ABSTRACT

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Title of the Thesis: Protein perturbations in diseases with emphasis on autophagy process: Insights from the mathematical modelling and network biology perspectives

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The proper functioning of the cellular mechanisms that underlie the makeup of living systems is governed by the intricate interactions between the proteins, which are frequently perturbed in disease conditions. The advancement of high-throughput technologies has led to an unprecedented wealth of quantitative data to trace these perturbations. It is of utmost importance to identify the key set of proteins responsible for modulating these perturbations to obtain the potential targets in a disease. Notably, systematic efforts to detect these core sets of proteins have spurred the expeditious growth of network biology, providing a framework ideal for describing disease characteristics and predicting prospective therapeutic targets. In addition, comprehending how these spatially and temporally dispersed perturbations culminate in imperative biological processes is crucial to understanding cellular homeostasis and, by extension, disease pathogenesis. One such cardinal biological process is autophagy, which remains at the crossroads of numerous other biological processes and pathways. Autophagy plays a crucial role in maintaining cellular homeostasis by degrading unwanted materials like damaged mitochondria and misfolded proteins. However, the contribution of autophagy toward a healthy cell environment is not limited to the cleaning process. It also assists in protein synthesis when the system lacks the amino acids' inflow from the extracellular environment due to diet consumption. Reduction in the autophagy process is associated with diseases like cancer, diabetes, non-alcoholic steatohepatitis, etc., while uncontrolled autophagy may facilitate cell death. In many diseases, therefore, autophagy is seen to act as Janus.

Nevertheless, despite decades of prominent research focus, it is still a puzzle with various missing pieces due to its complex mechanism in numerous biological processes and diseases. This necessitates the integration of systems biology into the autophagy scenario, which can investigate a system both in pieces and as a whole. The veracity of these investigations hinges on their capacity to capture effective system dynamics. The development of a purely theoretical algorithm may find crucial nodes in the network by resolving all spatiotemporal scales, often at a cost that ignores the effect on the clinical characteristics of a disease. At the same time, their findings may not allow for generalisation. Conversely, an algorithm that investigates only the primary network properties, or clinical characteristics, is limited by the inability to look at the in-depth association between proteins. Therefore, an unmet need exists for a systematic framework that bridges protein perturbations, large-scale theoretical simulations, autophagy, and clinical characteristics of a disease to learn effective disease pathophysiology. Addressing these piers, in this thesis, we have incorporated mathematical modelling and network biology approaches to develop computational frameworks to investigate the protein perturbations in diseases with an accentuation on the autophagy process. We first developed a framework for identifying autophagy-related targets in diabetic retinopathy by forming algorithmic alloys between disease and autophagic proteins. Investigating the perturbations of proteins at both the gene and metabolic levels and using network controllability, we developed a methodology to identify potential targets in NASH. We next incorporated a guilt-by-association methodology in the same disease, machine learning, constrained network controllability, and metabolic analysis to identify another set of potential targets. Intriguingly, we noted that a subset of the targets identified by both frameworks was either autophagy-related or was surrounded by autophagy-related proteins, suggesting an autophagy-mediated mode of operation for these targets. Finally, we formulated a mathematical model to investigate the mechanistic understanding of the autophagy process, where we addressed the interplay between DNA damage and autophagy. Overall, the study discussed in this thesis suggests some potential targets and therapeutic interventions which are either directly or indirectly autophagy-related. On one hand, the frameworks used in this study exploited a quintessential biological process by using an extensive clinical dataset and mathematical modelling, while, on the other hand, the protein perturbations at the gene and metabolic levels were investigated to identify potential therapeutic targets. The proposed methodologies in this thesis are general and can be applied to study any potential disease. We believe that learning the disease dynamics with these frameworks will provide potent novel modalities for accurately targeting diseases and, thereby will assist in the advancement of the drug-discovery process.

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