All is a matter of Energy: fission-fusion-mitophagy cycling of mitochondria in the NGF-dependent neuronal differentiation

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Keywords: NGF, differentiation, NAD+, energy, metabolism, mitochondrial dynamics, mitophagy

Abstract:

Nerve Growth Factor (NGF)-induced neuronal differentiation requires modification in biochemical and metabolic state of cells to sustain all anabolic pathways. In our previous work we demonstrated that NGF differentiation involves: i) regulation of mitochondrial dynamics to favor distribution of mitochondria along neurites, and ii) increase in mitochondrial respiration, energy production and autophagy flux. To test whether NGF differentiation enhance metabolic workload and the relevance of mitophagy and mitochondrial dynamics, we compared the effect of NGF to NAD^+, known to boost energy metabolism, mitophagy and neuroprotection against several toxic stimuli, in the differentiation of PC12 cells.

To this end, we used bright-field and fluorescence time-lapse imaging of cells stained by MitoTracker Green (MTG) and Lysotracker Red (LTR) and mitochondria quality assessing membrane potential. Surprisingly, we found that NAD^+ alone is able to induce PC12 differentiation by stimulating neurite sprouting even faster than NGF. Nonetheless, prolonged exposure to NAD^+ (> 24h) leads to neurite loss, ROS production and cell death, suggesting that boosting energy metabolism is not sufficient to induce a stable neuronal phenotype.

We also assessed the impact of NGF on energy metabolism. Remarkably, metabolic profiling of PC12 exposed to NGF identified 46 statistically significant metabolites; specifically, a significant increase in intermediates connected to glycolysis, TCA cycle, Pentose Phosphate pathway and redox balance.

Overall, our data indicate that neuronal differentiation imposes an important reprogramming of metabolic function to provide more energy on one side, while at the same time boosting the PPP and glutathione synthesis, which is the main neuronal scavenger system.