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Editorial

Redox signaling in neurodegeneration

Redox signaling is essential for normal function of cells (Packer and Cadenas, 2011; Butterfield et al., 2012) and often involves transient free radicals or free radical reaction products that bind to and change conformation and function of proteins and lipids (Subramaniam et al., 1997; Dodson et al., 2013). The mechanisms involved in redox signaling, while essential to convert cellular signals into chemical changes, are often quite complex. This complexity contributes to risk that something can (and unfortunately does in certain disorders) go awry, leading to cell death and subsequent disease. Well-known neurological disorders in which free radical damage to proteins, lipids, and nucleic acids exists include, among others, Alzheimer, Parkinson, Huntington diseases, and amyotrophic lateral sclerosis in addition to other neurological and cardiac disorders (Halliwell, 2007; Butterfield et al., 2014a; Sanders and Greenamyre, 2013).

When the redox status of neurons or glia is shifted to a more oxidized state, often the transcription factor Nrf2 is activated and translocated to the nucleus to bind to the antioxidant response element, which leads to the upregulation of Phase II antioxidant enzymes (Halliwell, 2007; Darley-Usmar et al., 1991; Farr et al., 2014). Hydrogen peroxide, cysteine modification by nitric oxide (NO) or oxidation to sulfenic, sulfinic, or sulfonic acids, NO-mediated tyrosine nitration, and insulin binding to its receptor, among other processes, are involved in or are inhibitory toward redox signaling in brain (Haskew-Laytona et al., 2010; Guo et al., 2014; Lipton et al., 1993; Gould et al., 2013; Radi, 2013; Butterfield et al., 2014b). When regulation of such signaling is compromised in the brain, neurodegenerative disorders can result (Packer and Cadenas, 2011; Butterfield et al., 2012).

Redox signaling and metabolism are intricately related in ways not fully understood (Dodson et al., 2013; Winkler and Hirrlinger, in press; Navarro-Yepes et al., 2014). This special issue of *Neurobiology of Disease* presents comprehensive reviews of redox signaling in neurodegeneration and neurodegenerative disorders. New insights into the role of redox signaling in neurodegenerative disorders are given in these outstanding reviews. In addition, two primary data papers are included in this Special Issue.

Alzheimer disease (AD) is a major public health crisis in many developed countries in which there is a large percentage of the elderly in the population, some examples being the USA, Japan, Southeast Asia, and European countries (Boffetta et al., 2014; Wee et al., 2015). AD is characterized pathologically by accumulation of amyloid β-peptide-rich senile plaques, neurofibrillary tangles [composed of aggregated hyperphosphorylated tau], and loss of synapses. A major clinical sign of AD is decreased glucose utilization in temporoparietal and other brain regions (Teune et al., 2014). Type 2 diabetes mellitus (T2DM) is a major risk factor for development of AD, and brains from subjects with AD and T2DM have elevated indices of oxidative and nitrosative stress (Hoyer, 2002; Craft, 2005; de Felice, 2013; de la Monte, 2009; Calvo-Ochoa and Arias, 2015; Butterfield et al., 2014b). Dr. Marsha Cole and her student, Catherine Cobb, focus on lipid peroxidation subsequent to oxidative or nitrosative stress in brain that trigger neuroinflammation secondary to T2DM or abnormal dopamine metabolism (Cobb and Cole, 2015). The authors posit that sustained oxidative and nitrosative stress and consequent neuroinflammation overwhelm cellular defenses leading to neurodegeneration and consequent damage to brain.

Studies of late middle-aged humans showed that insulin resistance predicts brain amyloid deposition (Willette et al., 2015), and Aβ oligomers cause oxidative stress, synaptic dysfunction, and loss of cognition (reviewed in Butterfield et al., 2013). Dr. Ralph Martins and colleagues examine the role of T2DM in neurodegeneration and outline a number of possible mechanisms that could be involved (Verdile et al., 2015). The authors provide strong literature support for the notion of altered redox signaling in neurodegenerative processes. Among these mechanisms might be activation of mTOR signaling downstream from Aβ-induced activation of PI3K/Akt signaling. Our group recently demonstrated altered PI3K/Akt signaling, activation of mTOR, and evidence for insulin resistance in brains form subjects with AD and, for the first time, in brain of subjects with amnestic mild cognitive impairment [MCI], arguably a prodromal stage of AD (Tramutola et al., 2015). Activation of mTOR has several sequelae, two of which relevant to the topic of this special issue are inhibition of autophagy and mTOR kinase-mediated phosphorylation of one of its downstream targets, p70SK6. Phosphorylation of 70SK6 leads this kinase to phosphorylate the insulin receptor substrate-1 [IRS-1] at Ser-307 to inhibit the function of IRS-1 and serve as a primary marker of insulin resistance (Tramutola et al., 2015). The inhibition of autophagy secondary to the crossroads between metabolic dysfunction and activation of mTOR is reviewed in this special issue of *NBD* by Dr. Marzia Perluigi and colleagues (Perluigi et al., 2015). These authors highlight that disturbance in mTOR signaling in brain affects many pathways such as glucose metabolism and subsequent decreased ATP production, mitochondrial dysfunction, altered cell growth, and especially autophagy and suggest that disturbances in mTOR signaling and consequent neurodegeneration lie at the intersection of metabolism and autophagy. In a separate contribution, Drs. Kenneth Hensley and Marni Harris-White also explore the interface between autophagy and redox biology, with emphasis on oxidative stress (Hensley and Harris-White, 2015). These authors suggest that targeting mTOR activation as a therapeutic target may offer new insights into AD pathogenesis. Among such potential therapeutic agents conceivably could be a cell-penetrating ester of the neuronal metabolite, lanthionine ketimine (LKE), which stimulates neuroprotective autophagy. An interesting original research contribution to

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this Special Issue of *Neurobiology of Disease* involving LKE-mediated neuroprotection in models of neurodegenerative disorders is provided by Dr. Hensley and colleagues (Hensley et al., 2015). These scientists show that LKE stimulates autophagy in RG2 glioma and SH-SY5Y neuroblastoma cells as evidenced by increased lipidation of microtubule-associated protein 1 light chain 3 (LC3) both in the absence and presence of bafilomycin-A1. These results discriminate between effects on autophagic flux versus blockage of autophagy clearance. LKE treatment caused changes in protein level or phosphorylation state of multiple autophagy pathway proteins including mTOR, p70S6K, unc-51-like-kinase-1, beclin-1, and LC3 in a manner essentially identical to effects observed after rapamycin treatment, the latter known to inhibit mTOR.

Drs. Barone and Butterfield review the potential involvement of heme oxygenase-1 [HO-1] in T2DM and AD (Barone and Butterfield, 2015). HO-1 and it partner, biliverdin reductase [BVR-A], lead to neuroprotective and antioxidant and anti-nitrosative bilirubin (Maines, 2010; Mancuso and Barone, 2009). Both enzymes are modified in brains of subjects with AD and MCI (Barone et al., 2014) and may contribute to the elevated oxidative stress in both these disorders (Butterfield et al., 2001; Butterfield et al., 2013; Nunomura et al., 2001). This review in this Special Issue compares and contrasts the beneficial aspects of stimulating HO-1 activity on the one hand and the recently posited notion of the potential involvement of HO-1 in insulin resistance, a prominent feature of AD as noted above, on the other hand. Much more research needs to be undertaken to determine whether such a scenario is applicable when HO-1 is oxidatively dysfunctional.

Other putative neuroprotective, redox-related signaling pathways in brain discussed in this Special Issue involve vitamin E- or vitamin D-related pathways. Drs. Lynn Ulatowski and Danny Manor review the role of vitamin E deficiency in neurodegeneration and decrements in normal properties of learning, memory and emotion (Ulatowski and Manor, 2015). These researchers point out that, while cerebellar neurodegeneration is the best-characterized consequence of vitamin E deficiency, recent studies using tocopherol transporter protein [TTP] knockout mice are consonant with the notion of vitamin E playing key roles in brain regions associated with higher cognitive function. Drs. Jeriel Keeney and D. Allan Butterfield critically evaluate the common links of brain modifications in vitamin D deficiency and elevated risk of Alzheimer disease, including altered redox signaling (Keeney and Butterfield, 2015). A growing literature is consistent with low vitamin D levels being correlated with several neurodegenerative disorders, including AD (McCarthy, 2014; Sakurai et al., 2014), though others are more skeptical (Anastasiou et al., 2014). Pathological and biochemical changes in brains of middle-aged to old-aged rats on a low vitamin D diet and associated elevated levels of 3-nitrotyrosine (an index of nitrosative stress) and cognitive impairment were reported recently from our group (Keeney et al., 2013). In the review of this Special Issue of *NBD*, common links to these same alterations in patients or subjects with AD, including some key redox signaling pathways, are discussed. This paper has relevance to the large number of people worldwide, including the USA, who are considerably vitamin D-deficient and conceivably have increased risk of development of AD.

A different process for nitrosative stress in brain other than tyrosine modification is S-nitrosylation, a topic reviewed in an interesting paper by Dr. Stuart Lipton and colleagues (Nakamura et al., 2015). These authors review the important roles played by protein S-nitrosylation in redox signaling mechanisms that modulate a diverse array of physiological processes, such as neuronal survival, synaptic plasticity, and transcriptional regulation. These authors also review how, in contrast, elevated nitrosative stress indexed by elevated S-nitrosylation secondary to aging, neurodegenerative disorders, or environmental factors, can lead to protein misfolding, mitochondrial dysfunction, transcriptional dysregulation, synaptic damage, and neuronal injury. The authors evaluate altered S-nitrosylation in brain of subjects with AD, Parkinson disease, and Huntington disease, with special emphasis on PD.

Dr. Oksana Berezovska and co-workers, in an original research contribution to this Special Issue (Arimon et al., 2015), report the use of a microdialysis method to find that the lipid peroxidation product, HNE, or 4,4′-dithiodipyridine [DTTP] infused into brain led to elevated Aβ42 levels and increased ratio of Aβ42/Aβ40 in the interstitial fluid 6 h after infusion. Pathogenic changes in presenilin-1, part of the γ-secretase complex, as well as to elevated BACE activity secondary to HNE-modification, are demonstrated. Both processes are consistent with elevated Aβ peptide. The authors posit the notion that oxidative stress precedes altered properties of Aβ-generating enzymes. It appears that Aβ, known to lead to elevated HNE in AD brain and in neurons (Markesbery, 1997; Lauderback et al., 2001; Sultana et al., 2013; Mark et al., 1997), can be part of a feed-forward vicious cycle to lead to more Aβ production. Such considerations are of clear importance to AD and redox signaling alterations.

Together, these papers in this special issue of *Neurobiology of Disease* on Redox Signaling in Neurodegeneration convincingly demonstrate that dysfunction of redox signaling pathways is coupled to changes in cellular metabolism, oxidative and nitrosative stress, autophagy, and other altered cellular processes in neurodegenerative disorders. Whether these changes in redox signaling are a cause or effect of these coupled processes and contribute to the pathology and clinical presentation of specific neurodegenerative disorders will require additional studies. This Special Issue of *Neurobiology of Disease* provides an excellent foundation from which these questions can be further investigated. On behalf of all the authors of this Special Issue, I hope you find these papers as interesting as I have.

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