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"Caspase Protease Inhibitors as Alzheimer's Disease Treatments"

ABSTRACT: Caspases are cysteine proteases that are major players in key cellular processes, including apoptosis and inflammation. Amongst the human caspases, caspase-6 has been implicated in playing a unique and critical role in the neurodegenerative pathways of Alzheimer's disease. Unfortunately, structural similarities between caspase-6 and other caspases have hampered precise targeting of caspase-6 uniquely. All caspases can exist in a canonical conformation, in which the substrate binds atop a beta-strand platform in the 130's region. This caspase-6 region can also adopt a helical conformation that has not been seen in any other caspases. We have shown that caspase-6 is inherently and dramatically more conformationally dynamic than closely related caspase-7. In contrast to caspase-7, which rests constitutively in the strand conformation before and after substrate binding, hydrogen/deuterium exchange data for the L2' and 130's regions suggested that prior to substrate binding, caspase-6 exists in a dynamic equilibrium between the helix and strand conformations. Caspase-6 transitions exclusively to the canonical strand conformation only upon substrate binding. Glu-135, which showed noticeably different calculated pK_as in the helix and strand conformations, appears to play a key role in the interconversion between the helix and strand conformations. We have also mapped the local changes in the conformational flexibility of procaspase-6 at the discrete states that reflect series of cleavage events that ultimately lead to the fully active, substrate-bound state. The prodomain region was found to be intrinsically disordered, independent of the activation step of caspase-6; however, its complete removal resulted in the protection of the adjacent 26-32 region, suggesting a regulatory role. The molecular details of caspase-6 dynamics in solution provide a comprehensive scaffold for strategic design of therapeutic approaches for neurodegenerative disorders. We have used this information to make the most potent caspase-6 inhibitor to date.

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