UNRAVELING THE METABOLIC AND MACHINERY CONSTRAINTS ON PROTEIN SECRETION THROUGH A NOVEL SYSTEMS BIOLOGY FRAMEWORK

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In mammalian cells, metabolism is a core process driving homeostasis, but variations in other cell processes largely define cell type identity and cell-type specific functions. The profile of secreted and membrane proteins show substantial cell-type specificity and drive many tissue specific functions. These proteins, encoded by up to 1/3 of mammalian protein-coding genes, include hormones, membrane proteins, and extracellular enzymes, and these are synthesized and trafficked through the secretory pathway. The pathway complexity, however, obfuscates its impact on the secretion of different proteins. Unraveling its impact on diverse proteins is particularly important since the pathway is implicated in many diseases and harnessed for biopharmaceutical production. Through the use of network reconstruction approaches and protein interaction assays, we have mapped out the core secretory pathway and integrated it with our genome-scale metabolic models of human1, mouse, and Chinese hamster ovary cells2. We first deploy graph-based approaches to evaluate the dependency of protein secretion on diverse human secreted proteins3. We then deployed constraint-based modeling to quantify the bioenergetic demands for the synthesis and secretion of these proteins4. Finally, we deployed these models to engineer mammalian cells for enhanced secretion of high-value biologic drugs. Thus, we present a platform that enables the study and engineering of the mammalian secretory pathway and metabolism for systems biotechnology.