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# Distribution and Structural Basis of the Native Strain in Human $\alpha_1$-Antitrypsin

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Metastability in the native form of proteins has been recognized as a mechanism of biological regulation. The strained native structure of serpins (serine proteinase inhibitors) is a typical example. The native strain of serpins is considered to be crucial to their physiological functions, such as plasma proteinase inhibition, hormone delivery, Alzheimer filament assembly, and extracellular matrix remodeling. To understand the structural basis and functional regulation of the native strain of serpins, various stabilizing amino acid substitutions of $\alpha_1$-antitrypsin ($\alpha_1$-AT), a prototype inhibitory serpin, were characterized. The stabilizing mutations are found in most domains of $\alpha_1$-AT, suggesting that the native strain of $\alpha_1$-AT is distributed throughout the whole molecule. Structural examination of the mutation sites revealed that various folding defects such as side-chain locking, buried polar groups in unfavorable hydrophobic environments, and cavities as the structural basis of native metastability. Interestingly, most of the stabilizing mutations did not affect the inhibitory activity, but the mutations that affect the activity is highly localized in a region where the reactive center loop is inserted upon interaction with a target enzyme. Implications on the strain-related functional regulation of serpins will be discussed.