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NIX-ing mitochondria: from development to pathology

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Hypoxia occurs physiologically in the developing body, and changing oxygen tensions are known to direct tissue differentiation; however, in the context of pathology, the same hypoxia-activated mechanisms may negatively affect tissue function. In this issue of *The EMBO Journal*, Esteban-Martínez *et al* (2017) report that programmed mitophagy, dependent on hypoxia-induced NIP-3-like protein X (BNIP3L, best known as NIX), is an essential step in differentiation of both retinal neurons and inflammatory macrophages.

See also: **L Esteban-Martínez *et al*** (June 2017)

During development, the body rapidly reshapes. At each moment, thousands of cells are formed and differentiate in synchrony, and the nature of the signals that govern this process so efficiently, yet so precisely, continues to baffle scientists. Various factors, including such offbeat mechanisms as mechanical force and electrical activity, were proposed to direct cell differentiation. The role of metabolism in this process is often overlooked, though phenotype transformation naturally requires integration of environmental and intracellular signals with the generation of energy and raw materials for new cellular structures. Mitophagy is a form of autophagy that was long considered a maintenance mechanism, whereby cells selectively degrade entire damaged mitochondria, a potential source of toxic reactive oxygen species (ROS; Ney, 2015). It is now appreciated that mitophagy can also occur as a part of cell differentiation, as for example, NIX-dependent programmed mitophagy removes mitochondria from reticulocytes during erythrocyte maturation (Zhang *et al*, 2012).

In this issue of *The EMBO Journal*, Esteban-Martínez *et al* (2017) unravel the mechanism of the prenatally occurring transition from proliferating neuroblasts to young retinal ganglion cells (RGCs)—the sole projecting neurons in the retina (Fig 1). The first critical step for RGC differentiation is hypoxia, which induces expression of NIX, a critical factor for mitophagy. Developing RGCs indeed exhibited decreased mitochondrial mass, and this was followed by a metabolic switch to glycolysis. Blocking this hypoxia-induced pathway at any step inhibited RGC maturation (Esteban-Martínez *et al*, 2017). Interestingly, differentiation and migration of olfactory bulb neurons during development also rely on autophagy signaling (Vázquez *et al*, 2012; Petri *et al*, 2017), and aerobic glycolysis (glycolysis in presence of oxygen) was proposed to occur in the human neonatal brain specifically in regions where synaptic growth rates are the highest (Goyal *et al*, 2014). Together, these findings suggest that brain neurons may undergo an analogous mitophagy-dependent metabolic switch during their differentiation.

Esteban-Martínez *et al* (2017) further demonstrated a similar metabolic rewiring governed by response to hypoxia- and NIX-dependent mitophagy in differentiation of pro-inflammatory (M1) macrophages (Esteban-Martínez *et al*, 2017; Fig 1). Inflammation and hypoxia often occur together, and there is significant cross talk between the cellular responses they elicit; thus, for example, hypoxia-inducible factors (HIFs) and NF-κB (an essential mediator of inflammation) have several common triggers, regulators, and targets (Biddlestone *et al*, 2015). Along the local immune response, inflamed tissue is initially characterized by the presence of M1 macrophages, which rely on glycolysis, while at later stages, the presence of M2 macrophages, which depend on oxidative phosphorylation, is associated with tissue regeneration (Jha *et al*, 2015). Here, involvement of mitophagy in M1 differentiation was only studied under *in vitro* conditions (Esteban-Martínez *et al*, 2017); *in vivo* experiments will elucidate whether hypoxia and mitophagy in immune cells can modulate immune responses and restoration of homeostasis. If so, the newly discovered mechanism can shed light on pathological conditions associated with hypoxia or a hypoxia-like response. According to the new findings, oxygen starvation and mitophagy in the brain could modulate the phenotype of both neuronal progenitors and of the brain's resident macrophages, the microglia.

Brain development and various neurological conditions are largely dependent on immunological factors. In particular, microglia are involved in diverse homeostatic functions during central nervous system formation and maintenance, and their altered activity was implicated in both neurodevelopmental and neurodegenerative conditions (Schwartz & Deczkowska, 2016). For example, microglia are critical for shaping neuronal circuitry during brain development in a process of synaptic pruning, whereby microglial cells use their phagocytic potential to eliminate weak synaptic connections between neurons. Under inflammatory conditions, for example, in brain aging, stroke, or in Alzheimer's disease, microglia assume a pro-inflammatory phenotype and

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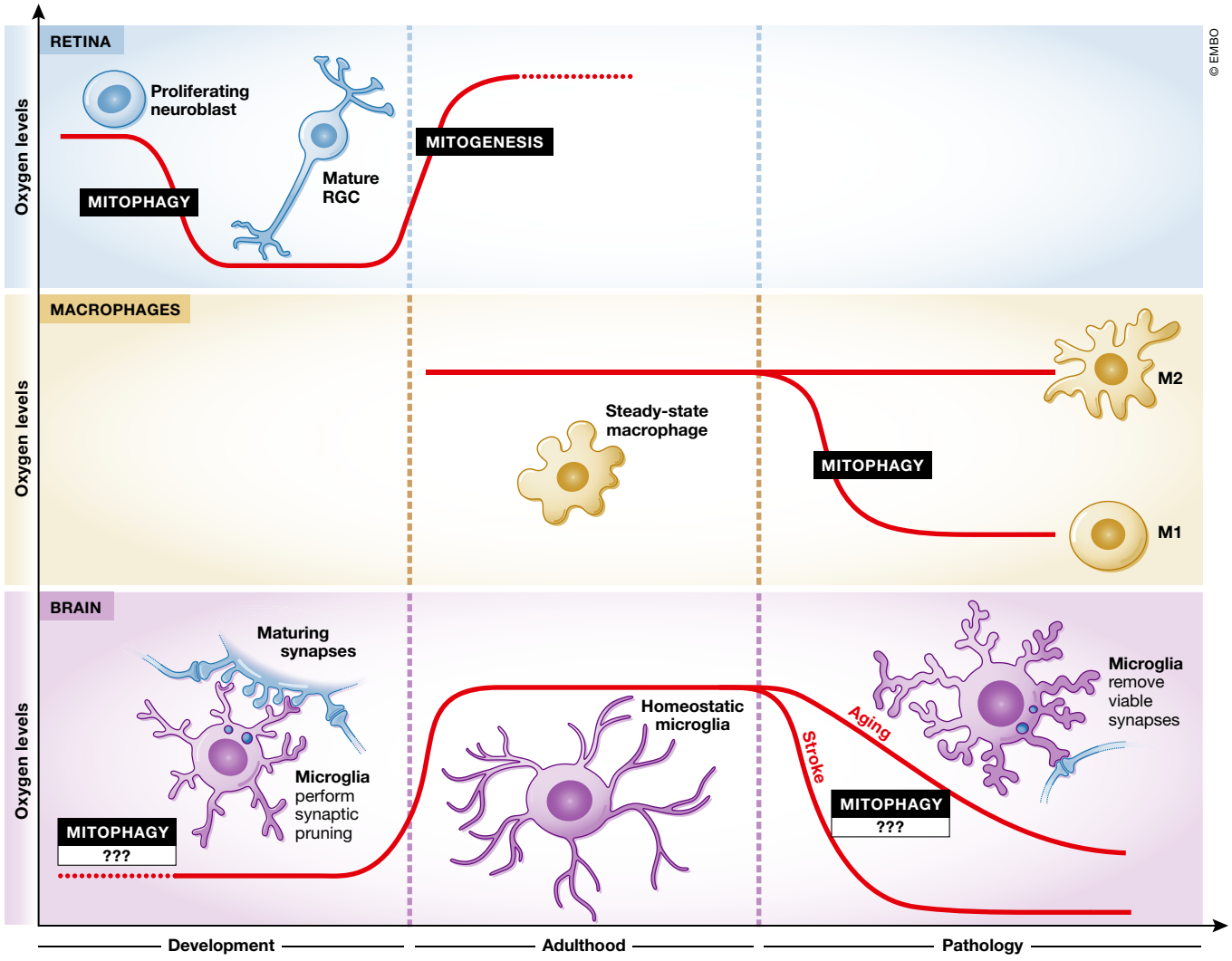

Figure 1. Hypoxia and mitophagy may direct cell differentiation in health and disease.
Hypoxia-induced mitophagy directs macrophage differentiation to pro-inflammatory M1 cells and maturation of RGCs in the retina. In the brain, hypoxic conditions temporally correlate with the periods of increased synaptic pruning activity, which shapes brain circuitry in development, but if over-activated in pathology, may eliminate viable synapses, thereby leading to brain function decline.

their synaptic pruning machinery is re-activated, leading to removal of viable synapses, and consequently, to cognitive loss (Stephan *et al*, 2012). Hypoxic conditions naturally occur in the brain during development, but brain aging was also associated with increased expression of HIF1α, probably in response to inefficient oxygen perfusion from the frail capillaries (Wang *et al*, 2012). Therefore, periods of intense microglia-mediated synaptic pruning and a hypoxia response in the brain seem to be temporally correlated (Fig 1). In addition, transient ischemia (a model of ischemic stroke) leads to increased synaptic clearance by microglia (Wake *et al*, 2009), further suggesting that hypoxia may determine synaptic pruning intensity, and therefore, brain function, throughout life. Future studies will determine whether low oxygen tensions in these cases led to synaptic clearance due to synapse inactivity, or due to induction of microglial pro-inflammatory phenotype upon hypoxia, and whether mitophagy has a role in this process.

Overall, changing oxygen tensions and related metabolic switches emerge as unexpected forces during both development and under pathology, especially in the brain, an organ extremely sensitive to deviations from homeostasis. Given the tremendous burden caused by brain pathologies, this new discovery may inspire future research on the possible involvement of such hypoxia-associated pathomechanisms in neurological diseases.

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