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Metabolic Interactome: The Missing Link between Single Cell Approach and Systems Biology Approach

V Krishnan Ramanujan*

Metabolic Photonics Laboratory, Departments of Surgery and Biomedical Sciences, Cedars-Sinai Medical Center, 8700 Beverly Blvd., D6067, Los Angeles, CA 90048, USA

Metabolism is a single common paradigm that connects all aspects of life – from prokaryotes to eukaryotes. It refers to all the chemical reactions that take place in an organism. Metabolic pathways conserved across various species provide a comprehensive map of how we evolved from the simplest life form while the newer elements of metabolic partners yield valuable information how adaptation to environmental conditions has played a key role in our ability to gain novel functions along the way. Living systems orchestrate an ensemble of structural and functional hierarchy of metabolic networks in order to regulate homeostasis. A useful guide to understand this complex labyrinth of energy landscapes is to exploit steady-state approximation which states that under homeostatic conditions, the rate of generation of any excess metabolite/cofactors is equal to the rate of removal of such perturbations. In this paradigm, the function of external/internal stimuli is to enable living systems *to explore new steady states* by means of transient perturbations. Unfavorable conditions during this exploration process may affect the bioenergetics of the living system reversibly or irreversibly. These changes form the basis of onset of disease process and the pathophysiology. The real question is: *is this paradigm good enough for understanding human health and its breakdown as manifested in various diseases?* Recent studies in single cell metabolism have revealed exciting new features that are far from our conventional linear thinking and point out clearly that the aforementioned paradigm is not only insufficient but also inaccurate in many cases. This brief editorial is an attempt to outline this state of affairs.

In contemporary biology, human disease is viewed as a natural manifestation of breaking down of key regulatory steps in any particular organ and chronic/acute insults (e.g., environmental) to the edifice of healthy organs form the foundation of such misregulation in the respective organ function. This model might as well explain certain situations such as liver failure after repeated exposure to alcohol or skin diseases after prolonged exposure to UV radiation and/or chemicals. Another viewpoint from the laboratory research may emphasize on the role of key genes and their relative changes in expression/function – leading to disease phenotypes. Last few decades of cancer research has been primarily rooted on this genetic basis of cell transformation and despite the incompleteness, this model has saved thousands of lives by novel methods of cancer therapy and interventions. Despite the success of such a reductionist approach, a comprehensive understanding of energy metabolism at the level of whole organism is still lacking. We believe that this problem may stem from our lack of appreciation of nonlinear dynamical behaviors in cellular function. The rationale for this view point is as follows: a typical cell contains thousands of macromolecules most of which are part of various metabolic pathways which in turn, have their own hierarchy of interactions in the overall cellular function. Any perturbation to the cell will result in a collective response of all these metabolic hubs but our limitations in experimentally probing only a selective, desired pathway response will naturally blind us to the other metabolic pathways. In order to understand the synergetic roles of the interacting partners and the emergent behavior of the various networks, it is imperative to investigate the response of the networks as a whole in addition to conventional methods.

Our laboratory was one of the first to experimentally demonstrate that living hepatocytes can exhibit nonlinear scaling behavior in enzyme cofactor (NAD(P)H) fluctuations by a comprehensive time-series analysis [1]. We further explored the utility of these methods in unraveling free radical dynamics in aging cells and pH-dependent fluorescence fluctuations in cancer cells [2,3]. More exhaustive theoretical developments in this direction have been published since – including the dissipative metabolic network models [4]. More recently, novel approaches for constructing human diseases network based on cell metabolism have already yielded intriguing insights into the disease comorbidity and such 'network disease" models have great potential to bridge the gap between single cell metabolism and the system approaches such as human genome and human proteome projects [5-8]. We need therefore an initiative that mobilizes interdisciplinary research expertise in single cell metabolic imaging, genomics and proteomics and computational biology to rope in the various experimental inputs to construct a comprehensive model of metabolic interactomes. We are certainly entering an era of global understanding of human metabolic network without sacrificing our technological abilities to probe single cell metabolism with high resolution. Like every new epoch in scientific history, it is the realization of incompleteness that paves way to strive towards completeness.

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***Corresponding author:** V Krishnan Ramanujan, Ph.D, Assistant Professor, Metabolic Photonics Laboratory, Departments of Surgery and Biomedical Sciences, 8700 Beverly Blvd., Suite D6067, Los Angeles, CA 90048, USA, Tel: (+1) 310-423-7666; E-mail: Ramanujanv@csmc.edu

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