Mitochondria dysfunction and differentiation of oligodendrocytes.

Is iron a candidate factor?

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Multiple sclerosis (MS) is a neurological disorder of the central nervous system characterized by demyelination and neurodegeneration (Dhib- Jalbut, 2007; Arthur et al., 2008). Although the pathogenesis of MS is not completely understood, various studies suggest that immune-mediated loss of myelin and mitochondrial dysfunction are associated with the disease (Ghafourifar et al., 2008). In particular, mitochondrial functions might be required for proper oligodendrocyte differentiation and myelination (Su et al., 2009). Specifically, it has been demonstrated that i) mitochondrial transcripts and copy number are induced by oligodendroglial differentiation, ii) slight mitochondrial inhibition inhibits differentiation, and iii) stronger mitochondrial inhibition selectively decreases viability of differentiating oligodendroglia but not undifferentiated cells (Schoenfeld et al., 2010).

It is now well established that mitochondria play a pivotal role in cell survival in large part because of their participation in the dynamic regulation of cellular Ca^{2+} (Pinton et al., 2008). Under normal conditions, the accumulation of Ca^{2+} in mitochondria stimulates oxidative metabolism (Jouaville et al., 1999). However, overload of mitochondria with Ca^{2+}, as a consequence of pathological stimuli, results in dramatic alterations in mitochondrial function, including decreased ATP production and increased generation of reactive oxygen (Pinton et al., 2008). Recent reports have

documented impaired activity of several mitochondrial respiratory complexes in MS plaques (Forte et al., 2007).

Malfunction of mitochondria is reported in several works and frequently is associated with demyelinization. This event occurs in multiple mitochondrial diseases, including Leber's Hereditary Optic Neuropathy, Friedreich's ataxia, Dominant Optic Atrophy, Periventricular Leukomalacia, and MS (Kalman, et al., 1995).

We investigated Ca^{2+} homeostasis in oligodendrocytes during conditions that mimic inflammation.

In particular, we evaluated the effects of TNFalpha and IFNgamma on intracellular Ca^{2+}homeostasis in oligodendrocytes, as these inflammatory cytokines are the major players in the autoimmune reaction against oligodendrocytes. Only TNFalpha alters intracellular Ca^{2+} homeostasis, whereas IFNgamma has no effect. Moreover, the TNFalpha effects are restricted to the mitochondrial compartment, suggesting specific effects on mitochondrial physiology. Last, but not least, the reduction of mitochondrial Ca^{2+} responses (a well known readout of mitochondrial damage) involved exclusively oligodendrocyte precursor cells (OPCs) and no other glial cell types such as astrocytes. Then, we evaluated mitochondrial membrane potential (MMP) in control and TNFalpha treated cells. The results indicated a strong reduction of MMP in cells treated with TNFalpha suggesting a significant reduction of activity of the mitochondrial respiratory chain. Finally, we found that OPCs forced to differentiate and pretreated with subtoxic doses of TNFalpha reveal a significant reduction of the percentage of cells that differentiate, in respect to OPCs forced to differentiate but not pretreated with the inflammatory cytokine.

Taken together, these results suggest that TNFalpha impair oligodendrocyte differentiation by altering mitochondrial functions.

Abnormal iron accumulation is frequently noted in MS and compelling evidence exists that iron is involved in inflammatory reactions (Todorich et al., 2009). In future experiments, we will investigate if iron status of these cells will significantly impact the outcome of the effects of TNFalpha treatment with particular attention on the mitochondrial homeostasis and in turn on oligodendrocyte differentiation.

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