Front. Biol. 2015, 10(1): 107–116
DOI 10.1007/s11515-015-1351-5

MINI-REVIEW

Metabolic regulation of adult stem cell-derived neurons

Ruth Beckervordersandforth, Benjamin M. Häberle, D. Chichung Lie (✉)

Institute of Biochemistry, Emil Fischer Center, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Abstract **The discovery of continuous generation of functional neurons throughout life has emerged as a major contributor to plasticity in defined regions of the adult mammalian brain. Work over the past decades identified cellular constituents of the distinct adult neurogenic niches as well as numerous signaling pathways, transcriptional and epigenetic regulators that exert tight control over the production of new neurons from resident stem cells. Recent studies uncovered developmental stage-specific adaptations of metabolic circuits and have provided evidence for their central regulatory function in the adult neurogenic lineage. Moreover, there is increasing evidence for a regulatory impact of a wide range of systemic metabolic factors including exercise induced metabolic changes and diet on the development of adult-born neurons. Here, we will summarize current knowledge and emerging principles underlying the metabolic control of neuronal maturation in adult neurogenesis.**

Keywords metabolism, adult neurogenesis, mitochondria, diet

Introduction

The lifelong generation of functional neurons from neural stem cells has emerged as a significant contributor to neural network plasticity in restricted regions of the adult mammalian brain (Ming and Song, 2011). Over the past two decades, adult neurogenesis has been consistently observed in rodents and primates in two brain regions, the subventricular zone (SVZ) of the lateral ventricles where stem cells give rise to immature neurons that migrate through the rostral migratory stream (RMS) to integrate as interneurons into the olfactory bulb circuit, and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) where stem cells generate new dentate granule cells. Notably, convincing evidence has also been presented that neurogenesis continues in the human hippocampus throughout adulthood (Eriksson et al., 1998; Spalding et al., 2013). Besides the "classical" neurogenic regions, neurogenesis has also been repeatedly reported in the hypothalamus adjacent to the third ventricle wall (Kokoeva et al., 2005; Kokoeva et al., 2007; Pierce and Xu, 2010; Lee and Blackshaw, 2012; Lee et al., 2012; Lee et al., 2014).

Received December 4, 2014; accepted February 11, 2015
Correspondence: D. Chichung Lie
E-mail: chi.lie@fau.de

The neurogenic lineages in the adult DG and SVZ/OB system have been characterized in great detail [for a comprehensive overview we refer the reader to the excellent review by Ming and Song (2011)]. Despite a number of region-specific characteristics in the neurogenic lineage, both neurogenic systems share the basic principle that neurons are generated from largely quiescent glia-like stem cells via a stereotypic sequence of proliferation, differentiation, migration and maturation steps, that culminate in the integration of the newborn neuron into a pre-existing neural circuit. It is also common to both neurogenic systems that cells of the neurogenic lineage are embedded into a niche with specialized cellular cytoarchitecture, vascularization pattern, and extracellular matrix properties. Niche-derived signals exert major regulatory control over the formation of neurons from stem cells by initiating or modulating developmental programs and are crucial to adapt the rate and timing of neurogenesis to complex behavioral stimuli. In past years, efforts to decipher the regulatory logic in adult neurogenesis have primarily focused on classical developmental signals, transcription factors and epigenetic regulators for their impact on neuronal development; there has also been a strong bias to investigate trophic factors/cytokines and cytoskeleton-associated proteins as downstream targets to explain the role of signaling pathways and transcriptional and epigenetic regulators on adult neurogenesis (Zhao et al., 2008; Ming and Song, 2011).

Metabolic control and development: an emerging player in the regulation of adult neurogenesis

It is appropriate to assume that the developmental programs underlying specialization of a quiescent glia-like stem cell into a functional neuron will encompass coordinated remodeling of cell biological, biochemical, and molecular pathways according to the changing demands of the developing neuron.

Fundamental differences regarding the metabolic requirements between proliferative and differentiated cells have long been reported especially in the context of cancer cells (Ward and Thompson, 2012). The investigation of distinct metabolic signatures between stem cells, precursor cells and fully differentiated cells have received major attention not least because of the increasing evidence that differential activity of metabolic circuits – rather than being a passive response to cellular function – may in fact represent a major driving force to attain or maintain a specific cellular phenotype (Mihaylova et al., 2014). The regulatory function of metabolic programs in adult neurogenesis has only very recently been appreciated. A landmark study by Knobloch and colleagues (2013) uncovered the importance of a lipogenic switch to recruit quiescent stem cells in the adult hippocampus into proliferation. Furthermore, *in vitro* studies linked activity of the Pentose Phosphate Pathway and glutaminolysis to long-term maintenance of the adult neural stem cell pool and implied mitochondrial integrity as an important factor for adult neural stem/precursor cell proliferation and neuronal fate determination (Stoll et al., 2011; Yeo et al., 2013). An in-depth review of the metabolic control of stem cell maintenance and proliferation is provided in this issue by Knobloch and Jessberger.

The development of recombinant mouse-moloney leukemia virus (MMLV) for birth dating and visualization of proliferating precursor cells in the adult neurogenic regions has significantly advanced our understanding of the timeline of adult-born neuron maturation *in situ* (van Praag et al., 2002; Zhao et al., 2006). This timeline has been extensively analyzed in adult mice. During the first three weeks after their birth from stem/precursor cells, new neurons undergo rapid dendritic and axonal growth to extend a dendritic tree with complex arborization in the molecular layer and to project axons toward the CA3 area (Zhao et al., 2006; Sun et al., 2013). GABAergic synaptic inputs are detected as early as one week after neuronal birth (Ge et al., 2006). Morphological and electrophysiological evidence for glutamatergic synaptic inputs and for mossy fiber synaptic outputs to hilar and CA3 neurons is observed during the third week after neuronal birth (Espositó et al., 2005; Ge et al., 2006; Zhao et al., 2006; Toni et al., 2008). Around the same time the initial depolarizing (excitatory) action of GABA is converted into hyperpolarization (inhibition) due to a decrease in the intracellular chloride concentration in maturing neurons (Ge et al., 2006). Over the following weeks the synaptic integration and neurophysiological properties of newborn neurons are constantly refined. Approximately four to six week-old neurons exhibit enhanced synaptic plasticity compared to older DG neurons, mediated at least in part by the expression of NR2B-containing NMDA receptors and the protracted development of GABAergic inhibition (Schmidt-Hieber et al., 2004; Ge et al., 2007; Marín-Burgin et al., 2012).

Functionally integrated neurons have high energy needs. Maintenance and restoration of ion gradients dissipated by the repeated generation of postsynaptic potentials and action potentials, and the neurotransmitter cycle, are the main cause of neuronal energy demands (Attwell and Laughlin, 2001; Alle et al., 2009). Neurons are metabolically coupled to their environment and in particular to astrocytes in multiple ways. Astrocytes are an essential cellular component of the blood-brain barrier, contact blood vessels through specialized endfeets, and contribute to the regulation of cerebral blood flow through the activity-dependent release of vasoactive substances, thereby providing active brain regions with sufficient substrates for energy production (Alvarez et al., 2013). Thus, astrocytes may contribute to metabolic regulation of adult neurogenesis through the control of access to circulating factors.

The energy requirement of the adult brain is mainly met by glucose. An increasing body of evidence, however, suggests that neurons do not directly utilize glucose for energy production, but prefer lactate as an oxidative substrate (Itoh et al., 2003). According to the Astrocyte-Neuron-Lactate-Shuttle model, lactate is supplied to neurons by astrocytes, which i) take up glucose from the circulation, ii) metabolize glucose into lactate via glycolysis and conversion of pyruvate, iii) release lactate into the extracellular space, from where it is taken up by neurons (Pellerin and Magistretti, 1994; Rouach et al., 2008; Bélanger et al., 2011).

Astrocytes and neurons are in addition metabolically coupled in neurotransmitter recycling. A large proportion of the glutamate released at the synapse is taken up by astrocytes in an energy consuming process that triggers astrocytic glucose uptake and consumption. Astrocytes transfer glutamate back to neurons by converting glutamate into glutamine and release of glutamine, which is taken up and converted back to glutamate via by neuronal glutaminase (Schousboe et al., 2014).

Finally, the high activity of oxidative metabolism in neurons generates high levels of toxic reactive oxygen species. Astrocytes support detoxification by supplying neurons with precursors for the synthesis of gluthathione, the most abundant antioxidant molecule in the brain. In addition, supply of lactate by astrocytes for energy consumption enables neurons to spare glucose as substrate for generation of NADPH in the Pentose-Phosphate pathway (PPP). NADPH can then be used to recycle reduced glutathione from oxidized glutathione, which is formed via

the detoxification of ROS (Herrero-Mendez et al., 2009; Rodriguez-Rodriguez et al., 2012).

Neurons and adult neural stem cells exhibit profound differences in the prevalent metabolic circuits; consequently, metabolic transition will be important during the maturation of adult-generated neurons (Fig. 1). Moreover, the importance of metabolic-coupling of neurons with the local astrocyte network for neuronal function and maintenance strongly suggests that metabolic integration into the local environment plays a major role during functional maturation of adult-born neurons. It will be interesting to determine if and when the metabolism of adult-born neurons and their surrounding environment become intertwined (Fig. 1).

In the following we will discuss emerging evidence and concepts on the impact of cellular metabolism on maturation and functional integration of adult generated neurons.

Key regulators of neuronal maturation are linked to metabolic pathways

Several studies have linked the activity of the mammalian target of rapamycin (mTOR) and of the cyclic AMP response element binding protein (CREB) to the regulation of neuronal maturation in adult neurogenesis. mTOR is a highly conserved serine/threonine kinase that as part of two large biochemical complexes, mTORC1 and mTORC2, directly regulates protein synthesis, transcription, autophagy, and stability of the actin cytoskeleton (Lipton and Sahin, 2014). Notably, aberrant mTOR activity in developing adult-born hippocampal neurons accelerates dendritic development and synaptic integration and produces hypertrophied neurons with excessive dendritic arborization (Kim et al., 2009; Kim et al., 2012; Amiri et al., 2012; Zhou et al., 2013).

CREB is a neuronal activity-regulated transcription factor. CREB-signaling is highly active in immature adult-generated neurons of the DG and the olfactory bulb/RMS system (Nakagawa et al., 2002; Giachino et al., 2005; Jagasia et al., 2009; Merz et al., 2011; Herold et al., 2011). Activity of the CREB pathway is at least in immature DG neurons controlled by GABA-mediated excitation, a key driver of neuronal maturation. Pharmacological enhancement of CREB-signaling promotes dendrite outgrowth of newborn neurons in the adult hippocampus (Fujioka et al., 2004); in contrast inhibition of CREB-signaling broadly interferes with the maturation of adult-generated neurons by impairing dendrite development, maintenance of neurogenic expression programs and survival of newborn neurons (Giachino et al., 2005; Jagasia et al., 2009; Herold et al., 2011).

Intriguingly, mTOR and CREB-dependent pathways have direct links to the regulation of metabolic pathways in other cellular systems. mTORCs represent metabolic rheostats as they not only integrate nutrient availability and growth factor signaling but also regulate mitochondrial biogenesis, and lipid and glucose metabolism through their transcriptional and translational targets (Mihaylova et al., 2014). CREB and its co-activators are essential regulators of energy balance on the organismal level. Here, CREB serves as sensor for hormonal and metabolic signals and regulates the transcription of enzymes, which catalyze key steps of glucose metabolism (Altarejos and Montminy, 2011). In addition, CREB impacts on mitochondrial biogenesis and mitochondrial respiratory chain function by directly controlling the expression of nuclear-encoded respiratory genes and through the induction of the expression of PGC1α, the central transcriptional regulator of mitochondrial biogenesis (Spiegelman, 2007). Notably, PGC1α was recently demonstrated to be central to spine formation and maintenance in the adult hippocampus (Cheng et al., 2012).

The importance of mTOR- and CREB-dependent signaling to the regulation of adult-born neuron maturation on one hand and their documented regulatory function in organismal and cellular metabolism on the other hand are strongly suggestive that metabolic adaptation is closely intertwined with neuronal maturation in adult neurogenesis.

Importance of mitochondria-dependent metabolism in controlling adult-born neuron maturation

The first evidence for the regulatory function of metabolism in controlling adult-born neuron maturation came from morphological analysis of mitochondria and manipulation of their function.

MMLV-mediated expression of mitochondria-targeted fluorescent protein allowed visualization of these organelles during distinct stages of adult hippocampal neurogenesis (Steib et al., 2014) (Fig. 2). Morphometric analyses revealed that *in vivo* maturation is paralleled by increases in mitochondrial mass. This increase in total mitochondrial content is largely due to a continuous increase in dendritic arbor-localized mitochondria. Notably, dendritic mitochondrial content increases after the neuron has established its full dendritic arbor, suggesting that the mitochondrial content is not simply the consequence of the increasing cell size but may also reflect the growing dependence of the functional neuron on mitochondrial metabolic pathways.

While mitochondria in the growing and fully developed dendritic arbor are almost exclusively of globular shape, mitochondria in the soma and the proximal dendritic segment show distinct morphologies at different maturation stages. Early after neuronal fate determination, mitochondria form large tubular structures. During the phases of rapid dendritic and axonal growth and synaptogenesis, mitochondria in the cell body and the dendritic shaft are of mixed tubular and globular shape. Mitochondria in the soma of fully mature adult-born neurons display heterogeneous morphologies: in the majority of neurons mitochondria are of mixed tubular and globular shape; occasionally, however, a prominent

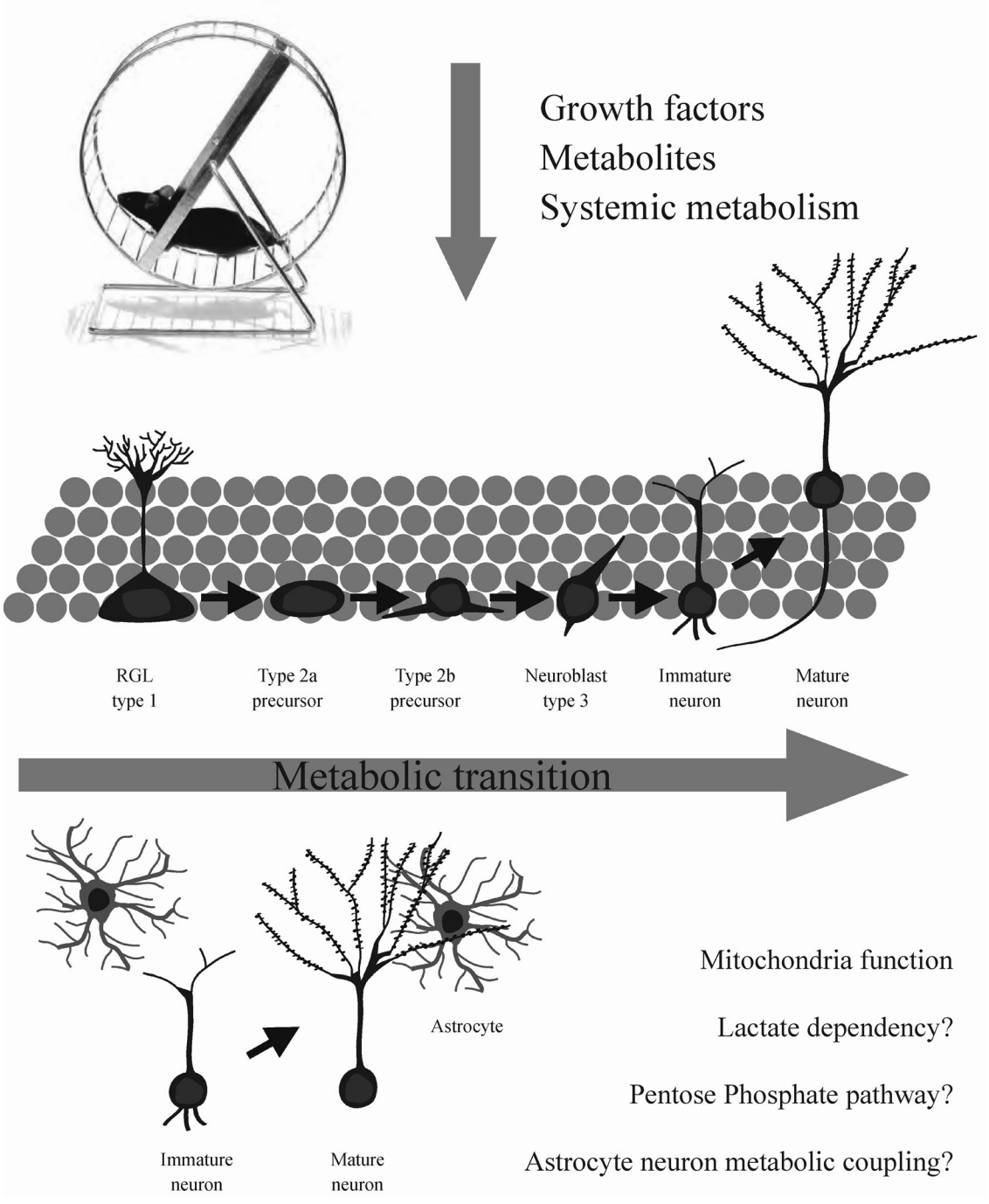

Figure 1 Metabolism and regulation of adult neurogenesis. Systemic metabolism and metabolites may directly impact on the development of adult-born hippocampal neurons. Exercise – a powerful behavioral stimulus of neurogenesis – may modulate adult hippocampal neurogenesis via expression of growth factors, alteration of systemic metabolism and metabolites. The development of stem cells into functional neurons is accompanied by adaptation of cellular metabolism. Adaptations of the functional neuron may include the increasing reliance on mitochondrial function, the Pentose Phosphate Pathway, lactate as a primary energy source, and metabolic coupling to astrocytes.

interconnected network is observed, which extends into the dendritic shaft.

Mitochondrial biogenesis and mitochondrial dynamics, i.e., the balance between mitochondrial fusion and fission processes, are major determinants of mitochondrial morphology. Rather than being generated *de novo*, mitochondria are generated by growth of preexisting mitochondria and subsequent fission (Attardi and Schatz, 1988; Osman et al., 2011). The differential distribution of tubular and globular mitochondria may therefore reflect that mitochondrial biogenesis in developing neurons occurs close to the soma and that new mitochondria are distributed from there into the

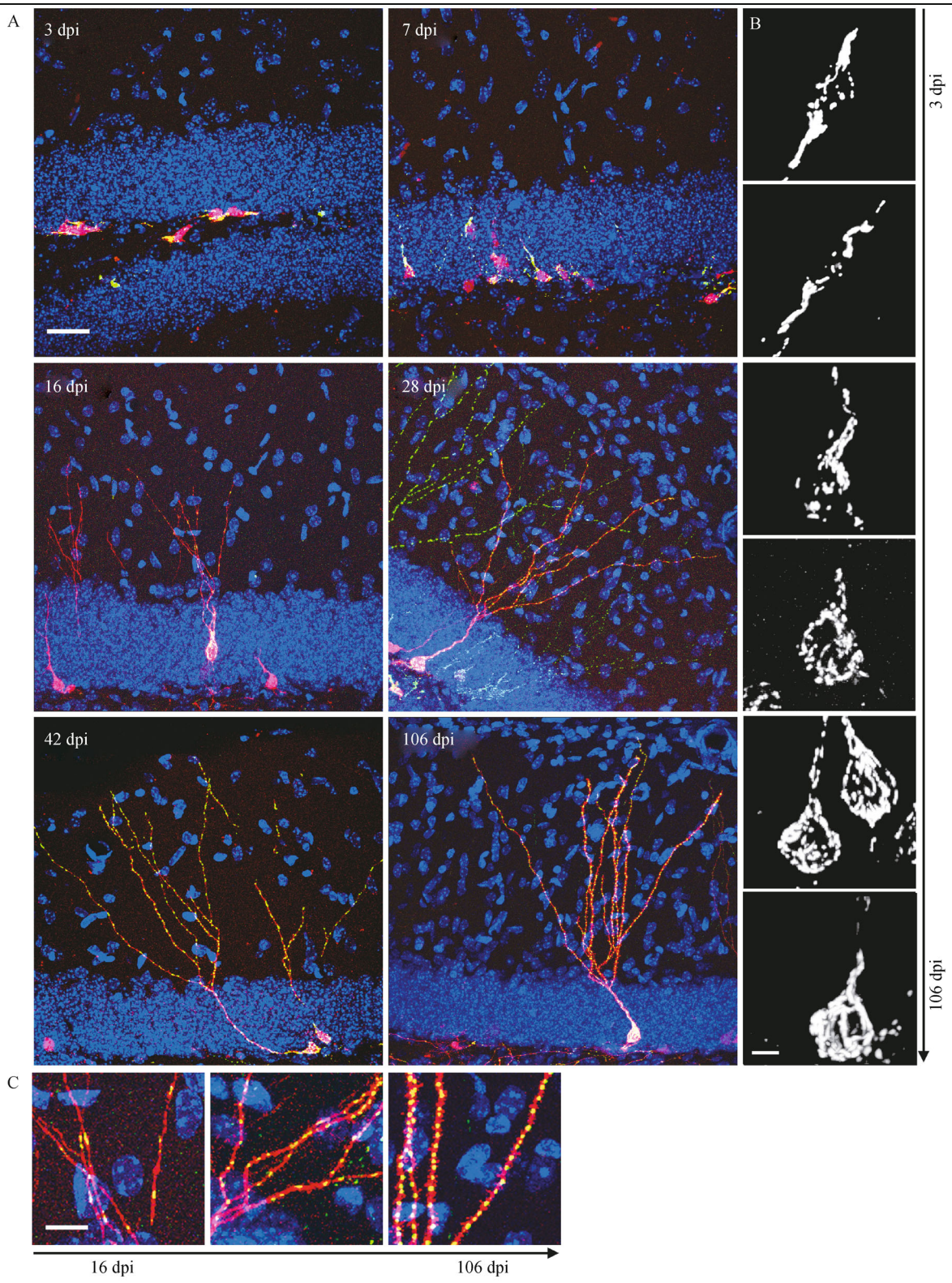

Figure 2 Extensive remodelling of the mitochondrial compartment accompanies maturation of adult-generated DG neurons. Analysis of adult-born DG neurons at different days after retrovirus mediated birthdating. (A) Development of adult-born neurons (red) is paralleled by increase in mitochondria mass (mitochondria in green). Scale bar 25 µm. (B) Higher magnification reveals distinct morphologies of somatic mitochondria: At early stages mitochondria predominantly formed large tubular structures. Between 16 days post retroviral injection (dpi) and 42 dpi mitochondria were of mixed tubular and globular shape. At 106 dpi, mitochondria in some adult-generated neurons formed an interconnected network. Note the dense packing of the dendritic shaft with mitochondria at all developmental time points. Scale bar 3 µm. (C) Higher magnification of the dendritic mitochondria at 16, 28, and 106 dpi, reveals increasing presence of round mitochondria. Scale bar 8 µm. Figure and legend reproduced from Steib et al. (2014).

dendritic arbor. In this scenario, mitochondrial fission would be essential to efficiently supply the dendritic arbor with new mitochondria (Li et al., 2004). Inhibition of mitochondrial fission via expression of a dominant-negative mutant of the fission factor Drp1, indeed, reduces overall mitochondrial number and the dendritic distribution of mitochondria in adult-born neurons. On the cellular level, impaired fission was associated with compromised neuronal fate maintenance or determination, dendrite development, and survival (Steib et al., 2014). Hence, balancing mitochondrial dynamics is crucial to ensure development of adult-born neurons.

The importance of mitochondrial dynamics is not confined to biogenesis and distribution of the organelle. Mitochondrial dynamics is also essential to sustain the pool of functional mitochondria by segregating damaged mitochondria and facilitating mitophagy (Mishra and Chan, 2014). Given the impact of deficient mitochondrial quality control on neuronal maintenance and plasticity in aging and neurodegeneration (Tatsuta and Langer, 2008), it is tempting to speculate that impaired segregation of dysfunctional mitochondria may also affect the development of adult-born neurons. Mitochondrial fusion and fission impact on mitochondrial membrane potential, thereby modulating reactive oxygen species (ROS) generation, the sequestration of cytosolic calcium, and electron transport chain activity. *In vitro* studies have not only implied mitochondria distribution, but also mitochondrial bioenergetics and calcium buffering in the regulation of neuronal morphogenesis and synaptogenesis (Li et al., 2004; Dietrich et al., 2008; Macaskill et al., 2009; Wang and Schwarz, 2009; MacAskill et al., 2010; Li et al., 2010; Dickey and Strack, 2011; Cheng et al., 2012; Steketee et al., 2012; Bertholet et al., 2013; Courchet et al., 2013). Regulation of dendritic Ca^{2+} buffering capacity in adult-generated hippocampal granule cells was proposed to contribute to their activity-dependent dendritic growth and synaptogenesis (Stocca et al., 2008). Moreover, knockdown of the electron transport chain complex I protein NDUFV2 results in defective dendritic arborization of adult-generated DG cells, indicating that electron transport chain activity and ATP supply by mitochondria are essential for dendrite growth and morphogenesis in adult neurogenesis (Oruganty-Das et al., 2012).

In sum, mitochondrial function is emerging as a crucial determinant of maturation in the adult neurogenic lineage. Future studies will have to address, which of the manifold mitochondria-dependent metabolic pathways are active during neuronal maturation and contribute to the regulation of neurogenesis.

Systemic factors with links to metabolism modulate adult neurogenesis

Since the discovery of adult neurogenesis and the first indications that adult-generated neurons are essential for circuit plasticity, the observation that adult neurogenesis may be powerfully modulated by systemic factors have gathered major attention. Notably, a number of these systemic factors possess close links to systemic and cellular metabolism.

Physical activity results in complex alterations of systemic metabolism (Hawley et al., 2014). An extensive body of literature indicates that physical activity enhances cognitive performance [as reviewed in (Mattson, 2012)]. Exercise-induced cognitive enhancement has been attributed to the stimulation of angiogenesis, synaptic plasticity, and neurogenesis (Pereira et al., 2007); in fact, voluntary exercise is the most potent behavioral stimulus to increase the proliferative activity of stem and precursor cells in the hippocampal neurogenic niche of adult rodents (Fig. 1) (van Praag et al., 1999; Fabel and Kempermann, 2008; Fabel et al., 2009). Among the signals proposed to mediate the exercise-induced neurogenic response are serotonin (Klempin et al., 2013) as well as the growth factors IGF-1 and VEGF. Importantly, it was shown that blockade of peripheral VEGF and IGF-1 inhibits the exercise-induced neurogenic response, which indicates that systemic circulating factors can exert major control over adult neurogenesis (Trejo et al., 2001; Fabel et al., 2003). Both VEGF and IGF-1 have bi-directional links to metabolism. On one hand their expression is modulated by metabolic factors such as hypoxia, glucose metabolism and lipid metabolism, on the other hand, VEGF and IGF-1 signaling induce complex changes in cellular and systems metabolism (Arai et al., 2009; Broughton and Partridge, 2009; Kivelä et al., 2014; Kumar et al., 2014; Wu et al., 2014).

A particularly compelling example for regulation of adult neurogenesis by systemic metabolism is observed in adult hypothalamic neurogenesis. The presumed precursors of the adult hypothalamic neurogenic lineage express receptors and signal transduction systems that allow them to respond to nutritional signals (Frayling et al., 2011; Orellana et al., 2012). Dietary factors modulate adult hypothalamic neurogenesis. High fat diet, for example, was reported to increase proliferation and to stimulate generation of neurons expressing anorexigenic peptides (Lee et al., 2012; Gouazé et al., 2013). It was also observed that ablation of cell genesis resulted in accelerated weight gain and obesity onset under high fat diet (Pierce and Xu, 2010; Lee et al., 2012; Gouazé et al., 2013). Thus, it is hypothesized that modulation of adult neurogenesis in accordance to the nutritional status serves to maintain energy homeostasis through the control of food intake and bodyweight (Sousa-Ferreira et al., 2014).

Metabolic pathologies and diet also inflict on the rate of adult hippocampal neurogenesis. Stranahan and colleagues (2008) described impaired hippocampal plasticity and hippocampal neurogenesis in rat and mouse models for diabetes, and provided evidence that the negative impact was conferred by increased glucocorticoid signaling. A wide variety of dietary factors including trace elements, vitamins, complex diets and plant-derived compounds were reported to

alter the rate of hippocampal neurogenesis. The mechanism underlying the neurogenic effect of dietary factors, however, has not been conclusively established [for a comprehensive review on diet and neurogenesis see (van Praag, 2009) and (Zainuddin and Thuret, 2012)].

Current research mainly describes the impact of systemic physiology, dietary and metabolic factors on the rate of neurogenesis. Several observations, however, suggest that systemic metabolism and metabolites also modulate maturation and function of adult-generated neurons. The increased generation of hypothalamic neurons expressing anorexigenic peptides following high fat diet may be the consequence of enhanced neuronal maturation (Gouazé et al., 2013). Voluntary exercise increases the speed of maturation of adult-born neurons as evidenced by accelerated dendritic growth, initiation of spinogenesis, and mature neuronal marker expression (Piatti et al., 2011; Steib et al., 2014). Morphometric analysis of mitochondria in adult-generated hippocampal neurons revealed that exercise has a developmental stage specific impact on mitochondrial content. Thus, continuous exposure to voluntary exercise increased total mitochondrial mass in developing neurons during the phase of rapid dendritic and axonal growth to a level that is comparable to the one in mature adult-generated neurons. This exercise-induced increase in mitochondrial content is transient and is not observed in mature adult-generated neurons that developed under continuous voluntary exercise conditions or that were exposed to exercise conditions at the mature stage. Yet, mitochondria show a different distribution pattern: in the developing neuron the majority of mitochondria were located in the soma and dendritic shaft whereas in mature neurons the bulk of the mitochondria localized to the dendritic arbor (Steib et al., 2014).

Interestingly, enhancement of mitochondrial fission, which facilitates mitochondrial movement and distribution, further accelerates exercise-induced dendritic growth, spinogenesis, and mature marker expression; enhanced fission under non-exercising conditions, however, had no discernible effect on neuronal maturation. Finally, impaired mitochondrial fission and dendritic distribution decrease survival of newborn neurons under basal conditions, and impede on morphological development and expression of neuron-specific markers during exercise-induced neurogenesis. Overall these observations revealed an intriguing interplay between exercise, mitochondrial biogenesis and distribution, and maturation of adult-born neurons (Steib et al., 2014).

Conclusions

The adaptation of cell-intrinsic metabolic circuits to developmental stage-specific metabolic requirements is emerging as a key contributor to the development of adult-born neurons. Another important question to solve is, how coordination between adaptation of metabolic circuits with signaling pathways, transcriptional, and epigenetic regulators of the development of adult-born neurons is achieved. Here, metabolic circuits may not only be positioned downstream of genetic regulatory circuits, but could also directly influence regulatory pathways, e.g., by generating substrates for epigenetic modifications. There are also indications that systemic metabolism and metabolites represent powerful signals to modulate adult neurogenesis under physiological and pathological conditions, yet the underlying molecular mechanisms remain to be established: are signaling intermediates involved? What is their identity? Do nutrient supply and metabolites directly impact on the developing neuron or do they impact on the neurogenic niche?

Impairment of adult hippocampal neurogenesis is suggested to contribute to learning and memory deficits and mood disturbances in neurodegenerative and neuropsychiatric disorders (Aimone et al., 2011; Sahay et al., 2011; Winner et al., 2011; Kheirbek et al., 2012). As metabolism unfolds as a key regulator of adult neurogenesis, strategies targeting metabolic pathways may represent a new therapeutic concept to enhance neurogenesis and neural plasticity (Pieper et al., 2010; Cheng et al., 2010; Kim et al., 2014).

Acknowledgements

This work was supported by the Bavarian Research Network on Human induced Pluripotent Stem Cells “FORIPS,” the University Hospital Erlangen [Interdisciplinary center for clinical research (IZKF) grants E12 and E16 to DCL] and the Deutsche Forschungsgemeinschaft (BE 5136/1-1 to RB). The authors declare no competing financial interests.

Compliance with ethics guidelines

R. Beckervordersandforth, B. M. Häeberle, and D. C. Lie declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

Aimone J B, Deng W, Gage F H (2011). Resolving new memories: a critical look at the dentate gyrus, adult neurogenesis, and pattern separation. Neuron, 70(4): 589–596

Alle H, Roth A, Geiger J R (2009). Energy-efficient action potentials in hippocampal mossy fibers. Science, 325(5946): 1405–1408

Altarejos J Y, Montminy M (2011). CREB and the CRTC co-activators: sensors for hormonal and metabolic signals. Nat Rev Mol Cell Biol, 12(3): 141–151

Alvarez J I, Katayama T, Prat A (2013). Glial influence on the blood brain barrier. Glia, 61(12): 1939–1958

Amiri A, Cho W, Zhou J, Birnbaum S G, Sinton C M, McKay R M, Parada L F (2012). Pten deletion in adult hippocampal neural stem/progenitor cells causes cellular abnormalities and alters neurogenesis.

J Neurosci, 32(17): 5880–5890

Arai Y, Kojima T, Takayama M, Hirose N (2009). The metabolic syndrome, IGF-1, and insulin action. Mol Cell Endocrinol, 299(1): 124–128

Attardi G, Schatz G (1988). Biogenesis of mitochondria. Annu Rev Cell Biol, 4(1): 289–333

Attwell D, Laughlin S B (2001). An energy budget for signaling in the grey matter of the brain. J Cereb Blood Flow Metab, 21(10): 1133–1145

Bélanger M, Allaman I, Magistretti P J (2011). Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab, 14(6): 724–738

Bertholet A M, Millet A M, Guillermin O, Daloyau M, Davezac N, Miquel M C, Belenguer P (2013). OPA1 loss of function affects *in vitro* neuronal maturation. Brain, 136(Pt 5): 1518–1533

Broughton S, Partridge L (2009). Insulin/IGF-like signalling, the central nervous system and aging. Biochem J, 418(1): 1–12

Cheng A, Hou Y, Mattson M P (2010). Mitochondria and neuroplasticity. ASN Neuro, 2(5): e00045

Cheng A, Wan R, Yang J L, Kamimura N, Son T G, Ouyang X, Luo Y, Okun E, Mattson M P (2012). Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines. Nat Commun, 3: 1250

Courchet J, Lewis T L Jr, Lee S, Courchet V, Liou D Y, Aizawa S, Polleux F (2013). Terminal axon branching is regulated by the LKB1-NUAK1 kinase pathway via presynaptic mitochondrial capture. Cell, 153(7): 1510–1525

Dickey A S, Strack S (2011). PKA/AKAP1 and PP2A/Bβ2 regulate neuronal morphogenesis via Drp1 phosphorylation and mitochondrial bioenergetics. J Neurosci, 31(44): 15716–15726

Dietrich M O, Andrews Z B, Horvath T L (2008). Exercise-induced synaptogenesis in the hippocampus is dependent on UCP2-regulated mitochondrial adaptation. J Neurosci, 28(42): 10766–10771

Eriksson P S, Perfilieva E, Björk-Eriksson T, Alborn A M, Nordborg C, Peterson D A, Gage F H (1998). Neurogenesis in the adult human hippocampus. Nat Med, 4(11): 1313–1317

Espósito M S, Piatti V C, Laplagne D A, Morgenstern N A, Ferrari C C, Pitossi F J, Schinder A F (2005). Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J Neurosci, 25 (44): 10074–10086

Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo C J, Palmer T D (2003). VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur J Neurosci, 18(10): 2803–2812

Fabel K, Kempermann G (2008). Physical activity and the regulation of neurogenesis in the adult and aging brain. Neuromolecular Med, 10 (2): 59–66

Fabel K, Wolf S A, Ehninger D, Babu H, Leal-Galicia P, Kempermann G (2009). Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. Front Neurosci, 3: 50

Frayling C, Britton R, Dale N (2011). ATP-mediated glucosensing by hypothalamic tanycytes. J Physiol, 589(Pt 9): 2275–2286

Fujioka T, Fujioka A, Duman R S (2004). Activation of cAMP signaling facilitates the morphological maturation of newborn neurons in adult hippocampus. J Neurosci, 24(2): 319–328

Ge S, Goh E L, Sailor K A, Kitabatake Y, Ming G L, Song H (2006). GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature, 439(7076): 589–593

Ge S, Pradhan D A, Ming G L, Song H (2007). GABA sets the tempo for activity-dependent adult neurogenesis. Trends Neurosci, 30(1): 1–8

Giachino C, De Marchis S, Giampietro C, Parlato R, Perroteau I, Schütz G, Fasolo A, Peretto P (2005). cAMP response element-binding protein regulates differentiation and survival of newborn neurons in the olfactory bulb. J Neurosci, 25(44): 10105–10118

Gouazé A, Brenachot X, Rigault C, Krezymon A, Rauch C, Nédélec E, Lemoine A, Gascuel J, Bauer S, Pénicaud L, Benani A (2013). Cerebral cell renewal in adult mice controls the onset of obesity. PLoS ONE, 8(8): e72029

Hawley J A, Hargreaves M, Joyner M J, Zierath J R (2014). Integrative biology of exercise. Cell, 159(4): 738–749

Herold S, Jagasia R, Merz K, Wassmer K, Lie D C (2011). CREB signalling regulates early survival, neuronal gene expression and morphological development in adult subventricular zone neurogenesis. Mol Cell Neurosci, 46(1): 79–88

Herrero-Mendez A, Almeida A, Fernández E, Maestre C, Moncada S, Bolaños J P (2009). The bioenergetic and antioxidant status of neurons is controlled by continuous degradation of a key glycolytic enzyme by APC/C-Cdh1. Nat Cell Biol, 11(6): 747–752

Itoh Y, Esaki T, Shimoji K, Cook M, Law M J, Kaufman E, Sokoloff L (2003). Dichloroacetate effects on glucose and lactate oxidation by neurons and astroglia *in vitro* and on glucose utilization by brain *in vivo*. Proc Natl Acad Sci USA, 100(8): 4879–4884

Jagasia R, Steib K, Englberger E, Herold S, Faus-Kessler T, Saxe M, Gage F H, Song H, Lie D C (2009). GABA-cAMP response element-binding protein signaling regulates maturation and survival of newly generated neurons in the adult hippocampus. J Neurosci, 29(25): 7966–7977

Kheirbek M A, Klemenhagen K C, Sahay A, Hen R (2012). Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. Nat Neurosci, 15(12): 1613–1620

Kim D Y, Rhee I, Paik J (2014). Metabolic circuits in neural stem cells. Cell Mol Life Sci, 71(21): 4221–4241

Kim J Y, Duan X, Liu C Y, Jang M H, Guo J U, Pow-anpongkul N, Kang E, Song H, Ming G L (2009). DISC1 regulates new neuron development in the adult brain via modulation of AKT-mTOR signaling through KIAA1212. Neuron, 63(6): 761–773

Kim J Y, Liu C Y, Zhang F, Duan X, Wen Z, Song J, Feighery E, Lu B, Rujescu D, St Clair D, Christian K, Callicott J H, Weinberger D R, Song H, Ming G L (2012). Interplay between DISC1 and GABA signaling regulates neurogenesis in mice and risk for schizophrenia. Cell, 148(5): 1051–1064

Kivelä R, Bry M, Robciuc M R, Räsänen M, Taavitsainen M, Silvola J M, Saraste A, Hulmi J J, Anisimov A, Mäyränpää M I, Lindeman J H, Eklund L, Hellberg S, Hlushchuk R, Zhuang Z W, Simons M, Djonov V, Knuuti J, Mervaala E, Alitalo K (2014). VEGF-B-induced vascular growth leads to metabolic reprogramming and ischemia resistance in the heart. EMBO Mol Med, 6(3): 307–321

Klempin F, Beis D, Mosienko V, Kempermann G, Bader M, Alenina N (2013). Serotonin is required for exercise-induced adult hippocampal neurogenesis. J Neurosci, 33(19): 8270–8275

Knobloch M, Braun S M, Zurkirchen L, von Schoultz C, Zamboni N, Araúzo-Bravo M J, Kovacs W J, Karalay O, Suter U, Machado R A, Roccio M, Lutolf M P, Semenkovich C F, Jessberger S (2013). Metabolic control of adult neural stem cell activity by Fasn-

dependent lipogenesis. Nature, 493(7431): 226–230

Kokoeva M V, Yin H, Flier J S (2005). Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. Science, 310(5748): 679–683

Kokoeva M V, Yin H, Flier J S (2007). Evidence for constitutive neural cell proliferation in the adult murine hypothalamus. J Comp Neurol, 505(2): 209–220

Kumar V B, Binu S, Soumya S J, K H, Sudhakaran P R (2014). Regulation of vascular endothelial growth factor by metabolic context of the cell. Glycoconj J, 31(6-7): 427–434

Lee D A, Bedont J L, Pak T, Wang H, Song J, Miranda-Angulo A, Takiar V, Charubhumi V, Balordi F, Takebayashi H, Aja S, Ford E, Fishell G, Blackshaw S (2012). Tanycytes of the hypothalamic median eminence form a diet-responsive neurogenic niche. Nat Neurosci, 15 (5): 700–702

Lee D A, Blackshaw S (2012). Functional implications of hypothalamic neurogenesis in the adult mammalian brain. Int J Dev Neurosci, 30 (8): 615–621

Lee D A, Yoo S, Pak T, Salvatierra J, Velarde E, Aja S, Blackshaw S (2014). Dietary and sex-specific factors regulate hypothalamic neurogenesis in young adult mice. Front Neurosci, 8: 157

Li Z, Jo J, Jia J M, Lo S C, Whitcomb D J, Jiao S, Cho K, Sheng M (2010). Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. Cell, 141(5): 859–871

Li Z, Okamoto K, Hayashi Y, Sheng M (2004). The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell, 119(6): 873–887

Lipton J O, Sahin M (2014). The neurology of mTOR. Neuron, 84(2): 275–291

MacAskill A F, Atkin T A, Kittler J T (2010). Mitochondrial trafficking and the provision of energy and calcium buffering at excitatory synapses. Eur J Neurosci, 32(2): 231–240

Macaskill A F, Rinholm J E, Twelvetrees A E, Arancibia-Carcamo I L, Muir J, Fransson A, Aspenstrom P, Attwell D, Kittler J T (2009). Miro1 is a calcium sensor for glutamate receptor-dependent localization of mitochondria at synapses. Neuron, 61(4): 541–555

Marín-Burgin A, Mongiat L A, Pardi M B, Schinder A F (2012). Unique processing during a period of high excitation/inhibition balance in adult-born neurons. Science, 335(6073): 1238–1242

Mattson M P (2012). Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab, 16(6): 706–722

Merz K, Herold S, Lie D C (2011). CREB in adult neurogenesis—master and partner in the development of adult-born neurons? Eur J Neurosci, 33(6): 1078–1086

Mihaylova M M, Sabatini D M, Yilmaz O H (2014). Dietary and metabolic control of stem cell function in physiology and cancer. Cell Stem Cell, 14(3): 292–305

Ming G L, Song H (2011). Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron, 70(4): 687–702

Mishra P, Chan D C (2014). Mitochondrial dynamics and inheritance during cell division, development and disease. Nat Rev Mol Cell Biol, 15(10): 634–646

Nakagawa S, Kim J E, Lee R, Chen J, Fujioka T, Malberg J, Tsuji S, Duman R S (2002). Localization of phosphorylated cAMP response element-binding protein in immature neurons of adult hippocampus. J Neurosci, 22(22): 9868–9876

Orellana J A, Sáez P J, Cortés-Campos C, Elizondo R J, Shoji K F, Contreras-Duarte S, Figueroa V, Velarde V, Jiang J X, Nualart F, Sáez J C, García M A (2012). Glucose increases intracellular free Ca^{2+} in tanycytes via ATP released through connexin 43 hemi-channels. Glia, 60(1): 53–68

Oruganty-Das A, Ng T, Udagawa T, Goh E L, Richter J D (2012). Translational control of mitochondrial energy production mediates neuron morphogenesis. Cell Metab, 16(6): 789–800

Osman C, Voelker D R, Langer T (2011). Making heads or tails of phospholipids in mitochondria. J Cell Biol, 192(1): 7–16

Pellerin L, Magistretti P J (1994). Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci USA, 91(22): 10625–10629

Pereira A C, Huddleston D E, Brickman A M, Sosunov A A, Hen R, McKhann G M, Sloan R, Gage F H, Brown T R, Small S A (2007). An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA, 104(13): 5638–5643

Piatti V C, Davies-Sala M G, Espósito M S, Mongiat L A, Trinchero M F, Schinder A F (2011). The timing for neuronal maturation in the adult hippocampus is modulated by local network activity. J Neurosci, 31(21): 7715–7728

Pieper A A, Xie S, Capota E, Estill S J, Zhong J, Long J M, Becker G L, Huntington P, Goldman S E, Shen C H, Capota M, Britt J K, Kotti T, Ure K, Brat D J, Williams N S, MacMillan K S, Naidoo J, Melito L, Hsieh J, De Brabander J, Ready J M, McKnight S L (2010). Discovery of a proneurogenic, neuroprotective chemical. Cell, 142 (1): 39–51

Pierce A A, Xu A W (2010). De novo neurogenesis in adult hypothalamus as a compensatory mechanism to regulate energy balance. J Neurosci, 30(2): 723–730

Rodriguez-Rodriguez P, Fernandez E, Almeida A, Bolaños J P (2012). Excitotoxic stimulus stabilizes PFKFB3 causing pentose-phosphate pathway to glycolysis switch and neurodegeneration. Cell Death Differ, 19(10): 1582–1589

Rouach N, Koulakoff A, Abudara V, Willecke K, Giaume C (2008). Astroglial metabolic networks sustain hippocampal synaptic transmission. Science, 322(5907): 1551–1555

Sahay A, Wilson D A, Hen R (2011). Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. Neuron, 70(4): 582–588

Schmidt-Hieber C, Jonas P, Bischofberger J (2004). Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature, 429(6988): 184–187

Schousboe A, Scafidi S, Bak L K, Waagepetersen H S, McKenna M C (2014). Glutamate metabolism in the brain focusing on astrocytes. Adv Neurobiol, 11: 13–30

Sousa-Ferreira L, de Almeida L P, Cavadas C (2014). Role of hypothalamic neurogenesis in feeding regulation. Trends Endocrinol Metab, 25(2): 80–88

Spalding K L, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner H B, Boström E, Westerlund I, Vial C, Buchholz B A, Possnert G, Mash D C, Druid H, Frisén J (2013). Dynamics of hippocampal neurogenesis in adult humans. Cell, 153(6): 1219–1227

Spiegelman B M (2007). Transcriptional control of mitochondrial energy

metabolism through the PGC1 coactivators. Novartis Found Symp, 287: 60–63, discussion 63–69

Steib K, Schäffner I, Jagasia R, Ebert B, Lie D C (2014). Mitochondria modify exercise-induced development of stem cell-derived neurons in the adult brain. J Neurosci, 34(19): 6624–6633

Steketee M B, Moysidis S N, Weinstein J E, Kreymerman A, Silva J P, Iqbal S, Goldberg J L (2012). Mitochondrial dynamics regulate growth cone motility, guidance, and neurite growth rate in perinatal retinal ganglion cells in vitro. Invest Ophthalmol Vis Sci, 53(11): 7402–7411

Stocca G, Schmidt-Hieber C, Bischofberger J (2008). Differential dendritic Ca^{2+} signalling in young and mature hippocampal granule cells. J Physiol, 586(16): 3795–3811

Stoll E A, Cheung W, Mikheev A M, Sweet I R, Bielas J H, Zhang J, Rostomily R C, Horner P J (2011). Aging neural progenitor cells have decreased mitochondrial content and lower oxidative metabolism. J Biol Chem, 286(44): 38592–38601

Stranahan A M, Arumugam T V, Cutler R G, Lee K, Egan J M, Mattson M P (2008). Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. Nat Neurosci, 11(3): 309–317

Sun G J, Sailor K A, Mahmood Q A, Chavali N, Christian K M, Song H, Ming G L (2013). Seamless reconstruction of intact adult-born neurons by serial end-block imaging reveals complex axonal guidance and development in the adult hippocampus. J Neurosci, 33(28): 11400–11411

Tatsuta T, Langer T (2008). Quality control of mitochondria: protection against neurodegeneration and ageing. EMBO J, 27(2): 306–314

Toni N, Laplagne D A, Zhao C, Lombardi G, Ribak C E, Gage F H, Schinder A F (2008). Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci, 11(8): 901–907

Trejo J L, Carro E, Torres-Aleman I (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci, 21(5): 1628–1634

van Praag H (2009). Exercise and the brain: something to chew on. Trends Neurosci, 32(5): 283–290

van Praag H, Kempermann G, Gage F H (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci, 2(3): 266–270

van Praag H, Schinder A F, Christie B R, Toni N, Palmer T D, Gage F H (2002). Functional neurogenesis in the adult hippocampus. Nature, 415(6875): 1030–1034

Wang X, Schwarz T L (2009). The mechanism of Ca^{2+} -dependent regulation of kinesin-mediated mitochondrial motility. Cell, 136(1): 163–174

Ward P S, Thompson C B (2012). Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. Cancer Cell, 21(3): 297–308

Winner B, Kohl Z, Gage F H (2011). Neurodegenerative disease and adult neurogenesis. Eur J Neurosci, 33(6): 1139–1151

Wu L E, Meoli C C, Mangiafico S P, Fazakerley D J, Cogger V C, Mohamad M, Pant H, Kang M J, Powter E, Burchfield J G, Xirouchaki C E, Mikolaizak A S, Stöckli J, Kolumam G, van Bruggen N, Gamble J R, Le Couteur D G, Cooney G J, Andrikopoulos S, James D E (2014). Systemic VEGF-A neutralization ameliorates diet-induced metabolic dysfunction. Diabetes, 63(8): 2656–2667

Yeo H, Lyssiotis C A, Zhang Y, Ying H, Asara J M, Cantley L C, Paik J H (2013). FoxO3 coordinates metabolic pathways to maintain redox balance in neural stem cells. EMBO J, 32(19): 2589–2602

Zainuddin M S, Thuret S (2012). Nutrition, adult hippocampal neurogenesis and mental health. Br Med Bull, 103(1): 89–114

Zhao C, Deng W, Gage F H (2008). Mechanisms and functional implications of adult neurogenesis. Cell, 132(4): 645–660

Zhao C, Teng E M, Summers R G Jr, Ming G L, Gage F H (2006). Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci, 26(1): 3–11

Zhou M, Li W, Huang S, Song J, Kim J Y, Tian X, Kang E, Sano Y, Liu C, Balaji J, Wu S, Zhou Y, Zhou Y, Parivash S N, Ehninger D, He L, Song H, Ming G L, Silva A J (2013). mTOR Inhibition ameliorates cognitive and affective deficits caused by *Disc1* knockdown in adult-born dentate granule neurons. Neuron, 77(4): 647–654