SFB 1078

Protonation Dynamics in Protein Function

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Freie Universität Berlin

via WebEx

Colloquium

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The Interplay of Electrostatics and Chemical Positioning in the Evolution of Antibiotic Resistance in TEM beta-Lactamases

Although substantial efforts have been made to design more efficient antibiotics, the use and misuse of these drugs has led to the appearance of super-resistant bacteria. As such, providing new biophysical understanding to the processes of evolution is necessary to develop new antibacterial strategies. Towards this goal, we sought to provide insight into how evolution utilizes the concept of electrostatic catalysis in TEM β-lactamases to shift its narrow spectrum penicillinase activity in TEM-1 towards extended spectrum activity in TEM-52, leading to the emergence of resistance against 3rd generation cephalosporin antibiotics. Using the concept of the vibrational Stark effect, we quantify the active site electric fields from the point of view of initial and final substrates, i.e., penicillin G and cefotaxime, and compare these results to a detailed mass spectrometry-based kinetic analysis and structural insights from molecular dynamics simulations. We observe that, like ketosteroid isomerase, a prime example of electrostatic catalysis, the enzyme utilizes immense preorganized electric fields of up to -180 MV/cm for both substrates, which serves as the catalytic basis to fine tune substrate-dependent chemical re-positioning and active site fluctuations during evolution. This integrated approach provides insights into the role of active site electrostatics on enzyme evolvability with implications for the emergence of antibiotic resistance, enzyme design, and protein evolution.

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