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Oxidative stress in multiple sclerosis: Central and peripheral mode of action

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ABSTRACT

Accumulating evidence suggests that oxidative stress plays a major role in the pathogenesis of multiple sclerosis (MS). Reactive oxygen species (ROS), which if produced in excess lead to oxidative stress, have been implicated as mediators of demyelination and axonal damage in both MS and its animal models. One of the most studied cell populations in the context of ROS-mediated tissue damage in MS are macrophages and their CNS companion, microglia cells. However, and this aspect is less well appreciated, the extracellular and intracellular redox milieu is integral to many processes underlying T cell activation, proliferation and apoptosis. In this review article we discuss how oxidative stress affects central as well as peripheral aspects of MS and how manipulation of ROS pathways can potentially affect the course of the disease. It is our strong belief that the well-directed shaping of ROS pathways has the potential to ameliorate disease progression in MS.

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1. Introduction to the disease

1.1. General remarks

Multiple sclerosis (MS) is the most frequent neurological disease in young adults with a complex and still uncertain pathogenesis. The most widely accepted hypothesis is that auto-reactive T cells and B-cells induce myelin damage, neuroinflammation and neurodegeneration (Compston and Coles, 2008; Fletcher et al., 2010; Trapp and Nave, 2008). However, primary oligodendrocyte dysfunction has also been considered as a potential disease-promoting or disease-triggering factor (Barnett and Prineas, 2004). Whatever the trigger factors for lesion

Abbreviations: APCs, antigen-presenting cells; ARE, antioxidant response element; DMF, dimethyl fumarate; FAEs, fumaric acid esters; GSH, glutathione; HO, heme oxygenase; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; Keap1, Kelch ECH associating protein 1; MDSC, myeloid-derived suppressor cells; MMF, monomethyl fumarate; NQO1, NAD(P)H: quinone oxidoreductase 1; Nrf2, nuclear factor (erythroid-derived 2)-like 2; RNS, reactive nitrogen species; ROS, reactive oxygen species; S1P, sphingosine 1-phosphate; TGF, transforming growth factor; T_h, T helper cell; T_{reg}, regulatory T cell; Trx, thioredoxin.

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formation in MS are, we now know that both, central and peripheral cellular components are critically involved in the disease process. Despite being of unknown etiology, the (histo-) pathological hallmarks of MS lesions are well-defined. They include focal as well as diffuse demyelination, oligodendrocyte loss, activation of brain resident immune cells such as microglia and astrocytes, and damage of the neuro-axonal unit. Such cellular alterations can be found in various brain regions including diverse white and gray matter areas (Bo et al., 2006; Kipp and Amor, 2012). The fast activation of brain intrinsic cells, in particular microglia followed by the activation of astrocytes, is most frequently linked to the expression and release of oxidative-stress related molecules.

In this review article we first give a brief definition of "oxidative stress" and "reactive oxygen species (ROS)" and then describe the pathways and factors involved in this ubiquitous cellular state. Since MS pathogenesis is characterized by the interplay of central and peripheral cellular elements, we then go on to explain how both compartments are regulated by ROS. Finally, we will argue that currently approved treatment options, most importantly Fumaric acid esters (FAEs), interfere with oxidative stress pathways and by this mechanism exert their beneficial function. However, modulation of central and peripheral ROS pathways might result in side effects.

2. Reactive oxygen species and oxidative stress

2.1. Definition of oxidative stress and ROS

Oxygen is pivotal for multicellular life. At the same time, it is one of the most reactive and life-threatening agents known. However, at least for aerobic organisms, oxidation has become the main means of energy generation. To guard against the possible deleterious effects of oxygen, intracellular homeostasis is maintained by a balancing of oxidation and reduction (redox) reactions, the so-called "intracellular redox equilibrium". In extreme cases, when metabolic processes or toxic insults lead to a situation where pro-oxidants outbalance the anti-oxidative counterparts, a state of "oxidative stress" is reached. This breakdown of cellular homeostasis results in oxidation-induced damage to lipids, proteins, carbohydrates and nucleic acids, eventually leading to cell death.

The agents inducing oxidative stress are chemical compounds classed as reactive oxygen species (ROS) or reactive nitrogen species (RNS). ROS/RNS are both instable, and mostly exist in a radical form, which means that they contain unpaired electrons on the outer orbital. The best-studied ROS/RNS include radicals of oxygen [superoxide anion (O_2^-), hydroxyl radicals ($OH^\cdot$), and peroxyradicals ($ROO^\bullet$)] or nitrogen [nitric oxide ($NO^\cdot$)] as well as non-radical species, such as hydrogen peroxide (H_2O_2) and singlet oxygen. Nitric oxide, itself less reactive and generally non-damaging, can rapidly react with a superoxide anion to form peroxinitrate ($ONOO^-$), one of the most deleterious ROS/RNS known. ROS and RNS have long been implicated in the pathogenesis of a plethora of diseases such as stroke, Parkinson's disease or Alzheimer's disease (Lin and Beal, 2006). On the other hand, and this aspect of ROS/RNS has been less well studied, low levels of ROS/RNS can act as second messengers for signal transduction/amplification and fulfill specific intracellular functions (Reth, 2002). Key transcription factors regulated by ROS include p53, AP-1 (c-Jun, c-Fos), NF-κB and, as discussed in this review article, the transcription factor Nrf2.

2.2. Cellular ROS-defense mechanisms

All cells are equipped with an intrinsic mechanism that neutralizes excess ROS and protects against oxidative injury. This so-called oxidative stress response is mainly, but not exclusively, controlled by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Nrf2 plays a vital role in maintaining cellular homeostasis, especially upon exposure of cells to chemical or oxidative stress, through its ability to regulate basal and inducible expression of a multitude of antioxidant proteins, detoxification enzymes and xenobiotic transporters (Kensler et al., 2007). In anti-oxidative stress responses, Nrf2 upregulates phase II detoxifying enzymes and antioxidant proteins. This Nrf2-induced enzymatic machinery includes enzymes mediating glutathione (GSH) synthesis, the thioredoxin (Trx) enzyme system and detoxifying enzymes like heme oxygenases (HO), or NAD(P)H: quinone oxidoreductase 1 (NQO1).

How do these components protect the cell? Reduced GSH acts by scavenging oxidative species such as superoxides, hydroxyl radicals, nitrogens, and ONOO (Forman et al., 2009). The crucial cysteine molecule is the key to the protection afforded by GSH. Its sulfur atom scavenges destructive molecules (peroxides and free radicals) converting them to harmless compounds, such as water. Trx plays an important role in maintaining a reduced environment in the cells through thiol-disulfide exchange reactions and, thus, protects cells and tissues from oxidative stress. NQO and HO are important as catalysts of heme and quinone degradation. Free heme is liberated under oxidative conditions and mediates ROS production. Quinones are highly redox active and also lead to formation of ROS. Since NQO and HO eliminate heme and quinone, they can exert an anti-oxidative function. Besides the induction of anti-oxidative factors, Nrf2 also contributes to different cellular functions such as differentiation, proliferation, inflammation and lipid synthesis, and there is increasing evidence of an association between aberrant expression and/or malfunctioning of Nrf2 and diverse pathologies including cancer, neurodegeneration or cardiovascular disease.

2.3. The Nrf2–Keap1–ARE pathway and its relevance for inflammation and degeneration

Having outlined the protective potential of the transcription-factor Nrf2, we will now describe its mode of action. The Nrf2 cell defense pathway is tightly regulated. Under quiescent conditions, Nrf2 is retained and degraded in the cytosol by Kelch ECH associating protein 1 (Keap1) (Zhang and Hannink, 2003) (Fig. 1). Various stress-associated stimuli, such as oxidative stress, induce conformational changes in Keap1 that result in the release of Nrf2 from its Keap1-binding. Subsequently, Nrf2 trans-locates into the nucleus where it trans-activates the expression of genes containing an antioxidant response element (ARE) in their promoter regions (Kensler et al., 2007). Although it is well established that Nrf2 activity is controlled, in part, by the cytosolic protein Keap1, the nature of this pathway and the

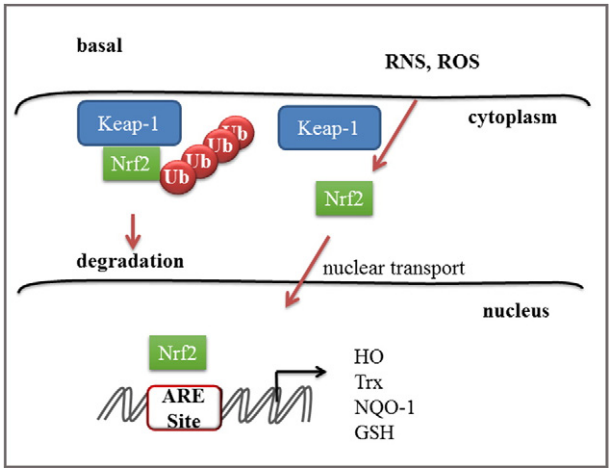

Fig. 1. Scheme of Nrf2 activation. Under basal conditions, Nrf2 interacts with Keap1, which results in degradation of Nrf2. In response to cellular stress, Nrf2 is liberated from its cytosolic inhibitor, trans-locates into the nucleus and binds to antioxidant response elements (AREs) in the promoters of target genes. Nrf2-regulated genes mainly include genes coding for antioxidative and detoxifying enzymes.