Chemical hypoxia-induced unfolded protein response activation in oligodendrocytes is mediated by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (NRF2)

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Abstract

The extent of remyelination in multiple sclerosis (MS) lesions is often incomplete. Injury to oligodendrocyte progenitor cells can be a contributing factor for such incomplete remyelination. The precise mechanisms underlying insufficient repair remain to be defined. Oxidative stress appears to be involved. Here, we used immortalized oligodendrocyte cell lines as model systems to investigate a causal relation of oxidative stress and endoplasmic reticulum stress signaling cascades.

OLN93 and OliNeu cells were subjected to chemical hypoxia by blocking the respiratory chain at various levels. Mitochondrial membrane potential and oxidative stress levels were monitored by flow cytometry. Endoplasmic reticulum stress was monitored by the expression induction of activating transcription factor 3 and 4 (*Atf3, Atf4*), DNA damage-inducible transcript 3 protein (*Ddit3*) and glucose-regulated protein 94 (*Grp94*). Lentiviral silencing of nuclear factor (erythroid-derived 2)-like 2 (*Nrf2*) or kelch-like ECH associated protein 1 (*Keap1*) was applied to study the relevance of NRF2 for endoplasmic reticulum stress responses.

We demonstrate that inhibition of the respiratory chain induces oxidative stress in cultured oligodendrocytes which is paralleled by the expression induction of distinct mediators of endoplasmic reticulum stress response, namely *Atf3*, *Atf4* and *Ddit3*. *Atf3* and *Ddit3* expression induction is potentiated in *Keap1*-deficient cells and absent in cells lacking the oxidative-stress related transcription factor *Nrf2*.

This study provides strong evidence that oxidative stress in oligodendrocytes activates endoplasmic reticulum stress response in a NRF2-dependent manner and, in consequence, might regulate oligodendrocyte degeneration in MS and other neurological disorders.