EVOLUTION OF PROTEIN DYNAMICS OVER 3.5 BILLION YEARS AT THE HEART OF ENZYME CATALYSIS AND REGULATION

Dorothee Kern, HHMI/ Brandeis University, Dept. of Biochemistry, Waltham, USA
dkern@brandeis.edu

As a direct manifestation of molecular kinetic energy, temperature is a fundamental evolutionary driver for chemical reactions. However, it is currently not understood how the natural evolution of catalytic efficiency responds to dramatic changes in environmental temperatures. Using Ancestral Sequence Reconstruction (ASR) we resurrect and biophysically characterize the oldest common ancestral kinase and enzymes along the evolutionary path to modern kinases. Strikingly, enzymes coped with an inherent drop in catalytic speed caused as the earth cooled down over 3.5 billion years by accelerating protein dynamics and adapting thermostability by unexpected mechanisms, as characterized by NMR. Tracing the evolution of enzyme activity and stability from the hot-start towards modern hyperthermophilic, mesophilic and psychrophilic organisms illustrates active pressure versus passive drift in evolution on a molecular level (1). In the second part of my talk I will describe our experimental exploration of the evolution of two allosteric regulation mechanisms widely found in the modern protein kinase superfamily, phosphorylation of the activation loop and binding of a regulatory partner protein. The results reveal the origins of allosteric activation including surprising mechanistic features. Moreover, ASR enabled identification of the underlying allosteric network in modern kinases that spans from the N-terminal to the C-terminal lobes. We are currently exploiting this knowledge for the development of allosteric inhibitors and activators. This latter approach delivered novel kinase inhibitors and activators with extreme specificity and high affinity thereby opening the road to new cancer treatment.

(1) V. Nguyen, C. Wilson, M. Hoemberger, J. Stiller, R. Agafonov, J. English, S. Kutter, D. Theobald and D. Kern “Evolutionary Drivers of Thermoadaptation in Enzyme Catalysis” Science 2017, 355