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COMMENTARY

Thrombin is bad, accepted; but is smoking good to prevent restenosis?

B. R. BINDER
Department of Vascular Biology and Thrombosis Research, Centre for Biomolecular Medicine and Pharmacology, Medical University of Vienna, Vienna, Austria

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See also Chen D, Weber M, Shiels PG, Dong R, Webster Z, McVey JH, Kemball-Cook G, Tuddenham EGD, Lechler RI, Dorling A. Postinjury vascular intimal hyperplasia in mice is completely inhibited by CD34+ bone marrow-derived progenitor cells expressing membrane-tethered anticoagulant fusion proteins. This issue, pp 2191–8.

The dramatic beneficial effects of percutaneous transluminal coronary angioplasty, which was introduced in the late 1970s, can be severely reduced by renarrowing of the treated arteries. Such restenosis occurs in 30–60% of all patients within 6 months after angioplasty. Although the use of coronary stents has reduced the incidence to 20–30%, restenosis after angioplasty and stenting is still an unresolved problem that can adversely affect the outcome of treatment of occlusive vascular diseases [1,2]. Since the introduction of angioplasty, additional therapeutic measures have been evaluated for their effectiveness in preventing restenosis. However, success has been limited: Casterella *et al.* [3] reviewed all these attempts and found that over 100 drugs and devices that were tested were preclinical or clinical failures. Brachytherapy using beta or gamma irradiating sources or radioactive stents [4,5] did prevent or delay restenosis in some cases. In fact, by the late 1990s, intracoronary brachytherapy had become the 'gold standard' therapy for the treatment of in-stent restenosis (ISR) in bare metal stents. Nowadays, drug-eluting stents represent the therapy of choice and in fact decrease the rate of restenosis substantially [6,7]. However, there is still a need for additional drug therapy based on an understanding of the pathophysiology of neointima formation, the major cause of ISR.

Neointima formation can be regarded as a response of the vascular wall to injury, and the experimental models used to study neointima formation are based upon that notion. In agreement with the different phases of healing of the vascular wound (Fig. 1A), several systems have been implicated in the process of neointima formation: among these are growth factor-dependent smooth muscle cell (SMC) proliferation, protease-dependent migration of cells into the wounded area, cytokine-initiated matrix deposition, and progression of the atherosclerotic disease itself [8–13]. Restenosis also involves, to a significant degree, inflammation [14–17], factors of the coagulation and fibrinolysis cascades, and protease-activated receptors [18–23]. With respect to the cells involved in neointima formation, in addition to resident monocytes, fibroblasts, platelets and monocytes recruited from the bloodstream, bone marrow-derived precursor cells are also involved [24,25]. In fact, their angioplasty-induced [26] release seems to be beneficial for re-endothelialization and neointima formation [27], whereas inhibition of the recruitment of monocyte lineage cells suppresses experimental restenosis [28].

In the article by Chen *et al.* in this issue [29], a novel and interesting aspect of the vascular response to injury is described (Fig. 1B). In an elegant study using mice transgenic for membrane-anchored anticoagulant fusion proteins under an α-smooth muscle actin promoter, they showed that bone marrow-derived cells enter the wounded area, express the anticoagulant protein, and completely inhibit neointima formation. This inhibition of neointima formation is harbored in CD34+ cells derived from the bone marrow that differentiate in the wound to SMCs and locally inhibit thrombin. As a consequence, tissue factor (and perhaps other markers of inflammation) is also not expressed in the neointima. Interestingly, when bone marrow of wild-type mice is transplanted into transgenic recipients expressing the anticoagulant in resident SMCs, inhibition of neointima formation is not seen.

This new pathophysiologic pathway is of potential major importance for novel therapeutic strategies. It implies that local thrombin inhibition is not enough, but that the specific site (cell) where thrombin formation or activity is inhibited is decisive. What are the consequences of this finding for systemic antithrombotic therapy after angioplasty? It might be that the local concentration of the antithrombotic at a specific site determines the success or failure of such measures.

However, there are also open questions with respect to the mechanism. Is thrombin important only at the beginning (local thrombus formation after injury) or during the process (tissue factor expression and thrombin generation). The report by

Correspondence: Bernd. R. Binder, Department of Vascular Biology and Thrombosis Research, Centre for Biomolecular Medicine and Pharmacology, Medical University of Vienna, Austria Schwarzspanierstr. 17, 1090 Vienna, Austria.
Tel.: +43 1 4277 62501; fax: +43 1 4277 9625; e-mail: bernd.binder@meduniwien.ac.at

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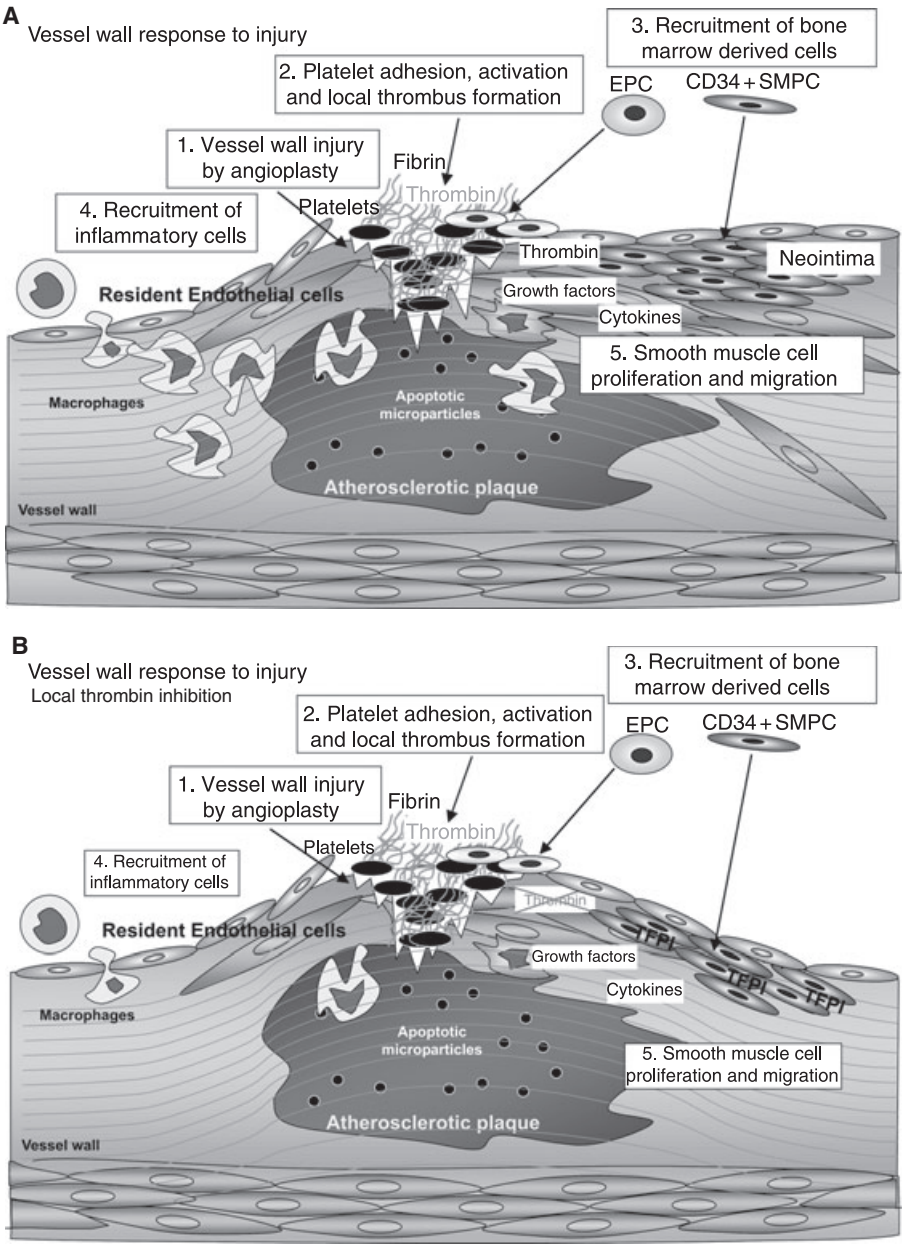

Figure 1. Vessel wall response to injury. (A) After injury (i), platelets adhere and are activated, local thrombin is formed and a local thrombus forms (ii). This leads to growth factor and cytokine release from resident cells and in turn recruitment of bone marrow-derived cells (iii) that are involved in healing (endothelial precursor cells, EPC) but might also sustain the inflammatory response (CD34+ cells and smooth muscle precursor cells, SMPC) by recruitment of bloodborne inflammatory cells (iv) and local thrombin formation. These processes finally lead to smooth muscle cell proliferation (v) and cell accumulation. (B) When local thrombin formation is inhibited, as in the experiments by Chen *et al.*, this vicious circle is disrupted and less neointima is formed.

Chen *et al.* indicates that thrombin plays a major role not only at the beginning, but also during the response to injury process. Furthermore, does thrombin initiate the inflammatory and growth factor cascades, which both need to be inhibited to abolish neointima formation, or is thrombin a major 'executor' acting on the target SMCs to initiate proliferation and migration? Which are the real target cells for thrombin? It might be that these are the very same bone marrow-derived CD34+ smooth muscle precursor cells. If this is the case, would inhibition of precursor release from the bone marrow be beneficial? This is in contrast to the earlier literature [27], where bone marrow-derived endothelial precursor cells have been reported to contribute to endothelial repair and inhibit neointima formation, but would be consistent with the description of host bone marrow cells as a source of intimal smooth muscle-like cells [24,25], and the fact that inhibition of recruitment of monocytic lineage cells also inhibits restenosis. Smoking reduces stem cell release from the bone marrow, and in fact there are reports – although conflicting [30] – that restenosis is somewhat ameliorated in smokers as compared to

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non-smokers [31,32]. This would be in line with the inhibitory effect of sirolimus on circulating vascular progenitor cells [33], which might mediate, at least in part, the beneficial effects of such drug-eluting stents. Does the report by Chen *et al*. support and explain that notion?

As always in science, exciting novel findings never close a chapter in research, but open up new fields.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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