Insight ... blocking the interaction between CD40L and Mac1, an interaction that was previously described to be crucial in atherosclerosis, does not affect restenosis

CD40-CD40L: a Janus-faced interaction

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The common denominator of arterial diseases is inflammation. Co-stimulatory molecules are essential to propagate and modulate immune reactions and thus the inflammatory response (1). In diseases such as atherosclerosis and restenosis, the co-stimulatory CD40-CD40L dyad plays a pivotal role. However, both CD40 and CD40L have Janus-faced properties. In the majority of studies, genetic or pharmacological inhibition of either CD40 or CD40L ameliorates vascular disease. However, in some cases, interventions within the CD40-CD40L system result in zero or even detrimental effects on the course of vascular pathologies. This ambiguity is caused by the versatile properties of CD40-CD40L interactions. First, especially CD40L is promiscuous in terms of receptor-ligand interactions. CD40L not only binds to CD40, but also can bind to Mac1 and αIIβ3 (2).

Second, CD40L and CD40 have different effects, depending on the cell-type that is studied, and third, the interaction between CD40 and its TNF receptor associated factor (TRAF) 2/3/5 or TRAF6 binding site directs its pro-inflammatory functions (1, 3).

In the current issue of Thrombosis and Haemostasis, Willecke et al. report the surprising observation that blocking the interaction between CD40L and Mac1, an interaction that was previously described to be crucial in atherosclerosis, does not affect restenosis (4). Administration of cM7, a peptide that binds the CD40L binding domain on Mac1 did not decrease neointimal area or ameliorated vascular remodelling. Interestingly, deficiency of CD40, the classical receptor of CD40L, did reduce neointima formation and vascular wall expansion, which was attributed to the observation that CD40-deficient platelets form less platelet-leukocyte aggregates with CD40-deficient leukocytes, produce less CXCL4, inhibit vascular smooth muscle cell (VSMC) proliferation and induce VSMC apoptosis.

The data reported here reveal an important feature of the CD40-CD40L co-stimulatory dyad in restenosis, and provide us with novel therapeutic leads. In contrast to atherosclerosis, in which CD40L-Mac1, as well as CD40L-CD40 interactions are involved, restenosis is only dictated by the classic CD40L-CD40 interaction, which makes therapeutic strategies to inhibit CD40 in restenosis of particular interest.

Conflicts of interest
None declared.

References