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CRYSTAL STRUCTURE OF AN UNCLEAVED α_1-ANTITRYPSIN V. SEVEN STABILIZING MUTATIONS AT 2.7 Å RESOLUTION

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α_1-antitrypsin, a member of the serpin (serine protease inhibitor) family, undergoes a large structural rearrangement upon the cleavage and insertion of the reactive site loop. This conformational change is driven by the metastability of the native serpin structures and has an important role in the regulation of the inhibitory-serpin function. Some mutations of α_1-antitrypsin generated by random mutagenesis stabilize the native conformation and retard the insertion of the reactive site loop. We determined the three dimensional structure of an uncleaved α_1-antitrypsin with seven such stabilizing mutations (hepta α_1-antitrypsin) at 2.7 Å resolution to understand the atomic level nature of the metastability. From the comparison of the structure with other serpin structures, we found a novel conformational strain due to unfavorable overlaps of Van der Waals radii in the central hydrophobic core of the native uncleaved serpins. The F51L mutation, which has relatively high stabilizing effect among the mutations, stabilizes the native state of α_1-antitrypsin by releasing such conformational strain. The compressed structure of the hydrophobic core in the native α_1-antitrypsin can contribute to the opening of a major β-sheet like a spring.