Apaf-1 deficient cortical neurons exhibit defects in axonal growth

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The apoptotic protease activating factor-1 (Apaf-1) is a key player in mitochondria-mediated apoptosis a process that is a prerequisite for nervous system development. It has recently been shown also that Apaf-1 is necessary not only for the death of the cells, but also for their survival.
Mouse primary cortical neurons (PCN) obtained from cerebral cortices of Apaf1+/+ (WT) and Apaf1-/- (KO) E14.5 embryos were cultured and analyzed after different days in vitro (DIV) by IF, while proteins and RNA were extracted to perform Western blot analysis and qPCR.
Here we have found that Apaf-1 plays an additional function in cortical neurons, where its deficiency specifically impairs axonal growth. Given the central role played by centrosomes and microtubules in the polarized extension of the axon, our data suggest that Apaf1-deletion affects axonal outgrowth through an impairment of centrosome organization. In line with this, centrosomal protein expression, as well as their localization proved to be altered upon Apaf1-deletion. We found that Apaf1-loss affects trans-Golgi components and leads to a robust activation of AMP-dependent protein kinase (AMPK), this confirming the stressful conditions induced by Apaf1-deficiency. Since AMPK hyper-phosphorylation is known to impair a proper axon elongation, our finding contributes to explain the effect of Apaf1-deficiency on axogenesis. We also discovered that the signaling pathways mediating axonal growth and involving glycogen synthase kinase-3b, liver kinase B1, and collapsing-response mediator protein-2 are altered in Apaf1-KO neurons. Overall, our results reveal a novel non-apoptotic role for Apaf1 in axonal outgrowth, suggesting that the neuronal phenotype due to Apaf1-deletion could not only be fully ascribed to apoptosis inhibition, but might also be the result of defects in axogenesis. Thus, due to alternative roles of some proteins like Apaf-1, the risk and benefit of each available pro- or anti-apoptosis treatment must be *carefully* evaluated. The discovery of new molecules involved in axonal elongation has a clinical relevance since it might help to explain neurological abnormalities occurring during early brain development. Although further investigations are needed to fully elucidate the sequence of events triggered by Apaf1-deficiency and leading to axonal elongation defects, the discovery of additional molecular players involved in axonal growth has a clinical relevance in that it might help to explain neurological abnormalities caused by stressful conditions during early brain development.