Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial commentary: Could shear stress mimetics delay complications in COVID-19?

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Coronavirus disease of 2019 (COVID-19) continues to plague the world, and it is likely here to stay indefinitely, even if vaccines are successful. Covid-19 is in fact both a pulmonary and endothelial disease [1]. SARS-CoV2 uses the angiotensin converting enzyme 2 (ACE2) to facilitate entry into cells, and ACE2 is present widely on lung type II alveolar cells and on ECs throughout the body. Continuous endothelium, as found in heart and muscle, is infected by SARS-CoV prior to crossing to underlying parenchyma. Endotheliitis is a hallmark of end-stage disease [2]. Micro and macrovascular EC dysfunction leads to vasoconstriction, pro-coagulant and pro-inflammatory states, and ultimately to end-organ dysfunction, all hallmarks of terminal COVID-19. Patients with pre-existing endothelial dysfunction, i.e. the aged, smokers, and subjects with hypertension or diabetes, are precisely the groups at highest risk for COVID-19 complications and mortality. There is thus strong rationale for using strategies of endothelial-targeted therapy or vascular normalization to prevent or delay complications, allowing time for immunological responses to clear the virus. The only vasculo-protective approach taken to date has been with 3–hydroxy-3-methyl-glutrayl-coenzyme A reductase inhibitors (statins), with mixed results. Another interesting consideration would be to somehow promote endothelial sheer stress (ESS) signaling.

ESS is defined as the tangential force exerted upon the endothelial surface by friction from flowing blood. ESS is proportional to the viscosity of blood and its velocity at the vessel wall. The velocity at the vessel wall, in turn, is dictated by the magnitude of blood flow in the vessel and by the nature of the flow. Blood flow velocity in vessels ranges from 100 cm/s in aorta to 0.5 mm/s in capillaries, a 2000-fold range. The rate of change of flow, i.e. acceleration, is also important to ESS, and can be as high as 6000 cm/s^2, the equivalent of 6 g-force (6 times earth's gravity). Flow is pulsatile in arterial vessels, due to the cardiac cycle, and can even be oscillatory, for example in diastolic reversal of coronary artery flow, or with aortic valve insufficiency. Flow can be laminar, usually in large and regular vessels, or turbulent, for example at bifurcations or vessel irregularities. Turbulent flow is more likely to occur with high blood flow and low viscosity, as found in large arteries. Pulsatile and turbulent flow patterns disappear in the microvasculature, but intermittent flow can still occur there because of the anatomical vascular plexus and dynamic changes in flow patterns. Under turbulent flow, ESS is diminished and chaotic.

ESS has powerful effects on endothelial biology and disease, promoting numerous favorable remodeling events, including effects on endothelial morphology, vasodilation, permeability, adhesion, proliferation, inflammatory response, and thrombotic and fibrinolytic homeostasis. The important contribution of low and oscillatory shear stress to the progression of atherosclerosis, first posited in 1969 [3], is now well-established. Atherosclerotic plaques preferentially develop at arterial bifurcations, branches, and curvatures where low and turbulent ESS is exposed [4]. Turbulent flow has also been implicated in thrombosis and aortic valvular disease [5]. In contrast, high and laminar ESS occurs in relatively straight arterial vessels and promotes anti-inflammation [6], anti-thrombosis, endothelial quiescence and barrier function [7], and under certain circumstances angiogenic sprouting [8]. Increases in laminar ESS likely contribute, for example, to the vasculo-protective benefits of exercise.

In light of the fundamental impact of ESS on vertebrate biology, and on human disease, understanding how ECs sense and transduce ESS is imperative. ECs express a number of mechanoreceptors that can sense ESS, leading to activation of complex intracellular signaling pathways, a process known as mechanotransduction. Numerous mechanoreceptors have been identified to date, including mechanosensitive GPCRs [9], ion channels (e.g. PIEZO) [10,11], tyrosine kinase receptors [12], and integrins [13]. The precise identity and relative dominance of these EC mechanoreceptors remains somewhat controversial, and depends on context, but GPCRs are likely a primary class of EC mechanoreceptors. In this issue of TCM, Li et al. [14] provide a comprehensive review of how GPCRs sense ESS and consequently promote vasodilation. Multiple GPCRs have potential mechanosensing properties, including GPR68 [15], the Sphingosine-1-phosphate receptors (S1PR) [16], the histamine receptors [17], and the bradykinin receptors [18]. GPCRs are widely expressed transmembrane proteins that, in general, bind to agonists that cause transmission of information to the intracellular milieu via allosteric changes in the receptor, leading to recruitment of intracellular signaling molecules such as heterotrimeric G-proteins or β-arrestins. Xiucun Li et al. [14] discuss in depth potential mechanisms of mechanosensing by different GPCRs, both agonist-dependent and agonist-independent, including conformational changes that can be triggered by ESS-induced

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changes in plasmalemma tension and membrane fluidity. Xiucun Li et al. also discuss the connection between reactive hyperemia (RH) and GPCRs. Although the mechanism of how the post-occlusive RH works has been controversial, GPCR Gαq/11-mediated signaling that releases endothelium-derived hyperpolarization factor (EDHF) or nitric oxide (NO) seem to be responsible for the hyperemic response. In addition to GPCRs, a few ion channels including PIEZO1 [19] and transient receptor potential vanilloid-4 (TRPV4) [20] have been identified as mechanosensitive and contribute significantly to the regulation of vascular tone by working synergistically with GPCRs.

Could there be a use for pharmacological activation of ESS pathways, i.e. ESS mimetics, in treating the current global COVID-19 scourge? There is indirect evidence for the idea that ESS mimetics might be protective against COVID-19 complications. The biological consequences of activated mechanotransduction in ECs are complex and differ contextually, but a major and consistent result is the activation of NO production by endothelial NO synthase (eNOS). NO, in turn, promotes vascular relaxation, and is also strongly anti-inflammatory, anti-thrombotic, and anti-apoptotic. NO decreases with age and with diabetes, the two groups most affected by COVID-19. Interestingly, NO has been shown to inhibit SARS-CoV1 replication [21,22]. Inhaled NO has shown potential benefit in SARS-CoV1 infections [23], and case studies suggest possible benefit in COVID-19 [24-26]. Phase 2 clinical trials with inhaled NO in COVID-19 are ongoing (NCT04388683, NCT04338828, NCT04397692, NCT04456088). Putative ESS mimetics would be expected to activate NO production, in addition to numerous other vasculo-protective pathways described above, thus yielding similar benefit as NO, if not more. GPCRs are eminently tractable pharmaceutical targets, accounting for ~30% of FDA-approved drugs, and >$150 billion annual sales worldwide. Targeting GPCRs that mediate ESS, guided by Li et al. [14], could thus be an attractive alternative to promote vasculoprotection in COVID-19.

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