Dynamics, regulation and inhibitor binding of the African swine fever virus topoisomerase

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Topoisomerases modulate DNA topology during transcription, replication and chromosome segregation [1]. Extensive studies have focused on the structural bases of catalytic mechanism and inhibitor development, mostly by X-ray crystallography on the cleavage core until recently [1,2]. African swine fever virus, a major threat in worldwide agriculture, consists of a type II topoisomerase (AsfvTop2) still with unknown structure or substrate specificity. Here we use cryo-EM and full-length AsfvTop2 to show highly dynamic features for the apo state, and distinct inhibitor binding modes for DNA complexes. In the apo form, six conformers were resolved which belong to three main conformational states (DNA gate open/C gate closed; both closed; and closed/open), suggesting that AsfvTop2 can pre-exist in multiple conformations resembling some intermediate states of the catalytic cycle (Fig. 1). Then we elucidated the cleavage site specificity of AsfvTop2. Structures of the AsfvTop2-DNA-inhibitor complexes with etoposide (Fig. 2a) and m-AMSA display binding modes differing from the corresponding complexes of Top2 from other sources, providing valuable information for future development of antiviral agents. In addition, we found that the ATPase activity can be inactivated by a unique disulfide bond (Fig. 2b), providing a regulatory mechanism and another potential drug target for AsfvTop2.

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