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Energy Loading in the Metastable Native Structure of Inhibitory Serpins

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To understand structural and functional basis of loaded energy in the metastable native structure of inhibitory serpins (serine protease inhibitors), we characterized mutations that decreased the loaded energy of a1-antitrypsin and simultaneously influenced its inhibitory activity. Various folding defects such as side-chain locking, buried polar groups in unfavorable hydrophobic environment, and cavities were found as the structural basis of the metastability of a1-antitrypsin in a region presumably directly involved in the formation of complex between the inhibitor and a target protease. Functional analyses suggest that, in addition to the loaded energy, other structural features like flexibility are also critical.