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Vav family exchange factors: Potential regulator in atherosclerosis

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ABSTRACT

The Vav family of guanosine nucleotide exchange factors (GEFs) regulates the phosphorylation of tyrosinase, influencing various physiological and pathological processes by modulating the binding of Rho GTPases to GDP/GTP. Recent research has highlighted the critical role of Vav family activation in tumorigenesis, neurological disorders, immune-related dysfunctions, and other diseases. This review offers a comprehensive overview of the structure and function of Vav proteins and their significant impact on the pathophysiology of atherosclerosis. In addition, we pay attention to the development of diagnostic and therapeutic targets centered around Vav proteins.

1. Introduction

The Vav proteins, comprising Vav1, Vav2, and Vav3, are signaling molecules that regulate the phosphorylation of tyrosinase. As guanosine nucleotide exchange factors (GEFs), they act as enzymes that regulate the activity of Rho GTPase protein in cell signal transduction. The Vav family converts the combined state between Rho GTPase and GTP/GDP, further transferring Rho GTPase from the inactive state (GDP bound) to the active state (GTP bound). Beyond their GT-pase-dependent functions, Vav proteins also participate in various signaling pathways through GTPase-independent pathways [1–3].

Vav1 was the first member of the Vav family to be discovered. It was discovered by Barbacid et al. when searching for new oncogenes [4]. Vav2 and Vav3 were subsequently identified and separated by researchers using standard cloning procedures [5–7]. Studies have shown that Vav1 was only expressed in bone marrow-derived cells, while Vav2 and Vav3 are broadly distributed among cells and exert more biological effects.

Multiple studies have linked the Vav family to the development of various diseases, including cardiovascular disorders. Genetic polymorphism analyses have found that the Vav2 rs602990 genotype and the Vav3 rs7528153 genotype are closely associated with increased risk for obesity, hypertension, and retinal arteriosclerosis [8,9]. Moreover, Vav-deficient mice exhibit significantly reduced atherosclerosis in animal models, further indicating a close relationship between the Vav gene and the occurrence and progression of atherosclerosis [10–15].

Vav proteins participate in several key cellular functions related to atherosclerosis, such as macrophage migration [16–19], lipid accumulation [19–21], cytoskeletal remodeling [19,20,22–24], and the overproduction of reactive oxygen species [19,21,25,26]. This review provides a comprehensive overview of the Vav family, including its structure, functions, signaling pathways, and specific roles in the pathogenesis of atherosclerosis.

2. Structure and functions of the Vav family

Each Vav protein exhibits a conserved structural network, comprising an N-terminal calponin-homology (CH) domain, an acidic (Ac) domain, a catalytic Dbl-homology (DH) domain, a pleckstrin-homology (PH) domain, a C1 subtype zinc finger (ZF) domain, a proline-rich region (PRR), and an SH1-SH2-SH3 domain composition. The DH, PH, and ZF domains constitute a common enzyme core essential for catalytic ability (Fig. 1A and B) [27–29]. This core also establishes phosphorylation-dependent interactions with the CH-Ac and CSH3

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regions [27,30]. In its non-phosphorylated state, the Vav protein adopts a closed conformation due to extensive intramolecular interactions between CH-Ac, CSH3, and the DH–PH–ZF box, occluding the GTPase binding site. Upon stimulation, multiple tyrosine phosphorylations within the Ac (Tyr142, Tyr160, Tyr174), ZF (Tyr541, Tyr544), and CSH3 (Tyr836) domains disrupt these interactions, leading to an "open" conformation that allows Vav proteins to bind to their substrates and exert biologic functions, a process known as the catalysis-dependent approach (Fig. 1C) [5,27,30,31].

In atherosclerosis, Vav primarily functions through the catalysis-dependent approach, interacting with substrates, such as Rac, RhoA, and Cdc42 within the Rho GTPase superfamily, including Ncf2 and calmodulin [32–34].

In addition to the catalysis-dependent approach, Vav proteins can also exert biological effects through a non-catalysis-independent mechanism. A prime example is the activation of the nuclear factor of activated T cells (NFAT) in T lymphocytes. Although the exact mechanism remains to be fully elucidated, it involves the CH domain of Vav proteins inducing the activation of the PLCγ–IP3–Ca^{2+} axis, leading to Ca^{2+}-dependent calcineurin activation and NFAT dephosphorylation and nuclear translocation [31,33–37].

The non-catalytic effect of Vav1 also extends to other biological processes, such as integrin-mediated signal transduction in T cells and the stabilization of Slp-76 microclusters following T cell receptor (TCR) activation. Furthermore, the SH2 domain of Vav1 negatively regulates the intracellular active fragments of Notch1 (ICN1), promoting the formation of a cytoplasmic complex between ICN1 and the E3 ubiquitin ligase Cbl-B. This tumor suppressor-like function is closely associated with the occurrence of T-cell leukemia [38–40]. However, current studies have not identified a non-catalysis-independent role for Vav in the pathological of atherosclerosis.

3. Vav family in atherosclerosis

Atherosclerosis, the underlying cause of acute cardiovascular and cerebrovascular events, such as myocardial infarction and cerebral embolism, involves a complex interplay of pathological processes. These include vascular endothelial injury, lipid accumulation in monocytes and macrophages, and vascular smooth muscle cell proliferation and phenotypic transformation. As atherosclerosis progresses, vascular calcification and inflammation within the plaque exacerbate the process, leading to increased plaque hardness and fragility, ultimately resulting in acute cardiovascular events.

In the context of atherosclerosis, the Vav gene exerts its effects primarily through a catalysis-dependent mechanism, with no reported non-catalytic roles. Genetic polymorphism studies have explored the impact of different Vav2 and Vav3 alleles on cardiovascular diseases. In addition, basic research has demonstrated the extensive involvement of the Vav family in the initiation and progression of atherosclerosis by influencing downstream Rho GTPases via a catalysis-dependent approach.

In this chapter, we will describe the functions of the Vav family in the pathological process of atherosclerosis such as lipid metabolism disorders, inflammatory cell migration, vascular calcification, and platelet activation and aggregation (Table 1).

3.1. Disturbance of lipid metabolism and foam cell formation

Hyperlipidemia, a key risk factor for atherosclerosis, is characterized by the initial accumulation of lipids in blood vessels. Low-density lipoprotein (LDL) deposited on the vascular wall aggravates endothelial cell dysfunction, leading to the recruitment of monocytes to the subendothelial layer. These monocytes engulf lipids, transforming into foam cells, which further accelerates vascular dysfunction, lipid streak formation, and the progression of atherosclerosis [41–43].

Chen et al. demonstrated the significant impact of Vav proteins on blood lipid stabilization in mice. Compared with wild-type $ApoE^{-/-}$ mice, $Vav1^{-/-}ApoE^{-/-}$ mice and $Vav1/Vav3^{-/-}ApoE^{-/-}$ mice exhibited markedly lower serum cholesterol and LDL levels under high-fat feeding conditions, accompanied by reduced plaque areas around the aortic root [12,14]. Although the blood lipids and plaque areas of $Vav2^{-/-}ApoE^{-/-}$ mice reduced as well, the extent of reduction was less pronounced than in $Vav1^{-/-}ApoE^{-/-}$ and $Vav1/Vav3^{-/-}ApoE^{-/-}$ mice [11].

In vitro experiments revealed that Vav proteins primarily mediate

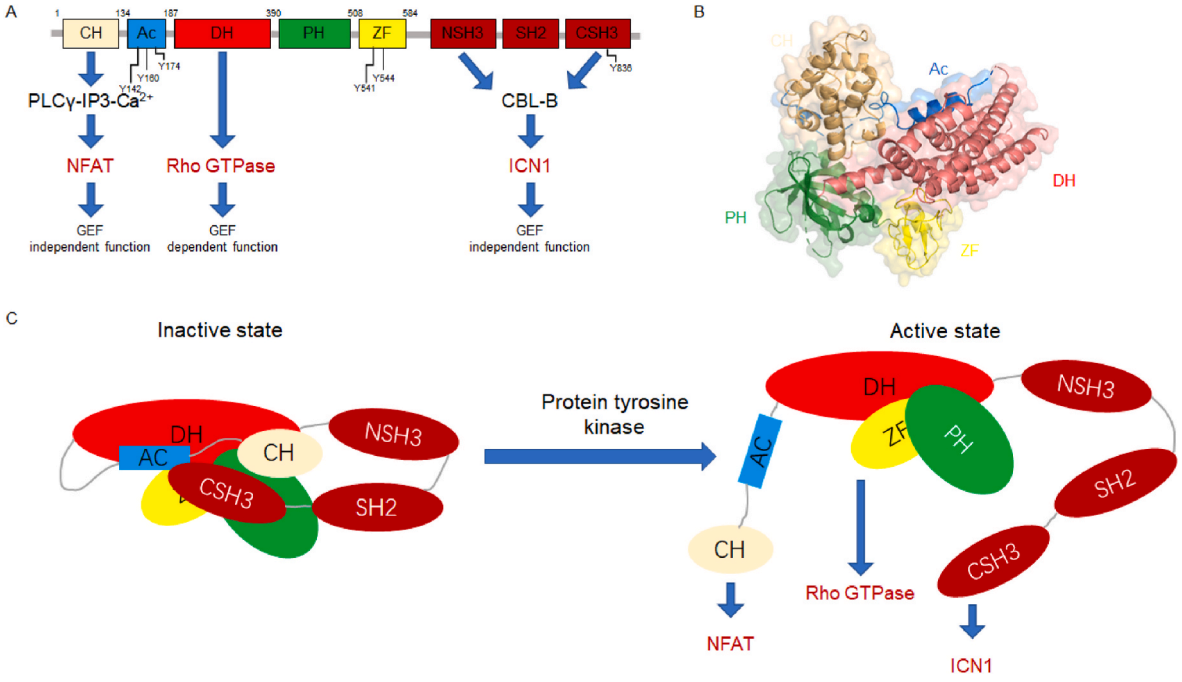

Fig. 1. Structure and mechanism of activation of Vav proteins. (A) Depiction of the structure, the main phosphorylation site, and the main downstream pathways were shown at the bottom of the domain of Vav protein. (B) Crystal structure of the autoinhibited Vav1 CH-Ac–DH–PH–ZF region (PDBID:3KY9). (C) A model for activation of Vav protein from non-phosphorylation state to phosphorylation state based on recently described structural and biochemical data.

Table 1
Pathological phenomenon and cell types related in Vav-mediated Rho GTPase in atherosclerosis.

Rho GTPase	Cell types	Pathological phenomenon	Related signal pathway	Reference
Rac1	Macrophage	Foam cell formation	CD36-Src	Singh et al. (2019)
	Macrophage	Monocyte recruitment	Vav-Rac1-Rock	Bhavsar et al. (2009)
	leukocytes	Migration of leukocytes	$\alpha_v\beta_3$-Vav-Rac1	Gao et al. (2005)
	neutrophils	Migration of neutrophils	Vav1/3-Rac1-PAK	Gakidis et al. (2004)
	Macrophage	Diabetic macrophage migration	CML-Vav1-Rac1	Bao et al. (2020)
	Platelet	Platelet activation	Vav1/3-PLCγ-Rac1	Pearce et al. (2007)
Rac2	Osteoclast	Osteoclast differentiation	Vav1-Rac2	Jang et al. (2019), Kang et al. (2020)
Cdc42	Macrophage	Foam cell formation	CD36-Src	Singh et al. (2019)
	neutrophils	Migration of neutrophils	Vav1/3-Cdc42-PAK	Gakidis et al. (2004)
RhoA	neutrophils	Migration of neutrophils	Vav1/3-RhoA-PAK	Gakidis et al. (2004)
	leukocytes	Migration of leukocytes	$\alpha_v\beta_3$-Vav-RhoA	Gao et al. (2005)
	VSMC	Calcification	Vav2-DDR1-RhoA	Ngai et al. (2020)
Dynamin 2	Macrophage	Foam cell formation	Vav1-Fyn-Dynamin 2	Rahaman et al. (2011)

intracellular signaling through the CD36-Src axis activation during the formation of macrophage-derived foam cells induced by oxidized (oxLDL) [13,44–46]. Vav proteins play key roles in ligand–receptor binding and internalization [19–21]. Rahaman et al. observed that Vav protein deficiency in macrophages impaired the maturation of oxLDL-laden endocytic vesicles, thereby impairing lipid accumulation [15]. Dynamin 2, a macromolecular GTPase, was found to co-localize with internalized oxLDL and Vav1 in macrophage-derived foam cells, suggesting the critical role of Vav1 in mediating foam cell formation [13]. In addition, Rahaman et al. identified a Ca^{2+}-mediated feedback mechanism in the SFK-Vav-PLCγ1 pathway in oxLDL-CD36 signaling, indicating the importance of Ca^{2+} in Vav family activation [13]. Singh et al. found that Vav proteins interact with Cdc42 to promote the formation of the lysosomal synapse (LS) in the cytoskeleton, which in turn facilitates the uptake of aggregated LDL (AgLDL) [10].

Huang et al. conducted unbiased whole-genome RNA sequencing on three types of macrophages with Vav gene defects independently and discovered that each gene defect up-regulated the expression of other Vav genes. Moreover, the deficiency of any individual Vav protein broadly affected the expression of proteins related to cell function, including cell cycle, cell adhesion, metabolism, and phagocytosis [11]. Genomic and bioinformatics analysis led Huang et al. to propose that Vav1, Vav2, and Vav3 form a ternary complex. The loss of one Vav protein disrupted the function of the complex, explaining the indispensability of each Vav member protein in foam cell formation. Further experiments revealed that the absence of one Vav protein could diminish CD36 internalization, consequently modifying lipid uptake and foam cell signaling [11]. However, direct protein–protein interactions between the three Vav proteins have not been definitively demonstrated through techniques such as co-immunoprecipitation.

Another study revealed that Siglecs, a family of sialic acid-binding immunoglobulin-like receptors predominantly expressed on immune cells, can inhibit oxLDL uptake by interacting with CD36, thereby suppressing Vav phosphorylation and downstream signaling pathways. In Siglec-E-deficient mice, higher Vav phosphorylation levels were observed, suggesting that Siglec-E reduces foam cell formation and the progression of atherosclerosis by inhibiting Vav activity [47].

Studies mentioned above have indicated that Vav proteins play essential roles in the lipid regulation of atherosclerosis. The effect of Vav proteins on lipid metabolism primarily depended on CD36 signaling and the activation of downstream Rho GTPase. Various studies have documented that the activation of downstream Rho GTPase was diverse and complex; however, whether these different research results can be attributed to the difference in irritants (such as agLDL and oxLDL) needs further exploration. In addition, due to the diversity of irritants in human atherosclerotic plaques, the downstream targets of Vav proteins remain indefinite. Therefore, future studies should focus on obtaining direct evidence of Vav protein activation in human atherosclerosis.

3.2. Migration of inflammatory cells

The pathological process of early atherosclerosis involves the activation, recruitment, and migration of monocytes to the subendothelial layer under the influence of vascular endothelial inflammatory factors [41,48]. The efflux of lipid-laden macrophages from blood vessels to perivascular lymph nodes contributes to the regression of atherosclerotic plaques [49,50].

Using in vivo fluorescence imaging and intravital video microscopy, Silverstein et al. observed that Vav1-deficient monocytes were less adhesive to the vascular wall and decreased plaque infiltration [14]. In vitro experiments demonstrated that under the stimulation of No2-LDL, a specific ligand for CD36, the migration of macrophages was inhibited. It was found via live cell imaging that this effect of No2-LDL was exerted by inhibiting the aggregation of the cytoskeleton and the formation of lamellar pseudopodia [13]. Compared with wild-type macrophages, $Vav1^{-/-}$ and $Vav1^{-/-}Vav3^{-/-}$ macrophages displayed reversed cell polarity and impaired migration ability [49]. The interaction between Vav proteins and integrins represents another pivotal link in cell migration. This interaction transmits signals to the downstream Rac1, which mediates cytoskeletal polymerization and affects macrophage migration. In the leukemia cell line K562, Vav1 directly interacts with β3 integrin to induce cell adhesion, while Vav1 mutants impair the activation of RhoA, Rac1, and Cdc42, influencing cell migration [51–53]. Our previous study revealed that the activation of Vav1 inhibits the migration of macrophages from the inside to the outside of the vascular wall, primarily mediated by the downstream Rac1 protein. These findings suggest that the Vav family plays a negative role in the migration of various immune cells in atherosclerosis, promoting their adhesion and preventing their egress from the blood vessel wall, thereby contributing to the development of atherosclerosis [49].

These studies demonstrate that Vav proteins not only influence lipid metabolism in macrophages but also regulate the migration ability of inflammatory cells. It is worth noting that under the stimulation of oxLDL, the Vav family binds with Cdc42 to induce macrophages to engulf lipids. However, Silverstein's research shows they activate Rac1 in Rho GTPase instead of Cdc42 or RhoA under No2-LDL stimulation.

These contrasting findings remind us that the mechanism of Vav activation in atherosclerosis is more than complicated. Analogous stimuli, such as ox-LDL and No2-LDL, activate different downstream molecules, leading to different biological effects. Given the variety of stimulating factors in humans, therefore, further exploration of the activation targets and mechanisms of the Vav family is warranted.

3.3. Vascular calcification

Vascular calcification is a process in which arterial mesenchymal cells transdifferentiate into osteogenic–chondrogenic cell phenotype under the influence of various pathological factors, inducing calcium salt deposition and calcified foci formation. This process mainly depends on various mechanisms. These include the formation of nucleation sites

from apoptotic bodies and necrotic fragments released from dying inflammatory cells, the involvement of matrix vesicles and circulating nucleation complexes, the formation and secretion of osteoclasts, and the transformation of vascular smooth muscle cells and pericytes into calcified phenotype [50,54,55].

Ngai et al. found that Vav2 phosphorylation in vascular muscle smooth cells was enhanced by high matrix stiffness and promoted collagen-I-dependent stress fiber formation. Furthermore, they identified a direct interaction between Vav2 and DDR1, regulating the effect of the DDR1-RhoA axis on vascular calcification. Vav2 knockdown decreased DDR1 protein level by 40 %, suggesting a potential Vav2-dependent regulation of DDR1 expression [56]. Unfortunately, they only focused on the downstream RhoA but did not work on other Rho GTPases like Rac1 and Cdc42, which are known contributors to vascular calcification [57].

Osteoclasts, derived from the mononuclear macrophage system, are specialized cells for bone digestion. Their function depends on lamellipodia, F-actin core polymerization, αvβ3 integrin, and dynamic adhesion structures surrounded by cytoskeletal proteins, including vinblastin and talin [58]. During bone resorption, mature osteoclasts polarize and undergo morphological changes, comprising the formation of actin loops and wrinkled boundaries around the resorption area, which facilitate bone destruction [59]. Studies have found that Vav3-deficient osteoclasts showed impaired actin cytoskeleton, cell polarization, diffusion, and absorption due to defects in the M-CSF receptor and αvβ3 integrin downstream signaling [60–62]. *In vitro* studies illustrated that $Vav3^{-/-}$ osteoclasts fail to form actin loops, hindering their ability to perform bone phagocytosis [63]. Rac1 and Rac2, effector molecules of α(v)β(3) integrin, were also affected. Surprisingly, Vav1 deficiency promoted both the transformation of bone marrow mononuclear cells (BMMCs) into osteoclasts and bone resorption, contrasting with the effects of $Vav3^{-/-}$ [64]. The study by Kang et al. found that the expression of Vav3 was significantly increased in Vav1-deficient mice, suggesting a compensatory relationship between the two genes [65], which was not explained in previous studies.

Although no dedicated research on the role of Vav proteins in osteoclasts of atherosclerosis exists, we speculate that Vav proteins may regulate the infiltration of macrophages and promote plaque regression in mice atherosclerosis, potentially masking their effects on osteoclasts. However, further investigation is needed to substantiate this inference.

3.4. Platelet aggregation

Platelets are non-nuclear fragments derived from megakaryocytes, shedding into the blood circulation to perform biological functions. Upon activation, platelets change from a disc shape or plate shape (resting state) to a dendritic shape, accompanied by the release of prothrombin and other factors. Adenosine diphosphate (ADP) and thromboxane are key players in platelet aggregation, initiating a cascade of events that lead to platelet cross-linking and the formation of a fibrin network.

In platelet suspension treated with thrombin and collagen, the tyrosine phosphorylation level of Vav1 increased significantly, whereas stimulation with the thromboxane mimic U46619 or ADP had a minimal effect [66]. In addition, increased platelet adhesive fibrinogen stimulated by the platelet integrin GPIIb-IIIa led to a strong elevation of Vav1 phosphorylation [67]. Pearce et al. proposed for the first time that Vav1 and Vav3 deficiency rendered platelets resistant to GPVI-induced activation [65,68]. Integrin αIIbβ3 activates intracellular signals including Src kinase, Syk, SLP-76, and PLCγ2 in platelets [69–73] and regulates the spreading and movement of platelets on fibrin. Studies show that the spread of normal platelets on fibrinogen requires Vav1 and Vav3, which was caused by αIIbβ3-mediated PLCγ2 activation and reduced $Ca2^{+}$ efflux [62,66]. Under physiological conditions, the limited diffusion of platelets triggered by αIIbβ3 was enhanced by G protein-coupled receptor agonists (such as ADP and thrombin), resulting in Rac activation and Rac-dependent perfect diffusion. Unlike in other cells, Vav1 and Vav3 deficiency in platelets does not affect the G protein-coupled receptors of Rac and RhoA agonists but rather induces agonist proteins [66]. This suggests that a protein expansion disorder may not be involved in platelet spreading disorder.

Vav family deficiency likewise affects the interaction between platelets and other cells. Pan et al. observed that the expression of P-REX/Vav GEF in platelets plays an important role in neutrophil migration to inflammatory sites, possibly related to the formation of complexes involving pro-inflammatory platelets, white blood cells, and the secretion of soluble factors under inflammatory conditions [60,61]. Vav1/Vav3-deficient mice exhibited reduced platelet PSGL1 levels, inhibiting L-selectin signaling in neutrophils and E-selectin signaling in endothelial cells, which resulted in a decrease in neutrophils integrin affinity and vascular adhesion [61].

In the pathological process of atherosclerosis, the adhesion molecules of platelets and inflammatory factors collaborate to thicken blood viscosity and promote thrombosis. Chen et al. found that high-fat diet (HFD)-induced platelet hyperreactivity in $ApoE^{-/-}$ mice was dependent on the phosphorylation of Vav1 and Vav3 [14]. In vitro studies also showed that platelet hyperreactivity induced by oxLDL-CD36 interaction relied on Vav1/Vav3. Chen et al. further demonstrated that Vav1 and Vav3 deficiencies decreased the carotid occlusion time in the occlusive thrombi model, intimating that Vav1 and Vav3 may play critical roles in protecting hyperlipidemic mice from occlusive thrombi [14].

The “interaction” between platelets and other atherosclerotic cells is also strongly coupled with the occurrence and development of coronary heart diseases [74–76]. Platelets were stimulated by ox-LDL, GDPI, and fibrin in this process and worked as an adaptor to activate the downstream PI3K/Akt pathway through Lyn signaling, which in turn promotes platelet aggregation [77]. Pearce et al. found that the lack of Vav1 and Vav3 resists fiber-induced platelet activation, while Vav2 deficiency reacts paradoxically [65,68]. There was an increase in Vav2 phosphorylation during platelet activation induced by PDGF. Therefore, whether all three proteins work in the pathological process of atherosclerosis remains unclear [61].

With the growing understanding of platelet interactions with other inflammatory cells, more platelet functions have been discovered [78]. Current studies have revealed that Vav proteins interact with platelets differently compared with other cells, that is to say, the Vav family did not affect Rac1 or other Rho GTPases but influenced the spread of platelet cytoskeleton and its rolling on the surface of fibrin instead. Therefore, the specific mode of Vav proteins in platelet function remains to be fully elucidated, necessitating further research into their downstream targets and mechanisms.

4. Therapeutic values

The above studies have shown that atherosclerosis regression could be observed in Vav gene knockout mice, and there have been various studies explaining the important role of expression and activation of Vav protein in atherosclerosis. Particularly, Silverstein’s discovery of Vav proteins in CD36-induced lipid phagocytosis makes Vav a potential target for the treatment of atherosclerosis and modulation of lipid metabolism. However, to become a de facto treatment or measurement, there is still a long way to go. Data from $Vav1^{-/-}ApoE^{-/-}$ deficient mice suggested that loss of Vav proteins inhibited the progression of hyperlipidemia and atherosclerosis [11,12,14], suggesting that the Vav family may serve as a potential target for lowering blood lipids. Meanwhile, $Vav1^{-/-}Vav3^{-/-}$ mice were resistant to FeCl3-induced carotid thrombosis (5 of the 8 animals studied failed to form occlusive thrombi), and the other 3 mice had the carotid artery occlusion time prolonged from 14.1 min in wild-type mice to 23.2 min, suggesting that inhibitors against Vav proteins may act as antithrombotic treatment [14]. Despite these promising findings, several challenges still need to be solved.

Research has found that Vav gene knockout may cause great side effects due to its role in regulating Rho GTPase activity. According to the data from knockout mice, these side effects may include hypertension, metabolic syndrome, and immunosuppression [36,79–82]; however, in $Vav1^{-/-}ApoE^{-/-}$ and $Vav3^{-/-}ApoE^{-/-}$ mice, these side effects have not been reported.

To mitigate these side effects, Rodriguez-Fdez et al. built a $Vav2^{L332A}$ mutant mice model (70 % Vav2 inhibition rate) by constructing a point mutation (L332A) in the catalytic site of the DH domain [83]. The enzymatic activities of Rac1 and RhoA were reduced by 70 % and 100 %, respectively, in $Vav2^{L332A}$ mutant mice. Compared with $Vav2^{-/-}$ mice, there was no hypertension in these mutant mice. In addition, the thickness of the aorta, the area of myocardial cells, and the content of collagen in the kidney had no significant difference with wild-type mice [60,84]. Likewise, $Vav2^{+/-}$ mice (50 % Vav2 inhibition rate) also showed similar situations, suggesting that the side effects of Vav family inhibition appeared to be dose-dependent. These findings have not been applied in model mice of atherosclerosis; however, it is worth noting that $Vav2^{L332A}$ mutant mice developed severe hyperlipidemia at 6 months [83], which implied the target spot L332A was not suitable for the treatment of atherosclerosis. Nevertheless, it provides us with a new treatment idea by looking for new targets, so that a "window dose" of Vav protein inhibitor can be obtained, which both inhibits atherosclerosis progression and reduces complications.

5. Conclusion

The Vav family regulates cardiovascular homeostasis through a variety of biological mechanisms. To develop effective therapeutic strategies targeting Vav proteins and their pathways, a comprehensive understanding of them is essential. Vav proteins act simultaneously on multiple levels, including lipid metabolism, inflammation, vascular calcification, and platelet aggregation, which demonstrate their significant impacts on atherosclerosis. Although there are studies on the influence of Vav gene polymorphism in atherosclerosis and other cardiovascular complications, more samples and in-depth clinical studies are still needed to evaluate the clinical utility of Vav proteins as diagnostic or therapeutic tools.

CRediT authorship contribution statement

Yu Zhang: Writing – review & editing, Writing – original draft. **Yongwei Ren:** Writing – review & editing. **Tao Zhou:** Writing – review & editing. **Zhengtao Qian:** Data curation. **Zhengyang Bao:** Conceptualization.

Data availability

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] K.L. Rossman, C.J. Der, J. Sondek, GEF means go: turning on RHO GTPases with guanine nucleotide-exchange factors, Nat. Rev. Mol. Cell Biol. 6 (2) (2005) 167–180.
[2] X.R. Bustelo, V. Sauzeau, I.M. Berenjeno, GTP-binding proteins of the Rho/Rac family: regulation, effectors and functions in vivo, Bioessays : news Rev. Mol. Cell. Dev. Biol. 29 (4) (2007) 356–370.
[3] X.R. Bustelo, RHO GTPases in cancer: known facts, open questions, and therapeutic challenges, Biochem. Soc. Trans. 46 (3) (2018) 741–760.
[4] S. Katzav, D. Martin-Zanca, M. Barbacid, vav, a novel human oncogene derived from a locus ubiquitously expressed in hematopoietic cells, EMBO J. 8 (8) (1989) 2283–2290.
[5] N. Movilla, X.R. Bustelo, Biological and regulatory properties of Vav-3, a new member of the Vav family of oncoproteins, Mol. Cell Biol. 19 (11) (1999) 7870–7885.
[6] E.P. Henske, M.P. Short, S. Jozwiak, C.M. Bovey, S. Ramlakhan, J.L. Haines, D. J. Kwiatkowski, Identification of VAV2 on 9q34 and its exclusion as the tuberous sclerosis gene TSC1, Ann. Hum. Genet. 59 (1) (1995) 25–37.
[7] K.E. Schuebel, X.R. Bustelo, D.A. Nielsen, B.J. Song, M. Barbacid, D. Goldman, I. J. Lee, Isolation and characterization of murine vav2, a member of the vav family of proto-oncogenes, Oncogene 13 (2) (1996) 363–371.
[8] K. Chen, W. Li, J. Major, S.O. Rahaman, M. Febbraio, R.L. Silverstein, Vav guanine nucleotide exchange factors link hyperlipidemia and a prothrombotic state, Blood 117 (21) (2011) 5744–5750.
[9] R. Huang, G. Guo, L. Lu, R. Fu, J. Luo, Z. Liu, Y. Gu, W. Yang, Q. Zheng, T. Chao, L. He, Y. Wang, Z. Niu, H. Wang, T. Lawrence, M. Malissen, B. Malissen, Y. Liang, L. Zhang, The three members of the Vav family proteins form complexes that concur to foam cell formation and atherosclerosis, J. Lipid Res. 60 (12) (2019) 2006–2019.
[10] S.O. Rahaman, W. Li, R.L. Silverstein, Vav Guanine nucleotide exchange factors regulate atherosclerotic lesion development in mice, Arterioscler. Thromb. Vasc. Biol. 33 (9) (2013) 2053–2057.
[11] S.O. Rahaman, W. Swat, M. Febbraio, R.L. Silverstein, Vav family Rho guanine nucleotide exchange factors regulate CD36-mediated macrophage foam cell formation, J. Biol. Chem. 286 (9) (2011) 7010–7017.
[12] S.O. Rahaman, G. Zhou, R.L. Silverstein, Vav protein guanine nucleotide exchange factor regulates CD36 protein-mediated macrophage foam cell formation via calcium and dynamin-dependent processes, J. Biol. Chem. 286 (41) (2011) 36011–36019.
[13] R.K. Singh, A.S. Haka, P. Bhardwaj, X. Zha, F.R. Maxfield, Dynamic actin reorganization and vav/cdc42-dependent actin polymerization promote macrophage aggregated LDL (Low-Density lipoprotein) uptake and catabolism, Arterioscler. Thromb. Vasc. Biol. 39 (2) (2019) 137–149.
[14] X.R. Bustelo, Vav proteins, adaptors and cell signaling, Oncogene 20 (44) (2001) 6372–6381.
[15] M. Phillipson, B. Heit, S.A. Parsons, B. Petri, S.C. Mullaly, P. Colarusso, R. M. Gower, G. Neely, S.I. Simon, P. Kubes, Vav1 is essential for mechanotactic crawling and migration of neutrophils out of the inflamed microvasculature, J. Immunol. (Baltimore, Md 182 (11) (2009) 6870–6878, 1950.
[16] D.R. Spurrell, N.A. Luckashenak, D.C. Minney, A. Chaplin, J.M. Penninger, R. S. Liwski, J.L. Clements, K.A. West, Vav1 regulates the migration and adhesion of dendritic cells, J. Immunol. 183 (1) (2009) 310–318.
[17] C.M. Wells, P.J. Bhavsar, I.R. Evans, E. Vigorito, M. Turner, V. Tybulewicz, A. J. Ridley, Vav1 and Vav2 play different roles in macrophage migration and cytoskeletal organization, Exp. Cell Res. 310 (2) (2005) 303–310.
[18] S. Malhotra, S. Kovats, W. Zhang, K.M. Coggeshall, B cell antigen receptor endocytosis and antigen presentation to T cells require Vav and dynamin, J. Biol. Chem. 284 (36) (2009) 24088–24097.
[19] B. Wilkinson, J. Koenigsknecht-Talboo, C. Grommes, C.Y. Lee, G. Landreth, Fibrillar beta-amyloid-stimulated intracellular signaling cascades require Vav for induction of respiratory burst and phagocytosis in monocytes and microglia, J. Biol. Chem. 281 (30) (2006) 20842–20850.
[20] I. Hornstein, A. Alcover, S. Katzav, Vav proteins, masters of the world of cytoskeleton organization, Cell. Signal. 16 (1) (2004) 1–11.
[21] B. Riteau, D.F. Barber, E.O. Long, Vav1 phosphorylation is induced by beta2 integrin engagement on natural killer cells upstream of actin cytoskeleton and lipid raft reorganization, J. Exp. Med. 198 (3) (2003) 469–474.
[22] M. Villalba, K. Bi, F. Rodriguez, Y. Tanaka, S. Schoenberger, A. Altman, Vav1/Rac-dependent actin cytoskeleton reorganization is required for lipid raft clustering in T cells, J. Cell Biol. 155 (3) (2001) 331–338.
[23] D.B. Graham, C.M. Robertson, J. Bautista, F. Mascarenhas, M.J. Diacovo, V. Montgrain, S.K. Lam, V. Cremasco, W.M. Dunne, R. Faccio, C.M. Coopersmith, W. Swat, Neutrophil-mediated oxidative burst and host defense are controlled by a Vav-PLCgamma2 signaling axis in mice, J. Clin. Invest. 117 (11) (2007) 3445–3452.

[24] A.V. Miletic, D.B. Graham, V. Montgrain, K. Fujikawa, T. Kloeppel, K. Brim, B. Weaver, R. Schreiber, R. Xavier, W. Swat, Vav proteins control MyD88-dependent oxidative burst, Blood 109 (8) (2007) 3360–3368.
[25] J.E. Chrencik, A. Brooun, H. Zhang, I.I. Mathews, G.L. Hura, S.A. Foster, J.J. Perry, M. Streiff, P. Ramage, H. Widmer, G.M. Bokoch, J.A. Tainer, G. Weckbecker, P. Kuhn, Structural basis of guanine nucleotide exchange mediated by the T-cell essential Vav1, J. Mol. Biol. 380 (5) (2008) 828–843.
[26] J. Rapley, V.L. Tybulewicz, K. Rittinger, Crucial structural role for the PH and C1 domains of the Vav1 exchange factor, EMBO Rep. 9 (7) (2008) 655–661, https://doi.org/10.1038/embor.2008.80.
[27] B. Yu, I.R. Martins, P. Li, G.K. Amarasinghe, J. Umetani, M.E. Fernandez-Zapico, D. D. Billadeau, M. Machius, D.R. Tomchick, M.K. Rosen, Structural and energetic mechanisms of cooperative autoinhibition and activation of Vav1, Cell 140 (2) (2010) 246–256.
[28] M. Barreira, S. Fabbiano, J.R. Couceiro, E. Torreira, J.L. Martínez-Torrecuadrada, G. Montoya, O. Llorca, X.R. Bustelo, The C-terminal SH3 domain contributes to the intramolecular inhibition of Vav family proteins, Sci. Signal. 7 (321) (2014) ra35.
[29] K.E. Schuebel, N. Movilla, J.L. Rosa, X.R. Bustelo, Phosphorylation-dependent and constitutive activation of Rho proteins by wild-type and oncogenic Vav-2, EMBO J. 17 (22) (1998) 6608–6621.
[30] J.L. Zugaza, M.A. López-Lago, M.J. Caloca, M. Dosil, N. Movilla, X.R. Bustelo, Structural determinants for the biological activity of Vav proteins, J. Biol. Chem. 277 (47) (2002) 45377–45392.
[31] C.O. Jacob, M. Eisenstein, M.C. Dinauer, W. Ming, Q. Liu, S. John, F.P. Quismorio, A. Reiff, B.L. Myones, K.M. Kaufman, D. Mccurdy, J.B. Harley, E. Silverman, R. P. Kimberly, T.J. Vyse, P.M. Gaffney, K.L. Moser, M. Klein-Gitelman, L. Wagner-Weiner, C.D. Langefeld, D.L. Armstrong, R. Zidovetzki, Lupus-associated causal mutation in neutrophil cytosolic factor 2 (NCF2) brings unique insights to the structure and function of NADPH oxidase, Proc. Natl. Acad. Sci. U.S.A 109 (2) (2012) E59–E67.
[32] M.R. Kuhne, G. Ku, A. Weiss, A guanine nucleotide exchange factor-independent function of Vav1 in transcriptional activation, J. Biol. Chem. 275 (3) (2000) 2185–2190.
[33] Z. Zhou, J. Yin, Z. Dou, J. Tang, C. Zhang, Y. Cao, The calponin homology domain of Vav1 associates with calmodulin and is prerequisite to T cell antigen receptor-induced calcium release in Jurkat T lymphocytes, J. Biol. Chem. 282 (32) (2007) 23737–23744.
[34] L.F. Reynolds, L.A. Smyth, T. Norton, N. Freshney, J. Downward, D. Kioussis, V. L. Tybulewicz, Vav1 transduces T cell receptor signals to the activation of phospholipase C-gamma1 via phosphoinositide 3-kinase-dependent and -independent pathways, J. Exp. Med. 195 (9) (2002) 1103–1114.
[35] A. Saveliev, L. Vanes, O. Ksionda, J. Rapley, S.J. Smerdon, K. Rittinger, V. L. Tybulewicz, Function of the nucleotide exchange activity of vav1 in T cell development and activation, Sci. Signal. 2 (101) (2009) ra83.
[36] V.L. Tybulewicz, Vav-family proteins in T-cell signalling, Curr. Opin. Immunol. 17 (3) (2005) 267–274.
[37] J. Wu, S. Katzav, A. Weiss, A functional T-cell receptor signaling pathway is required for p95vav activity, Mol. Cell Biol. 15 (8) (1995) 4337–4346.
[38] X.R. Bustelo, L.F. Lorenzo-Martín, M. Cuadrado, I. Fernández-Pisonero, J. Robles-Valero, An unexpected tumor suppressor role for VAV1, Mol. Cellular Oncol. 5 (3) (2018) e1432257.
[39] J. Robles-Valero, L.F. Lorenzo-Martín, I. Fernández-Pisonero, X.R. Bustelo, Rho guanosine nucleotide exchange factors are not such bad guys after all in cancer, Small GTPases 11 (4) (2020) 233–239.
[40] J. Robles-Valero, L.F. Lorenzo-Martín, M. Menacho-Márquez, I. Fernández-Pisonero, A. Abad, M. Camós, M.L. Toribio, L. Espinosa, A. Bigas, X.R. Bustelo, A paradoxical tumor-suppressor role for the Rac1 exchange factor Vav1 in T cell acute lymphoblastic leukemia, Cancer Cell 32 (5) (2017) 608–623.e9.
[41] M.A. Gomez-Marcos, R. Gonzalez-Sarmiento, J.I. Recio-Rodríguez, C. Agudo-Conde, L. Gamella-Pozuelo, N. Perretta-Tejedor, C. Martínez-Salgado, L. García-Ortiz, Relationship between target organ damage and blood pressure, retinal vessel calibre, oxidative stress and polymorphisms in VAV-2 and VAV-3 genes in patients with hypertension: a case-control study protocol (LOD-Hipertension), BMJ Open 4 (4) (2014) e005112.
[42] N. Perretta-Tejedor, J. Fernández-Mateos, L. García-Ortiz, M.A. Gómez-Marcos, J. I. Recio-Rodríguez, C. Agudo-Conde, E. Rodriguez-Sánchez, A.I. Morales, F. J. López-Hernández, J.M. López-Novoa, R. González-Sarmiento, C. Martínez-Salgado, Association of VAV2 and VAV3 polymorphisms with cardiovascular risk factors, Sci. Rep.-UK 7 (2017) 41875.
[43] T. Kuznetsova, K. Prange, C.K. Glass, M. de Winther, Transcriptional and epigenetic regulation of macrophages in atherosclerosis, Nat. Rev. Cardiol. 17 (4) (2020) 216–228.
[44] P. Natarajan, T.S. Collier, Z. Jin, A. Lyass, Y. Li, N.E. Ibrahim, R. Mukai, C. P. Mccarthy, J.M. Massaro, R.B. D'Agostino, H.K. Gaggin, C. Bystrom, M.S. Penn, J. L. Januzzi, Association of an HDL apolipoproteomic score with coronary atherosclerosis and cardiovascular death, J. Am. Coll. Cardiol. 73 (17) (2019) 2135–2145.
[45] X.H. Yu, D.W. Zhang, X.L. Zheng, C.K. Tang, Cholesterol transport system: an integrated cholesterol transport model involved in atherosclerosis, Prog. Lipid Res. 73 (2019) 65–91.
[46] M. Febbraio, E.A. Podrez, J.D. Smith, D.P. Hajjar, S.L. Hazen, H.F. Hoff, K. Sharma, R.L. Silverstein, Targeted disruption of the class B scavenger receptor CD36 protects against atherosclerotic lesion development in mice, J. Clin. Invest. 105 (8) (2000) 1049–1056.
[47] E.A. Podrez, M. Febbraio, N. Sheibani, D. Schmitt, R.L. Silverstein, D.P. Hajjar, P. A. Cohen, W.A. Frazier, H.F. Hoff, S.L. Hazen, Macrophage scavenger receptor CD36 is the major receptor for LDL modified by monocyte-generated reactive nitrogen species, J. Clin. Invest. 105 (8) (2000) 1095–1108.
[48] E.A. Podrez, E. Poliakov, Z. Shen, R. Zhang, Y. Deng, M. Sun, P.J. Finton, L. Shan, M. Febbraio, D.P. Hajjar, R.L. Silverstein, H.F. Hoff, R.G. Salomon, S.L. Hazen, A novel family of atherogenic oxidized phospholipids promotes macrophage foam cell formation via the scavenger receptor CD36 and is enriched in atherosclerotic lesions, J. Biol. Chem. 277 (41) (2002) 38517–38523.
[49] A.S. Daoud, J. Jarmolych, J.M. Augustyn, K.E. Fritz, Sequential morphologic studies of regression of advanced atherosclerosis, Arch. Pathol. Lab Med. 105 (5) (1981) 233–239.
[50] J. Llodrá, V. Angeli, J. Liu, E. Trogan, E.A. Fisher, G.J. Randolph, Emigration of monocyte-derived cells from atherosclerotic lesions characterizes regressive, but not progressive, plaques, Proc. Natl. Acad. Sci. U.S.A 101 (32) (2004) 11779–11784.
[51] S.O. Rahaman, D.J. Lennon, M. Febbraio, E.A. Podrez, S.L. Hazen, R.L. Silverstein, A CD36-dependent signaling cascade is necessary for macrophage foam cell formation, Cell Metabol. 4 (3) (2006) 211–221.
[52] Z. Zhao, M.C. de Beer, L. Cai, R. Asmis, F.C. de Beer, W.J. de Villiers, D.R. van der Westhuyzen, Low-density lipoprotein from apolipoprotein E-deficient mice induces macrophage lipid accumulation in a CD36 and scavenger receptor class A-dependent manner, Arterioscler. Thromb. Vasc. Biol. 25 (1) (2005) 168–173.
[53] G. Bories, N. Leitinger, Macrophage metabolism in atherosclerosis, FEBS Lett. 591 (19) (2017) 3042–3060.
[54] P.J. Bhavsar, E. Vigorito, M. Turner, A.J. Ridley, Vav GEFs regulate macrophage morphology and adhesion-induced Rac and Rho activation, Exp. Cell Res. 315 (19) (2009) 3345–3358.
[55] M.A. Gakidis, X. Cullere, T. Olson, J.L. Wilsbacher, B. Zhang, S.L. Moores, K. Ley, W. Swat, T. Mayadas, J.S. Brugge, Vav GEFs are required for beta2 integrin-dependent functions of neutrophils, J. Cell Biol. 166 (2) (2004) 273–282.
[56] C. Gao, E. Schaefer, M. Lakkis, S.D. Blystone, Beta3 tyrosine phosphorylation and alphavbeta3-mediated adhesion are required for Vav1 association and Rho activation in leukocytes, J. Biol. Chem. 280 (15) (2005) 15422–15429.
[57] Z. Bao, L. Zhang, L. Li, J. Yan, Q. Pang, Z. Sun, Y. Geng, L. Jing, C. Shao, Z. Wang, εN-Carboxymethyl-Lysine negatively regulates foam cell migration via the vav1/rac1 pathway, J. Immunol. Res. 2020 (2020) 1906204.
[58] K.A. Lomashvili, S. Cobbs, R.A. Hennigar, K.I. Hardcastle, W.C. O'Neill, Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin, J. Am. Soc. Nephrol. : JASN (J. Am. Soc. Nephrol.) 15 (6) (2004) 1392–1401.
[59] F. Otsuka, K. Sakakura, K. Yahagi, M. Joner, R. Virmani, Has our understanding of calcification in human coronary atherosclerosis progressed? Arterioscler. Thromb. Vasc. Biol. 34 (4) (2014) 724–736.
[60] C.M. Shanahan, Inflammation ushers in calcification: a cycle of damage and protection? Circulation 116 (24) (2007) 2782–2785.
[61] D. Ngai, M. Lino, K.E. Rothenberg, C.A. Simmons, R. Fernandez-Gonzalez, M. P. Bendeck, DDR1 (discoidin domain receptor-1)-RhoA (ras homolog family member A) Axis senses matrix stiffness to promote vascular calcification, Arterioscler. Thromb. Vasc. Biol. 40 (7) (2020) 1763–1776.
[62] S. Cheng, B. Ramachandran, A. Behrmann, J. Shao, M. Mead, C. Smith, K. Krchma, Y. Bello Arredondo, A. Kovacs, K. Kapoor, L.M. Brill, R. Perera, B.O. Williams, D. A. Towler, Vascular smooth muscle LRP6 limits arteriosclerotic calcification in diabetic LDLR−/− mice by restraining noncanonical wnt signals, Circ. Res. 117 (2) (2015) 142–156.
[63] S.L. Teitelbaum, F.P. Ross, Genetic regulation of osteoclast development and function, Nat. Rev. Genet. 4 (8) (2003) 638–649.
[64] O. Destaing, F. Saltel, J.C. Géminard, P. Jurdic, F. Bard, Podosomes display actin turnover and dynamic self-organization in osteoclasts expressing actin-green fluorescent protein, Mol. Biol. Cell 14 (2) (2003) 407–416.
[65] P.T. Lakkakorpi, H.K. Väänänen, Kinetics of the osteoclast cytoskeleton during the resorption cycle in vitro, J. Bone Miner. Res. : of. J. Am. Soc. Bone Miner. Res. 6 (8) (1991) 817–826.
[66] K. Cichowski, J.S. Brugge, L.F. Brass, Thrombin receptor activation and integrin engagement stimulate tyrosine phosphorylation of the proto-oncogene product, p95vav, in platelets, J. Biol. Chem. 271 (13) (1996) 7544–7550.
[67] A. Zambonin-Zallone, A. Teti, M. Grano, A. Rubinacci, M. Abbadini, M. Gaboli, P. C. Marchisio, Immunocytochemical distribution of extracellular matrix receptors in human osteoclasts: a beta 3 integrin is colocalized with vinculin and talin in the podosomes of osteoclastoma giant cells, Exp. Cell Res. 182 (2) (1989) 645–652.
[68] A.C. Pearce, J.I. Wilde, G.M. Doody, D. Best, O. Inoue, E. Vigorito, V.L. Tybulewicz, M. Turner, S.P. Watson, Vav1, but not Vav2, contributes to platelet aggregation by CRP and thrombin, but neither is required for regulation of phospholipase C, Blood 100 (10) (2002) 3561–3569.
[69] C. Page, S. Pitchford, Neutrophil and platelet complexes and their relevance to neutrophil recruitment and activation, Int. Immunopharm. 17 (4) (2013) 1176–1184.
[70] D. Pan, R.T. Amison, Y. Riffo-Vasquez, D. Spina, S.J. Cleary, M.J. Wakelam, C. P. Page, S.C. Pitchford, H.C. Welch, P-Rex and Vav Rac-GEFs in platelets control leukocyte recruitment to sites of inflammation, Blood 125 (7) (2015) 1146–1158.
[71] S.L. Teitelbaum, The osteoclast and its unique cytoskeleton, Ann. Ny. Acad. Sci. 1240 (2011) 14–17.
[72] J.S. Jang, I.S. Kang, Y.N. Cha, Z.H. Lee, M.C. Dinauer, Y.J. Kim, C. Kim, Vav1 inhibits RANKL-induced osteoclast differentiation and bone resorption, BMB Rep. 52 (11) (2019) 659–664.
[73] I.S. Kang, J.S. Jang, C. Kim, Opposing roles of hematopoietic-specific small GTPase Rac2 and the guanine nucleotide exchange factor Vav1 in osteoclast differentiation, Sci. Rep.-UK 10 (1) (2020) 7024.

[74] A. Obergfell, K. Eto, A. Mocsai, C. Buensuceso, S.L. Moores, J.S. Brugge, C. A. Lowell, S.J. Shattil, Coordinate interactions of Csk, Src, and Syk kinases with [alpha]IIb[beta]3 initiate integrin signaling to the cytoskeleton, J. Cell Biol. 157 (2) (2002) 265–275.
[75] A.C. Pearce, Y.A. Senis, D.D. Billadeau, M. Turner, S.P. Watson, E. Vigorito, Vav1 and vav3 have critical but redundant roles in mediating platelet activation by collagen, J. Biol. Chem. 279 (52) (2004) 53955–53962.
[76] I. Goncalves, S.C. Hughan, S.M. Schoenwaelder, C.L. Yap, Y. Yuan, S.P. Jackson, Integrin alpha IIb beta 3-dependent calcium signals regulate platelet-fibrinogen interactions under flow. Involvement of phospholipase C gamma 2, J. Biol. Chem. 278 (37) (2003) 34812–34822.
[77] B.A. Judd, P.S. Myung, A. Obergfell, E.E. Myers, A.M. Cheng, S.P. Watson, W. S. Pear, D. Allman, S.J. Shattil, G.A. Koretzky, Differential requirement for LAT and SLP-76 in GPVI versus T cell receptor signaling, J. Exp. Med. 195 (6) (2002) 705–717.
[78] J.M. Pasquet, L. Quek, C. Stevens, R. Bobe, M. Huber, V. Duronio, G. Krystal, S. P. Watson, Phosphatidylinositol 3,4,5-trisphosphate regulates Ca(2+) entry via btk in platelets and megakaryocytes without increasing phospholipase C activity, EMBO J. 19 (12) (2000) 2793–2802.
[79] A. Poole, J.M. Gibbins, M. Turner, M.J. van Vugt, J.G. van de Winkel, T. Saito, V. L. Tybulewicz, S.P. Watson, The Fc receptor gamma-chain and the tyrosine kinase Syk are essential for activation of mouse platelets by collagen, EMBO J. 16 (9) (1997) 2333–2341.
[80] K. Suzuki-Inoue, O. Inoue, J. Frampton, S.P. Watson, Murine GPVI stimulates weak integrin activation in PLCgamma2-/- platelets: involvement of PLCgamma1 and PI3-kinase, Blood 102 (4) (2003) 1367–1373.
[81] P. Wonerow, A.C. Pearce, D.J. Vaux, S.P. Watson, A critical role for phospholipase Cgamma2 in alphaIIbbeta3-mediated platelet spreading, J. Biol. Chem. 278 (39) (2003) 37520–37529.
[82] A.C. Pearce, O.J. Mccarty, S.D. Calaminus, E. Vigorito, M. Turner, S.P. Watson, Vav family proteins are required for optimal regulation of PLCgamma2 by integrin alphaIIbbeta3, Biochem. J. 401 (3) (2007) 753–761.
[83] M. Chatterjee, D. Rath, J. Schlotterbeck, J. Rheinlaender, B. Walker-Allgaier, N. Alnaggar, M. Zdanyte, I. Müller, O. Borst, T. Geisler, T.E. Schäffer, M. Lämmerhofer, M. Gawaz, Regulation of oxidized platelet lipidome: implications for coronary artery disease, Eur. Heart J. 38 (25) (2017) 1993–2005.
[84] H.S. Elbatarny, S.J. Netherton, J.D. Ovens, A.V. Ferguson, D.H. Maurice, Adiponectin, ghrelin, and leptin differentially influence human platelet and human vascular endothelial cell functions: implication in obesity-associated cardiovascular diseases, Eur. J. Pharmacol. 558 (2007) 7–13.