

Mapping Protein Selectivity Landscapes

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Abstract : Characterizing the binding selectivity landscape of interacting proteins is crucial both for elucidating the underlying mechanisms of their interaction and for developing selective inhibitors. However, current mapping methods are laborious and cannot provide a sufficiently comprehensive description of the landscape. Here, we introduce a distinct and efficient strategy for comprehensively mapping the binding landscape of proteins using a combination of experimental multi-target selective library screening and in silico next-generation sequencing analysis. We map the binding landscape of a non-selective trypsin inhibitor, the amyloid protein precursor inhibitor (APPI), to each of four human serine proteases (kallikrein-6, mesotrypsin, and anionic and cationic trypsins). We then use this map to dissect and improve the affinity and selectivity of APPI variants toward each of the four proteases. Our strategy can be used as a platform for the development of a new generation of target-selective probes and therapeutic agents based on selective protein-protein interactions.

Keywords : drug design, directed evolution, protein engineering, protease inhibition.

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