α-Ketoglutarate dehydrogenase complex moonlighting: ROS signalling added to the list

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It is well established that alterations in energy metabolism are present in most neurodegenerative disorders. Some of these alterations are due to mitochondrial dysfunctions that occur in parallel to an exacerbated production of reactive oxygen species (ROS). From a quantitative viewpoint, mitochondria are thought to be the largest contributors to intracellular ROS production in most cell types. Under specific circumstances, mitochondria produce excess ROS (mROS) leading cells to undergo oxidative stress and apoptotic death. Amongst the different mROS sources, the mitochondrial respiratory chain complexes I and III appear to be important. However, increasing evidence now suggest the important contribution of certain metabolic enzymes of the mitochondrial matrix, such as pyruvate dehydrogenase complex and the tricarboxylic acid (TCA) cycle enzyme 2-oxoglutarate dehydrogenase complex (KGDHC), or embedded in the inner mitochondrial membrane, such as glycerolphosphate dehydrogenase and the flavoprotein-ubiquinone oxidoreductase mitochondrial system (Holmström and Finkel, 2014).

KGDHC is one of the key regulatory enzymes of the TCA cycle, and its activity is mainly controlled by the cellular redox state, by ATP and by the KGDHC product, succinyl-CoA. In brain tissue, KGDHC is also involved in neurotransmitter biosynthesis. Thus, α-ketoglutarate (α-KG) is the precursor of glutamate and glutamine biosynthesis, in neurons and astrocytes, respectively, and of GABA synthesis in GABAergic neurons. Therefore, three major tasks of the brain cells, namely neurotransmitter biosynthesis, energy conservation, and redox homeostasis, are potentially linked to mROS metabolism by the KGDHC activity. However, the significance, mechanism and regulation of KGDHC-mediated ROS production have remained elusive.

Chen and colleagues (2016) now show that transient up- or down-modulation of KGDHC activity can play a protective role against exogenously excess ROS. In essence, they propose that perturbation in metabolism caused by transient reductions in KGDHC would activate cellular antioxidant systems to overcome a prospective increase in ROS. Moreover, they also show that decreasing KGDHC activity –either acutely *in vivo*, or chronically *in vitro*- triggers KGDHC-mediated excess ROS. Thus, increases in

the mitochondrial NADH/NAD^+ ratio switch KGDHC to a less active ROS-production mode that is self-protected against excess ROS. This is performed by KGDHC glutathionylation (McLain et al. 2013), a process that occurs during increased oxidized glutathione (GSSG) concentrations caused by excess ROS. Thus, KGDHC activity can plays a key role in mROS homeostasis.

In previous reports, the authors had shown that specific inhibition of KGDHC in intact cerebellar granule neurons increased α-KG, increased transamination of α-KG with valine, leucine and GABA (Santos, et al. 2006), increased GABA shunt and produced changes in glycolysis (Shi, et al. 2009, Nilsen, et al. 2011). Interestingly, glycolysis activation in neurons triggers glutathione oxidation to GSSG due to a shift of the pentose phosphate pathway (PPP) (Herrero-Mendez et al. 2009; Rodriguez-Rodriguez et al. 2012). Whether such an increase in glycolysis is consequence of KGDHC inhibition, or is part of an overall increase in glucose metabolism that takes place during PPP impairment, may be worth elucidating. Furthermore, it is interesting to note the apparent link between KGDHC activity and endoplasmic reticulum Ca^{2+} stores observed by Chen et al. (2016), although the underlying mechanism still remains to be fully elucidated. Thus, the authors previously described the accumulation of bombesin-released Ca^{2+} stores (BRCS) by exogenous ROS, which resembles those observed in neurodegenerative disorders. Now, the authors show that the chronic inhibition of KGDHC *in vivo* potentiates the effect of the free-radical donor tert-butylhydroperoxide (t-BHP) on BRCS in primary neurons, an effect that is rescued by the over-expression of the KGDHC subunit, 2-oxoglutarate dehydrogenase. These results clearly show that the response of BRCS to externally added ROS is modulated by KGDHC activity. However, whether the observed effect on BRCS is an indirect consequence of KGDHC activity-mediated ROS, or its takes place by different, yet unknown mechanism(s), remains to be investigated.

Taken together, the results presented by Chen et al. (2016) adds novel functions to the long list of metabolic tasks of KGDHC, thus raising the possibility to consider the pharmacological control of KGDHC activity as a therapeutic strategy against the bioenergetics deficiency of neurodegenerative disorders.

Acknowledgements
J.P.B. is funded by the MINECO (SAF2013-41177-R), the Instituto de Salud Carlos III (RD12/0043/0021), the E.U. SP3-People-MC-ITN programme (608381), the EU BATCure grant (666918), and the NIH/NIDA (1R21DA037678-01).

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Figure 1 legend

Outline diagram of the main conclusion by Chen et al. (2016). Tuning KGDHC activity progressively controls mROS production with different cellular outcomes. Long-term KGDHC inhibition releases harmful excess mROS, whereas short-term inhibition or mild activation of KGDHC either slightly increases or decreases, respectively, neuroprotective mROS.

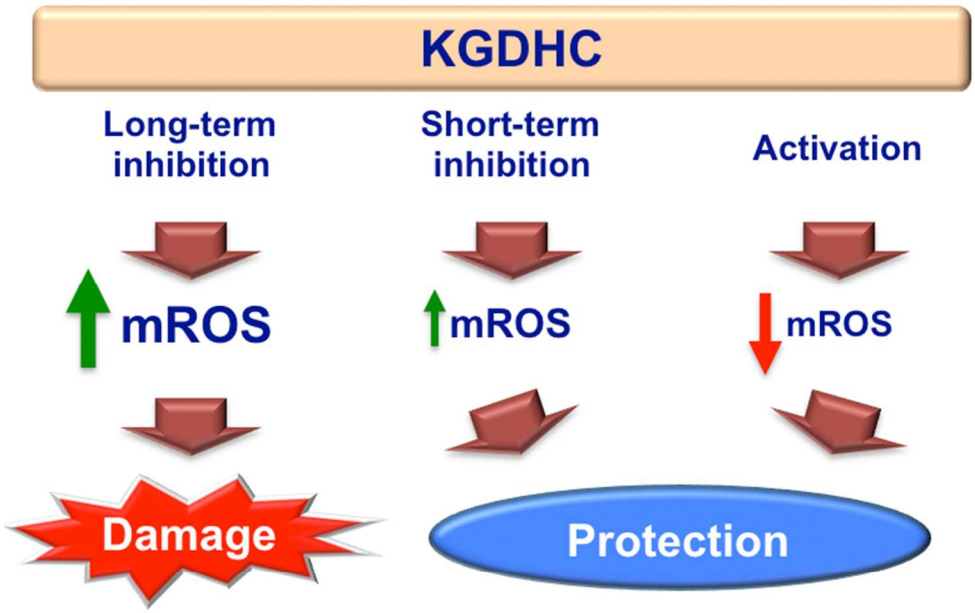

Figure 1

281x189mm (72 x 72 DPI)