Brief summary on the Research Work of the Applicant duly signed by the Nominator

Understanding kinetic control of biological processes is as important as identifying components that constitute pathways. Insulin-signaling (IS) is central for almost all metazoans and its perturbations are associated with various developmental disorders, metabolic diseases and aging. While temporal phosphorylation changes and kinetic constants have provided some insights, constant or variable parameters that establish and maintain signal topology are poorly understood. Here, we report kinetic parameters that encode insulin concentration and nutrient dependent flow of information, using iterative experimental and mathematical simulation-based approaches. Our results illustrate how dynamics of distinct phosphorylation events collectively contribute to selective kinetic gating of signals and maximum connectivity of the signaling cascade under normo-insulinemic but not hyper-insulinemic states. In addition to identifying parameters that provide predictive value for maintaining the balance between metabolic and growth-factor arms, we posit a kinetic basis for the emergence of insulin resistance. Given that pulsatile insulin secretion during a fasted state precedes a fed response, our findings reveal rewiring of insulin signaling akin to memory and anticipation, which was hitherto unknown. Striking disparate temporal behavior of key phosphorylation events that destroy the topology under hyper-insulinemic states underscores the importance of unraveling regulatory components that act as bandwidth filters. In conclusion, besides providing fundamental insights, our study will help in identifying therapeutic strategies that conserve coupling between metabolic and growth-factor arms, which is lost in diseases and conditions of hyper-insulinemia.

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