Letter to the Editor

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The S-Nitrosylation of Septin2 (SNO-Septin2) axis: A novel potential therapeutic target for treating aneurysms and dissection

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SUMMARY Aortic aneurysm and aortic dissection (AAD) are severe life-threatening cardiovascular disorders for which no approved pharmaceutical therapies are currently available. Protein S-nitrosylation (SNO) is a typical redox-dependent posttranslational modification whose role in AAD has yet to be described. Recently, Zhang *et al*. revealed for the first time that SNO modification of macrophage cytoskeletal protein septin2 promotes vascular inflammation and extracellular matrix degradation in aortic aneurysm. Mechanically, the TIAM1-RAC1(T lymphoma invasion and metastasis-inducing protein 1-Ras-related C3 botulinum toxin substrate 1) axis participates in the progression of AAD induced with S-nitrosylated septin2. More importantly, developing R-ketorolac and NSC23766 compounds that specifically target the TIAM1-RAC1 pathway may be new a potential strategy for alleviating AAD.

Keywords aneurysms and dissection, SNO-Septin2, TIAM1-RAC1 axis, macrophage

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Recently, Zhang *et al*. (*1*) revealed for the first time that S-nitrosylation (SNO) modification of macrophage cytoskeletal protein septin2 promotes vascular inflammation and extracellular matrix (ECM) degradation in aortic aneurysms. Mechanically, the TIAM1-RAC1 (T lymphoma invasion and metastasis-inducing protein 1-Ras-related C3 botulinum toxin substrate 1) axis participates in the progression of aortic aneurysm and dissection (AAD) induced with S-nitrosylated Septin2. More importantly, developing R-ketorolac and NSC23766 compounds that specifically inhibit the TIAM1-RAC1 pathway may be a new potential strategy for alleviating AAD. Taken together, SNO-septin2 may likely to an effective strategy for treating AAD by modulating the TIAM1-RAC1 axis.

AAD is a cardiovascular disease with a significant risk of aortic rupture, leading to uncontrolled bleeding and even death (*2*). Its varied risk factors include being elderly, being male, hypertension, smoking, and dyslipidemia. These factors lead to degeneration of the aorta and promote aortic wall fragility, ultimately diminishing the aorta's ability to withstand blood flow and resulting in AAD (*3*). The pathological characteristics of AAD formation include endothelial dysfunction and smooth muscle cell (SMC) loss occurring in the damaged aortic wall. A point worth noting is that infiltration of inflammatory cells such as macrophages may contribute to the progression of AAD *via* the ECM and inflammation (*4*). At present, surgical procedures including open surgical repair and minimally invasive treatments have clinically proven to be the most effective methods of treating AAD. Some drugs, such as β-blockers, have also been used to eradicate the high risk of aortic rupture in clinical settings, but an insufficient understanding of AAD's pathogenesis currently limits the prevention and treatment of this condition (*5*). Therefore, further exploration of the molecular mechanisms of and development of novel strategies to prevent and treat the progression of AAD are urgently needed and are of great importance.

Protein SNO is a ubiquitous redox-related post-translational modification involving attachment of nitric oxide (NO) to cysteine thiol, resulting in NO bioactivity. SNO has been found to play an essential role in cardiovascular disorders, including myocardial hypertrophy, heart failure, and atherosclerosis (*6,7*). In human patients and mouse models, SNO-Septin2 levels are significantly elevated in macrophages. Septin2 has been identified as a new S-nitrosylated protein. Septin2 belongs to the Septin family of conserved GTP-binding proteins found in eukaryotes and mammalian. The pathogenesis of Septin2 in infection and cancer has been well-documented (*8,9*). However, the potential role of SNO-Septin2 in AAD remains unclear.

Zhang *et al*. first identified SNO of Septin2 at cysteine 111 (Cys111) in angiotensin II (Ang II)-induced AA and β-aminopropionitrile (BAPN)-induced AAD in

vivo. The mutation of Cys111 in Septin2 significantly reversed this effect. Moreover, the Cys111 mutation of Septin2 alleviates inflammation and ECM degradation in macrophages. Moreover, iNOS is the main source of activation by NO-induced SNO-Septin2 in macrophages. Collectively, SNO of Septin2 at the Cys111 site promotes macrophage inflammation and ECM degradation, leading to the development of AAD.

However, the molecular mechanisms underlying how SNO-Septin2 regulates macrophage inflammation need to be further explored. TIAM1 is a specific guanine nucleotide exchange factor (GEF) and is an activator of the small GTPase RAC1. TIAM1-RAC1 has been found to play a pivotal role in various biological processes, such as cytoskeletal activities, endocytosis, membrane transport, cell survival, proliferation, migration, and invasion (*10*). This novel finding expands the biological functions of the TIAM1-RAC1 pathway in SNO-Septin2-induced inflammation of macrophages that results in the progression of AAD. NSC23766, an inhibitor of the TIAM1-RAC1 axis, significantly alleviates macrophage inflammation and migration and it limits the development of AAD. Ketorolac is a nonsteroidal anti-inflammatory drug that has been approved by the US FDA for preventing AAD formation *via* a pharmacological blockade of RAC1 activation. Overall, this evidence indicates that the RAC1-TIAM1 signaling pathway represents a potential therapeutic target for AAD induced with SNO-Septin2.

To date, mounting evidence has revealed that SNO-Septin2 induces vascular inflammation and ECM degradation in macrophages (*11,12*). Endothelial dysfunction and SMC loss are also known to play an essential role in AAD pathologies. Nevertheless, the role of SNO-Septin2 in endothelium and SMCs needs to be further explored. A question worth asking is whether other factors affect vascular inflammation, resulting in the development of AAD. In the future, researchers should focus on the clinical safety of the drug R-ketorolac in humans since it is a potential novel therapy for the development of AAD. Platelet-activating factor increases the permeability of endothelial cells by activating the TIAM1-RAC1 signaling pathway. The increased permeability of endothelial cells affects the broadening of the inflammatory response, thus leading to atherosclerosis. Whether the role of TIAM1-RAC1 in endothelial damage contributes to atherosclerosis warrants further exploration.

In summary, Zhang *et al*. provide the first evidence that Septin2 is a novel S-nitrosylated protein. Prompted by pathogenic factors, SNO of Septin2 at the Cys111 site promotes substantial inflammation and ECM degradation in macrophages, resulting in AngII or BAPN-induced AAD formation and development. Mechanistically, increased SNO-Septin2 alletes its interaction with TIAM1 and activates the TIAM1-RAC1 axis and thus the NF-κB signaling pathway. More importantly, both R-ketorolac and NSC23766 attenuate the progression of AAD by inhibiting the TIAM1-RAC1 signaling pathway (Figure 1, Created with BioRender.com). Overall, the pharmacological blockade of RAC1 may therefore represent a potential treatment for cardiovascular diseases such as AAD in both patients and murine models.

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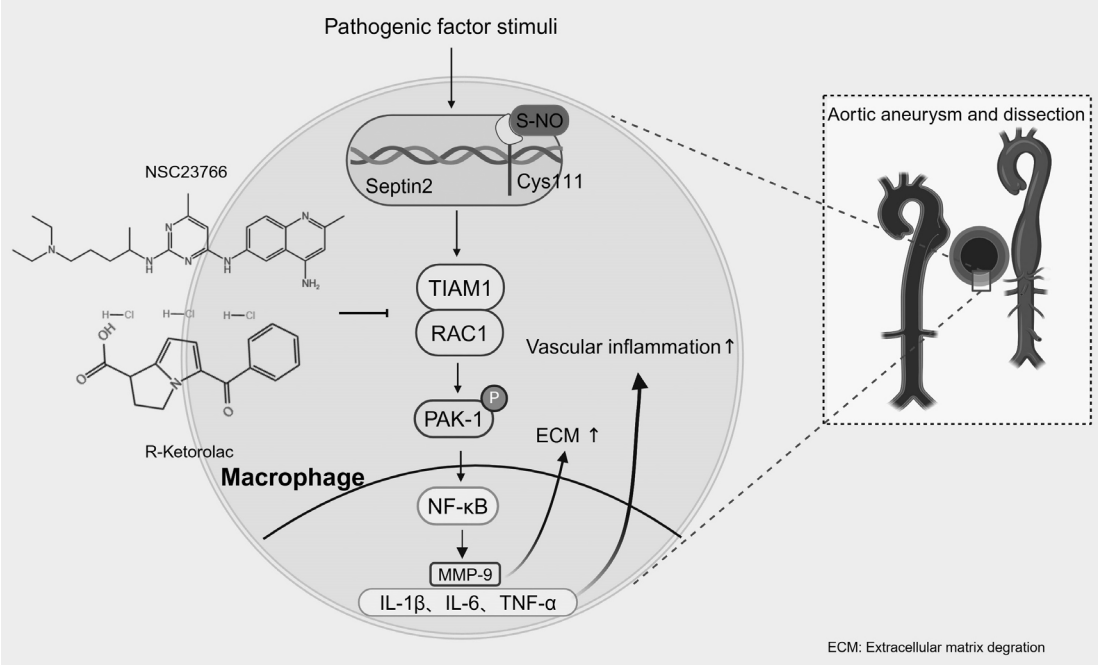

Figure 1. Schematic illustration of the involvement of SNO-Septin2 in the progression of AAD.

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