Cysteine-less natural thrombin inhibitors: flexible but effective

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The mechanisms leading to blood clotting rely on a complex signal amplification cascade, where serine proteinase zymogens are sequentially activated to generate thrombin, a central player with both pro- and anticoagulant roles. Given their peculiar lifestyle, hematophagous animals need to counter the hemostatic mechanisms of their hosts. To this purpose, they evolved a true arsenal of specific and highly effective inhibitors of the serine proteinases that participate in blood clotting. Due to its central role in hemostasis, thrombin is a common target of this molecular weaponry, and a number of unique mechanisms of recognition and inhibition have been identified among natural anticoagulants aimed at this enzyme. Despite their diverse mechanisms of action, most characterized natural thrombin inhibitors display common and disulfide-rich structural scaffolds. However, a small subset of these molecules is particularly intriguing: the elusive cysteine-less thrombin inhibitors. These small (32-80 amino acids) and flexible polypeptides, belonging to MEROPS families I53, I64, I72, I74, I76, and I77, are disordered in solution. Notwithstanding, they can specifically inhibit thrombin with high affinity and effectively impair blood clotting. In-depth biochemical and structural studies on variegin (I74), madanin (I53), and anophelin (I77) started to unveil the molecular mechanisms of action of this group of inhibitors, revealing an unsuspected diversity. Using a hybrid approach that effectively combines a number of biochemical and biophysical techniques, these studies are being taken a step further, uncovering unexpected aspects of the unique modes of action of cysteine-less thrombin inhibitors and the strategies employed by many hematophagous organisms to counter thrombin's role in blood clotting.

Keywords: anticoagulant; proteinase inhibitor; disordered.