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Mitochondrial Dysfunction, Oxidative Stress and Neuroinflammation in Huntington's Disease

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Abstract: Huntington's disease (HD) is a neurodegenerative disorder that gets worse over time. It's inherited in an autosomal dominant way and is triggered by an expansion of CAG repeats in the HTT gene. This leads to the production of a toxic form of the huntingtin protein, known as mutant huntingtin (mHTT) [1] [2] . Research using experimental models of Huntington's disease has found that issues with how mitochondria regulate calcium can arise pretty early on, sometimes even before we see any obvious behavioral or brain tissue changes. This points to the idea that mitochondrial dysfunction could be a key player in the early stages of the disease's progression [4] , mHTT-driven ROS production and inflammatory signaling actually feed off each other in a two-way relationship [2].

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I. INTRODUCTION TO HUNTINGTON'S DISEASE

Huntington's disease (HD) typically shows up with a combination of motor issues, cognitive decline, and psychiatric problems. The main culprit behind this degeneration is the striatal medium spiny neurons [5], [6]. The mutation involves an expansion of CAG repeats, which leads to an increase in polyglutamine in the huntingtin gene [7], mHTT misfolds, clumps together, and ends up in the nuclei and cytoplasm of neurons [2], [8]. Aggregation relies on both nucleation and the length of poly(Q), leading to the formation of amyloid-like fibrils [9]. The cleavage of proteins, especially at Arg(167), creates N-terminal fragments that play a key role in mediating toxicity. [10]. Further along, a chain reaction of oxidative stress, problems with mitochondria, excitotoxicity, and neuroinflammation leads to the death of neurons. [2], [6].

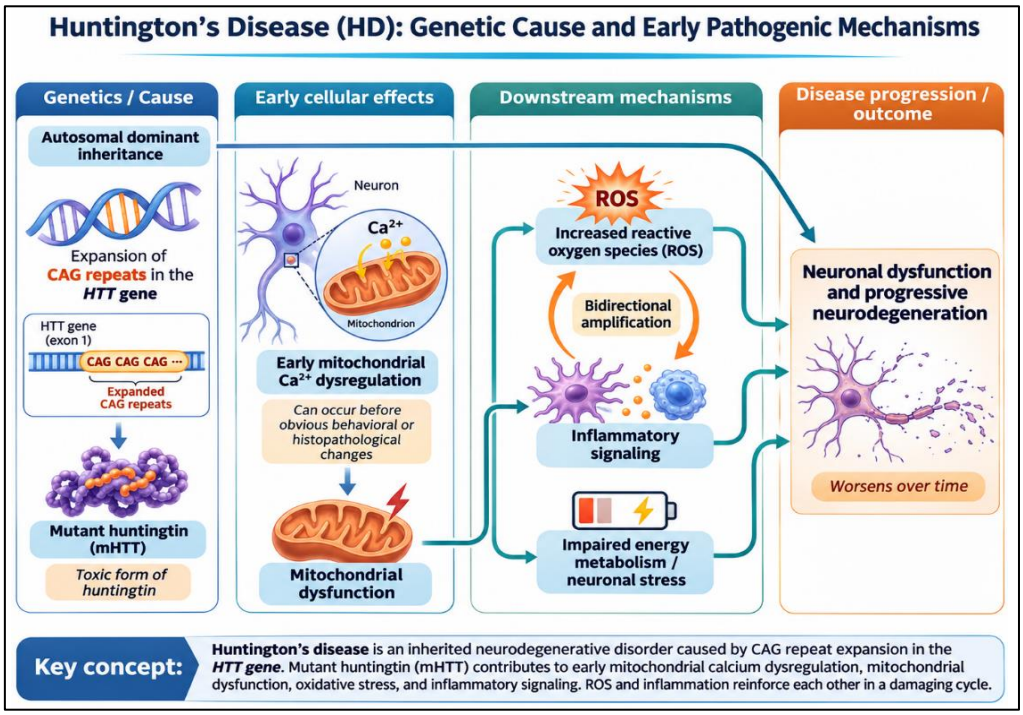


Fig 1 Genetic Basis and Early Pathogenic Mechanisms of Huntington's Disease (HD)

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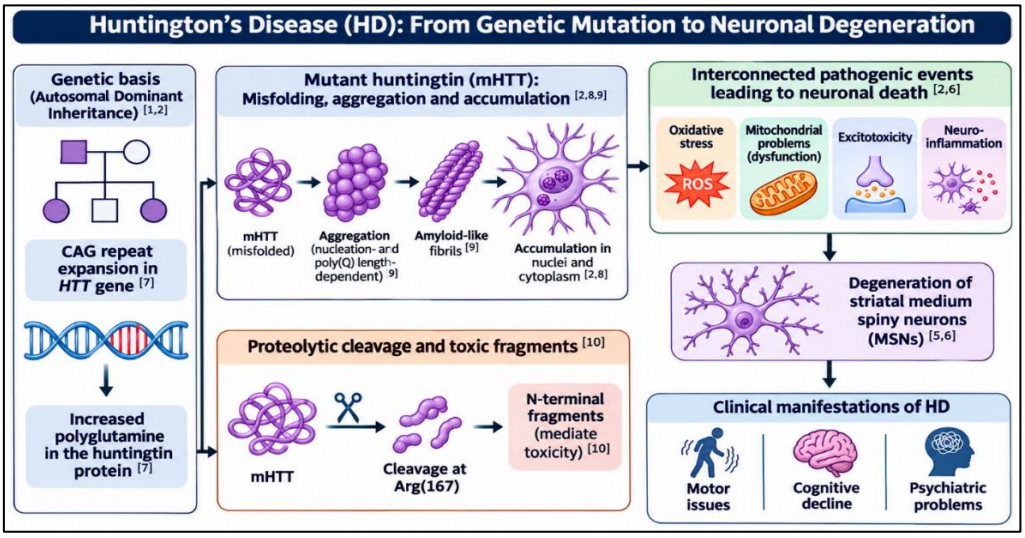


Fig 2 Molecular Mechanisms Underlying Mutant Huntingtin Aggregation and Neuronal Degeneration in Huntington's Disease (HD)

➢ *Mitochondrial Dysfunction*

Mitochondria play a key role in the development of Huntington's disease. Since the brain requires a lot of oxygen, it's particularly susceptible to energy-related issues [1], [6]. The Nature Neuroscience study attached is really key. It shows that lymphoblast mitochondria from patients with Huntington's Disease have a lower membrane potential and start to depolarize with less calcium than those in the control group. Interestingly, this same issue pops up in the brain mitochondria of transgenic mice months before any noticeable pathological or behavioral changes occur [4]. The N-terminal mHTT ends up in the membranes of neuronal mitochondria, and when a long polyglutamine fusion protein is introduced, it mimics the calcium issue seen in healthy mitochondria. This suggests that there's a direct impact on the organelle itself [4].

- mHTT disrupts calcium balance, messes with mitochondrial activity, and compromises mtDNA integrity [1], [11].
- When calcium flows in, it triggers the mPTP to open up, which leads to a drop in ATP levels and the release of cytochrome c [1].
- In HD mice, the activity of Complex IV drops when there's an increase in nitric oxide and superoxide levels [11].
- S-nitrosylation of Drp1 by mHTT boosts fission and fragmentation [11] .

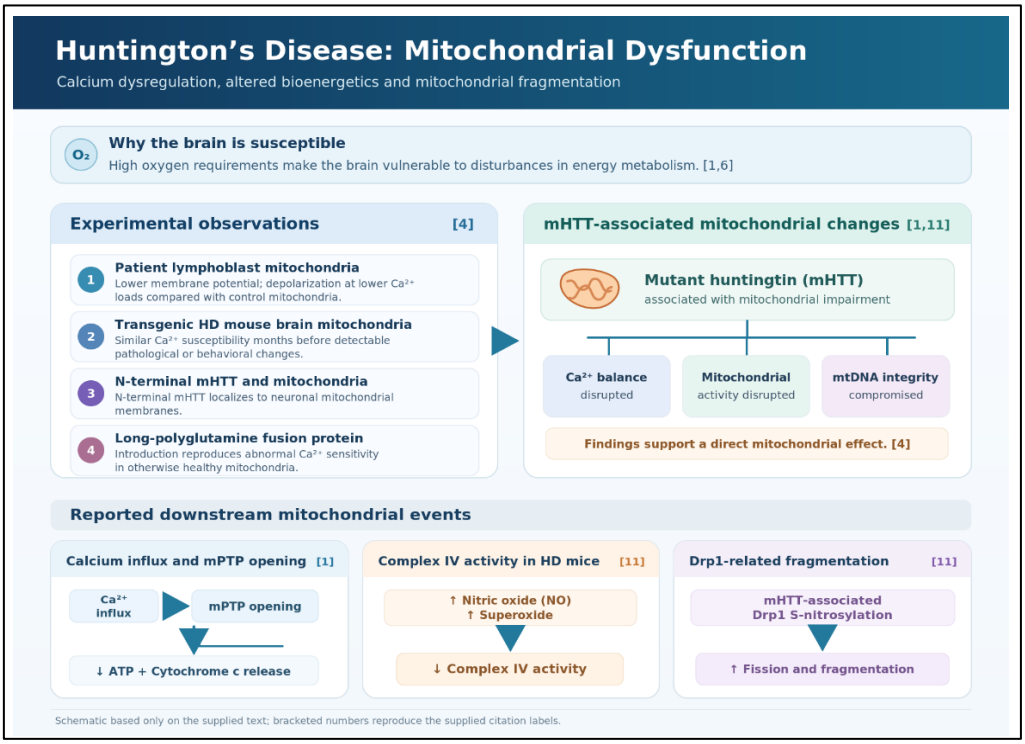


Fig 3 Mitochondrial Dysfunction in Huntington's Disease (HD): Evidence from Patient and Experimental Studies

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➢ *Oxidative Stress and Neuronal Injury*

Mitochondria generate energy, but in the process, some electrons might slip out of the electron transport chain and react with oxygen, leading to the creation of reactive oxygen species (ROS). Usually, our body's antioxidant defense system does a good job of managing these reactive molecules. But if there's too much ROS or if our antioxidant protection isn't up to par, it can result in oxidative stress, which can harm cellular components [1]. In HD mice, we can actually spot protein carbonylation, and it turns out that both VDAC1 and Hsp90 are getting oxidized. Plus, reactive oxygen species (ROS) are causing some damage to mitochondrial DNA [11]. Oxidative stress seems to play a role early on, acting as a key factor instead of just being a later result [2].

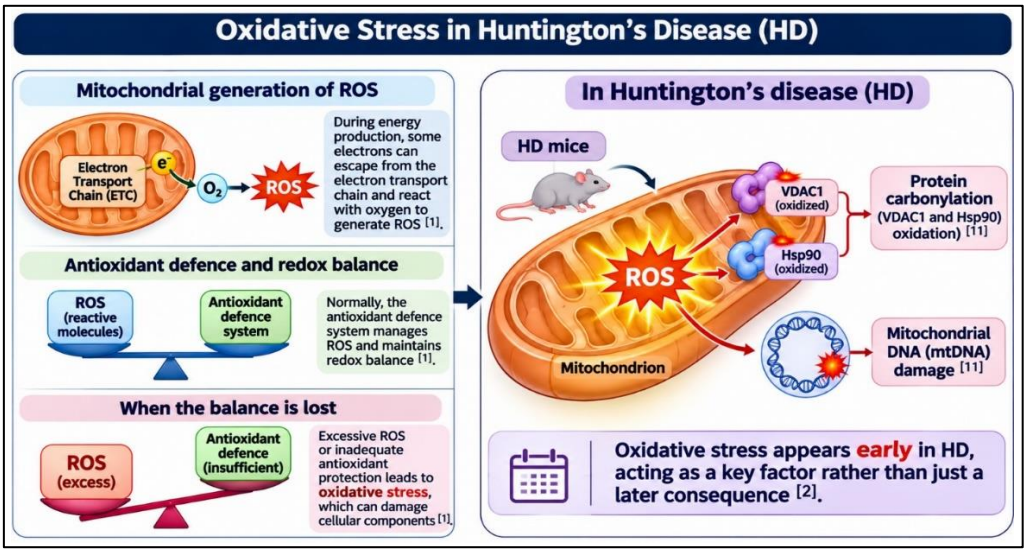


Fig 4 Role of Oxidative Stress in the Pathogenesis of Huntington's Disease (HD)

➢ *Neuroinflammation and Immune Activation*

Mitochondrial ROS signals to astrocytes and microglia, which then kick off the release of pro-inflammatory cytokines and Toll-like receptor proteins. This, in turn, boosts both ROS levels and calcium influx [1]. In a rat model using 3-nitropropionic acid (3NP), oxidative stress kicked off the activation of NF-κB p65. This activation in microglia and astrocytes then leads to an increase in TNF-α, IL-1β, IL-6, reactive oxygen species (ROS), and excitotoxins [12]. In a 3-NP-induced experimental model, researchers discovered that parthenolide can help lessen inflammation and reduce microglial activation. Plus, it seems to encourage changes in astrocytes that might actually shield neurons from potential harm [12]. Barbigerone lowered pro-inflammatory cytokines and also cut down on oxidative markers in that model [6]. Before neurodegeneration kicks in, there's a decline in astrocytic glutamate uptake due to reduced GLT1. This connection suggests that issues with glial cells might be tied to excitotoxicity [7].

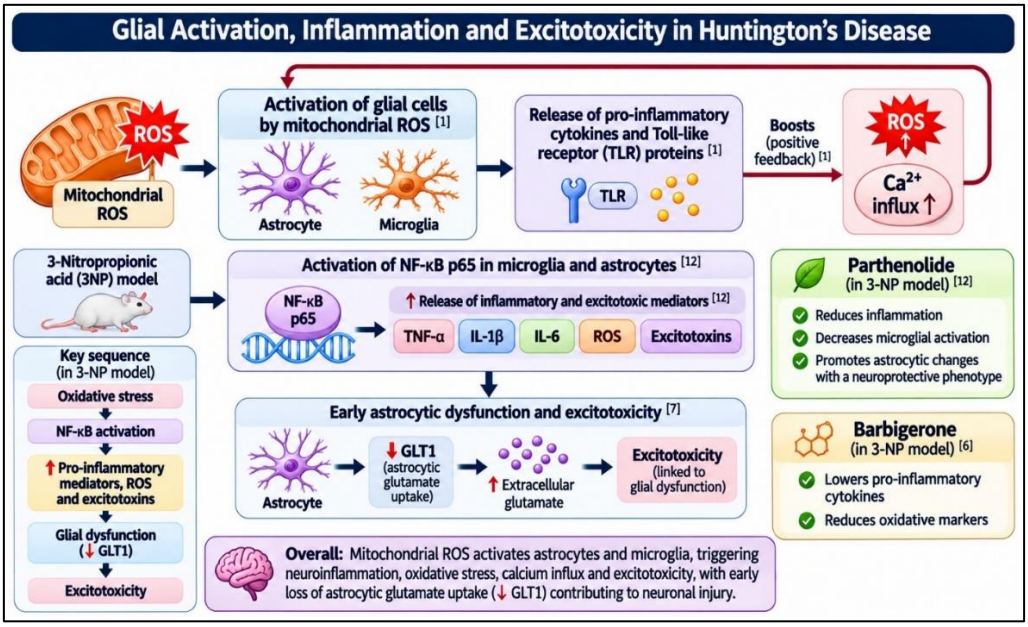


Fig 5 Interrelationship Between Mitochondrial Oxidative Stress, Glial Activation, Neuroinflammation, and Excitotoxicity in Huntington's Disease (HD)

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➢ *Interconnection Between these Mechanisms*

These three processes create a self-reinforcing loop. Pro-inflammatory cytokines ramp up ROS production through NADPH oxidase and inducible nitric oxide synthase, which in turn keeps stimulating the microglia due to oxidative damage—it's really a back-and-forth interaction [2]. Nrf2 signaling plays a key role in connecting redox reactions and inflammation. The Nrf2 and NF-κB pathways are tightly intertwined and can impact each other's functions. When Nrf2 is activated, it boosts the cell's antioxidant defenses and helps manage inflammation. On the flip side, if there's an imbalance between oxidants and antioxidants, it can ramp up NF-κB activity, which might trigger a more intense inflammatory response [12]. Excitotoxicity plays a role here as well. In the striatum of HD mice, there's an increase in extrasynaptic NMDAR activity, which hinges on the cleavage of mHTT by caspase-6. Interestingly, memantine has been shown to reverse these deficits [13]. In living organisms, having too much NR2B actually makes striatal degeneration worse in Hdh(CAG)150 mice [5]. When the recognition of autophagy cargo is impaired, it makes it even harder for mHTT to be cleared away [14].

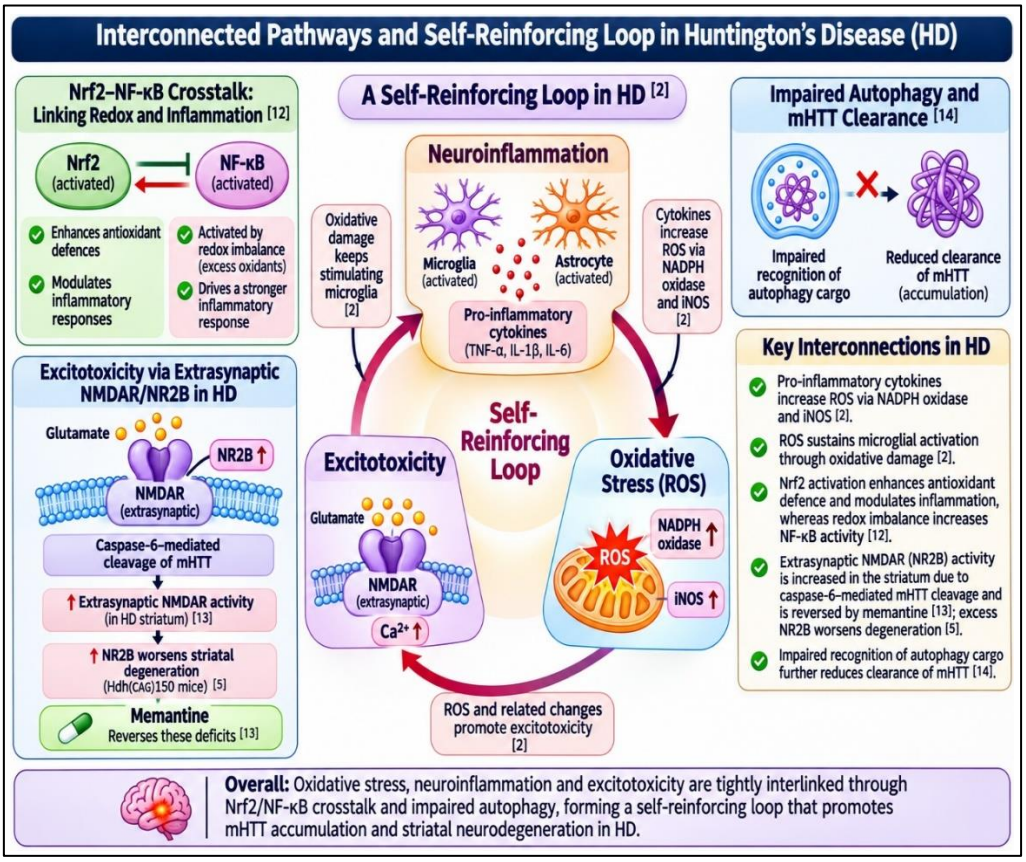


Fig 6 Interconnected Mechanisms of Oxidative Stress, Neuroinflammation, Excitotoxicity, and Impaired Autophagy in Huntington's Disease (HD)

➢ *Emerging Neuroprotective Strategies*

Therapeutic approaches focus on each part of the loop. For mitochondrial-targeted strategies, options like MitoQ, coenzyme Q10, and NAD precursors are available [3], together with calcium modulators and agents that boost mitochondrial dynamics [1]. The IGF-1/Akt pathway helps to prevent neuronal death caused by mHTT, and for that to happen, huntingtin needs to be phosphorylated by Akt first [15]. Immunomodulatory treatments feature options like anti-TNF-α antibodies and fingolimod [2]. Phytochemicals like Aegle marmelos help activate Nrf2/ARE, while also blocking NF-κB. On top of that, they support mitochondrial biogenesis through PGC-1α [2]. Gene editing and stem cell techniques provide tailored solutions for individuals [1].

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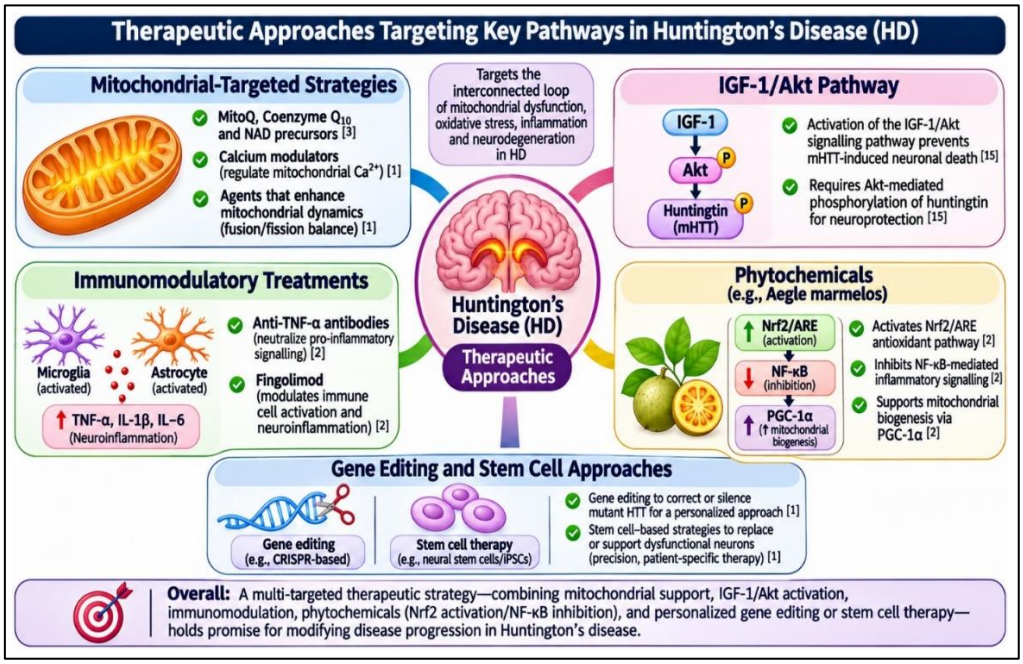


Fig 7 Therapeutic Strategies Targeting Mitochondrial Dysfunction, Neuroinflammation, and Neuroprotective Signaling Pathways in Huntington's Disease (HD)

➢ *Challenges and Future Perspectives*

Translating findings into real-world applications is still a tough challenge. Many antioxidant molecules that looked good in early studies haven't made it through clinical trials [11]. NMDARs aren't the best targets because they play crucial roles in our body. This suggests we probably need really selective NR2B antagonists to make any progress [5], [13]. Somatic CAG expansion modifiers like FAN1 and MLH1 point to a unique pathway for disease modification [16]. We really need to focus on creating standardized formulations, optimizing pharmacokinetics, and validating biomarkers [2].

II. CONCLUSION

Mitochondrial dysfunction, oxidative stress, and neuroinflammation in Huntington's disease aren't just separate issues; they actually form an interconnected network. In this setup, mHTT directly disrupts how mitochondria manage calcium. At the same time, reactive oxygen species (ROS) can trigger inflammatory signals, and then inflammation, in turn, messes with redox balance [2], [4]. Multi-target strategies like mitochondrial antioxidants, Nrf2 activators, inflammasome inhibitors, and selective NMDAR modulators seem really promising. Still, the big hurdle is figuring out how to translate these findings into clinical practice [3], [11].

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