Are you *TORCing tau* me? Amyloid- β blocks the conversation between lysosomes and mitochondria

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How amyloid- β (A β) and tau exacerbate Alzheimer's disease (AD) at a subcellular level is only incompletely understood. Norambuena *et al* (2018) report crosstalk between mitochondria and lysosomes and identify a role for lysosomal mTORC1 in the nutrient-induced activation of mitochondria. This lysosomal signalling pathway is strongly inhibited by oligomeric A β through the tau-dependent activation of plasma membrane-localized mTORC1. Together, these results identify a further role for tau in mediating A β toxicity.

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See also: A Norambuena *et al* (November 2018)

Type 2 diabetes and Alzheimer's disease (AD) are progressive, chronic disorders, with the former being a major risk factor for the latter (Schrijvers *et al*, 2010). Two major causes of type 2 diabetes have been identified: increased insulin resistance of the organs of the body and a loss in the capacity of the pancreas to generate sufficient amounts of insulin to meet cellular energy demands. A link between type 2 diabetes and AD has been established with the finding that insulin dysregulation occurs in brain tissue from AD patients and mouse models for AD (Schrijvers *et al*, 2010; Vandal *et al*, 2015). A key molecule in the insulin signalling pathway is the protein kinase mammalian target of rapamycin (mTOR): its hyperactivation mediates insulin resistance (Um *et al*, 2004), whereas a decrease in its

activity extends the lifespan and slows the ageing process in multiple organisms (Johnson *et al*, 2013). This central role of mTOR (which signals through ribosomal S6 kinase 1, S6K1) is not surprising given its crucial function in pathways that are involved in both sensing nutrients and controlling the response to their fluctuations in the environment (Efeyan *et al*, 2015).

Alzheimer's disease is a brain disorder that is characterized by the aggregation of two molecules which constitute its hallmark lesions: the peptide amyloid- β (A β) and the protein tau. They both impair neuronal functions at multiple levels, including many aspects of mitochondrial function (Polanco *et al*, 2018). Lysosomes have historically been considered as both degradative and recycling centres. Lysosomal dysfunction has been linked to AD pathogenesis through promotion of the accumulation of insoluble and toxic protein aggregates, such as A β and tau, in the brain (Nixon, 2017). However, we now know that lysosomes also play a key role in nutrient sensing (Efeyan *et al*, 2015). Furthermore, the discovery of direct contact sites between lysosomes and mitochondria has sparked hypotheses of a potential cooperation between these two organelles under physiological conditions, as well as in the development of neurodegenerative diseases (Wong *et al*, 2018). In this issue, Norambuena *et al* (2018) provide evidence that oligomeric forms of A β (A β os) disrupt the functional crosstalk between lysosomes and mitochondria, thereby contributing to the early stages of AD.

Mitochondrial dysfunction impairs lysosomal structure and function in a manner that depends on the levels of mitochondrial reactive oxygen species (ROS; Demers-Lamarche *et al*, 2016). Norambuena *et al* (2018) demonstrate that there is also an opposite information flow, with mitochondria receiving signals from lysosomes via a mechanism that is dependent on mTORC1, a multiprotein signalling complex nucleated by mTOR and bound to the cytosolic side of lysosomes. This lysosome-associated mTORC1 was shown to be activated by insulin and amino acids, leading to what the authors have termed "nutrient-induced mitochondrial activation (NiMA)", reflected by increased oxygen consumption and the mitochondrial production of ROS. This lysosomal signalling was strongly inhibited by A β os and was found to depend on the activation of mTORC1 by a mechanism that requires tau (Fig 1).

Nutrient-induced mitochondrial activation was detected by measuring the ratio between the mitochondrial coenzymes NADH and NADPH using two-photon fluorescence lifetime imaging (2P-FLIM). This visualization technique allowed the authors to demonstrate that starved neurons increase their mitochondrial production of NADPH as a response to insulin or amino acids. The involvement of mTORC1 signalling was demonstrated using Torin 1, a potent and selective ATP-competitive inhibitor of mTOR that effectively blocks the phosphorylation of mTORC1, and by an shRNA-mediated specific knockdown of essential mTORC1 subunits. Importantly, mTORC1 not only is found on lysosomes, but also is located at

Figure 1. A β blocks signalling from lysosomes to mitochondria.

(A) Under physiological conditions, the hormone insulin or amino acids activate mitochondria in a process that depends on lysosomal mTORC1. This process has been termed NiMA (nutrient-induced mitochondrial activity) and reveals a role for an increased localization of mTORC1 to the cytoplasmic surface of lysosomes in this process. (B) Oligomeric A β (that accumulates under pathological conditions such as AD) causes a reduction in NiMA in a process that involves plasma membrane-localized mTORC1. Tau has a role in this negative regulation. The question marks (?) indicate areas that remain to be investigated.

the plasma membrane and even in mitochondria. In order to determine the subcellular localization of the mTORC1 that regulates NiMA, several experimental approaches were undertaken, including the overexpression of mTORC1 subunits that forced its accumulation preferentially on lysosomes or the plasma membrane, or the shRNA-mediated knockdown of the mitochondrial protein Bcl-xL to block the direct binding of mTORC1 to mitochondria. Collectively, the data revealed that NiMA occurs when mTORC1 is targeted to lysosomes.

Nutrient-induced mitochondrial activation was blocked by A β os, but not when mTORC1 was targeted preferentially to lysosomes. Given the capacity of A β os to activate mTORC1 at the plasma membrane (Norambuena *et al*, 2017), it was concluded that the abrogation of NiMA by A β os was caused by an activation of mTORC1 in this

location (Fig 1). This activation has previously been shown to cause aberrant neuronal cell cycle re-entry, another pathological mechanism in AD (Norambuena *et al*, 2017). Interestingly, activation of lysosomal mTORC1 by insulin can prevent neurons from re-entering the cell cycle, and it appears that A β os reduce neuronal insulin signalling in a vicious cycle that augments A β o toxicity by forcing neuronal cell cycle re-entry (Norambuena *et al*, 2017). This might in part explain why systemic diabetes is a strong risk factor for AD.

Many toxic effects of A β os have been shown to be mediated through tau (Polanco *et al*, 2018). This also holds true for NiMA, as this process was not blocked by A β os in tau knockout neurons (Norambuena *et al*, 2018). This reinforces the view that tau acts as a scaffolding protein, facilitating the formation of signalling complexes that affect

neuronal function in several ways (Polanco *et al*, 2018). What remains to be accomplished is the isolation and characterization of these putative complexes that are "TORCing" to tau. A β os activate numerous signalling cascades that contain kinases other than mTOR, such as Fyn, PKA and CaMKII (Li & Götz, 2017; Norambuena *et al*, 2017; Polanco *et al*, 2018), but, again, these signalling complexes have not been fully identified. Work from our laboratory has shown that A β os initiate a pathological cascade that results in the *de novo* synthesis of tau protein and its pathological phosphorylation; this occurs via activation of S6K1, albeit in an mTOR-independent manner (Li & Götz, 2017). The new findings by Norambuena *et al* (2018) potentially identify an early signature of AD, pointing at a convergence of various signalling pathways and presenting a reduction in mTOR activity as a

valid therapeutic approach for the treatment of AD (Caccamo *et al.*, 2018). Interestingly, suppression of mTOR has also been reported to increase health and lifespan in several organisms (Johnson *et al.*, 2013), and it would not be surprising if in our journey to treat AD we also have a strong positive effect on its major risk factor, ageing.

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