Insight CX₃CL1 promotes platelet reactivity
CX₃CL1, a special deputy at the intersection of platelets and the vessel wall

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Chemokines are small chemoattractive cytokines that govern leukocyte responses and play crucial roles during immune surveillance and inflammation. Among the approximately 50 chemokines, CX₃CL1 (fractalkine) is special in a sense that it is the only member of the CX₃C-class and a transmembrane chemokine. Transmembrane-bound CX₃CL1 mediates direct cell-cell adhesion by engaging its receptor CX₃CR1. However, the chemokine domain of CX₃CL1 can be separated from the membrane anchor through the action of a disintegrin and metalloprotease (ADAM)-10 and -17. The released soluble CX₃CL1 can then mediate classical responses such as chemotaxis.

The involvement of the CX₃CL1–CX₃CR1 axis in the pathophysiology of cardiovascular disease is well documented in the literature (1). In mice, CX₃CL1 is expressed in early and advanced atherosclerotic lesions and might contribute to plaque progression by recruiting monocytes directly through CX₃CR1 as well as by promoting their survival once emigrated (2, 3). In patients with advanced heart failure, plasma levels of soluble CX₃CL1 were predictive of all-cause mortality (4). Moreover, a mutation in the CX₃CR1 gene causing a reduced activity in monocyte arrest was associated with a lower risk for cardiovascular disease (5). Notably, platelets also express CX₃CR1 upon activation, and platelets in hyperlipidaemic mice showed increased expression of CX₃CR1, enhancing platelet-leukocyte interactions (6).

In this issue of Thrombosis and Haemostasis, Hildemann et al. add a new dimension to the role of the CX₃CL1–CX₃CR1 axis in cardiovascular disease (7). In this study, a connection was identified between platelet reactivity and response to the well-established antiplatelet drug clopidogrel and an enhanced expression of CX₃CL1 during congestive heart failure (CHF). The authors demonstrated an increase in CX₃CL1 levels and expression in a rat model of CHF in serum, urine, hearts and aorta. This increased availability of CX₃CL1 led to an impaired relaxation of aortic segments of CHF animals, compared to controls, reflecting an endothelial dysfunction mediated by CX₃CL1. In addition, platelets from rats with CHF showed an increase in CX₃CR1 expression, similar to previously observations during hyperlipidemia (6). These platelets also displayed an increased responsiveness to ADP and to a combination of ADP and CX₃CL1. Interestingly, rats with CHF were less susceptible to platelet antagonism with clopidogrel. Finally, patients with low response to clopidogrel have higher levels of circulating CX₃CL1 than normal responders and serum CX₃CL1 levels also appeared to be associated with cardiac ejection fraction and severity of CHF.

As a whole, this article provides a mechanistic basis for previous studies that indicated an aggravating effect of CX₃CL1 in patients with cardiac insufficiency (4). In addition, the current findings also implicate CX₃CR1 as an auxiliary receptor for ADP-induced platelet activation, with the potential to counteract the pharmacologic of P2Y₁₂ receptor blockade by clopidogrel.

However, a still open question concerns the dissection of the roles of the soluble bloodstream, and the vascular cell-expressed membrane-bound forms of CX₃CL1 in the pathophysiology of cardiovascular disease.

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Conflict of Interest
None declared.

References