Insight  Stimulated in vivo synthesis of PAI-1 in adipose tissue

Adipose tissue-derived PAI-1: A molecular link for thrombo-inflammatory disease states?

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Adipose tissue (particularly the visceral adipose tissue of the omentum) was long thought to be a passive, fat-storing cell clump; however, many years ago this view became out-dated. Numerous studies made us aware of the actual character of this contour-determining part of our body: Adipose tissue is considered to be a true organ capable of producing multiple types of hormones, pro- and anti-inflammatory mediators such as adipokines and other components that are relevant for metabolic control and vascular homeostasis. No wonder that fat tissue-derived factors are dynamically involved in obesity-associated diseases, play an important part in insulin resistance or metabolic syndrome, and are relevant control elements of the cardiovascular system (1). Adipokines constitute a heterogenous group of macromolecules and are divided into those produced by fat cells (such as leptin or adiponectin) and those released by non-fat cells, including several interleukins, tumour necrosis factor (TNF-α) as well as plasminogen activator inhibitor-1 (PAI-1) (2, 3). Moreover, the repertoire of adipokines, particularly when released under stimulatory/inflammatory conditions, may differ considerably between omental and subcutaneous fat tissue. Thus, adipose tissue-derived factors may act in a paracrine fashion at the interface with other organs or tissues, as was proposed for the fat–bone relationship (4).

Against this background, in this issue of Thrombosis and Haemostasis, Ekström et al. (5) provide experimental evidence in humans for a potential cross-talk between an acute inflammatory situation (such as open heart surgery in a small group of patients) and fat. This situation lead to a significant stimulation of PAI-1 gene expression in omental adipose tissue, accompanied by increased plasma levels of PAI-1 antigen over several hours during the post-operative period (5). Consequently, the authors propose that such inflammation-provoked elevated PAI-1 levels would diminish the t-PA-mediated fibrinolytic potential in these patients, resulting in an increased risk of myocardial infarction. As the origin of chronically elevated PAI-1 levels in situations of spontaneous arterial thrombosis or early vein graft rejection is largely unknown, this first study in human subjects offers a promising approach to define mechanistic relations between adipose tissue and other disturbed organs with regard to the thrombo-inflammatory axis.

Yet, one should be careful to over-interpret these findings (as already indicated by the authors), since several aspects may limit the conclusions of this small study. Further experimental work is required to clarify the following issues: (a) Although the elevation in PAI-1 antigen may also imply increased PAI-1 activity and enhanced inhibition of t-PA (with an increase in t-PA:PAI-1 complexes), these parameters were not determined, indicating that an impact on fibrinolysis may be assumed but was not experimentally demonstrated; (b) in addition to omental tissue being a major origin of the protease inhibitor, elevated plasma PAI-1 levels could be derived from activated platelets as well, which would fit with the known inflammatory role of platelets in different vascular diseases (6); (c) although quantitatively less pronounced when compared to omental fat tissue, epicardial adipose tissue may very well be responsive to acute inflammatory situations during open heart surgery, particularly due to its close proximity to the organ under operation. Here, further analysis to clarify mechanisms of a paracrine crosstalk provoked by adipokines may be worth considering. And finally, (d) the authors did not mention any PAI-1 targeting approaches that may add to an anti-inflammatory regimen with antagonists towards interleukins or TNF-α; here, PAI-1 inhibitors may very well be suitable to limit the risk of vascular diseases, including myocardial infarction, in the post-operative period and beyond (7).

Together with their first study in human patients the authors provide some clues for a thrombo-inflammatory connection between open heart surgery and increased PAI-1 production in adipose tissue. These initial findings may stimulate further translational investigations as to the potential role of adipokines and their direct or indirect contribution in thrombosis and haemostasis.

Conflicts of interest
None declared.

References
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