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Principles of Lipid Droplets and Transcriptional Response

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Description

Developmental Biology embodies some of the most fundamental questions in Biology and can trace its roots back to several thousand years ago; the last 100 years have been particularly extraordinary. In part the advances have been fuelled by new technical advances and knowledge in many other areas, which have contributed to shaping the field as truly interdisciplinary. During those 100 years some of our predecessors identified some key questions and a few important principles especially by trying to find general rules that govern what cells are able to do and how they choose between different options, as well as principles of experimental design that can be used to uncover those rules even before we know their physicochemical underpinnings. But the field has been changing rapidly in the last two decades. Here I present a brief overview of some of the changes that have taken place over the last Century and a personal view of current directions. The picture that emerges is of some dark clouds on the horizon, so this is also a call to arms for our colleagues to try to regain what the field has been losing.

Lipid Droplets

Lipid Droplets (LDs) are phospholipid monolayer-bound organelles found in most eukaryotes and some prokaryotes. These organelles store neutral lipids, such as triacylglycerols and cholesterol esters, that can be used to generate metabolic energy or cell membranes. Specific proteins, including many important lipid metabolism enzymes (TG synthesis and degradation enzymes), bind to LD surfaces. Due to their important function in metabolism, alterations in LD biology are causal or implicated in diseases, such as lipodystrophy, atherosclerosis, obesity, and related disorders. Type 2 diabetes mellitus, Nonalcoholic Fatty Liver Disease (NAFLD), and nonalcoholic steatohepatitis (NASH). Moreover, alterations in LD metabolism are implicated in cancer, neurodegeneration, and immune function.

Kinetoplastid protozoa possess properties that are highly divergent from the mammalian, yeast and bacterial cells more commonly used in synthetic biology and represent a tantalisingly untapped source of bioengineering potential. Trypanosoma brucei, an established model organism for studying the Kinetoplastida, is non-pathogenic to humans and provides an interesting test case for establishing synthetic biology in this phylogenetic class.

Vertebrate embryos establish their primary body axis in a conserved progressive fashion from the anterior to the posterior. During this process, a posteriorly localized neuromesodermal cell population called Neuromesodermal Progenitors (NMps) plays a critical role in contributing new cells to the spinal cord and mesoderm as the embryo elongates. Defects in neuromesodermal population development can cause severe disruptions to the formation of the body posterior to the head. Given their importance during development and their potential, some of which has already been realized, for revealing new methods of in vitro tissue generation, there is great interest in better understanding NMp biology. The zebrafish model system has been instrumental in advancing our understanding of the molecular and cellular attributes of the NM cell population and its derivatives. In this review, we focus on our current understanding of the zebrafish NM population and its contribution to body axis formation, with particular emphasis on the lineage potency, morphogenesis, and niche factors that promote or inhibit differentiation.

Transcriptional Response

Cells store excess lipids, such as fatty acids or sterols, as neutral lipids in LDs, a process that we named the “lipid storage response”. One component of the LSR is a rewiring of transcription to facilitate LD formation and lipid storage and utilization. This opened the door for two main disciplines to start contributing: Genetics (especially from the work of Thomas Hunt Morgan and his followers) and Experimental Embryology (arising mainly from the pioneering work of Wilhelm Roux). Genetics uncovered how “mutations”, heritable changes in the germ line, could affect development and body form and, through early attempts at mapping (notably by Morgan's student Alfred Sturtevant), the notion that some of the causative genes were present in some physical sequence in the genetic material whose nature was at that time still unknown.

The LD-Portal also includes data on subcellular protein localization based on protein correlation profiling for the majority of proteins across organelles in the C57BL/6J

murine liver (Krahmer et al., 2018). These studies were performed in mice fed with chow or HFDs, and by examining proteins across different cell fractions; they revealed how nutrient overload leads to organellar reorganization. Of the 6,163 proteins quantified across cellular fractions, 5,878 gave reproducible profiles for organelle assignment. Diet-dependent relocalization was found for 901 proteins and protein-expression changes for 258.

The reproducibility of this dataset was assessed by calculating the Pearson correlation of profiles derived from the same biological conditions and between different diets, and this revealed Pearson's coefficients of 0.86 and 0.78 for protein levels and relocalization patterns, respectively. For the murine liver samples, 787 protein profiles showed a characteristic peak in the top fraction after organelle separation by density centrifugation, indicating localization on the LDs or in LD-associated membranes.

Most of these proteins localized to multiple organelles, and only 94 had a unique LD localization. Of the 787 LD proteins, 308 showed a significant profile shift under HFD feeding. For instance, the proteins RAB7A, HSD17B11, DHRS1, and RAB1A underwent HFD-induced relocalization to LDs. Wilhelm Roux noted that the surviving cell in two-cell-stage embryos in which the other cell had been killed (in his own experiments) behaved differently from the equivalent cell in embryos where the other cell had been carefully removed (in contemporary experiments by Hans Driesch and Hans Spemann): in the first case it formed a half-embryo whereas in the second case it was able to "regulate", giving rise to a complete but miniature embryo. Roux's reflections on these experiments first pointed clearly to the principle that experimental approaches could be used to explore what cells can do and to compare this to what cells do in normal development.