CD40L-Positive Platelets Induce CD40L Expression De Novo in Endothelial Inflammation: Adding a Loop to Microvascular Inflammation

To the Editor:

We read with great interest the article by Wagner et al, in which the authors elegantly showed that membrane bound CD154 (CD40 ligand [L]) expressed by T-cells can effectively trigger CD40L expression by endothelial cells. More importantly, the authors demonstrated a functional activity of endothelium-associated CD40L, thus revealing a novel costimulatory activity in monocyte–endothelial interactions. We have recently performed a series of experiments that aimed to study CD40L induction by endothelial cells, in particular assessing the consequences of the interactions between CD40L positive platelets with CD40 bearing endothelial cells.

CD40L expression was evaluated by flow cytometry in human intestinal microvascular endothelial cells (HIMEC) cultured alone, with resting and thrombin activated platelets, or stimulated with different activators, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and interferon (INF)-γ. Functional CD40L–CD40L interactions were interrupted by using anti-CD40L specific antibodies, as reported.

We found that CD40L was virtually absent in resting HIMEC (Figure A), and that all the potent proinflammatory molecules, such as IL-1β, TNF-α, and INF-γ, failed to induce CD40L expression, even though they were able to trigger HIMEC activation by upregulation of adhesion molecules (not shown). Resting platelets only slightly induced membrane bound endothelial CD40L (Figure B); in contrast, when endothelial cells were cultured with thrombin-positive CD40L platelets, HIMEC strongly upregulated CD40L expression (Figure C). Specificity of the CD40L activation was demonstrated by platelet-C40L blockade, as addressed by the strong inhibition induced by the use of the anti-CD40L antibodies (Figure D).

Taken together, our results extend the findings by Wagner et al, suggesting that platelets are a novel cell type that could be implicated in mediating CD40L-endothelial expression, thus strengthening the concept that activated platelets trigger endothelial CD40-dependent inflammation. At sites of intense endothelial activation and inflammation, such as during atherosclerosis or chronic intestinal inflammation in inflammatory bowel disease, where platelets express CD40L and are at direct contact with CD40 bearing endothelium, CD40L upregulation by endothelial cells could be a novel element in immune response amplification and in mediating cross-talk and activation signals toward CD40 positive cells, such as monocytes, B-cells, T-cells, and platelets.

An extremely high number (~ 10^12) of platelets circulate in the peripheral blood, and their number and activation state is increased in several inflammatory conditions. Thus, because they express and are major source of CD40L in the blood, CD40L-platelet–dependent CD40L-endothelial upregulation might represent a new pathway in the amplification of endothelium-dependent inflammation. Furthermore, targeting these interactions could be considered a potential therapeutic approach to blocking vascular inflammation not only in atherosclerosis, but also in chronically inflamed tissues, where the endothelium regulates leukocyte traffic and influx into the interstitium.

Silvio Danese
Franco Scaldaferrri
Alfredo Papa
Roberto Pola
Antonio Gasbarrini
Department of Internal Medicine, Catholic University
Rome, Italy

Allesandro Sgambato
Achille Cittadini
Institute of General Pathology
“Giovanni XXIII” Cancer Research Center
Catholic University
Rome, Italy


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CD40L positive platelets induce CD40L-endothelial expression by HIMEC. HIMEC monolayers were left untreated (A) or cocultured with 10^8 resting (B) or 10^9 thrombin-activated (C) platelets from normal subjects in the absence (C) or presence (D) of CD40L blocking antibody. After 18 hours, the HIMEC monolayers were extensively washed to remove virtually all platelets and were then stained with CD40L antibody and analyzed by flow cytometry. Thrombin alone (0.5U/mL) didn’t affect CD40L expression by HIMEC (not shown). The black curves represent the background of the isotype.
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Silvio Danese, Franco Scaldaferrì, Alfredo Papa, Roberto Pola, Antonio Gasbarrini, Allesandro Sgambato and Achille Cittadini

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