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MEETING REVIEW

Metabolism in time and space – exploring the frontier of developmental biology

Alena Krejci[1,2,*] and Jason M. Tennessen[3,*]

ABSTRACT

Despite the fact that metabolic studies played a prominent role in the early history of developmental biology research, the field of developmental metabolism was largely ignored following the advent of modern molecular biology. Metabolism, however, has recently re-emerged as a focal point of biomedical studies and, as a result, developmental biologists are once again exploring the chemical and energetic forces that shape growth, development and maturation. In May 2017, a diverse group of scientists assembled at the EMBO/EMBL Symposium 'Metabolism in Time and Space' to discuss how metabolism influences cellular and developmental processes. The speakers not only described how metabolic flux adapts to the energetic needs of a developing organism, but also emphasized that metabolism can directly regulate developmental progression. Overall, and as we review here, this interdisciplinary meeting provided a valuable forum to explore the interface between developmental biology and metabolism.

KEY WORDS: Metabolism, Mitochondria, Aerobic glycolysis, Developmental plasticity, Nutrient sensing

Introduction

The origins of developmental biology are so firmly entrenched in studies of metabolism that, by 1931, Joseph Needham's book *Chemical Embryology* exceeded 2000 pages (Needham, 1931). This research was, however, largely forgotten when developmental biologists pivoted towards a more gene-centric approach. Many of the century-old questions highlighted by Needham figured prominently at the EMBO/EMBL Symposium 'Metabolism in Time and Space', which heralded the return of this long-neglected pillar of developmental biology. Over the course of three days, a notably diverse cast of scientists met in Heidelberg, Germany to discuss metabolic studies in organisms ranging from bacteria to humans; regardless of the system, a few major themes emerged. Metabolism must adapt to the energetic demands of cell proliferation, tissue growth and development, and as a result the rate and direction of metabolic flux will undergo dramatic changes during the life of any organism. However, metabolism does not simply respond to developmental signals; rather, individual metabolites can dramatically influence growth, differentiation and the timing of life history events, such as the onset of sexual maturation. Finally, organisms employ metabolic sensing mechanisms that gate cell fate decisions and developmental progression based on nutrient availability. These general themes fostered a sense of unity among the participants and stressed the importance of this type of interdisciplinary gathering.

Nutrient-sensing mechanisms

Growth and development are resource-intensive processes that depend on access to adequate nutrient supplies. As a result, developmental decisions are often gated by nutrient sensors, which ensure that growing organisms have sufficient metabolic stores. This relationship between nutrition and growth is exemplified in bacteria, where cell division is intimately linked with metabolic flux. In this regard, Uwe Sauer (ETH Zurich, Switzerland) described how his lab used real-time metabolomics to determine how carbon-starved *Escherichia coli* respond to pulses of glucose (Link et al., 2015). By examining changes in metabolic flux at 10-second intervals, the Sauer lab not only observed that glucose is quickly metabolized and shunted into biosynthetic pathways, but also uncovered a mechanism by which carbon-starved cells decide to divide upon exposure to glucose.

Just as bacterial proliferation depends on the ability to accurately measure glycolytic flux, eukaryotic growth, too, is dependent on the ability to monitor nutrient availability. A classic example of this metabolic necessity was provided by Alison Smith (John Innes Centre, Norwich, UK), who explained how plants store photosynthetic starch during the day and use it at night. Smith and colleagues determined that *Arabidopsis* sets the rate of nocturnal starch usage based on leaf starch content and a circadian clock that predicts the duration of night, thereby ensuring that starch stores will last until dawn (Scialdone et al., 2013). Their model also indicates that plants are capable of quantifying starch, and working towards the goal of elucidating this mechanism, the Smith lab has discovered an *Arabidopsis* protein, ESV1, that influences the rate of starch turnover by physically interacting with and controlling the structure of starch granules (Feike et al., 2016).

Animal development also must respond to metabolic cues, and a number of labs are using *Drosophila* as a model for studying nutrient sensing. Carla Margulies (Ludwig-Maximilians Universität, Munich, Germany) explained how her lab used cell type-specific ChIP to identify transcriptional targets of the sugar-responsive transcription factor Mondo, which is the *Drosophila* homolog of carbohydrate-responsive element-binding protein (ChREBP, also known as MLXIPL). Their analysis revealed that Mondo binding sites are enriched near glycolytic and lipogenic genes, suggesting that Mondo promotes lipid synthesis in response to sugar. In addition, the Margulies lab has determined that CrebA, a member of the Creb3L family of transcription factors, is active in fed animals and regulates genes involved in the secretory machinery.

Pierre Leopold (CNRS, Paris, France) and Norbert Perrimon (Harvard Medical School, Cambridge, USA) extended the

[1]University of South Bohemia, Faculty of Science, Branisovska 31, 37005 Ceske Budejovice, Czech Republic. [2]Biology Centre, Institute of Entomology, Czech Academy of Sciences, Branisovska 31, 37005 Ceske Budejovice, Czech Republic. [3]Department of Biology, Indiana University, 1001 East Third Street, Bloomington, IN 47405, USA.

*Authors for correspondence (abruce@prf.jcu.cz; jtenness@indiana.edu)

A.K., 0000-0001-7589-4035; J.M.T., 0000-0002-3527-5683

Development (2017) 144, 3193-3198 doi:10.1242/dev.150573

discussion of nutrient sensing by describing the network of signals that control the secretion of *Drosophila* insulin-like peptides (Dilps) from insulin-producing cells (IPCs). Similar to human insulin, Dilps are key regulators of growth and metabolism, and the fly has thus proven to be a powerful model for studying the mechanisms controlling insulin secretion. Intriguingly, IPCs are not directly responsible for detecting individual metabolites; rather, nutrient-sensing mechanisms in peripheral tissues remotely regulate IPC function. The Leopold lab determined that the proteins Eiger (TNFα) and Stunted (F1-F0 ATP synthase) are secreted from the fat body in order to control Dilp release, albeit for opposite purposes. When larvae encounter a low-protein diet, decreased amino acid levels in the fat body result in Tor inhibition. Since the TNFα-converting enzyme TACE is normally inactivated by Tor, a low-protein diet results in TACE activation and induces the release of Eiger into the hemolymph. Eiger then binds the G protein-coupled receptor (GPCR) Grindelwald located on the surface of IPCs, leading to Jnk activation and inhibition of Dilp secretion (Agrawal et al., 2016). By contrast, a high-protein diet activates Tor signaling in the fat body and induces the release of Stunted, which signals to IPCs via the GPCR Methuselah and induces Dilp secretion (Delanoue et al., 2016).

Complementary studies by the Perrimon lab have discovered additional secreted factors that control Dilp signaling and systemic metabolism. For example, the fat body-derived protein ImpL2 is secreted into the hemolymph in order to sequester and inactivate circulating Dilps (Kwon et al., 2015). A chronic high-sugar diet induces Activin-β release from the midgut, which promotes adipokinetic hormone signaling in the fat body and results in hyperglycemia (Song et al., 2017). Notably, Perrimon also described their analyses of the *Drosophila* adipokine Unpaired 2 (Upd2), which acts as a functional leptin ortholog and is released from the fat body of fed animals to induce Dilp secretion from IPCs (Rajan and Perrimon, 2012). Perrimon and colleagues have now demonstrated that a nutrient-regulated unconventional secretion pathway controls Upd2 release. They further demonstrate that a key protein involved in this secretory machinery is phosphorylated in response to starvation, which serves to inhibit Upd2 secretion. Since this mechanism is also capable of regulating human leptin secretion from the *Drosophila* fat body, the Perrimon lab's findings suggest that a conserved mechanism controls adipokine secretion.

Finally, Andrea Brand (The Gurdon Institute, Cambridge, UK) described how quiescent neural stem cells (NSCs) are reactivated by insulin signaling during *Drosophila* larval development. Previous studies in the Brand lab demonstrated that larval feeding induces blood-brain barrier (BBB) glial cells to secrete Dilp6 (Ilp6), which triggers larval NSCs to re-enter the cell cycle (Chell and Brand, 2010). Her lab has now determined that Dilp6 signaling from BBB glia requires the gap junction proteins Inx1 (Ogre) and Inx2, which allow nutrient-dependent calcium oscillations to synchronize the activity of these cells (Spéder and Brand, 2014). Interestingly, insulin secretion from human pancreatic β-cells is also coordinated by calcium signaling and is dependent on gap junctions, suggesting similarities between systemic insulin signaling (from the human pancreas) and local signaling (in the *Drosophila* brain).

Metabolic and developmental plasticity

Cellular metabolism *in vivo* must adapt to changes in nutrient quality and quantity. Most metabolic experiments, however, are conducted using standardized growth conditions and, as a result, the mechanisms that regulate metabolic plasticity remain poorly understood. In an effort to understand how cells adapt to changes in nutrient availability, Wilhelm Palm (Memorial Sloan Kettering, New York, USA) examined how cells proliferate in the absence of free amino acids (AAs). As Palm explained, when free AAs are limiting, cells use macropinocytosis to take up extracellular proteins as an alternative AA source. If free AAs become available, however, AA-induced activation of mTor will inhibit lysosomal catabolism of macropinocytosed proteins. Therefore, mTor activation provides a metabolic switch that ensures continued growth despite fluctuations in AA availability.

Similar to the cell-based studies described by Palm, animal metabolism must adapt to a variety of nutrient sources. Marian Walhout (University of Massachusetts Medical School, Worcester, USA) emphasized this fact by describing how *C. elegans* can rewire entire metabolic pathways in response to dietary cues. Walhout's lab found that *C. elegans* larvae raised on a *Comamonas* DA1877 diet exhibit accelerated larval growth, reduced fecundity and shortened lifespan when compared with larvae raised on a standard *E. coli* OP50 diet (MacNeil et al., 2013). Using an interspecies systems biology approach, they demonstrated that these diet-dependent phenotypes stem from vitamin B12, which is abundant in DA1877 but limiting in an OP50 diet (Watson et al., 2014). Furthermore, vitamin B12 is required for breakdown of the toxic metabolite propionate, and the Walhout lab has determined that larvae reared on an OP50 diet must transcriptionally upregulate a vitamin-independent pathway to degrade this compound (Watson et al., 2016). Christian Rödelsperger (Max Planck Institute for Developmental Biology, Tübingen, Germany) also highlighted nematode developmental plasticity by describing how the genus *Pristionchus* is ideally suited to study diet-dependent life history decisions. During the course of development, *Pristionchus* are capable of both forming stress-resistant dauer larva and developing predatory mouthhooks in response to environmental cues. Since both of these developmental decisions are gated by internally synthesized pheromones, Rödelsperger is using a systems biology approach to determine how pheromone biosynthesis changes in response to the metabolic composition of different diets.

The importance of using natural diversity to study metabolic plasticity was also emphasized by Tadashi Uemura (Kyoto University, Japan), whose lab is studying how different *Drosophila* species develop on diets with either low or high protein:carbohydrate ratios. The Uemura lab has discovered that larvae from generalist species, such as *Drosophila melanogaster*, are able to grow on either diet, whereas specialist species fail to develop on a medium with a high carbohydrate content. A metabolomic comparison of these species revealed that generalists exhibit homeostasis on the carbohydrate-rich diet as compared with specialists, and implicates the *Drosophila* Activin homolog Dawdle as a regulator of these adaptive metabolic responses.

Irene Miguel-Aliaga (MRC LMS, Imperial College, London, UK) expanded upon the discussion of plasticity by describing how the intestine of *Drosophila* females is significantly larger than that of males. Since the gut is a key regulator of nutrient absorption, this sex-specific trait dramatically influences metabolism and physiology. Miguel-Aliaga's lab determined that the differences between male and female intestines result from a non-canonical sex determination pathway that functions within intestinal stem cells (ISCs) (Hudry et al., 2016). Moreover, her lab discovered that masculinizing the ISCs in adult females reduces intestinal size and prevents the resizing that normally occurs after mating, thereby revealing a novel mechanism that profoundly influences nutrient handling and reproductive output. Their ongoing work is now extending the study of sex differences to other intestinal cell types, characterizing them using cell type-specific metabolic and splicing sensors.

Development (2017) 144, 3193-3198 doi:10.1242/dev.150573

Environmental cues regulate plant development and auxin signaling

Any growing organism must adapt to environmental stress, but plants exhibit an exceptional level of plasticity because, unlike animals, they are immobile and must adapt to local nutrient deficiencies. In this regard, Ottoline Leyser (University of Cambridge, UK) described how low soil nitrate levels inhibit branching in *Arabidopsis* by indirectly regulating auxin transport. Auxin is produced by growing leaves at the shoot apex and transported down the stem by the PIN family of auxin efflux proteins, which localize to the basal membrane of cells. Under normal growth conditions, new shoots form when auxin flows from the bud apex into the main stem. The Leyser lab discovered that the hormone strigolactone allows plants to tune their branching in response to limited nutrient availability by inducing the endocytosis of PIN1 and PIN7 in stems, reducing auxin flow and inhibiting bud activation (de Jong et al., 2014).

Developmental plasticity in the root is also controlled by PIN-dependent directional auxin transport, which, as explained by Ben Scheres (Wageningen University, The Netherlands), controls both rapid trophic responses and long-term maintenance of root developmental zones. Using *Arabidopsis*, the Scheres lab discovered that PLETHORA (PLT) transcription factors are key determinants of developmental zones within the root meristem and are only expressed in cells that experience prolonged exposure to high auxin levels (Mähönen et al., 2014). As a result, PLT expression maintains the long-term identity of zones within the root meristem even as local auxin concentrations experience short-term fluctuations, such as during the gravitropic response, where the auxin gradient is temporarily redistributed to the lower site of the root. These results, together with the research described by Leyser, provided an elegant snapshot of how environmental cues influence plant development by modulating the movement of a single molecule.

Metabolic regulation of development and the cell cycle

Many of the speakers emphasized the fact that metabolism is not simply a passive target of growth factor signaling, but rather directly regulates development. This point was highlighted by Peter Carmeliet (VIB-KU Leuven, Belgium), who described how endothelial cell (EC) metabolism controls angiogenesis in mammals. Previous work by the Carmeliet lab demonstrated that the enzyme PFKFB3 promotes vascular sprouting by inducing high levels of EC glycolysis (De Bock et al., 2013; Schoors et al., 2014). Yet, despite the glycolytic nature of ECs, Carmeliet's lab has found that CPT1A, which represents a rate-limiting enzyme in fatty acid β-oxidation, is also required for blood vessel formation. The role of CPT1A in this context, however, is not in ATP production; rather, ECs use fat catabolism for *de novo* nucleotide synthesis (Schoors et al., 2015). These results, together with other unpublished studies from the Carmeliet lab, emphasize that metabolism is an essential regulator of angiogenesis and highlight the importance of studying how metabolic processes directly influence tissue growth.

Matthias Heinemann (University of Groningen, The Netherlands) further explored metabolic regulatory functions in budding yeast. By examining the metabolism of individual cells, the Heinemann lab determined that NAD(P)H and ATP oscillate in opposite phase, once per cell cycle (Papagiannakis et al., 2017). Remarkably, these oscillations also continued in cell cycle-arrested cells, indicating that the metabolic oscillations are autonomous. In normally dividing cells, S phase consistently started at the time when NAD(P)H levels increase, and mitotic exit occurred at the trough in NAD(P)H signal, indicating coupling of metabolism with the cell cycle. However, when cells were shifted from a low-glucose to a high-glucose medium, the resulting increase in NAD(P)H levels reset the timing of the cell cycle, such that mitotic exit was delayed to maintain synchrony with NAD(P)H oscillations. These results reveal that metabolic flux has a previously unappreciated role in controlling the cell cycle and suggest that metabolic oscillations could profoundly influence cell proliferation.

A spotlight on lipids

Lipids are among the most abundant metabolites within a eukaryotic cell and control a variety developmental processes. Anne-Claude Gavin (EMBL, Heidelberg, Germany) explained how these molecules act within discrete cellular compartments to influence membrane structure, metabolism and signal transduction. Since lipids are hydrophobic, the mechanisms that move individual lipid species throughout the cytosol are also key regulators of their activity. By purifying lipid-transfer proteins from yeast, Gavin's lab determined that the oxysterol-binding proteins Osh6 and Osh7 transport phosphatidylserine from the endoplasmic reticulum to the plasma membrane (Maeda et al., 2013). Intriguingly, these families of proteins are associated with a number of human diseases, indicating that the sorting of lipids can profoundly influence metabolism and physiology.

The importance of studying lipid metabolism was further emphasized by Alex Gould (The Francis Crick Institute, London, UK), whose lab examined how oxidative stress influences *Drosophila* larval growth. The Gould lab found that while hypoxia induces cell cycle arrest in most larval tissues, neuroblasts continue dividing under low oxygen tension (Bailey et al., 2015). This sparing of neuroblast proliferation is dependent upon hypoxia-induced accumulation of lipid droplets (LDs) in glial cells, which are formed when polyunsaturated fatty acids (PUFAs) and other fatty acids are redistributed from the plasma membrane to glial LDs. Since oxidative stress induces the peroxidation of PUFAs, which can subsequently damage proteins and other macromolecules, their findings suggest that LD formation protects PUFAs and limits damage caused by reactive oxygen species within both the glia and neighboring neuroblasts.

Finally, Aurelio Teleman (German Cancer Research Center, Heidelberg, Germany) described how stearic acid (C18:0) acts as a signaling molecule during *Drosophila* development (Senyilmaz et al., 2015). The Teleman lab mutated the *Drosophila* gene *Elovl6* (*Baldspot*), which encodes a fatty acid elongase required for synthesizing C18:0. While characterizing this mutant, they discovered that animals lacking C18:0 display mitochondrial fusion defects and are hypersensitive to mitotoxins. These phenotypes, however, are not the result of a defect in mitochondrial membrane structure. In both *Drosophila* and human cells, C18:0 regulates the ubiquitylation and activity of mitofusin, which controls mitochondrial fusion. In human cells, C18:0 is required to stearolylate and inactivate the transferrin receptor (TFR1, or TFRC). In the absence of C18:0, TFR1 activates JNK, leading to mitofusin ubiquitylation and inactivation and mitochondrial fragmentation. Overall, the Teleman lab's unexpected results emphasize how a seemingly common lipid can directly influence cell signaling, growth and metabolism.

New roles for the Warburg effect

Nearly a century ago, Otto Warburg noted that tumors consume an exceptionally high level of glucose and tend to convert pyruvate to lactate, regardless of oxygen availability. This phenomenon, which is known as aerobic glycolysis or the Warburg effect, is ideally suited to support growth and biosynthesis. Jared Rutter (University

Development (2017) 144, 3193-3198 doi:10.1242/dev.150573

of Utah, Salt Lake City, USA) highlighted the importance of the Warburg effect while describing how his lab discovered the molecular identity of the mitochondrial pyruvate carrier (MPC). This conserved protein complex is responsible for transporting pyruvate into the mitochondrial matrix and represents the key metabolic link between glycolysis and oxidative phosphorylation (Bricker et al., 2012). Consistent with Warburg's observations, the Rutter lab found that many cancers exhibit decreased MPC1 expression, which results in an enhanced glycolytic state and increased tumor growth (Schell et al., 2014). Furthermore, Rutter also described unpublished data which reveal that the MPC promotes stem cell proliferation in the intestine, thereby implicating MPC as a key developmental regulator.

The Rutter lab's findings were echoed in talks by Nicole Prior (Aulehla lab, EMBL, Heidelberg, Germany) and Olivier Pourquié (Harvard Medical School, Cambridge, USA), who described a posterior-to-anterior gradient of glycolysis in the presomitic mesoderm (PSM) of the vertebrate tail bud (Bulusu et al., 2017; Oginuma et al., 2017). Using a combination of metabolomics, transcriptomics and a pyruvate FRET sensor, their labs found that the posterior PSM exhibits elevated levels of glycolytic flux and lactate production, suggesting that it relies on aerobic glycolysis to maintain an undifferentiated state. Consistent with this possibility, both groups determined that inhibition of glycolytic flux in the PSM leads to developmental abnormalities. The purpose of glycolysis in this region remains unclear however, as unpublished data from the Aulehla lab revealed that only a minimal amount of glucose is required to support mesodermal patterning. As Prior explained, the trace amount of glucose used in this experiment does not affect the accumulation of glycolytic metabolites, suggesting that aerobic glycolysis in the PSM has a non-canonical function. One clue as to how aerobic glycolysis promotes PSM development independently of biosynthesis comes from the Pourquié group, who demonstrated that the gradient of FGF/MAPK signaling present within this tissue regulates the transcription of several glycolytic enzymes. Intriguingly, FGF also controls Wnt signaling in the PSM, and the inhibition of glycolysis in this tissue phenocopies the loss of Wnt signaling in the tail bud. Therefore, Pourquié's group tested the possibility that FGF influences Wnt signaling via glycolytic flux and, indeed, found that Wnt targets are downregulated after the inhibition of glycolysis. Together, the data argue for a model in which FGF signaling establishes a glycolytic gradient across the developing tail bud that is, in turn, required to maintain Wnt signaling.

In addition to the newfound relationship between aerobic glycolysis, FGF, and Wnt signaling, Alena Krejci (University of South Bohemia, Ceske Budejovice, Czech Republic) reported that the Notch signaling pathway is also capable of promoting a glycolytic state. Krejci's group discovered that many *Drosophila* metabolic genes contain binding sites for the Notch-specific transcription factor Suppressor of Hairless and that a short pulse of Notch activity in S2N tissue culture cells elicits long-lasting metabolic remodeling towards the Warburg effect (Slaninova et al., 2016). Furthermore, the expression of several genes involved in glucose metabolism is regulated by Notch in the wing disc, and Notch may use this mechanism to promote the growth of this developing tissue. Considering that the Notch pathway is active in other contexts in which cells or tissues display elevated levels of glycolysis, these observations suggest that Notch could regulate aerobic glycolysis in a variety of settings.

The role of the Warburg effect in development was further explored by Jason Tennessen (Indiana University, Bloomington, USA), whose lab found that *Drosophila* larvae use aerobic glycolysis to synthesize the putative oncometabolite L-2-hydroxyglutarate (Li et al., 2017). Since this compound influences histone and DNA methylation, it has the potential to act as a metabolic signal during larval development. When considered in the context of Prior's and Pourquié's presentations, the Tennessen lab's observations emphasize that aerobic glycolysis can potentially influence developmental growth independently of biosynthesis.

Metabolism and immunity

A common theme that emerged at the symposium was that similar metabolic mechanisms control cell fate decisions during both development and the immune response. For example, just as the Warburg effect is associated with tumors and undifferentiated tissues, activated effector T cells (T_E) rely on aerobic glycolysis, whereas memory T cells (T_M) tend to utilize oxidative metabolism. The group of Erika Pearce (Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany) has determined that these differences in T cell metabolism depend on mitochondrial structure (Buck et al., 2016). As Pearce described, the more glycolytic T_E cells have punctate mitochondria, whereas T_M cells display mitochondria that are fused into networks. Since these structural changes precede the metabolic changes, their observations argue that mitochondrial morphology controls the cellular metabolic state. Indeed, the Pearce lab demonstrated that the inner mitochondrial membrane protein Opa1 promotes mitochondrial fusion in T_M cells and induces T_M cell fate even in culture conditions that normally program T_E cell differentiation. Furthermore, these observations suggest that mitochondrial fusion-promoting drugs might create metabolically fit T cells and improve adaptive cellular immunotherapy against tumors.

As mentioned by Pearce, the crosstalk between metabolism and immunity is of particular interest in the cancer field. Towards the goal of further exploring this relationship, Lisa Kelly (University of Edinburgh, UK) and colleagues are using zebrafish as a model to elucidate the metabolic signals involved in the recruitment of innate immune cells during early cancer development. Their data argue that developing pre-neoplastic cells exhibit changes in mitochondrial dynamics and related metabolic processes, which alter respiratory capacity. Kelly is now using transgenic zebrafish reporter lines combined with live imaging to understand how these metabolic signals recruit immune cells.

Two members of Dominique Ferrandon's lab (University of Strasbourg, France) further explored the topic of immune responses by describing how animal intestines respond to acute toxin exposure. First, Catherine Socha described how the pore-forming bacterial toxin hemolysin leads to a thinning of the gut epithelium in *Drosophila*, honey bees and humans (Lee et al., 2016). Surprisingly, this thinning results from the extrusion of apical cytoplasm from enterocytes (intestinal cells) into the gut lumen, thereby providing these cells with a mechanism to maintain barrier function against bacterial invasion. Socha also explained how the gut endothelium recovers a few hours after toxin exposure and provided details of the mechanisms that underlie this process. Second, Adrien Franchet presented results showing that the *Drosophila* gut epithelium reacts to the exposure to some xenobiotic substances by extruding LDs. His observations suggest that extruded LDs protect the organism from the detrimental action of xenobiotics and complement the Gould lab's discovery that glial LDs protect neuroblasts from oxidative damage.

Metabolism in the moonlight

Many of the enzymes involved in metabolism were first described nearly a century ago. Yet, despite decades of research, only recently

Development (2017) 144, 3193-3198 doi:10.1242/dev.150573

have the 'moonlighting' functions of these well-studied proteins begun to emerge. Non-canonical enzyme function figured prominently in the presentation by Matthias Hentze (EMBL, Heidelberg, Germany), whose lab recently demonstrated that many of the enzymes involved in central carbon metabolism serve as RNA-binding proteins (termed enigmRBPs) (Beckmann et al., 2015). Although the function of most enigmRBPs remains poorly understood, Hentze described unpublished results which reveal that the autophagy receptor protein p62 (SQSTM1) binds vault RNAs (vtRNAs). This interaction prevents p62 from inducing autophagy – a result that both reveals a novel RNA-based mechanism for regulating autophagy and suggests that the hundreds of enigmRBPs are likely to have important and diverse functions.

While Hentze highlighted the moonlighting function of metabolic enzymes, Avinash Patel (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany) revealed that even ATP has non-metabolic roles (Patel et al., 2017). Patel and colleagues found that, under physiological conditions (2-8 mM), ATP promotes protein solubility and inhibits the formation of protein aggregates. Notably, this hydrotrope function is independent of the more canonical role of ATP as an energy carrier and suggests that the age-related decline in ATP concentration might be a cause of the enhanced pathological protein aggregation observed in neurodegenerative diseases. While these observations are exciting in themselves, a broader interpretation of Patel's results suggest that many well-studied metabolites are likely to have as yet undiscovered functions.

Emerging technologies and future directions

A major takeaway message was that development and metabolism are inseparably linked. This is an important point for developmental biologists, who often treat metabolic enzymes as either housekeeping genes or as the downstream targets of signal transduction cascades. Moving forward, our community must make a concerted effort to understand how individual metabolites control cell signaling and developmental progression. Furthermore, we must move beyond genomic and proteomic approaches, and embrace emerging metabolomic technologies to understand how the distribution and abundance of metabolites change during development. With these goals in mind, the meeting highlighted a number of technological advances that will significantly expand the developmental biologists' metabolic toolkit. For example, Kai Johnsson (EPFL, Lausanne, Switzerland) described fluorescent protein sensors that allow for real-time metabolite measurements, while Theodore Alexandrov (EMBL, Heidelberg, Germany) explained how emerging metabolomic techniques can visualize the spatial distribution of metabolites within developing tissues (Palmer et al., 2017). Such advances in metabolomics, metabolite imaging, and the modeling of metabolic networks are providing new opportunities to study the biochemical forces that shape growth and development. The future is bright for this re-emerging field, and nearly 90 years after the publication of Needham's treatise, we are once again exploring the metabolic basis of developmental biology.

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Competing interests

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