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Views & Comments

Extending the "Paracentral Dogma" of Biology with the Metabolome: Implications for Understanding Genomic–Glycomic–Metabolic–Epigenomic Synchronization

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The central dogma of biology holds that the transcription of DNA into RNA and the translation of RNA into proteins forms the primary axis of biological activity [1]. Following major advances in the description of the complex glycan and lipid chains that are added onto these basic building blocks, the glycome and lipidome have recently been added to this doctrine as an exciting new extension named the "paracentral dogma" [2]. However, it has been pointed out that biological systems can include many layers, which are described in modern omics technology platforms relating to both cell-intrinsic and cell-extrinsic layers of control, including metabolomic, microbiomic, immunological, epigenomic, epitranscriptomic, proteomic and phosphoproteomic layers [3].

It is well known that stem and progenitor cells have a metabolism that is based on glycolysis and glutaminolysis [4]. Although this provides less energy to the cell than oxidative phosphorylation, it suffices for these cells' needs, since such cells are generally relatively quiescent and normally suppress energy-intensive processes such as genome duplication and transcription. Moreover, it has been shown that the high intracellular lactate levels involved in such states not only inhibits the key gatekeeper enzymes of oxidative phosphorylation (i.e., pyruvate dehydrogenase and carnitine palmitoyl acyltransferase) but also actually covalently modifies them by lactylation in order to maintain this inhibited metabolic–epigenomic state [5]. In addition, intermediate metabolism and nutrients are the source of the very extensive library of post-translational modifications to DNA, RNA, and proteins, as well as supplying cellular energy for many of the required reactions. Hence, the metabolic state locks in and reinforces the epigenomic state, and the metabolome and epigenome thereby play mutually reinforcing roles. This self-reinforcing coordination explains why it is so difficult to generate induced pluripotent cells and is a contributory explanation for why the described protocols typically have such low cellular yields.

These concepts become even more important when it is considered that cancer cells are de-differentiated, similarly rely on glycolysis and glutaminolysis, and are similarly metabolically–epigenomically–genomically synchronized. The disruption of this metabolic system is a key focus of mechanistic cancer research.

These important considerations imply that the descriptive and predictive power of the newly described "paracentral dogma" of biology may be usefully and meaningfully extended by including the metabolome, along with the genome, transcriptome, proteome, glycome, and lipidome, to describe cell-intrinsic regulation—not only in terms of another omics analytical layer but also as a fully predictive and interactive partner in the symphonic-like multilayer coordination that evidently comprises cellular regulatory layering.

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