
A3**Regulatory Role of the Serpin Strain**

Eun Joo Seo and Myeong-Hee Yu

National Creative Research Initiatives, Protein Strain Research Center, Institute of Science and Technology, P. O. Box 131, Cheongryang, Seoul 130-650, Korea

The native forms of common globular proteins are in their most stable state but the native forms of plasma serpins (serine protease inhibitors) show high-energy state interactions. The high-energy state strain of α_1 -antitrypsin, a prototype serpin, is distributed throughout the whole molecule, but the strain that regulates the function directly appears to be localized in the region where the reactive site loop is inserted during complex formation with a target protease. To examine the functional role of the strain at other regions of α_1 -antitrypsin, we increased the stability of the molecule greatly via combining various stabilizing single amino acid substitutions that did not affect the activity individually. The results showed that a substantial increase of stability, over 13 kcal mol⁻¹, affected the inhibitory activity with a correlation of 11% activity loss per kcal mol⁻¹. Addition of an activity-affecting single residue substitution in the loop insertion region to these very stable substitutions caused a further activity decrease. The results suggest that the native strain of α_1 -antitrypsin distributed throughout the molecule regulates the inhibitory function in a concerted manner.