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The many domains of TFPI

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If tissue factor pathway inhibitor (TFPI) were a product like a smart phone or computer operating system, no doubt we would all be complaining that it came in too many versions. This relatively small (32 kDa) protein, thought to be the major plasma inhibitor of the initiation of clotting (reviewed by Broze and Girard (1)), has five domains: an acidic N-terminal domain, three Kunitz-type protease inhibitor domains, and a basic C-terminal domain. TFPI exists in multiple versions in plasma, including the “full-length” TFPI α molecule as well as various C-terminally truncated forms, some of which are in mixed disulfides with LDL. Although the latter have little or no anticoagulant activity, they are the predominant TFPI species in plasma. An alternatively spliced variant, TFPI β , is on the surface of endothelial cells and other cell types; it lacks the Kunitz 3 and basic C-terminal domains and instead is GPI-anchored via an alternate C-terminal sequence (2). Other alternatively spliced TFPI mRNAs have also been detected, although it is not clear if they are expressed into protein.

The first two Kunitz domains of TFPI function as protease inhibitors, with Kunitz 1 inactivating factor VIIa and Kunitz 2 inactivating factor Xa. The Kunitz 3 domain, N-terminal acidic domain and C-terminal basic domain are all thought to contribute to TFPI function, as removing them diminishes TFPI anticoagulant activity (1).

In the present issue of *Thrombosis and Haemostasis*, Peraramelli et al. employ chemical synthesis of peptides (including the use of peptide ligation to assemble them into larger proteins) to create versions of TFPI that contain just the isolated Kunitz 2 domain of TFPI, as well as combinations of Kunitz domains 1 and 2, or of Kunitz domains 2 and 3. They then utilize these precisely defined truncations of TFPI to explore the contributions of Kunitz domains 1 and 3, as well as the basic C-terminal domain, to the inactivation of factor Xa—which appears to be the major target of this protease inhibitor. This clever approach confirms previous studies of the functional contributions of the various TFPI domains (1), and extends them to identify, among other things, which portions of TFPI outside Kunitz domain 2 contribute to the initial encounter complex, and which contribute to the isomerization of TFPI bound to factor Xa to bring about the formation of the tightly-bound (and fully inhibited) TFPI/factor Xa complex.

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Conflict of Interest
None Declared.

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