Biological - Framework 8 : Redox dysfunction model for neurodegeneration

Type 4- An EOAD model and an ApoE stratified model of LOAD- Dr. Cruchaga et al

Type 1 - The Brain Signals Distress Long Before It Breaks - Dr. Lado et al.

The brain does not fail abruptly.

It drifts out of balance slowly—and it signals that imbalance long before damage becomes irreversible.

Across disorders such as treatment-resistant depression, Alzheimer's disease, and Parkinson's disease, a common early pattern keeps emerging: oxidative stress. Not simply as cellular damage, but as a signal that the brain is struggling to maintain homeostasis.

When redox balance shifts, microglia remain activated longer than they should. Inflammatory signaling increases. Reactive oxygen and nitrogen species accumulate. Neuronal mitochondria become less efficient, and neuroplasticity quietly declines. Over time, neurons and glial cells reinforce each other's stress, forming a feed-forward loop that becomes increasingly difficult to interrupt.
By the time symptoms are clinically obvious, we are often treating downstream effects—neurotransmitter imbalance, cognitive decline, behavioral change—rather than the process that initiated the disease.

In our recent publication in Frontiers in Aging Neuroscience, we describe how oxidative stress, neuroinflammation, and bioenergetic failure converge into a single systems-level mechanism underlying both neurodegenerative and severe psychiatric illness. This framework aligns with foundational work by Heneka and colleagues on microglial-driven neuroinflammation, as well as Butterfield's work linking oxidative stress to metabolic and mitochondrial dysfunction.

This perspective shifts the clinical goal:

• From symptom suppression to restoring homeostasis
• From late intervention to early detection
• From isolated molecular targets to circuit- and energy-based care

It also raises a deeper question. If oxidative stress is an early signal rather than indiscriminate damage, what if we could intervene without disrupting physiological redox balance?

What if a molecule could act as a selective detector—neutralizing pathological scavenger radicals while preserving normal redox signaling?

I am currently exploring a theoretical small-molecule framework built around this idea. Details remain intentionally undisclosed, but the concept is chemically plausible and, in principle, synthesizable. The challenge is not whether such a molecule can exist—it is whether we move beyond blunt antioxidant strategies and begin designing with redox intelligence.

Progress often begins by listening to the signal—and asking the right question.

Lado, L.A., Misir, A. The Interplay of Homeostasis, Inflammation, and Oxidative Stress in Neurodegenerative Disorders.Frontiers in Aging Neuroscience, Sec. Neuroinflammation and Neuropathy, Vol. 17, 2025. Published January 8, 2026. doi:10.3389/fnagi.2025.1607669
Link to paper

Heneka, M.T., et al. Neuroinflammation in Alzheimer's disease. The Lancet Neurology, 2015.

Butterfield, D.A., Halliwell, B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nature Reviews Neuroscience, 2019.

Homeostatic decompensation mechanisms converge on biological pathways that include:

1. Neuronal excitotoxicity with dysregulation of glutaminergic `and noradrenergic networks that are influenced bt GABA and acetylcholine inhibitory neurons,, resulting in Synaptopathy , Endo-Lysosomal Dysfunction, Ferroptosis, Mitochondrial Dysfunction due to dysfunctional Respirasome with excessive ROS/Oxygen Superoxide Production , and an altered Mitochondrial TCA -Pentose Phosphate Shunt function causing intracellular FADH/FAD, NADH/NAD, and ATP/AMP imbalances, Stressed Cytosolic Mitochondrial DNA released from distressed Mitochondria activates of c-GAS signalling system which activates the senescent transcriptome signature and innate immune cytokine profiles.
2. Over activated Nutrient and Growth Factors induce over activation of mTOR1\mTOR2 which contributes to the aging pathways.
3. TNF alpha is involved as part of the neuroinflammatory response.
4. sEV communications between (neurons, T cells, astrocytes, endothelial cells, muscle cells, liver cells, microglia, OPC-Oligodendrocytes, T/B Cells, Monocytes, and Macrophages) is changed.
5. glucose , lactose, glucosamine, and lipid dyshomeostasis,
6. Chromatin remodeling,
7. RNA splicing alterations due to inherited SNPs, altered circRNA production, Changes in transcription due to type I and III RNA polymerase - resulting in altered ce RNA. RNA binding factors and DNA binding transcription factors are also altered with AD.

8. Alterations are seen in cell type specific
    a. autophagy
    b. mitophagy
    c. Ferroapoptosis and other Apoptosis Molecular Systems,
    d. Key Kinases are involved in controlling many of the pathological processes including GSK-3b,
    e. Inflammasome-NLRP3 hyperactivation occurs from Repetition Recognizing Receptor Systems, and
    f. STRESS Granules form due to Oxidation, Metabolic, and Hormonal Stressors.

    The presence of stress granules in Neurons, OPCs, Microglia, and Astrocytes is one of the earliest visual pathological signs of the disease.

Notes:

1. Cytokine defined Inflammation is paradoxically an initiator, driver, and resilience factor in the disease.
2. Neurotropic viruses and prion proteins play a significant role in subtypes of the disease.