Brian G Miller, J Biotechnol Biomater 2017, 7:1(Suppl)
http://dx.doi.org/10.4172/2155-952X.C1.070

Allokairic regulation of enzyme function

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Human glucokinase (GCK), the body's primary glucose sensor and a major determinant of glucose homeostatic diseases, displays a unique form of allosteric-like behavior that is manifested as a cooperative kinetic response to glucose. The allosteric-like behavior of GCK is particularly intriguing since the enzyme is monomeric and contains only one glucose binding site. Recent work in our laboratory has shown that millisecond timescale order-disorder transitions within the enzyme's small domain govern cooperativity. Here, we present the results of biophysical studies that elucidate the structural and dynamic origins of the time-dependent, allokairic properties of GCK. Using high-resolution nuclear magnetic resonance, we identify two distinct mechanisms by which GCK can be activated, both of which result in hyperinsulinemia. The first activation mechanism alters the equilibrium distribution of GCK conformers in favor of a single-state, whereas the second mechanism alters the intrinsic dynamics of the enzyme without perturbing the relative distribution of states in the structural ensemble. Time-resolved fluorescence measurements map the dynamic conformational landscape of GCK and provide evidence for three distinct conformations of the enzyme in the absence of glucose. Together our findings provide a framework for understanding the origins of time-dependent changes in activity in other regulatory enzymes.

Biography

Brian Miller is an Associate Professor of Biochemistry at the Florida State University, USA. He did his PhD from the University of North Carolina, Chapel Hill in the year 2001. His research interest is protein structure, function and evolution.

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