Crystal structure of chymotrypsin in complex with guamerin, a leech protease inhibitor

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Guamerin, a serine protease inhibitor which belongs to antistasin-type inhibitor family, represents a specific inhibitor towards elastase and chymotrypsin. However, it shows the weak inhibitory preference to other trypsin-type proteases such as trypsin, kallikrein and factor Xa. To provide the structural basis of specific inhibitory activity of guamerin and possible application of guamerin as a potent protese-inhibitor, we determined the crystal structure of chymotrypsin in complex with guamerin at 2.5 Å resolution. The overall structure of guamerin and its binding mode to chymotrypsin is similar with those of previously determined protease inhibitors such as bdellastasin, antistasin and hirustasin. The crystal structure of the complex showed that the C-terminal region of guamerin (residues 30-43) is involved in interacting with chymotrypsin. Clearly, the hydrogen bonds between the oxyanion hole of protease, formed by the NH groups of residues 193 and 195, and carbonyl oxygen atom of P1 residue (Met36), stabilize the binding of inhibitor to the enzyme. In addition, crystal structure also revealed the P1 residue (Met36) of guamerin fits into the substrate specificity pocket of chymotrypsin, explaining the inhibitory specificity of guamerin towards elastase and chymotrypsin.