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MEETING REVIEW

Metabolism meets development at Wiston House

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ABSTRACT

It is becoming increasingly clear that cellular metabolite levels regulate the activity of signaling pathways, and conversely that signaling pathways affect cellular physiology and growth via metabolic pathways. Thus, metabolism and signaling mutually influence each other. The Company of Biologists' Workshop 'Metabolism in Development and Disease' brought together people studying signaling and development with people studying metabolism, particularly in a cancer context. This Meeting Review discusses examples of talks that illustrated this principle.

KEY WORDS: Development, Disease, Metabolism

Introduction

Eighty years ago, metabolism was at the center of biological research, and was thought to control most biological processes. It was within this context that Otto Warburg proposed that cancer originates from altered cellular metabolism due to mitochondrial dysfunction (Warburg, 1956). In subsequent decades, as genes were cloned and sequenced, and signaling pathways were pieced together, focus shifted away from metabolic regulation. Instead, more recently, biological processes have been thought to be controlled by signaling pathways. The Company of Biologists' Workshop 'Metabolism in Development and Disease' (organized by Suzanne Eaton, Wilhelm Palm and Craig Thompson and held 15-18 May 2016 at the beautiful Wiston House in Sussex, England; Fig. 1) brought together people studying metabolism (particularly in a cancer context) with those studying development, merging these two fields. A key takeaway message was that metabolism and signaling are intertwined, with each one influencing the other. Both signaling and metabolism can play instructive roles in development and disease. Furthermore, metabolism can be very plastic, and can be re-wired both during normal development and in cancer. Examples of the talks that illustrated these principles are discussed below.

Metabolism and metabolites can play instructive roles in development and disease

Several talks at the meeting presented beautiful examples of how metabolites can play instructive roles both in normal development and in disease. For instance, during development tissues are patterned by morphogen gradients – gradients of signaling proteins belonging, for instance, to the BMP/TGFβ or Wnt families – that act in a concentration-dependent manner. Carlos Carmona-Fontaine (Memorial Sloan Kettering Cancer Center, NY, USA) presented data showing that in tumors, spontaneous gradients of oxygen and lactate are formed (Carmona-Fontaine et al., 2013). These gradients can pattern macrophages in a concentration-dependent manner that depends on the distance from blood vessels. In essence, this example shows that metabolites can act in an instructive manner similar to a morphogen. This builds on a significant body of work, presented by Peter Ratcliffe (University of Oxford, UK), on how cells sense hypoxia, and how these mechanisms are used by cancer cells (Ratcliffe, 2013).

During vertebrate somite formation, oscillations of FGF and Wnt signaling pattern the mesoderm, leading to waves of signaling that start at the posterior tip of the presomitic mesoderm and move towards the anterior to create somites. Olivier Pourquié (Harvard Medical School, Boston, MA, USA; Brigham and Women's Hospital, Cambridge, MA, USA) showed that glycolytic flux and metabolites link the FGF and the Wnt gradients in the embryonic tail bud, providing an example of how a metabolic pathway is integrated into an intricate signaling network.

The Hedgehog signaling pathway plays an important patterning role throughout development of animals. Hedgehog binding to its receptor Patched relieves inhibition of the seven-pass transmembrane protein Smoothened, leading to activation of Gli transcription factors and downstream gene expression. How and why Smoothened is repressed in the absence of Patched was not well understood. Using the *Drosophila* wing as a model system, Suzanne Eaton's group (Max Planck Institute of Molecular Biology and Genetics, Dresden, Germany) found that very low-density lipoprotein particles in serum repress Hedgehog signaling. From fractionation experiments, they identified endocannabinoids as the active compound and showed that these bind directly to Smoothened and inhibit it; this activity is conserved from flies to humans (Khaliullina et al., 2015). This provides another beautiful example of a metabolite that plays an important signaling role, and of how metabolites and signaling components can be functionally intertwined.

Several talks at the meeting focused on metabolic regulation in the nervous system. Neuroblasts are large *Drosophila* neural stem cells (NSCs). They undergo asymmetric cell divisions to yield one large neuroblast daughter cell and a small differentiating daughter cell. During pupal life, the neuroblasts progressively reduce in size through successive divisions. Eventually, the cytoplasm is no longer large enough to support an asymmetric division, and the neuroblast undergoes one last symmetric division to yield two differentiated cells. This leads to a lack of NSCs in the adult fly. Catarina Homem [Chronic Diseases Research Center (CEDOC), Lisbon, Portugal] together with Jürgen Knoblich (Institute of Molecular Biotechnology, Vienna, Austria) discovered that the ecdysone pulse that induces pupation instigates a metabolic shift in neuroblasts, causing them to become less glycolytic and more dependent on oxidative phosphorylation. This metabolic shift, which is the opposite to that observed by Otto Warburg in growing cancer cells, causes neuroblasts to reduce their growth rate. Hence, the cessation of stem cell renewal is due to a metabolic shift to oxidative phosphorylation (Homem et al., 2014). This nicely illustrates the interconnections between development and metabolism, and provides an example of how the metabolic

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Fig. 1. The participants of The Company of Biologists' Workshop 'Metabolism in Development and Disease'. Organizers Craig Thompson, Wilhelm Palm and Suzanne Eaton are seated front center.

re-wiring found in cancer is a reversal of the differentiation process observed during normal development. On a similar theme, Jelle van den Ameele (Brand laboratory, Gurdon Institute, Cambridge, UK) also presented preliminary data on metabolic reprogramming and changes in mitochondrial morphology during *Drosophila* neurogenesis.

In the brain, glial cells provide important metabolic support for neurons. For instance, in *Drosophila*, glial cells form the blood–brain barrier, thereby regulating which nutrients gain access to the brain, and ensheath neurons and exchange metabolites with them. Christian Klämbt (University of Münster, Germany) talked about examples in which alterations in glial metabolite homeostasis cause specific changes in animal behavior. His lab has identified metabolism-related genes that, when manipulated in glia, cause distinct changes in larval locomotor behavior.

Metabolism and energetics also influenced development during animal evolution. Ben Steventon (University of Cambridge, UK) showed how energy supply differences between animals can explain the different modes of elongation of the posterior body during embryogenesis (Steventon et al., 2016).

Nutrient-sensitive post-translational modification of proteins

One particular situation in which nutrients play instructive roles in disease and development is when metabolite levels directly influence protein post-translational modifications. A number of such examples were presented at the meeting.

Triggering of the T-cell receptor on naive T lymphocytes leads to their activation. The group of Doreen Cantrell (University of Dundee, Scotland, UK) discovered that T-cell activation in mice only occurs if sufficient levels of the right nutrients are available. The main sources of carbon and nitrogen for vertebrate cells are glucose and glutamine, respectively. These two metabolites are required to form UDP-N-acetylglucosamine (UDP-GlcNAc). Hence, UDP-GlcNAc levels are a proxy for glucose and glutamine availability, making O-GlcNAcylation of proteins a nutrient-responsive post-translational modification. Cantrell's group found that immune activation induces expression of glucose and glutamine transporters in T cells, thereby fueling the production of UDP-GlcNAc. This leads to increased O-GlcNAcylation of Myc, thereby stabilizing Myc protein, which in turn is important for T-cell activation (Swamy et al., 2016). Interestingly, Myc forms part of a feedback loop in this context, as Myc activity upregulates the expression of genes required for glutamine uptake and utilization. Interestingly, regulation by metabolism might be a widespread phenomenon within the hematopoietic system. Naomi Taylor (Institut Génétique Moléculaire Montpellier, France) showed that glutamine-derived *de novo* nucleotide biosynthesis is required for erythroid differentiation of mouse and human hematopoietic stem cells (HSCs). HSCs require glutamine uptake via the ASCT2 (SLC1A5) glutamine transporter, and active glutamine metabolism for erythroid specification. If this is blocked, erythropoietin-stimulated HSCs are diverted to differentiate into myelomonocytic fates (Oburoglu et al., 2014).

Craig Thompson (Memorial Sloan Kettering Cancer Center, NY, USA) presented the concept that histone acetylation levels are regulated by nutrients (Wellen et al., 2009). When mammalian cells have sufficient carbon supply, acetyl-CoA levels increase due to activity of ATP citrate lyase. Acetyl-CoA is then used to acetylate

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histones. By contrast, when glucose supply is low, not only are acetyl-CoA levels low, hampering novel acetylation of histones, but reduced glycolytic flux also leads to elevated levels of the oxidised form of nicotinamide adenine dinucleotide (NAD^+), leading to elevated histone deacetylation via NAD^+-dependent deacetylases. Likewise, histone acetylation in yeast was also shown to be dependent on acetyl-CoA levels, and hence metabolic flux, by Ben Tu's lab (University of Texas Southwestern Medical Center, Dallas, TX, USA), showing conservation of biological principles from yeast to humans (Cai et al., 2011). As another example of nutrient sensing by post-translational modification of proteins, Tu further showed that levels of methionine, and its downstream metabolite S-adenosylmethionine (SAM), regulate autophagy via methylation of the catalytic subunit of PP2A (Sutter et al., 2013).

A further example was presented by Aurelio Teleman (German Cancer Research Center, Germany), who showed that a lipid metabolite, stearic acid, covalently modifies proteins, thereby affecting mitochondrial morphology and function (Senyilmaz et al., 2015).

Signaling regulates metabolism

The interconnections between signaling and metabolism go both ways, with metabolism regulating signaling and the other way around. Several talks, discussed above, revealed mechanisms whereby signaling affects metabolism. Wilhelm Palm from Craig Thompson's lab provided another beautiful example of this. Normally, cells preferentially uptake glucose and free amino acids from their environment to fuel metabolism and growth. Palm showed that under low-nutrient conditions, cultured human cells can also uptake whole proteins as a protein source from the medium via macropinocytosis (Palm et al., 2015). Interestingly, this cellular 'stress response' is inhibited by mTORC1 signaling, leading to the unexpected result that under certain nutrient conditions, cells proliferate better when mTORC1 activity is suppressed, with obvious possible implications for cancer therapy using mTORC1 inhibitors.

Of development and cancer

Our understanding of cancer biology has benefitted tremendously from research on the basic biological mechanisms of development. For instance, most of the signaling pathways that have been genetically dissected and pieced together, mainly in *Drosophila*, such as Notch, Hedgehog and BMP/TGFβ signaling, play important roles in cancer development. Perhaps this is because cancer entails cell de-differentiation, reversing the progression and signaling events of normal development. This also applies to metabolism, and the metabolic shifts observed during cell differentiation and de-differentiation. Hence, one takeaway message of the meeting was that cancer biology and developmental biology can also learn from each other when it comes to metabolic regulation. This is particularly the case because metabolism can easily re-wire, and hence the metabolic patterns observed in cells growing in tissue culture do not necessarily reflect the *in vivo* situation. Thus, although our understanding of metabolic re-wiring during cancer is further advanced than our understanding of metabolic dynamics during development, model organisms that allow us to look at metabolic changes during development could contribute towards a better understanding of the *in vivo* situation in normal and disease conditions.

YaoYao Chen (University of Cambridge, UK) presented a project looking at the metabolic profiles of embryonic stem cells (ESCs) as they differentiate. She showed that ESCs have large amounts of mitochondria and respire actively. As they progress to primed pluripotent stem cells (EpiSCs), they gradually become more glycolytic as their oxygen consumption and mitochondrial membrane potential decrease. Finally, as EpiSCs differentiate, they once again rely more on respiration. Similarly, William Harris (University of Cambridge, UK) showed that also in the developing eye retina, the metabolic profile of cells depends on their state of differentiation (Agathocleous et al., 2012). The ciliary marginal zone (CMZ) of a developing eye contains the stem cells that proliferate and are in contact with blood vessels, and intermediate progenitors that proliferate and differentiate. Compared with the more centrally located differentiated cells of the retina, the proliferating stem cells consume less oxygen and are less dependent on respiration for ATP synthesis (Agathocleous et al., 2012). Even though they have access to oxygen, the stem cells of the CMZ are fermentative, reminiscent of the 'Warburg effect' seen in cancer. He then presented evidence for a nutrition-sensitive restriction point for proliferation and differentiation in the CMZ (Love et al., 2014) and that the hypoxia-activated HIF1 pathway can overcome this restriction (Khaliullina et al., 2016). These types of results may give insights into how and why de-differentiated cancer cells rely less on respiration compared with differentiated cells.

Laura Johnston (Columbia University, NY, USA) also presented a developmental biology project with likely cancer implications. In the *Drosophila* wing disc, the confrontation of cells with high Myc activity (and hence high proliferation capacity) with cells with low Myc activity, leads to 'cell-competition' whereby the low-Myc cells die, even though in a non-confrontation context they would survive. A similar situation might arise early in tumorigenesis when high-Myc tumor cells reside next to low-Myc non-tumor cells. Johnston showed that when in confrontation, high-Myc cells activate p53 (TP53), which stimulates oxidative phosphorylation and enhances their glycolytic flux, augmenting their proliferation capacity. High-Myc cells induce expression of Glut1 (Slc2a1), and increase glucose uptake and lactate production (de la Cova et al., 2014). p53 is also required in the high-Myc cells for their ability to transmit a death-inducing signal to low-Myc cells. By contrast, low-Myc cells lose p53 activity, leading to their death. Hence, changes in metabolism contribute to accentuating the comparison between 'winner' and 'loser' cells in such a confrontational context. Whether such cell competition might apply in the cancer context is an intriguing possibility worth studying in the future.

Re-wiring of metabolism

One theme that emerged is that metabolic networks can re-wire and metabolic flux can change within cells depending on circumstances, both during cancer and normal development. Several examples were presented in which cancer cells uptake metabolites from their surroundings, such as lactate or pyruvate, which non-cancer cells would normally secrete. The Gottlieb lab (Cancer Research UK, Beatson Institute, Glasgow, UK) showed that kidney cells lacking succinate dehydrogenase, which is associated with renal cell carcinoma, consume extracellular pyruvate, allowing them to divert glucose-derived carbons towards aspartate biosynthesis, used for making nucleotides (Cardaci et al., 2015). Lucas Sullivan from the Vander Heiden lab (Massachusetts Institute of Technology, Cambridge, MA, USA) presented a beautiful story showing that the major role of mitochondrial respiration is to provide electron acceptors for aspartate biosynthesis, and indeed respiratory chain defects can be rescued in cell culture by providing cells aspartate (Sullivan et al., 2015).

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The Chiarugi lab (Tuscan Tumor Institute, Italy) discovered that in prostate cancer, cancer-associated fibroblasts 'feed' lactate to tumor cells by increasing glucose uptake via the GLUT1 transporter, thereby fueling lactate production, and increasing its secretion via monocarboxylate transporter 4 (SLC16A3). Cancer cells, by contrast, have decreased GLUT1 expression and increased lactate uptake as a result of *de novo* expression of the lactate transporter MCT1 (SLC16A1) (Fiaschi et al., 2012). As a consequence, prostate cancer cells become independent of glucose consumption and dependent on lactate uptake for their proliferation. By infusing isotope-labeled nutrients prior to tumor resection, Ralph DeBerardinis (Children's Medical Center Research Institute, Dallas, TX, USA) demonstrated that non-small cell lung cancers can also uptake lactate (Hensley et al., 2016). Importantly, however, DeBerardinis showed that just as tumors are not homogeneous entities genetically, they are also not homogeneous metabolically, with metabolically heterogeneous regions identified both within and between tumors (Hensley et al., 2016).

One-carbon (1C) units are required for purine and thymidine biosynthesis. Normally, these are generated by a mitochondrial folate pathway. Gregory Ducker showed that when this pathway is blocked in cancer cells, they can re-wire and use a cytosolic pathway for 1C-unit production that is sufficient to support tumor growth *in vivo* (Ducker et al., 2016).

The talks described above focused on metabolic re-wiring in cancer. Alex Gould (The Francis Crick Institute, London, UK) showed that this also occurs during development. In the brain, glia are important for sustaining neuronal function and they also provide a niche that regulates the proliferation of NSCs. Working with *Drosophila*, the Gould laboratory discovered that in response to hypoxia or oxidative stress, glia divert polyunsaturated fatty acids away from membranes to the core of lipid droplets, which function as anti-oxidant organelles limiting the peroxidation chain reactions that would otherwise damage neuroblasts (Bailey et al., 2015). One could envisage a similar mechanism also being used by tumor cells that encounter significant oxidative stress. Teymuras Kurzchalia (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany) provided a fascinating and extreme example of metabolic reprogramming that allows *Caenorhabditis elegans* to survive complete dessication. To do so, animals need to be pre-conditioned in lower humidity for some time, during which the glyoxylate shunt (used for the biosynthesis of carbohydrates) was induced to synthesize trehalose, which protects the animals upon subsequent complete water loss (Erkut et al., 2016).

Compartmentalization of metabolism in space and time

Metabolism is compartmentalized both in space (intracellularly as well as intercellularly) and in time for a number of reasons. For instance, cyanobacteria need to both fix nitrogen, which is inhibited by oxygen, and perform photosynthesis, which produces oxygen. Hence, these processes are spatially segregated. Reducing equivalents used for energy production (NADH; reduced form of nicotinamide adenine dinucleotide) and for biosynthetic reactions (NADPH; nicotinamide adenine dinucleotide phosphate) are largely isolated from each other. Metabolites need to be channeled into particular pathways. Three examples of spatial or temporal compartmentalization of metabolism were provided at the meeting.

Pierre Magistretti (Ecole Polytechnique Fédérale de Lausanne, Switzerland; KAUST, Saudi Arabia) summarized a large body of work from his lab uncovering the segregation of metabolic tasks between neurons and supporting glia (Magistretti and Allaman, 2015). When neurons release glutamate at synapses, it is taken up by astrocytes via a process requiring ATP. These high energetic costs cause astrocytes to uptake glucose and to release lactate. The lactate is then used in neurons to convert it to pyruvate and to respire. Hence, astrocytes ferment whereas neurons respire. Lactate also acts as a signaling molecule by inducing the expression of genes involved in synaptic plasticity. This spatial compartmentalization of metabolism leads to a complex metabolic choreography between neurons and their support cells resulting in energetic homeostasis, which is crucial for synaptic plasticity, neuroprotection and memory. As discussed above, Ben Tu's lab showed that the spatial compartmentalization of acetyl-CoA levels in yeast is important for the regulation of histone acetylation (Cai et al., 2011). Diane Barber (University of California, San Francisco, CA, USA) showed that intracellular pH dynamics regulates activity of myriad proteins including metabolic enzymes, as well as cancer cell behaviors including dysplasia in the *Drosophila* eye (Grillo-Hill et al., 2015). In tumors, it is known that extracellular pH drops, activating metalloproteases, whereas intracellular pH increases. Thus, changes in the extracellular-intracellular pH gradient can affect cell behavior both in development and disease.

Conclusions and perspectives

In sum, several takeaway messages were distilled at the end of the meeting. First, owing to the compartmentalization of metabolism in space and time, there is a strong need for probes that can detect metabolite levels with high spatial resolution in living tissue in real time. Second, metabolism and signaling are strongly intertwined, with metabolites having the ability to play instructive roles similar to signaling components. Third, there are similarities between the metabolic shifts observed in cancer and those seen during normal development, perhaps because cancer cells re-use programs and mechanisms that originally evolved in an organism for other purposes. Hence, developmental biologists and cancer biologists studying metabolism will likely learn much by interacting further with each other.

Competing interests

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References

Agathocleous, M., Love, N. K., Randlett, O., Harris, J. J., Liu, J., Murray, A. J. and Harris, W. A. (2012). Metabolic differentiation in the embryonic retina. *Nat. Cell Biol.* **14**, 859-864.

Bailey, A. P., Koster, G., Guillermier, C., Hirst, E. M. A., MacRae, J. I., Lechene, C. P., Postle, A. D. and Gould, A. P. (2015). Antioxidant role for lipid droplets in a stem cell niche of drosophila. *Cell* **163**, 340-353.

Cai, L., Sutter, B. M., Li, B. and Tu, B. P. (2011). Acetyl-CoA induces cell growth and proliferation by promoting the acetylation of histones at growth genes. *Mol. Cell* **42**, 426-437.

Cardaci, S., Zheng, L., MacKay, G., van den Broek, N. J. F., MacKenzie, E. D., Nixon, C., Stevenson, D., Tumanov, S., Bulusu, V., Kamphorst, J. J. et al. (2015). Pyruvate carboxylation enables growth of SDH-deficient cells by supporting aspartate biosynthesis. *Nat. Cell Biol.* **17**, 1317-1326.

Carmona-Fontaine, C., Bucci, V., Akkari, L., Deforet, M., Joyce, J. A. and Xavier, J. B. (2013). Emergence of spatial structure in the tumor microenvironment due to the Warburg effect. *Proc. Natl. Acad. Sci. USA* **110**, 19402-19407.

de la Cova, C., Senoo-Matsuda, N., Ziosi, M., Wu, D. C., Bellosta, P., Quinzii, C. M. and Johnston, L. A. (2014). Supercompetitor status of Drosophila Myc cells requires p53 as a fitness sensor to reprogram metabolism and promote viability. *Cell Metab.* **19**, 470-483.

Ducker, G. S., Chen, L., Morscher, R. J., Ghergurovich, J. M., Esposito, M., Teng, X., Kang, Y. and Rabinowitz, J. D. (2016). Reversal of cytosolic one-

Development (2016) 143, 3045-3049 doi:10.1242/dev.138800

carbon flux compensates for loss of the mitochondrial folate pathway. *Cell Metab.* **23**, 1140-1153.

Erkut, C., Gade, V. R., Laxman, S. and Kurzchalia, T. V. (2016). The glyoxylate shunt is essential for desiccation tolerance in C. elegans and budding yeast. *eLife* **5**, e13614.

Fiaschi, T., Marini, A., Giannoni, E., Taddei, M. L., Gandellini, P., De Donatis, A., Lanciotti, M., Serni, S., Cirri, P. and Chiarugi, P. (2012). Reciprocal metabolic reprogramming through lactate shuttle coordinately influences tumor-stroma interplay. *Cancer Res.* **72**, 5130-5140.

Grillo-Hill, B. K., Choi, C., Jimenez-Vidal, M. and Barber, D. L. (2015). Increased H(+) efflux is sufficient to induce dysplasia and necessary for viability with oncogene expression. *eLife* **4**.

Hensley, C. T., Faubert, B., Yuan, Q., Lev-Cohain, N., Jin, E., Kim, J., Jiang, L., Ko, B., Skelton, R., Loudat, L. et al. (2016). Metabolic heterogeneity in human lung tumors. *Cell* **164**, 681-694.

Homem, C. C. F., Steinmann, V., Burkard, T. R., Jais, A., Esterbauer, H. and Knoblich, J. A. (2014). Ecdysone and mediator change energy metabolism to terminate proliferation in Drosophila neural stem cells. *Cell* **158**, 874-888.

Khaliullina, H., Bilgin, M., Sampaio, J. L., Shevchenko, A. and Eaton, S. (2015). Endocannabinoids are conserved inhibitors of the Hedgehog pathway. *Proc. Natl. Acad. Sci. USA* **112**, 3415-3420.

Khaliullina, H., Love, N. K. and Harris, W. A. (2016). Nutrient-deprived retinal progenitors proliferate in response to hypoxia: interaction of the hif-1 and mtor pathway. *J. Dev. Biol.* **4**, 17.

Love, N. K., Keshavan, N., Lewis, R., Harris, W. A. and Agathocleous, M. (2014). A nutrient-sensitive restriction point is active during retinal progenitor cell differentiation. *Development* **141**, 697-706.

Magistretti, P. J. and Allaman, I. (2015). A cellular perspective on brain energy metabolism and functional imaging. *Neuron* **86**, 883-901.

Oburoglu, L., Tardito, S., Fritz, V., de Barros, S. C., Merida, P., Craveiro, M., Mamede, J., Cretenet, G., Mongellaz, C., An, X. et al. (2014). Glucose and glutamine metabolism regulate human hematopoietic stem cell lineage specification. *Cell Stem Cell* **15**, 169-184.

Palm, W., Park, Y., Wright, K., Pavlova, N. N., Tuveson, D. A. and Thompson, C. B. (2015). The utilization of extracellular proteins as nutrients is suppressed by mTORC1. *Cell* **162**, 259-270.

Ratcliffe, P. J. (2013). Oxygen sensing and hypoxia signalling pathways in animals: the implications of physiology for cancer. *J. Physiol.* **591**, 2027-2042.

Senyilmaz, D., Virtue, S., Xu, X., Tan, C. Y., Griffin, J. L., Miller, A. K., Vidal-Puig, A. and Teleman, A. A. (2015). Regulation of mitochondrial morphology and function by stearoylation of TFR1. *Nature* **525**, 124-128.

Steventon, B., Duarte, F., Lagadec, R., Mazan, S., Nicolas, J.-F. and Hirsinger, E. (2016). Species-specific contribution of volumetric growth and tissue convergence to posterior body elongation in vertebrates. *Development* **143**, 1732-1741.

Sullivan, L. B., Gui, D. Y., Hosios, A. M., Bush, L. N., Freinkman, E. and Vander Heiden, M. G. (2015). Supporting aspartate biosynthesis is an essential function of respiration in proliferating cells. *Cell* **162**, 552-563.

Sutter, B. M., Wu, X., Laxman, S. and Tu, B. P. (2013). Methionine inhibits autophagy and promotes growth by inducing the SAM-responsive methylation of PP2A. *Cell* **154**, 403-415.

Swamy, M., Pathak, S., Grzes, K. M., Damerow, S., Sinclair, L. V., van Aalten, D. M. F. and Cantrell, D. A. (2016). Glucose and glutamine fuel protein O-GlcNAcylation to control T cell self-renewal and malignancy. *Nat. Immunol.* **17**, 712-720.

Warburg, O. (1956). On the origin of cancer cells. *Science* **123**, 309-314.

Wellen, K. E., Hatzivassiliou, G., Sachdeva, U. M., Bui, T. V., Cross, J. R. and Thompson, C. B. (2009). ATP-citrate lyase links cellular metabolism to histone acetylation. *Science* **324**, 1076-1080.