The mercury–sulfur bond mediated inhibition mechanism of sulfhydryl group reactive agents on DEDDh exonuclease

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Abstract

According to World Health Organization (WHO) statistics, in western Africa, the Lassa fever virus infects about 30-50 thousand people per year with a case fatality rate of ~1%, but without any vaccine or effective treatments by now. NP exonuclease of the Lassa fever virus is comprised by the N-terminal domain and C-terminal DEDDh exonuclease domain, which are responsible for cap-binding and immune evasion, respectively. The two functions are essential for viral replication and infection, therefore the inhibitors of NP exonuclease could be used as antiviral drugs. On the other hand, Sulfhydryl group reactive agents, such as p-hydroxymercuribenzoate (PCMB) and p-chloromercuriphenyl sulfate (PCMPS), which are inhibitors of various enzymes, including NP exonuclease. However, the inhibition mechanisms of PCMB or PCMPS on target enzymes remain unclear. In this study, we demonstrated that PCMB and PCMPS are inhibitors of NP exonuclease by inhibitor coupled nuclease activity assays and determined various crystal structures of PCMPS- and PCMB bounded NP exonuclease complexes. We also performed the molecular dynamics (MD) simulation for understanding the dynamic of apo- or ligand-bound NP exonuclease. Combing our biochemical, structural, and MD related studies, we reveal a unique inhibition mechanism of PCMB and PCMPS on NP exonuclease. Our results not only provide the inhibition mechanism of PCMB and PCMPS but also provide a guideline for using these sulfhydryl group reactive agents on in vitro protein functional studies.

Keywords - Organomercurial, NP exonuclease, DEDDh exonuclease, Inhibitor, Molecular dynamics

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