sensors to couple amino acid availability with mTORC1-mediated cell growth. This study is the first to identify a direct sensor for lactate. Although lactate has traditionally been viewed as a waste product of glycolysis, it is now increasingly appreciated that lactate can serve as a critical energy source, signaling molecule, and biosynthetic precursor in cells [7]. The study by Zhang and colleagues, therefore, will have a far-reaching impact on our understanding of lactate in physiology and disease and will surely motivate future studies to identify additional nutrient sensors in cellular metabolism. Moreover, elevated levels of LDHA or lactate have been reported in patients with viral infections [8,9], suggesting that the virus might hijack the glycolysis pathway to promote lactate production, thereby escaping from the host defense. Finally, cancer cells often exhibit increased lactate production, even under aerobic conditions (the Warburg effect) [4]. Considering the important roles of type I IFNs in cancer immunosurveillance [1], the Warburg effect might be used by cancer cells to dampen this immunosurveillance. Further studies will be directed to further testing these hypotheses and to translating these intriguing findings into novel treatments for cancer and viral infections.

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Spotlight

Neuron–Astrocyte Liaison to Maintain Lipid Metabolism of Brain

Soham Mukherjee[1] and S.N. Suresh[2,*]

Neuron–astrocyte crosstalk is a tightly regulated process that is essential for overall proper functioning of the brain. Maria S. Ioannou *et al.* (*Cell*, 2019) revealed a novel and compelling function of neuron–astrocyte crosstalk that explains how neurons cope with their accumulating toxic lipid particles under various scenarios.

Neurons and astrocytes coordinate a plethora of metabolic processes to ensure the homeostasis of the brain. In the 1980s, a seminal study showing trophic support by astrocytes to neurons indicated their probable crosstalk [1]. Unsurprisingly thereafter, the literature skyrocketed, demonstrating the synchronized operation of neurons and astrocytes as being quintessential for the well-being of organisms. Although the traditional belief is that astrocytes support the well-being of neurons, growing evidence pinpoints numerous inbuilt mechanisms helping neurons to cope with stress scenarios. Lipid droplets (LDs) are energy rich and fuel mitochondria-mediated β-oxidation followed by oxidative phosphorylation [2]. Hyperactive neurons generate peroxidated lipids and also have very low mitochondrial fatty acid consumption [3]. This poses the question: how do neurons tackle the accumulating lipids and their adducts? This led the authors to investigate whether astrocytes have any role to play at all in maintaining the lipid homeostasis of neurons, as the preceding literature indicates a bidirectional interaction of neurons and astrocytes. Such a possibility of astrocyte–neuron interaction in the context of lipid metabolism is not yet well characterized. Do neurons transfer lipids to astrocytes? If so, what are the mechanistic underpinnings facilitating such transfer? The current study by Maria S. Ioannou *et al.* in *Cell* sheds light on these questions that are important to perpetuate neuronal and, eventually, organismal homeostasis [4].

N-Methyl-D-aspartate (NMDA)-mediated excitotoxicity in neurons stimulates the formation of LDs. Increased neuronal autophagic flux liberates free fatty acids from lysosomes that amalgamate to form cytosolic LDs. Thus, autophagy assists LD biogenesis to evade lipotoxicity. This corroborates with a previous observation that diacylglycerol acyltransferase 1 (DGAT-1) and elevated autophagic flux mediate LD formation by channeling free fatty acids from lysosomes [5]. Despite autophagy inhibition, there is no exponential accumulation of LDs beyond a certain threshold, probably indicating the existence of an alternative pathway. Under

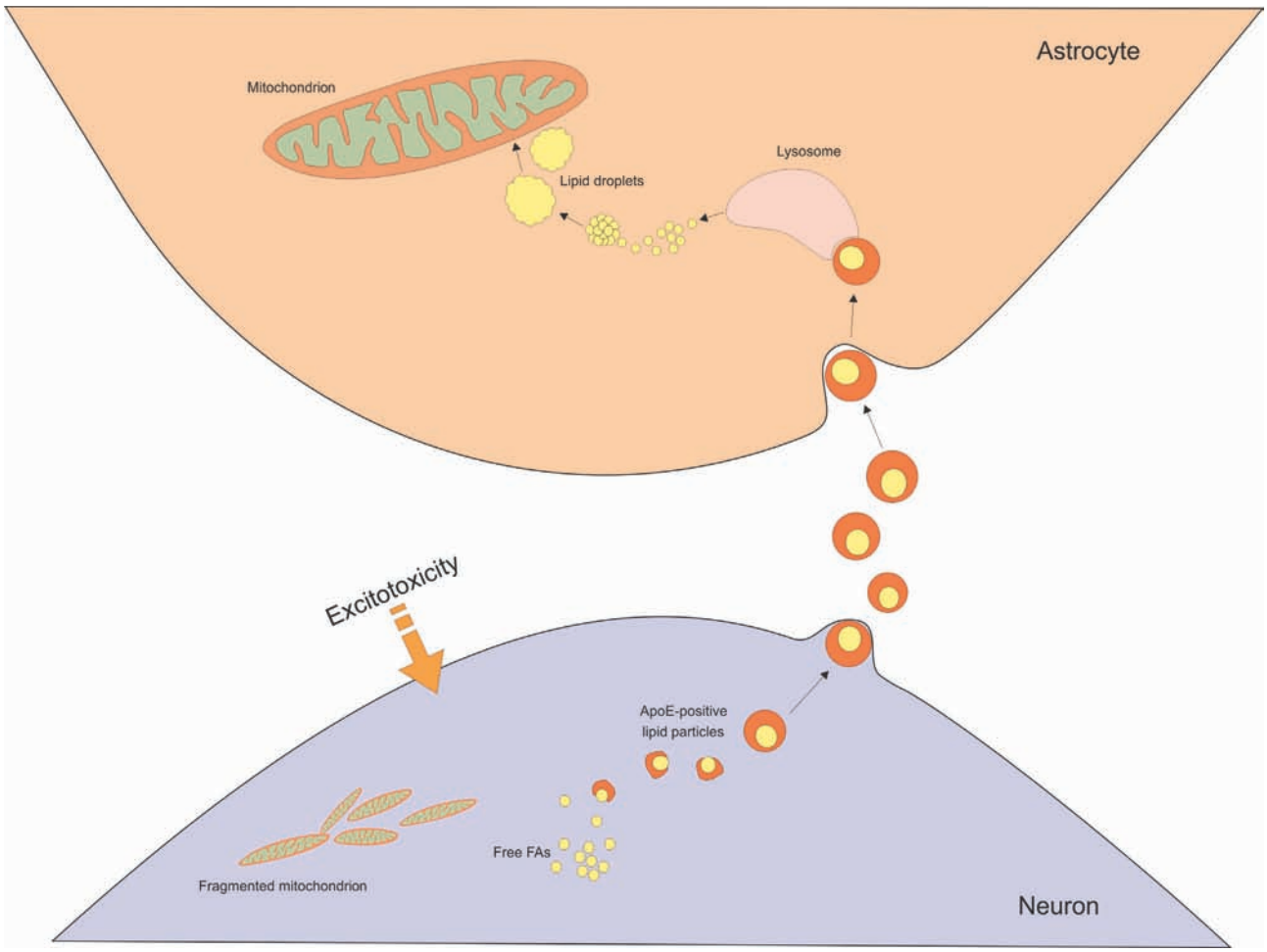

Figure 1. On Excitotoxicity, Neurons Accumulate Peroxidated Lipid Adducts That Are Exocytosed in an Apolipoprotein E (ApoE)-Dependent Manner. ApoE-positive vesicles are endocytosed by neighboring astrocytes for lysosomally mediated degradation of lipids to free fatty acids (FAs). The free FAs then adhere to form LDs that will be metabolized through mitochondrially mediated β-oxidation and oxidative phosphorylation.

excitotoxic conditions, neuronal mitochondria are highly fragmented, which is not feasible to metabolize LDs, ruling out the possibility of mitochondrially mediated LD consumption [6]. A previous study indicated that non-neuronal cells transfer LDs to neighboring cells [7]. Along these lines, Ioannou *et al.* tested the fate of hyperactive neuronally derived toxic lipid particles. Neuron–astrocyte coculture and lipid labeling techniques revealed that neuronal peroxidated lipids are transferred to glial fibrillary acidic protein (GFAP)-positive astrocytes. Concurrently, the lipoprotein particles are expelled via exocytosis from neurons and then endocytosed by astrocytes (Figure 1). Endocytic fatty acid transfer from hyperactive neurons was shown elegantly by blocking the lipoprotein receptors of astrocytes through competitive binding assays. Apolipoprotein E (apoE) is a lipid carrier in the central nervous system that is required for LD accumulation in astrocytes [8]. To understand whether apoE plays a role in LD release and uptake, the authors tested lipid release from apoE-null mutant cells. Notably, LD transfer from neurons to astrocytes is diminished, indicating the essentiality of apoE. Given that apoE is a seemingly pervasive risk factor for late-stage Alzheimer's disease (AD) and its related dementias, its compromised levels could significantly affect the ability of neurons to exocytose accumulating LDs over time. This provided an additional mechanism for how apoE disease variants contribute to AD pathogenesis. However, this study did not address the effect of different isoforms of apoE such as apoE3 and apoE4 that exert opposite effects in driving disease pathogenesis. Nevertheless, it opens an avenue to investigate the mechanisms of lipid transfer dynamics in disease variants of apoE3 and apoE4 that might explain

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the underlying dysfunctional lipid metabolism in AD.

The authors tested their hypotheses using two *in vivo* model systems, acute stroke and chemically mediated excitotoxicity. In these cases, consistent with *in vitro* data, LDs accumulate in astrocytes but not in neurons, indicating their transfer. Astrocytes dismantle LDs to fatty acids and then metabolize them through mitochondrially mediated β-oxidation. However, the β-oxidation adversely elevates reactive oxygen species (ROS) [2]. In contrast to neurons, ROS measurement indicated the absence of their accumulation in astrocytes. How do astrocytes handle the deleteriously increased production of ROS? Addressing this intriguing question, transcriptome profiling revealed that astrocytes upregulated oxidative stress-nullifying genes in response to lipid uptake. Notably, these genes were expressed at low levels in neurons, thus explaining their dependence on astrocytes to handle LD-mediated toxicity. However, future studies can explore the precise nature of the exchanged lipid particles that will add laurels to this field. In hyperactive neurons, the vicious cycle of elevated ROS and the accumulation of lipid particles and peroxide adducts could catapult the manifestation of pathophysiological conditions [8,9].

In future, it will be worth investigating the fate of lipid particles formed in different neuronal compartments such as the soma and/or its projections to dissect whether any differences exist in the molecular machineries/mechanisms and kinetics of exocytosis. Also, where precisely are lipid particles released from neurons? Do they prefer any particular domain of the plasma membrane? Understanding the consequences of excitotoxicity for astrocytes *per se* and their implications for neurons could reveal the mechanisms underlying neurodegeneration and neurodevelopmental disorders. Do similar mechanisms for expelling lipid particles exist in cortical neurons or other types? If they are different, this could explain why certain types of neurons are vulnerable in various neurodegenerative conditions. Could blocking neuron–astrocyte lipid transfer *in cellulo* and *in vivo* by genetic or pharmacological means result in neurodegenerative-like phenotypes such as accumulation of ubiquitin-positive aggregates and so on?

To summarize, hyperactive neurons exocytose LDs to evade lipid toxicity. Astrocytes take up these apoE-positive LDs via endocytosis to fuel mitochondria-mediated β-oxidation, and such coupling of lipid metabolism between neurons and astrocytes protects neurons from fatty acid toxicity. The finding of enhanced gene expression to combat increased ROS by astrocytes solves an important piece of the puzzle of how they handle oxidative stress efficiently unlike neurons. At the intracellular level, neurons wield a number of protective mechanisms to overcome accumulating toxic proteins and lipid biochemical intermediates. This study reveals an additional dimension of the intrinsic basic mechanisms of the neuron in how it combats accumulating peroxidized lipid adducts. The crucial function of 'neuronal transfer of lipoprotein particles to astrocytes' as a means to evade toxicity joins the long but important list of metabolic functions arising from neuron–astrocyte harmonization. Despite long years of investigating this harmonization, it continues to surprise us with new angles as we study it.

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Spotlight

Huntington's Disease: Astrocytes Shift to Fatty Acid Metabolism

Bennett Van Houten [1,2,*]

A recent study by Polyzos *et al.* (*Cell Metab.*, 2019) shows that astrocytes in a Huntington disease (HD) mouse model switch from glycolysis to fatty acid oxidation (FAO), causing increased superoxide radical anion production and loss of succinate dehydrogenase (SD) activity. Blocking mitochondria reactive oxygen species (ROS) with an antioxidant compound called XJB-5-151 reversed lipofuscin formation and protected the mice.