Intra- and intercellular functions of redoxins during neuroinflammation

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The essential role of redox regulation for physiological signaling within distinct cellular processes has been documented in various organisms and models. However, identified and characterized molecular mechanisms based on particular thiol switches are very rare.

Signaling processes via reversible oxidative posttranslational modifications of thiols need to be tightly controlled, e.g. by enzymes of the thioredoxin (Trx) family of proteins. The Trx family comprises more than 50 members in mammals, including Trxs, glutaredoxins (Grxs), peroxiredoxins (Prxs) (1, 2), which catalyze the reduction and oxidation of specific Cys residues and regulate the levels of H_2O_2.

Neuroinflammation describes the inflammation of the nervous system consisting of neurons and glial cells, i.e. oligodendrocytes, astrocytes and microglia. It occurs upon infection, trauma, ischemia or autoimmunity and in neurodegenerative diseases. Upon neuroinflammation, monocytes/macrophages, T and B lymphocytes pass the blood brain barrier and can activate local antigen presenting cells (3).

We have shown that macrophages secrete particular redoxins upon cytokine treatment, and that these redoxins can also act as cytokines (e.g. 4). We identified a Grx2-dependent mechanism protecting the myelin structure against nitric oxide induced damage in models mimicking neuroinflammation, e.g. cerebellar organotypic slice cultures (5). Moreover, we identified a Grx2-mediated differentiation block of oligodendroglial differentiation.

Within the scope of the priority program we will particularly focus on the translocation of redoxins and redoxin-induced translocation of substrates and characterize extracellular substrates and functions of secreted redoxins, analyze the impact of redoxins on/during reactive astrogliosis, and elucidate thiol switches controlling the differentiation and regeneration capacity of oligodendrocytes.

Including patient material, our data will have high importance for translational research and might even lead to new tools to diagnose and combat diseases linked to neuroinflammation like multiple sclerosis and Alzheimer´s disease, in the future.

References

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