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Mitochondrial Biology in Neuro-Autoimmune Disease Pathogenesis

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ABSTRACT

Oxidative stress plays a critical role in many neurodegenerative situations such as Alzheimer's disease, Parkinson's and Huntington's disease. Inflammation and oxidative stress are also supposed to promote tissue damage in multiple sclerosis (MS). Oxidative stress contributes to the cascade, leading to dopamine cell degeneration in Parkinson's disease. However, oxidative stress is closely linked to other components of the degenerative process, such as mitochondrial dysfunction, nitric oxide toxicity and inflammation. Oxidative stress was assessed by approximating lipid peroxidation product in the form of thiobarbituric acid reactive substances, nitric oxide in the form of nitrite & nitrate. In this review we focused the Amiloid beta and Reactive oxygen species (ROS) function as a mitochondrial function in neruo-outoimmunity disease.

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INTRODUCTION

Alzheimer's disease (AD):

AD is an advanced neurodegenerative disease that distresses the hippocampus and cortex. But the details are still unknown, a complex interplay of genetics, environment and aged likely culminate in disease. Although specific mutations involving the beta-amyloid precursor protein have been identified in early-onset familial AD [1-3]. Multiple genes and acquired mutations play an important role. It has been known for decades that apolipoprotein E allele variations are associated with the non-familial late-onset AD. The e4 allele discusses an increased risk whereas the e2 allele reduces the risk. There is growing evidence implicating the complement pathways in the pathogenesis of AD. In AD, the beta-amyloid (Aβ) peptide accrues in extracellular [4-6]. Reactive oxygen ROS are chemically reactive molecules containing oxygen and are produced in all aerobic cells. Oxidative stress happens when the generation of ROS in a system surpasses that system's ability to neutralize and to remove them. All organisms have developed adaptive responses to oxidative stress that involve defensive enzyme and molecular chaperones the expression of both being scored by stress-responsive transcription factors as well as antioxidant molecules [7]. Extreme production of ROS, and the resulting disruption of cellular redox balance, ambitions the oxidation of biological macromolecules, such as DNA, proteins, carbohydrates, and lipids, potentially leading to failure of biological functions [8, 9].

Many ROS possess unpaired electrons and are therefore free radicals. The generation of free radicals is carefully linked with the participation of trace metals, particularly copper and irons [5, 6]. Inside cells, "free pools" of copper and iron are evaded through their effective confiscate by metal-binding proteins [10-12]. The chelatable redox-active iron establishes the so-called labile iron pool (LIP), which serves as a transient source of iron [13-16]. However, whenever cells are exposed to stress conditions, an excess of superoxide anion radical acts as an oxidant of Fe-S clusters of several enzymes, releasing "free iron". The released iron can in turn participate in Fenton type reactions, producing the highly reactive hydroxyl radical [17]. During the oxidative spurt triggered during inflammatory processes, cells of the immune system produce both superoxide anion and nitric oxide (NO) free radicals. Nitric oxide is produced by the NO synthase family of enzymes. NO may directly react with its biological targets, as it is known to regulate the catalytic activity of various enzymes primarily by interacting with Fe-S clusters, oxidized copper centres, heme, and tyrosyl radicals [18]. NO also

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responds with superoxide ion (O 2−) or oxygen to form the nitrogen radical peroxynitrite (ONOO −). Reactive nitrogen species (RNS) are highly reactive towards biological macromolecules and are thought to be responsible for NO-mediated cell death. Mitochondrial dysfunction, which is associated with an accumulation of ROS, performs to play a role in the early events of AD pathology [19-21]. Some mice model studies ahowed that the metabolic changes, including increased fragmentation and decreased fusion, have been observed in the AD brain [22]. Mitochondria are essential for the formation and maintenance of synapses. Oxidation of mitochondrial DNA reduces it more susceptible to somatic mutation as oxidized bases are frequently misread during replication [23]. These mutations may pledge erroneous beta-amyloid processing [24]. The natural function of beta-amyloid may cause the early oxidative stress triggers and pathological lesions. Beta-amyloid peptide can inhibit cytochrome oxidase leading to disruption of the electron transport chain and production of ROS [25].

Parkinson and oxidative stress:

Mitochondrial dysfunction affects diverse cellular processes that can culminate in cell death. Mitochondrial dysfunction affects a number of cellular pathways, leading to damage of intracellular components and to cell death [26-28]. Abnormal metabolic function, abnormal morphology, and impaired fission–fusion balance have all been observed in mitochondria in at least some forms of Parkinson disease. Mitochondria are a major source of free radicals in the cell, resulting in oxidative stress, but mitochondria are also integral to the oxidative stress response. Increased oxidative stress can lead to impaired function of the UPS, thereby further affecting cell survival [29-31]. Mitochondria also sequester calcium when intracellular calcium levels rise during the excitotoxic process. The threshold for excitotoxicity might decrease if mitochondrial ATP production is impaired. Mitochondria also have a pivotal role in apoptotic cell death. Mitochondrial release of cytochrome c and other 'pro-apoptotic factors', such as AIF, into the cytoplasm triggers a cascade of events, culminating in cell death. Products of PD-associated are genes that affect mitochondrial function and oxidative stress [33-36].

Acquired somatic mutations affect mitochondrial electron transport chain function, and such mutations are increased in the substantia nigra in patients with PD. Rare inherited mutations in genes encoding electron transport chain components have been associated with parkinsonism[37]. Parkin, α-synuclein, PINK1, DJ-1, LRRK2 and HTRA2, are all encoded by nuclear genes, mutations in which can lead to PD, and all show a degree of localization to the mitochondria. Parkin is partially localized to the outer mitochondrial membrane, protects against oxidative stress, and has a hypothesized role in mitochondrial biogenesis [38-41]. LRRK2 associates, at least in part, with the outer mitochondrial membrane; its precise function in that location is unclear, but it is thought to interact with Parkin. HTRA2 is a mitochondrial serine protease, the release of which might be involved in apoptotic cell death. PINK1 is a mitochondrial serine–threonine kinase that affords protection against oxidative stress and acts with Parkin to regulate the balance of mitochondrial fission and fusion [42]. DJ-1 is relocated to mitochondria under conditions of oxidative stress and is thought to be neuroprotective under such conditions. The α-synuclein protein has an amino-terminal mitochondrial targeting sequence and, when overexpressed or under conditions of acidification, is at least partially associated with the inner mitochondrial membrane, where it might cause direct damage. High temperature requirement protein A2 (HTRA2; also known as OMI or PARK13) is a mitochondrial serine protease [43]. Mutations in HTRA2 are suggested to be a susceptibility factor for PD. Homozygous HtrA2 knockout mice progress striatal degeneration and parkinsonism 66 in the context of more-widespread neuronal loss. Expression of a mutation that causes the Gly399Ser substitution or a polymorphism that produces an Ala141Ser substitution, both of which have been found in individuals with PD, leads to mitochondrial swelling, decreased mitochondrial membrane potential, and increased risk of staurosporine induced cell death [44-45].

Multiple sclerosis (MS):

Oxidative stress is frequently occupied in the development of brain damage, and ROS contribute to several mechanisms original the pathogenesis of multiple sclerosis (MS) lesions [46]. It has been reported that ROS are produced upon interaction of monocytes with brain endothelium, which leads to tight-junction alterations, cytoskeleton rearrangements, loss of blood-brain barrier integrity, and subsequent extravasation of leukocytes into the CNS [47-48]. Furthermore, infiltrated leukocytes produce higher amounts of ROS, which induce myelin phagocytosis and break down by macrophages. The inflammatory environment in demyelinating lesions may lead to the generation of oxygen and nitrogen free radicals as well as proinflammatory cytokines that in turn exacerbates the inflammatory response. It is clear that during oxidative burst, activated macrophages produce elevated levels of ROS and RNS by up regulation of NADPH oxidase and inducible nitric oxide synthase (iNOS), respectively, producing O and NO radicals [49]. Together, O and NO form the very harmful peroxynitrite (ONOO2-·).

Peroxynitrite decays to yield oxidizing and nitrating species that react in complex ways with different relevant biomolecules. These reactive species not only induce lipid peroxidation and affect DNA or polysaccharide structure, but they also react with cellular proteins by tyrosine nitration [50]. Interestingly, iNOS is up-regulated in MS lesions [51] and in the cerebrospinal fluid of patients with MS. Mechanisms of oxidative

injury and cytoprotection in a demyelinating Central Nervous System (CNS) lesion. Free radicals comprise nitric oxide (NO) and reactive oxygen as well as nitrogen species (Reactive Oxygen Species (ROS) or Reactive Nitrogen Species (RNS), respectively) which are mainly produced by macrophages, microglia and astrocytes. ROS and RNS lead to damage of neurons, axons, myelin and oliogdendrocytes (indicated by arrows). This process also may involve mitochondrial damage. Black squares indicate mitochondria which accumulate in injured axons. The cytoptrotective transcription factor Nrf2 is present in neurons, oligodendrocytes and astrocytes as part of the cellular anti-oxidative response. Abbreviations: OL, oligodendrocyte; MP, myeloperoxidase.

RESULTS AND DISCUSSIONS

Oxidative stress is one of the hallmarks of tissue damage and plays an important role in neurodegenerative disease. In inflammatory diseases such as MS, oxidative stress mainly affects the degenerative phase of the disease which dominates later stages of the disease course. Oxidative damage also provides a good explanation for non-inflammatory aspects of MS pathogenesis. Such a mechanism may explain the preferential destruction of small calibre axons and the demisepredominantly in axons with low mitochondrial content and larger axonal surface area [52]. In summary, highly reactive free radicals seem to be involved in inducing and amplifying tissue injury in the initial stage of MS lesion formation but also during progressive expansion or in diffuse injury of the normal appearing white matter. Although AD and PD have the exact mechanism of disease progression or pathogenesis remains largely unknown. As outlined in this paper, several in vivo and in vitro studies point towards a role of oxidative stress in AD and PD pathogenesis. Nevertheless, whether it is a primary cause or simply a consequence of the neurodegenerative process is still an unanswered question. In addition, specifically concerning AD, there are quite a few contradictory reports regarding the role of oxidative stress in the disease. Indeed, it has been described that oxidative stress may as well lead to an increase in Aβ and in vivo studies showed a negative correlation between oxidative stress and Aβ, indicating an antioxidant role for Aβ.

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