Active or Inactive Human Granzyme B?

Insights through Molecular Dynamics Simulations

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Human granzyme B (hGzmB), which acts as the executive components of perforin/granzyme mediated apoptotic pathway [1], has attracted attention, due to its diverse pharmacological significance. Understanding the intricate details of reaction coupled motions in hGzmB can be highly crucial to facilitate the drug design [2]. In this work, long classical molecular dynamics (MD) simulations are employed to systematically analyze the structural dynamics of hGzmB in the interconversion of active and inactive conformation. The adopted protocol was validate by modeling the various stages of hGzmB catalytic cycle. Active and inactive conformations of hGzmB were modeled using hGzmB-substrate [3] and hGzmB-inhibitor complexes, respectively. Results demonstrate a systematic binding and unbinding phenomenon during the MD simulations, which correlated well with the available structural information for other members of this class of enzyme. Based on these observations a chain of intramolecular interactions (Figure 1) was proposed to be responsible for the conformational dynamics in hGzmB. The enzyme activation was associated with the formation of Asp103-Arg216 salt-bridge, which in turn caused the loss of His59···Asp103 H-bond. This sequence of events facilitated the accommodation of substrate near the catalytic triad. The proposed mechanism was also supported from *in silico* mutational studies, where Arg216Ala mutation resulted into the failure of substrate binding. This critical understanding of hGzmB activation at the atomic level is of prime importance for the identification of hGzmB modulating agents, by guided tailoring of structural features in therapeutic agents.

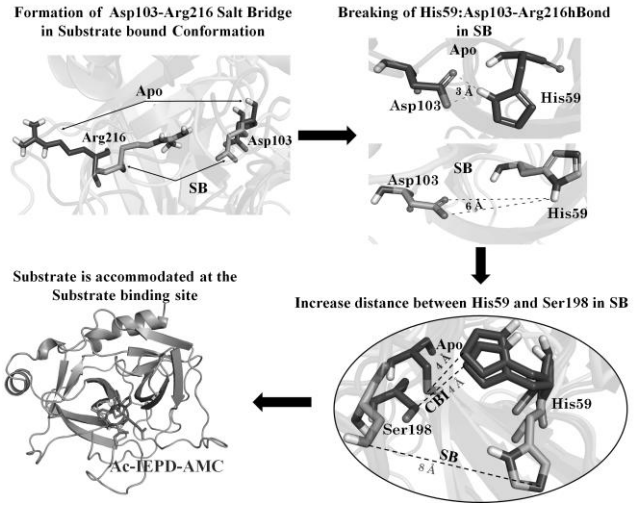

Figure 1. Sequence of events during enzyme activation. Apo: Apoform of hGzmB, SB: Substrate bound hGzmB, CBI: Inhibitor bound complex (covalent complexation).

Bibliography:

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