of the kinase structural domain facilitate the shuttling of FAK and Pyk2 between the nucleus and the cytoplasm. Key sites for tyrosine phosphorylation (P) are marked in yellow.

Biochemical Mechanisms for FAK Family Kinases Activation

FAK activation involves key steps such as autophosphorylation of Tyr397 and site-specific dimerization. The recruitment of FAK to the adhesion foci is facilitated by either the FAT or FERM structural domains. This recruitment leads to the dissociation of the latter from the catalytic structural domain, relieving autoinhibition and initiating initial kinase activation. Subsequently, dimer formation occurs via FERM-FERM or FERM-FAT interactions,²² allowing FAK autophosphorylation on Tyr397.²³ Tyr397, which is adjacent to the first proline-rich sequence, plays a significant role in mediating phosphorylation and triggering maximal activity of the FAK catalytic region. In addition, it serves as a docking site for highly active Src family kinases (SFKs).²⁴

Further, FAK is activated through growth factor signaling-mediated cell adhesion. It directly interacts with the cytoplasmic portion of various growth factor receptors, such as Met proto-oncogene receptor tyrosine kinase (rearranged during transfection), epidermal growth factor receptor, and vascular endothelial growth factor (VEGF). Integrin signaling, on the other hand, can activate FAK through the plasma membrane lipid phosphatidylinositol 4,5-bisphosphate. The binding of phosphatidylinositol 4,5-bisphosphate to a crucial region of the regulatory FERM structural domain triggers FAK aggregation in the lipid bilayer that induces FAK autophosphorylation. Phosphorylation of Src in the FAK activation loop results in release of the FERM/kinase chain and full catalytic activation of FAK.²⁵

Pyk2 activation does not rely solely on the recruitment of focal adhesions. The activation of Pyk2 is regulated by cytokines, growth factors, and, critically, by an elevation in cytoplasmic Ca²⁺ levels induced by various ligands, such as antidiuretic hormone and platelet-derived growth factor (PDGF).²⁶ Experimental evidence for the inhibitory interaction between the FERM domain and the structural domain of Pyk2 kinase remains unavailable,^{27,28} although key tyrosine residues within Pyk2 may play a crucial role in SFK-mediated phosphorylation.

Biological Functions of FAK Family Kinases

FAK and Pyk2, members of the FAK family kinases, serve as downstream substrates for kinase phosphorylation, transmit cellular signals, and act as scaffolding proteins in the assembly of signaling complexes. Activation of the FAK family kinases is modulated by various stimuli and plays a crucial role in regulating processes such as cell survival, proliferation, and motility.²⁹ FAK modulates the actin cytoskeleton to regulate cell adhesion and directional motility. Similarly, Pyk2 contributes to the regulation of cell phenotype and modulates the cytoskeleton during cell attachment and spreading.³⁰ FAK is actively involved in the growth and development of the heart, kidneys, and nervous system. Pyk2 does not affect embryonic growth or development. However, it plays a vital role in the developmental regulation of the immune system in mice, with Pyk2 deficiency leading to defective humoral immune responses in marginal B-zone cells.³¹ FAT of the Pyk2 structural domain is involved in regulating bone resorption, and its deficiency in mice contributes to AS development.³²

The FAK Family Kinases are Involved in Atherosclerosis

FAK family kinases are involved in atherosclerotic disease progression through multiple signaling cascades (Figure 2) that we will address in detail in subsequent sections to provide a theoretical basis for the use of the FAK family of kinases for treating AS.

Regulation of FAK Family Kinases in VSMCs

VSMCs are located in the medial layer of the arterial wall and play a crucial role in regulating vascular tone, blood pressure, and blood flow.³³ While VSMCs residing in mature vessels have low proliferative and migratory activity, VSMCs may migrate from the medial to the intimal layer of the arterial wall in response to physical and inflammatory stimuli that cause damage to the vascular endothelium and undergo a phenotypic switch from a “contractile” to a highly “synthetic” phenotype. This phenotypic transition involves the proliferation and migration of VSMCs and production of extracellular matrix components.³⁴ Targeted regulation of VSMC proliferation and migration is instrumental in effectively mitigating AS. FAK plays a critical role in regulating VSMC proliferation and migration. Inhibiting FAK

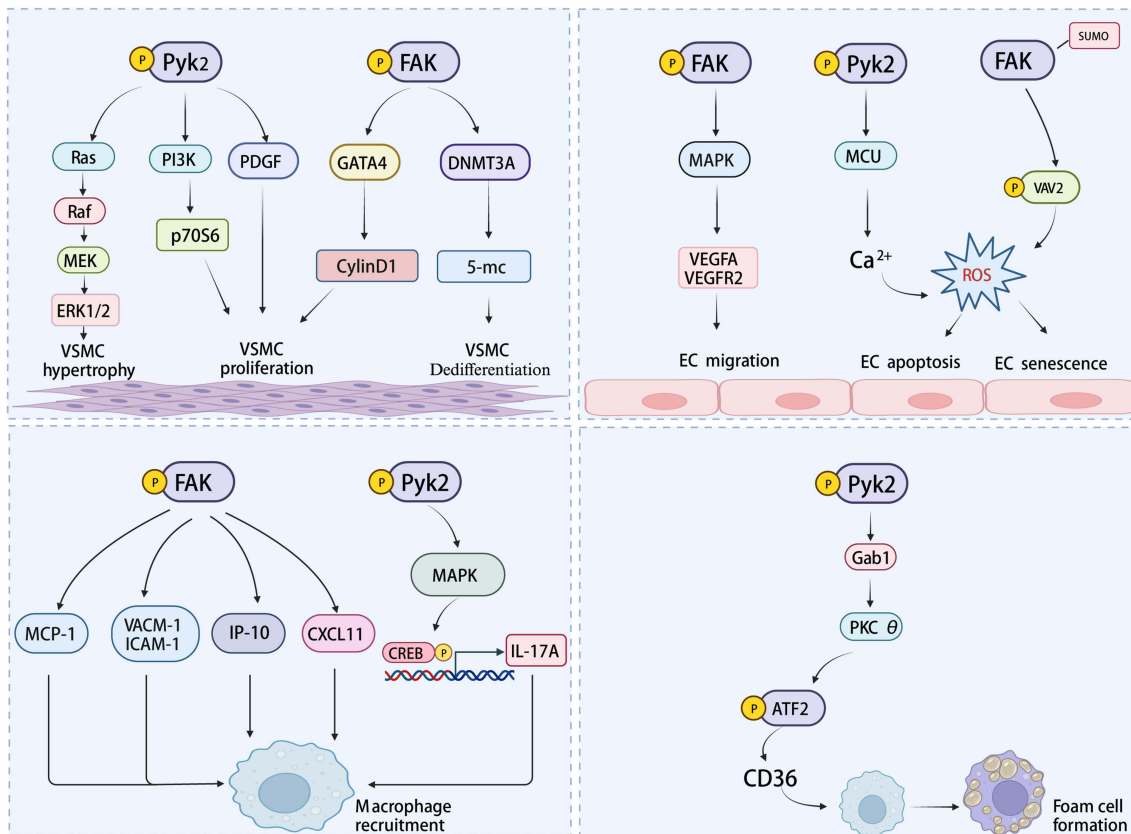


Figure 2 Potential role of FAK family kinases in atherosclerosis. FAK family kinases are involved in the pathogenesis of atherosclerosis by regulating VSMC phenotypic switching, EC dysfunction, foam cell formation, and inflammatory response mechanisms.

Abbreviations: Gab-1, grb2-associated binders; PKCθ, protein kinase Cθ; ATF2, activating transcription factor 2; MCP-1, monocyte chemoattractant protein-1; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cellular adhesion molecule-1; IP-10, induced protein 10; MAPK, mitogen-activated protein kinase; CREB, cyclic adenosine monophosphate response element-binding protein; IL-17, interleukin-17A; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated extracellular signal-regulated kinase; ERK1/2, extracellular signal-regulated kinases 1 and 2; PI3K, phosphatidylinositol 3-kinase; PDGF, platelet-derived growth factor; GATA4, GATA-binding protein 4; DNMT3A, DNA methyltransferases 3A; 5-mc, 5-methylcytosine; MAPK, mitogen-activated protein kinase; VEGFA, vascular endothelial growth factor A; VEGFR1, vascular endothelial growth factor R1; MCU, mitochondrial calcium uniporter; ROS, reactive oxygen species.

phosphorylation at the Tyr397 and Tyr925 sites and reducing Src phosphorylation (a downstream target of FAK) significantly attenuated VSMC migration and proliferation.^{35,36}

Role of FAK Family Kinases in VSMC Proliferation

FAK interacts with nuclear transcription factors, including tumor suppressor P53, GATA-binding protein 4 (GATA4), and TATA-box-binding protein-associated factor 9. Knockdown of GATA4 via shRNA attenuates endothelial hyperplasia induced by filamentous thread injury and promotes SMC proliferation by upregulating the transcription of the cell cycle protein D1³⁷ In healthy arteries, FAK is predominantly localized in the nuclei of smooth muscle cells. However, FAK is activated and redistributed to the cytoplasm after injury. Inhibition of FAK catalytic activity retains FAK in the nucleus, leading to reduced GATA4 protein expression in injured arteries. This inhibition also hampers GATA4-mediated transcription of the cell cycle protein D1, effectively blocking SMC proliferation and hyperplasia.¹⁴

Activation of FAK phosphorylation promotes cell-cell adhesion, cell-peripheral extracellular matrix adhesion, and cell proliferation, facilitating neointima formation. Deletion of Rac1, specifically in SMCs, leads to reduced cell proliferation and neointima formation following vascular injury. The Rho kinase family plays a role in focal adhesions and stress fiber formation, and inhibition of Rho kinase activity prevents neointima formation after vascular injury.³⁸ FAK governs the aforementioned cellular processes by activating the downstream small GTPases, Rac and Rho.

Pyk2 serves as an upstream regulator of multiple signaling pathways involved in Ang II-induced VSMC growth. The formation of the Pyk2-grb2/Src-shc-grb2 complex governs the ERK1/2 pathway by activating FAK. In addition,

Pyk2-dependent tyrosine phosphorylation, coupled with the interaction of p130 Cas, induces the activation of PI3K kinase.³⁹ By downregulating Pyk2 expression in Ang II-induced VSMCs, inhibition of both ERK1/2 and PI3K/Akt activation was achieved. Therefore, targeting Pyk2 phosphorylation is an essential molecular strategy for controlling VSMC growth.⁸

Role of FAK Family Kinases in VSMC Dedifferentiation

Under physiological conditions, VSMCs maintain a highly differentiated contractile resting state. However, in the presence of hypoxia and inflammation, VSMCs undergo dedifferentiation and transition from a contractile to a differentiated phenotype. This phenotypic switch is accompanied by reduced contractile capacity, enhanced proliferation and migration, and downregulated expression of SMC-specific contractile genes.⁴⁰ Inhibition of FAK leads to its nuclear translocation, resulting in reduced DNMT3A stability via ubiquitination and proteasomal degradation specificity. Consequently, this intervention reduces 5-mc levels, promotes SMC differentiation, and enhances the expression of SMC contractile genes.⁴¹

Role of FAK Family Kinases in VSMC Migration

Pyk2 downregulation hampers PDGF-induced AKT and ERK1/2 phosphorylation, inhibits cell cycle progression, and impedes VSMC proliferation.⁴² Hepatocyte growth factor (HGF) within the plaques acts as a chemokine for VSMCs, thereby stimulating their migration. In VSMCs, HGF induces a time-dependent activation of FAK and Pyk2 phosphorylation, thereby facilitating VSMC migration.⁴³

In conclusion, the FAK family kinases play an important role in regulating the phenotypic transition of VSMC during AS, making them a promising therapeutic target for AS.

Regulation of FAK Family Kinases in ECs

ECs are capable of producing vasodilators (such as NO, PG I₂, and H₂S) as well as vasoconstrictor molecules, which contribute to the regulation of arterial structure and remodeling by ensuring a balance between vasodilators and vasoconstrictors, thereby sustaining vascular tone.^{44,45} The microstructure of ECs, specifically the endothelial glycocalyx, plays a key role in maintaining their integrity.⁴⁶ Low endothelial permeability was observed under uniform flow conditions with high physiological shear stress in which the glycocalyx remained intact. Conversely, increased endothelial permeability has been observed in disturbed flow states with low physiological shear stress, leading to a reduction in the glycocalyx. Additionally, ECs exhibit metabolic activity and sustain their proliferation and vasodilatory functions through various metabolic pathways. Alterations in EC metabolism can induce EC proliferation and inflammation, thereby initiating AS.⁴⁷

Role of FAK Family Kinases in EC Migration

Enhanced neovascularization within atherosclerotic plaques can worsen plaque instability. Overexpression of Sema7A in human umbilical vein ECs (HUVECs) markedly upregulates VEGFA/VEGFR2, stimulating EC migration and promoting neovascularization within the plaques. Mechanistic studies have shown that Sema7A increases FAK expression through a β 1 integrin-dependent mechanism, thereby facilitating VEGFA/VEGFR2-mediated neovascularization. FAK inhibitors significantly inhibit EC migration and intraplaque neovascularization.⁴⁸

Role of FAK Family Kinases in EC Senescence

The disturbed flow (d-flow) promotes ROS production, EC inflammation, and apoptosis, ultimately contributing to endothelial cell dysfunction.⁴⁹ d-Flow stimulates ROS production through NADPH oxidase activity. In addition, it activates p90RSK, which upregulates FAK K152 SUMOylation and subsequent phosphorylation of VaV2, promoting FAK phosphorylation. Introducing a mutation at the lysine 152 site of FAK sumoylation to replace it with arginine demonstrated a significant reduction in apoptosis and diminished levels of the cellular senescence marker β -galactosidase (SA- β gal) induced by d-flow. In addition, it mitigated EC activation and senescence.¹⁵

Role of FAK Family Kinases in EC Apoptosis

Increased EC apoptosis is evident in regions susceptible to AS, and this apoptotic process can further worsen AS progression. ECs form a lining on the interior surface of blood vessels and are vulnerable to apoptosis triggered by external environmental stimuli such as hypoxia, hyperoxia, oxidative stress, and inflammatory factors,⁵⁰ which subsequently aggravate AS progression.⁵¹ The modulation of mitochondrial calcium uniporter (MCU) phosphorylation by Pyk2 participates in the regulation of mitochondrial Ca^{2+} uptake, ROS production, and EC apoptosis, thus contributing to the exacerbation of atherosclerotic disease progression. Pyk2/MCU protein expression is upregulated in a mouse model of AS. Similarly, increased levels of Pyk2/MCU were observed in a model of H_2O_2 -induced HUVEC injury. Additionally, shRNA targeting Pyk2 effectively shielded ECs from H_2O_2 -induced damage. Rosuvastatin exerted a protective effect in both the AS mouse model and the H_2O_2 -induced HUVEC injury model by inhibiting the Pyk2/MCU pathway, reducing mitochondrial damage and ROS generation, and preventing EC apoptosis. In conclusion, targeting the Pyk2/MCU pathway may represent a novel approach to prevent AS progression.⁵²

Taken together, these findings suggest that the FAK family kinases is capable of inducing EC dysfunction in response to a variety of stimuli and that inhibition of FAK activity reduces atherosclerotic lesions.

Involvement of the FAK Family Kinases in the Inflammatory Response to Atherosclerosis

AS is a progressive inflammatory disease of the blood vessel wall driven by innate immunity. During the early stages of AS, the inflammatory process begins with EC activation. These cells express inflammatory factors, including interleukin-8 (IL-8), ICAM-1, and monocyte chemoattractant protein-1 (MCP-1). During the advanced stages of AS, macrophages and other inflammatory cytokines infiltrate the vessel wall. They degrade collagen fibers within the extracellular matrix of plaques by secreting matrix metalloproteinases, resulting in plaque rupture and hemorrhage.⁵³ Consequently, modulation of inflammation mitigates the development of AS and its associated complications.⁵⁴

The suppression of FAK or Pyk2 expression results in decreased TNF- α -induced activation of ERK and JNK and reduced expression of CAMs. In a carotid artery ligation model using ApoE^{-/-} mice, activation of FAK/Pyk2 promoted the migration of macrophages to the vascular endothelium. Administration of dual inhibitors targeting FAK/Pyk2 resulted in decreased expression of inflammatory cell adhesion factors and reduced the recruitment of macrophages.⁵⁵

FAK facilitates NF- κ B activation, which leads to upregulation of VCAM-1 expression and promotes monocyte adhesion through the ERK-RSK-IKK β pathway.¹³ Inhibition of FAK activation in ECs exposed to oxidized low-density lipoprotein (ox-LDL) inhibits atherosclerosis by downregulating VCAM-1 and ICAM-1 expression and reducing monocyte adhesion.⁵⁶

Cyclic adenosine monophosphate response element-binding protein (CREB) plays a vital role in orchestrating the inflammatory response and facilitating THP1 cell migration and endothelial cell adhesion. CREB activation depends on the essential function of Pyk2 activity. 15(S)-HETE induces THP1 cell migration and adhesion, thereby initiating the activation of the Pyk2 signaling pathway that ultimately results in CREB activation and the production of IL-17.⁵⁷

Taken together, these findings suggest an important role for FAK family kinases in promoting AS and inflammation, and that inhibition of FAK activity reduces atherosclerotic lesions.

FAK Family Kinases are Involved in Lipid Accumulation in Atherosclerosis

Lipid uptake is facilitated by scavenger receptors such as CD36, lectin-like ox-LDL receptor-1 (LOX-1), and scavenger receptor A1.⁵⁸ Upon endothelial injury, LDL traverses the endothelial monolayer and undergoes modification, resulting in the formation of ox-LDL. Macrophages take up ox-LDL through scavenger receptor-mediated phagocytosis and cytophagocytosis at the cell membrane, leading to increased lipid accumulation and foam cell formation.⁵⁹ Strategies aimed at modulating lipid levels constitute mainstream therapies for AS, and targeting the reduction in foam cell formation by blocking lipid uptake holds promise for the treatment of this condition.

Prothrombin-induced foam cell formation was observed in peritoneal macrophages of ApoE^{-/-} mice. Immunofluorescence staining of cross-sections of mouse aortic roots showed increased Pyk2 phosphorylation and

CD36 expression in ApoE^{-/-} mice. In vitro studies showed that thrombin-induced CD36 expression in RAW264.7 cells, in a clock-dependent pattern resulted in foam cell formation. PYK2 activation plays a key role in thrombin-induced CD36 expression and foam cell formation. Thrombin promotes tyrosine phosphorylation of Pyk2 (Tyr402), and Pyk2 inhibition attenuates thrombin-induced activation of CD36 expression and foam cell generation.⁶⁰

In conclusion, regulation of lipid metabolism by inhibition of FAK family kinase activity is also a potential therapeutic strategy for AS.

FAK Family Kinases Inhibitors Find Various Applications

Currently, the development of FAK inhibitors is a research hotspot in academia and pharmaceutical companies, with a primary focus on oncology, where small molecules inhibit FAK phosphorylation, block intracellular signaling in the cell membrane, and inhibit cancer cell proliferation. To date, two compounds, namely GSK2256098 (NCT02523014, NCT02428270) and Defactinib (NCT01951690) are in Phase II trials, while Conteltinib (NCT05580445) is in Phase IB/II trials; VS-4718 (NCT01849744), PF-562271 (NCT00666926), IN10018 (NCT05327231), and APG-2449 (NCT03917043) are in Phase I trials. Many inhibitors are being investigated in preclinical studies, such as BJJ-03-025, PF-573228, and Y15.^{61–63} Although clinical trials on the association between FAK inhibitors and AS have not been widely conducted, the relevant basic research provides corresponding evidence for this. We reason that drug research targeting the regulation of FAK for the treatment of AS and cardiovascular diseases will progress significantly.

Pf-562271

PF-562271 is a dual inhibitor of FAK/Pyk2 that reduces VCAM-1 and ICAM-1 expression, monocyte migration, and macrophage recruitment in ApoE^{-/-} mice and HAOEC ECs. The FAK/Pyk2 inhibitor, PF-562271, has anti-inflammatory properties and shows promise as a potential therapeutic agent for atherosclerotic disease.⁵⁵

Vs-4718

GATA4 plays a role in SMC differentiation and vascular endothelial hyperplasia. The FAK inhibitor VS-4718 is currently in clinical development as a cancer therapy. In the femoral arterial wire injury model, VS-4718 induced a loss of FAK activity and increased nuclear FAK accumulation, thereby blocking neointimal hyperplasia via reduced GATA4 and cyclin D1 expression. These research findings suggest that VS-4718 may also be evaluated as a potential therapy for vessel wall-narrowing diseases.¹⁴

Acarbose

In a rabbit AS model, acarbose dose-dependently inhibited FAK phosphorylation, downregulated the PI3K/Akt signaling pathway, inhibited aberrant proliferation and migration of VSMCs, and attenuated the extent of aortic AS lesions.⁶⁴

Isatinidilol

The novel third-generation β -adrenergic receptor blocker, isatinidilol, demonstrated a dose-dependent inhibition of PDGF-induced proliferation in ECs. It also exhibited inhibitory effects on intimal hyperplasia and VSMC proliferation and migration in a rat carotid artery balloon injury model. Mechanistic investigations revealed that isatinidilol hindered Pyk2 phosphorylation in a concentration-dependent manner, reduced the coupling of PKC-ERK1/2 to Pyk2, reduced the intracellular calcium ion concentration, and attenuated intimal thickening by suppressing VSMC proliferation.⁶⁵

Pelargonidin

Pelargonidin is a novel FAK inhibitor that has demonstrated a dose-dependent inhibition of PDGF-BB-induced cell proliferation in HASMCs. Mechanistic studies have revealed that pelargonidin directly targets FAK and binds to it in an adenosine triphosphate-competitive manner. This binding inhibits the phosphorylation of FAK at the Tyr397, Tyr576, and Tyr577 sites induced by PDGF-BB. Consequently, pelargonidin effectively inhibits FAK activity and shows potential preventive effects against AS.⁶⁶ Similarly, petunidin, another anthocyanin, has a preventive effect on AS. In vivo studies showed that petunidin inhibited neointima formation induced by carotid balloon injury. In vitro studies showed its inhibitory effect on PDGF-BB-induced FAK phosphorylation and abnormal migration of HASMCs.¹²

Alginate Oligosaccharides

Alginate oligosaccharides (AOS) are polysaccharide polymers extracted from seaweed that inhibit the FAK/PI3K signaling pathway and protect HUVECs from H₂O₂-induced oxidative stress damage, providing a new alternative strategy for the prevention of AS.⁶⁷

Ginsenoside Rg3

Ginsenoside Rg3 effectively inhibited AS plaque formation and improved lipoprotein abnormalities in ApoE^{-/-} mice. In vivo studies revealed that ginsenoside Rg3 may protect ECs and inhibit AS by up-regulating PPAR γ via repressing FAK-mediated pathways, thus inhibiting the expression of VCAM-1 and ICAM-1 in intima, protect ECs, and inhibit AS.⁵⁶

Rubiaronone C

Rubiaronone C, the primary active ingredient of *Lobelia philippinensis*, belongs to the triterpenoid class. Recent studies have demonstrated that rubiarbonone C inhibits VSMC migration by suppressing FAK activation and reducing F-actin reorganization. Thus, rubiarbonone C shows great potential as a therapeutic candidate for the treatment of AS.⁶⁸

Mulberry Aqueous Extracts

Mulberry aqueous extracts contain polyphenolic compounds that have been shown to possess anti-hyperglycemic and lipid-modulating effects that help in the prevention of cardiovascular disease. The aqueous extract of mulberry was found to reduce the interaction between integrin- β 3 and FAK, inhibit VSMC migration, and prevent the development of high-cholesterol diet-induced AS in a rabbit model.⁶⁹

1-Deoxynojirimycin

1-Deoxynojirimycin (DNJ) is the active ingredient found in *Morus alba* that effectively inhibits lipid accumulation. In A7r5 cells cultured under a diabetic hyperglycemic condition, DNJ was found to reduce FAK phosphorylation and VSMC migration in a dose-dependent manner. DNJ was also found to inhibit glucose-stimulated migration of VSMCs by activating the AMPK/RhoB pathway and suppressing FAK pleiotropy.⁷⁰

In summary, current researchers have conducted a large number of studies on FAK inhibitors, but there are still gaps and shortcomings. First, the dose-response relationship of FAK inhibitors has yet to be explored, and some studies have shown that FAK inhibitors can promote angiogenesis and antagonize their own antitumor effects at low concentrations.⁷¹ Second, single-target FAK inhibitor therapy suffers from insufficient efficacy because the disease is associated with multiple abnormal mechanisms. In future, researchers should focus on multi-target drug development, such as FAK/Pyk2, FAK/IGF-1 receptor, FAK/EGF receptor, and FAK/CDK4/6 pathways. The application of computer-aided drug design, pharmacophore modeling, and molecular docking approaches to develop multi-target FAK inhibitors are other new directions in drug discovery. Finally, future studies still need to conduct in-depth research on regulatory mechanisms of the FAK family of kinases to assist in the development of novel and more selective inhibitors.

Discussion

The FAK family of kinases plays a crucial role in regulating many aspects of normal cellular behavior and has emerged as a promising therapeutic target for a wide range of diseases. This review summarizes the progress of research on FAK family kinases in AS, where activation of FAK phosphorylation has been found to exacerbate the progression of AS to various pathogenetic outcomes. However, there are some limitations to the current review. First, most animal models employed in current basic research only involve the early developmental stages of AS, and it is not clear whether FAK can regulate AS after plaque formation. There is also a lack of reports on the clinical application of FAK kinase inhibitors in AS, and the clinical efficacy of FAK kinase inhibitors needs to be verified by large-scale randomized controlled trials. Although the mechanism of action of FAK family kinases in AS has been extensively investigated, further studies are needed to address these open questions and overcome existing barriers. FAK is predominantly present in the nucleus of VSMCs in healthy arteries, and injury promotes FAK cytoplasmic relocalization and FAK activation in vivo. Little is known about how FAK re-localization occurs. Second, integrin signaling regulates FAK localization, and how integrins regulate FAK localization in different types of vascular cells in healthy and diseased states needs to be further

investigated and considered. Third, ER stress induces ox-LDL-mediated phenotypic transformation of VSMCs that involves reciprocal regulation between FAK and ER stress. Whether FAK is involved in the phenotypic transformation of VSMCs via reciprocal regulation with ER stress remains to be investigated. In conclusion, FAK family kinases are potential therapeutic targets for AS, and we hope to see more FAK and Pyk2 research within the AS field in the future.

Abbreviations

FAK, Focal adhesion kinase; Pyk2, proline-rich tyrosine kinase 2; VSMC, vascular smooth muscle cells; EC, endothelial cell; CVD, Cardiovascular disease; NLS, nuclear localization sequence; NEWS, nuclear export sequence; PRRs, proline-rich regions; VEGF, Vascular endothelial growth factor; SMC, smooth muscle cell; HGF, Hepatocyte growth factor; *Sema7A*, Signal protein 7A; ROS, Reactive oxygen species; d-flow, disturbed flow; IL, interleukin; MCP-1, Monocyte chemoattractant protein-1; HUVECs, human umbilical vein endothelial cells; ox-LDL, Oxidized low-density lipoprotein; LOX-1, lectin-like oxLDL receptor-1; AOS, Alginate oligosaccharides; DNJ, 1-deoxynojirimycin; Gab-1, grb2-associated binders; PKC θ , protein kinase C θ ; ATF2, activating transcription factor 2; MCP-1, monocyte chemoattractant protein-1; ICAM-1, Intercellular adhesion molecule 1; VCAM-1, Vascular cellular adhesion molecule-1; IP-10, induced protein 10; MAP, mitogen-activated protein kinase; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated extracellular signal-regulated kinase; ERK1/2, extracellular signal-regulated kinases 1 and 2; PI3K, phosphatidylinositol 3-kinase; PDGF, platelet-derived growth factor; GATA4, GATA-binding protein 4; DNMT3A, DNA methyltransferases 3A; 5-mC, 5-methylcytosine; MARK, mitogen-activated protein kinase; MCU, mitochondrial calcium uniporter.

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Disclosure

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References

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: update From the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76(25):2982–3021. doi:10.1016/j.jacc.2020.11.010
2. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. *Nat Rev Dis Primers*. 2019;5(1):56. doi:10.1038/s41572-019-0106-z
3. Lechner K, von Schacky C, McKenzie AL, et al. Lifestyle factors and high-risk atherosclerosis: pathways and mechanisms beyond traditional risk factors. *Eur J Preven Cardiol*. 2020;27(4):394–406. doi:10.1177/2047487319869400
4. Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*. 2006;47(8 Suppl):C7–12. doi:10.1016/j.jacc.2005.09.068
5. Hanks SK, Calalb MB, Harper MC, et al. Focal adhesion protein-tyrosine kinase phosphorylated in response to cell attachment to fibronectin. *Proc Natl Acad Sci USA*. 1992;89(18):8487–8491. doi:10.1073/pnas.89.18.8487
6. Whitney GS, Chan PY, Blake J, et al. Human T and B lymphocytes express a structurally conserved focal adhesion kinase, pp125FAK. *DNA Cell Biol*. 1993;12(9):823–830. doi:10.1089/dna.1993.12.823
7. Schaller MD, Hildebrand JD, Shannon JD, et al. Autophosphorylation of the focal adhesion kinase, pp125FAK, directs SH2-dependent binding of pp60src. *Mol Cell Biol*. 1994;14(3):1680–1688. doi:10.1128/mcb.14.3.1680-1688.1994
8. Rocic P, Lucchesi PA. Down-regulation by antisense oligonucleotides establishes a role for the proline-rich tyrosine kinase PYK2 in angiotensin ii-induced signaling in vascular smooth muscle. *J Biol Chem*. 2001;276(24):21902–21906. doi:10.1074/jbc.M101684200
9. Nowakowski J, Cronin CN, McRee DE, et al. Structures of the cancer-related Aurora-A, FAK, and EphA2 protein kinases from nanovolume crystallography. *Structure*. 2002;10(12):1659–1667. doi:10.1016/S0969-2126(02)00907-3
10. Ceccarelli DF, Song HK, Poy F, et al. Crystal structure of the FERM domain of focal adhesion kinase. *J Biol Chem*. 2006;281(1):252–259. doi:10.1074/jbc.M509188200
11. Sayers RL, Sundberg-Smith LJ, Rojas M, et al. FRNK expression promotes smooth muscle cell maturation during vascular development and after vascular injury. *Arteriosclerosis Thrombosis Vasc Biol*. 2008;28(12):2115–2122. doi:10.1161/ATVBAHA.108.175455
12. Son JE, Lee E, Jung SK, et al. Anthocyanidins, novel FAK inhibitors, attenuate PDGF-BB-induced aortic smooth muscle cell migration and neointima formation. *Cardiovasc Res*. 2014;101(3):503–512. doi:10.1093/cvr/cvt337

13. Yurdagul A Jr, Sulzmaier FJ, Chen XL, et al. Oxidized LDL induces FAK-dependent RSK signaling to drive NF- κ B activation and VCAM-1 expression. *J Cell Sci.* 2016;129(8):1580–1591. doi:10.1242/jcs.182097
14. Jeong K, Kim JH, Murphy JM, et al. Nuclear Focal Adhesion Kinase Controls Vascular Smooth Muscle Cell Proliferation and Neointimal Hyperplasia Through GATA4-Mediated Cyclin D1 Transcription. *Circ Res.* 2019;125(2):152–166. doi:10.1161/CIRCRESAHA.118.314344
15. Velatooru LR, Abe RJ, Imanishi M, et al. Disturbed flow-induced FAK K152 SUMOylation initiates the formation of pro-inflammation positive feedback loop by inducing reactive oxygen species production in endothelial cells. *Free Radic Biol Med.* 2021;177:404–418. doi:10.1016/j.freeradbiomed.2021.09.023
16. Lipfert L, Haimovich B, Schaller MD, et al. Integrin-dependent phosphorylation and activation of the protein tyrosine kinase pp125FAK in platelets. *J Cell Biol.* 1992;119(4):905–912. doi:10.1083/jcb.119.4.905
17. Guan JL, Shalloway D. Regulation of focal adhesion-associated protein tyrosine kinase by both cellular adhesion and oncogenic transformation. *Nature.* 1992;358(6388):690–692. doi:10.1038/358690a0
18. Guidetti GF, Torti M, Canobbio I. Focal Adhesion Kinases in Platelet Function and Thrombosis. *Arteriosclerosis Thrombosis Vasc Biol.* 2019;39(5):857–868. doi:10.1161/ATVBAHA.118.311787
19. Hall JE, Fu W, Schaller MD. Focal adhesion kinase: exploring Fak structure to gain insight into function. *Int Rev Cell and Mol Biol.* 2011;288:185–225.
20. Ossovskaya V, Lim ST, Ota N, et al. FAK nuclear export signal sequences. *FEBS Lett.* 2008;582(16):2402–2406. doi:10.1016/j.febslet.2008.06.004
21. Schlaepfer DD, Mitra SK, Ilic D. Control of motile and invasive cell phenotypes by focal adhesion kinase. *BBA.* 2004;1692(2–3):77–102. doi:10.1016/j.bbamer.2004.04.008
22. Brami-Cherrier K, Gervasi N, Arsenieva D, et al. FAK dimerization controls its kinase-dependent functions at focal adhesions. *EMBO J.* 2014;33(4):356–370. doi:10.1002/emj.201386399
23. Lietha D, Cai X, Ceccarelli DF, et al. Structural basis for the autoinhibition of focal adhesion kinase. *Cell.* 2007;129(6):1177–1187. doi:10.1016/j.cell.2007.05.041
24. Parsons JT. Focal adhesion kinase: the first ten years. *J Cell Sci.* 2003;116(Pt 8):1409–1416. doi:10.1242/jcs.00373
25. Goñi GM, Epifano C, Boskovic J, et al. Phosphatidylinositol 4,5-bisphosphate triggers activation of focal adhesion kinase by inducing clustering and conformational changes. *Proc Natl Acad Sci USA.* 2014;111(31):E3177–86. doi:10.1073/pnas.1317022111
26. Lev S, Moreno H, Martinez R, et al. Protein tyrosine kinase PYK2 involved in Ca(2+)-induced regulation of ion channel and MAP kinase functions. *Nature.* 1995;376(6543):737–745. doi:10.1038/376737a0
27. Dunty JM, Gabarra-Niecko V, King ML, et al. FERM domain interaction promotes FAK signaling. *Mol Cell Biol.* 2004;24(12):5353–5368. doi:10.1128/MCB.24.12.5353-5368.2004
28. Riggs D, Yang Z, Kloss J, et al. The Pyk2 FERM regulates Pyk2 complex formation and phosphorylation. *Cell Signal.* 2011;23(1):288–296. doi:10.1016/j.cellsig.2010.09.015
29. Gilmore AP, Owens TW, Foster FM, et al. How adhesion signals reach a mitochondrial conclusion—ECM regulation of apoptosis. *Curr Opin Cell Biol.* 2009;21(5):654–661. doi:10.1016/j.ccb.2009.05.009
30. Halder J, Kamat AA, Landen CN, et al. Focal adhesion kinase targeting using in vivo short interfering RNA delivery in neutral liposomes for ovarian carcinoma therapy. *Clin Cancer Res.* 2006;12(16):4916–4924. doi:10.1158/1078-0432.CCR-06-0021
31. Golubovskaya VM, Kweh FA, Cance WG. Focal adhesion kinase and cancer. *Histol Histopathol.* 2009;24(4):503–510. doi:10.14670/HH-24.503
32. Gil-Henn H, Destaing O, Sims NA, et al. Defective microtubule-dependent podosome organization in osteoclasts leads to increased bone density in Pyk2(-/-) mice. *J Cell Biol.* 2007;178(6):1053–1064. doi:10.1083/jcb.200701148
33. Rzuclidlo EM, Martin KA, Powell RJ. Regulation of vascular smooth muscle cell differentiation. *J Vascular Surg.* 2007;45(Suppl A):A25–32. doi:10.1016/j.jvs.2007.03.001
34. Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. *Physiol Rev.* 2004;84(3):767–801. doi:10.1152/physrev.00041.2003
35. Wu X, Bian F, Hu H, et al. Effects of Kindlin-2 on proliferation and migration of VSMC and integrin β 1 and β 3 activity via FAK-PI3K signaling pathway. *PLoS One.* 2020;15(6):e0225173. doi:10.1371/journal.pone.0225173
36. Ju S, Lim L, Ki YJ, et al. Oxidative stress generated by polycyclic aromatic hydrocarbons from ambient particulate matter enhance vascular smooth muscle cell migration through MMP upregulation and actin reorganization. *Part Fibre Toxicol.* 2022;19(1):29. doi:10.1186/s12989-022-00472-z
37. Molkenin JD. The zinc finger-containing transcription factors GATA-4, -5, and -6. Ubiquitously expressed regulators of tissue-specific gene expression. *J Biol Chem.* 2000;275(50):38949–38952. doi:10.1074/jbc.R000029200
38. Bae YH, Mui KL, Hsu BY, et al. A FAK-Cas-Rac-lamellipodin signaling module transduces extracellular matrix stiffness into mechanosensitive cell cycling. *Sci Signaling.* 2014;7(330):ra57. doi:10.1126/scisignal.2004838
39. Gomez D, Owens GK. Smooth muscle cell phenotypic switching in atherosclerosis. *Cardiovasc Res.* 2012;95(2):156–164. doi:10.1093/cvr/cvs115
40. Jeong K, Murphy JM, Kim JH, et al. FAK Activation Promotes SMC Dedifferentiation via Increased DNA Methylation in Contractile Genes. *Circ Res.* 2021;129(12):e215–e33. doi:10.1161/CIRCRESAHA.121.319066
41. Perez J, Torres RA, Roci P, et al. PYK2 signaling is required for PDGF-dependent vascular smooth muscle cell proliferation. *Am J Physiol Cell Physiol.* 2011;301(1):C242–51. doi:10.1152/ajpcell.00315.2010
42. Ma H, Calderon TM, Kessel T, et al. Mechanisms of hepatocyte growth factor-mediated vascular smooth muscle cell migration. *Circ Res.* 2003;93(11):1066–1073. doi:10.1161/01.RES.0000102867.54523.7F
43. Sharma A, Rizky L, Stefanovic N, et al. The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activator dh404 protects against diabetes-induced endothelial dysfunction. *Cardiovasc Diabetol.* 2017;16(1):33. doi:10.1186/s12933-017-0513-y
44. Rubanyi GM. The role of endothelium in cardiovascular homeostasis and diseases. *J Cardiovasc Pharmacol.* 1993;22(Suppl 4):S1–14. doi:10.1097/00005344-199322004-00002
45. Harding IC, Mitra R, Mensah SA, et al. Pro-atherosclerotic disturbed flow disrupts caveolin-1 expression, localization, and function via glycocalyx degradation. *J Transl Med.* 2018;16(1):364. doi:10.1186/s12967-018-1721-2
46. Feng S, Bowden N, Fragiadaki M, et al. Mechanical Activation of Hypoxia-Inducible Factor 1 α Drives Endothelial Dysfunction at Atheroprone Sites. *Arteriosclerosis Thrombosis Vasc Biol.* 2017;37(11):2087–2101. doi:10.1161/ATVBAHA.117.309249

47. Hu S, Liu Y, You T, Zhu L. Semaphorin 7A Promotes VEGFA/VEGFR2-Mediated Angiogenesis and Intraplaque Neovascularization in ApoE(-/-) Mice. *Front Physiol.* 2018;9:1718. doi:10.3389/fphys.2018.01718
48. Heo KS, Le NT, Cushman HJ, et al. Disturbed flow-activated p90RSK kinase accelerates atherosclerosis by inhibiting SENP2 function. *J Clin Invest.* 2015;125(3):1299–1310. doi:10.1172/JCI76453
49. Munshi N, Fernandis AZ, Cherla RP, et al. Lipopolysaccharide-induced apoptosis of endothelial cells and its inhibition by vascular endothelial growth factor. *J Immunol.* 2002;168(11):5860–5866. doi:10.4049/jimmunol.168.11.5860
50. Wu J, Hafner C, Schramel JP, et al. Cyclic and constant hyperoxia cause inflammation, apoptosis and cell death in human umbilical vein endothelial cells. *Acta Anaesthesiol Scandinavica.* 2016;60(4):492–501. doi:10.1111/aas.12646
51. Zhang Y, Yang X, Li Z, et al. Pyk2/MCU Pathway as a New Target for Reversing Atherosclerosis. *Front Cell Develop Biol.* 2021;9:651579. doi:10.3389/fcell.2021.651579
52. Zhu Y, Xian X, Wang Z, et al. Research Progress on the Relationship between Atherosclerosis and Inflammation. *Biomolecules.* 2018;8(3):80. doi:10.3390/biom8030080
53. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation.* 2002;105(9):1135–1143. doi:10.1161/hc0902.104353
54. Murphy JM, Jeong K, Rodriguez YAR, et al. FAK and Pyk2 activity promote TNF- α and IL-1 β -mediated pro-inflammatory gene expression and vascular inflammation. *Sci Rep.* 2019;9(1):7617. doi:10.1038/s41598-019-44098-2
55. Geng J, Fu W, Yu X, et al. Ginsenoside Rg3 Alleviates ox-LDL Induced Endothelial Dysfunction and Prevents Atherosclerosis in ApoE(-/-) Mice by Regulating PPAR γ /FAK Signaling Pathway. *Front Pharmacol.* 2020;11:500. doi:10.3389/fphar.2020.00500
56. Kotla S, Singh NK, Heckle MR, et al. The transcription factor CREB enhances interleukin-17A production and inflammation in a mouse model of atherosclerosis. *Sci Signaling.* 2013;6(293):ra83. doi:10.1126/scisignal.2004214
57. Yu XH, Fu YC, Zhang DW, et al. Foam cells in atherosclerosis. *Clin Chim Acta.* 2013;424:245–252. doi:10.1016/j.cca.2013.06.006
58. Chistiakov DA, Bobryshev YV, Orekhov AN. Macrophage-mediated cholesterol handling in atherosclerosis. *J Cell & Mol Med.* 2016;20(1):17–28. doi:10.1111/jcmm.12689
59. Raghavan S, Singh NK, Gali S, et al. Protein Kinase C θ Via Activating Transcription Factor 2-Mediated CD36 Expression and Foam Cell Formation of Ly6C hi Cells Contributes to Atherosclerosis. *Circulation.* 2018;138(21):2395–2412. doi:10.1161/CIRCULATIONAHA.118.034083
60. Groendyke BJ, Nabet B, Mohardt ML, et al. Discovery of a Pyrimidothiazolodiazepinone as a Potent and Selective Focal Adhesion Kinase (FAK) Inhibitor. *ACS Med Chem Lett.* 2021;12(1):30–38. doi:10.1021/acmedchemlett.0c00338
61. Slack-Davis JK, Martin KH, Tilghman RW, et al. Cellular characterization of a novel focal adhesion kinase inhibitor. *J Biol Chem.* 2007;282(20):14845–14852. doi:10.1074/jbc.M606695200
62. Hochwald SN, Nyberg C, Zheng M, et al. A novel small molecule inhibitor of FAK decreases growth of human pancreatic cancer. *Cell Cycle.* 2009;8(15):2435–2443. doi:10.4161/cc.8.15.9145
63. Chuang WY, Yu MH, Yang TY, et al. Acarbose attenuates migration/proliferation via targeting microRNA-143 in vascular smooth muscle cells under diabetic conditions. *J Food Drug Anal.* 2020;28(3):461–474. doi:10.38212/2224-6614.1241
64. Yeh JL, Liou SF, Chang YP, et al. Isoeugenodilol inhibits smooth muscle cell proliferation and neointimal thickening after balloon injury via inactivation of ERK1/2 pathway. *J Biomed Sci.* 2008;15(3):375–389. doi:10.1007/s11373-008-9236-0
65. Son JE, Jeong H, Kim H, et al. Pelargonidin attenuates PDGF-BB-induced aortic smooth muscle cell proliferation and migration by direct inhibition of focal adhesion kinase. *Biochem Pharmacol.* 2014;89(2):236–245. doi:10.1016/j.bcp.2014.02.015
66. Zhao J, Han Y, Wang Z, et al. Alginate oligosaccharide protects endothelial cells against oxidative stress injury via integrin- α /FAK/PI3K signaling. *Biotechnol. Lett.* 2020;42(12):2749–2758. doi:10.1007/s10529-020-03010-z
67. Park HS, Quan KT, Han JH, et al. Rubiarbonone C inhibits platelet-derived growth factor-induced proliferation and migration of vascular smooth muscle cells through the focal adhesion kinase, MAPK and STAT3 Tyr(705) signalling pathways. *Br J Pharmacol.* 2017;174(22):4140–4154. doi:10.1111/bph.13986
68. Chan K-C, Ho -H-H, Lin M-C, et al. Mulberry Water Extracts Inhibit Atherosclerosis through Suppression of the Integrin- β 3 /Focal Adhesion Kinase Complex and Downregulation of Nuclear Factor κ B Signaling in Vivo and in Vitro. *J Agric Food Chem.* 2014;62(39):823–830. doi:10.1021/jf502942r
69. Chan KC, Lin MC, Huang CN, et al. Mulberry 1-deoxynojirimycin pleiotropically inhibits glucose-stimulated vascular smooth muscle cell migration by activation of AMPK/RhoB and down-regulation of FAK. *J Agric Food Chem.* 2013;61(41):9867–9875. doi:10.1021/jf403636z
70. Reynolds AR, Hart IR, Watson AR, et al. Stimulation of tumor growth and angiogenesis by low concentrations of RGD-mimetic integrin inhibitors. *Nature Med.* 2009;15(4):392–400. doi:10.1038/nm.1941
71. Wang R, Zhao X, Yu S, et al. Discovery of 7H-pyrrolo[2,3-d]pyridine derivatives as potent FAK inhibitors: design, synthesis, biological evaluation and molecular docking study. *Bioorg Chem.* 2020;102:104092. doi:10.1016/j.bioorg.2020.104092

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