Analysis of glycolysis regulation through predictive optogenetic control of Akt and Erk pathways

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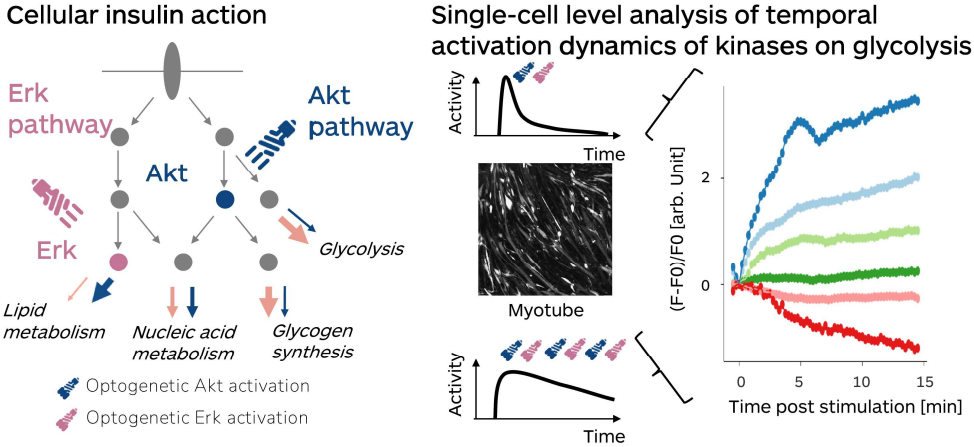
Postprandial metabolism is tightly regulated through the action of hormone insulin and its downstream signaling pathways. It has been suggested that different temporal insulin secretion patterns modulate the activation dynamics of various kinases such as Akt and Erk, controlling appropriate metabolic responses depending on the cellular nutrient availability. While our previous research in C2C12 myotube demonstrated that metabolic signaling network induced by the Akt isoform, Akt2,[1)] partially regulates glycolysis, the precise interplay between temporal kinase activation and glycolytic control remains elusive.

To address this, we developed an optogenetic system to precisely control the activities of kinases Akt and Erk using a simulation model that can predict the light-induced kinase activation thereby enabling induction of kinase activation dynamics. Since an optogenetic system for Akt was previously established, we newly developed an orthogonal optogenetic system for Erk and demonstrated that two kinases can be independently controlled using blue and red-light illumination. We then constructed an ordinary differentiation equation-based simulation model by estimating kinetic parameters in the equations based on the experimentally obtained Erk activation pattern with various light illumination patterns. Furthermore, we employed intracellular fluorescent lactate sensor[2)] to monitor the single-cell level regulation of glycolysis. By integrating these experimental and computational approaches, we aim to elucidate how distinct temporal activation patterns of Akt and Erk contribute to the regulation of glycolysis in response to physiological cues.



References: 1) Kawamura, et al., *Sci. Signal.* **16**, eabn0782 (2023)., 2) Nasu et al., *Nat. Commun.* **14**, 6598., (2023).