Huntington’s Disease

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Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by pathogenic expansions of the triplet cytosine-adenosine-guanosine (CAG) within the Huntingtin gene. These expansions lead to a prolongation of the poly-glutamine stretch at the N-terminus of Huntingtin causing protein misfolding and aggregation. Huntingtin and its pathological variants are widely expressed, but the central nervous system is mainly a ected, as proved by the wide spectrum of neurological symptoms, including behavioral anomalies, cognitive decline and motor disorders.

Other hallmarks of HD are loss of body weight and muscle atrophy. This review highlights some key elements that likely provide a major contribution to muscle atrophy, namely, alteration of the transcriptional processes, mitochondrial dysfunction, which is strictly correlated to loss of energy homeostasis, inflammation, apoptosis and defects in the processes responsible for the protein quality control. The improvement of muscular symptoms has proven to slow the disease progression and extend the life span of animal models of HD, underlining the importance of a deep comprehension of the molecular mechanisms driving deterioration of muscular tissue.

Keywords: Huntington disease ; skeletal muscle ; neurolodegenerative disease

1. Introduction

Huntington’s disease (HD) is a neurodegenerative pathology, caused by defects of the IT-15 gene encoding Huntingtin protein, a large 348 kDa protein predicted to form an elongated and flexible superhelix [1]. At its N-terminus, Huntingtin harbors an expandable poly-glutamines (polyQ) stretch, starting at amino acid 18, followed by a proline-rich domain. Huntingtin is conserved between Drosophila and mammals, but the number of glutamines increases with the evolution, with the longest known polyQ tract found in humans [2]. The proline-rich domain is found only in mammalian Huntingtin and it is crucial for the interactions with proteins containing homology region 3 (SH3) or tryptophane (WW) domains [2]. All Huntingtin orthologs contain HEAT repeats located downstream of the proline-rich domain. HEAT repeats (named according to four proteins in which they were first detected: Huntingtin, Elongation factor 3, regulatory A subunit of protein phosphatase 2A and TOR1) are formed by 40 amino acids that occur multiple times along the length of the protein and mediate protein-protein interaction [2]. Huntingtin is essential for murine embryogenesis [3][4][5] and interacts with an ever growing number of protein partners (to date they are more than 400) [6][7], being involved in many biological functions, including regulation of gene transcription, RNA splicing, protein degradation and vesicle transport [8].

HD is due to expansion of the triplet cytosine-adenosine-guanosine (CAG) within the exon 1 of the IT-15 gene generating an aberrant prolongation of the polyQ stretch [9]. Many studies reported that the CAG repeats length is inversely related to the age of HD onset [10][11]. Healthy subjects have fewer than 35 CAG repeats, with a number of CAG repeats usually comprised between 17 and 20 [12]; individuals with a number of CAG repeats comprised between 36 and 40 manifest the first symptoms in the fourth decade of life, while CAG repeats greater than 60 are associated to juvenile forms of HD [13]. The abnormal length of the polyQ stretch causes protein misfolding and aggregation, leading to alterations in the many protein-protein interaction networks in which Huntingtin is involved and a toxic gain-of-function [14][15]. Whether the toxicity of mutant Huntingtin is due to its aggregates or its soluble oligomers remains a matter of debate, since it has been proposed that mutant Huntingtin aggregates play a protective role, by removing the soluble oligomeric forms that represent the toxic species [16]. In any case, the formation of mutant Huntingtin containing aggregates is correlated with disease progression. In addition, mutant Huntingtin is particularly exposed to the activity of many proteases that generate proteolytic fragments with increased toxicity [17][18][19][20]. The enhanced proteolysis observed in HD is crucial for the pathogenesis and leads to the generation and accumulation of intracellular small toxic N-terminal fragments containing the polyQ stretch [21][22].

Typical symptoms of HD include psychiatric disorders, behavioral anomalies, cognitive decline and motor dysfunction, such as involuntary muscle contractions that cause irregular jerky movements (chorea), slow movements (bradykinesia), postural abnormalities (dystonia) and muscle rigidity [13][23][24].

When HD was identified, it was thought to be a neuronal pathology involving the central nervous system, but it soon became evident that it involves also peripheral tissues, although at different extents. Indeed, Huntingtin is widely expressed in neuronal cells, but also in many peripheral tissues, like heart, skeletal muscle, kidney, and liver, where its abundancy is comparable to that of the brain [25][26][27][28][29][30]. Dysfunction of peripheral cells also occurs when they are isolated in vitro suggesting that the pathogenesis of HD in peripheral tissues may be independent of the central nervous system. In fact, it has been shown that the same pathways that lead to neurodegeneration are also active in myoblast and blood cells cultures from HD patients and the peripheral manifestations of HD are thought to be a contributor to its morbidity and mortality [31][32]. Among peripheral tissues, skeletal muscle is heavily involved, as can be deduced by relevant clinical evidences displayed by HD patients and animal models of HD (Table 1) that experience muscular weakness [33][34] and progressive muscular wasting [35][36], which are not necessarily associated with alterations in brain functions [37][38].

The synoptic diagram is reported in Figure 1.

Figure 1. The scheme represents the main mechanisms contributing to muscle weakness and atrophy in HD and their interconnections. Dotted lines represent putative connections. **Htt**, Huntingtin. Created with BioRender.com.

2. Therapies for HD Treatment

A vast number of drugs is currently under study for treatment of different symptoms of HD, as reviewed in many worthy articles [39][40]. Inhibition of the myostatin/activin A signaling, by injecting in R6/2 mice a soluble inactive form of the activin type IIB receptor, which competes with the natural receptor for circulating agonists, restored the normal fiber diameter, muscular mass, contractile functions and number of motor units at the wild-type levels [41]. Myostatin is a secreted growth factor, belonging to the transforming growth factor β super family that modulates muscle size, through its binding to the activin type IIB receptor, and deletion of its gene leads to muscular hypertrophy [42][43]. Interestingly, the rescue of the normal phenotype occurred without reducing nuclear aggregates, but rather increasing the percentage of nuclei containing Huntingtin aggregates that were increased in size [41]. Probably, inhibition of the myostatin/activin A signaling re-activated some transcriptional patterns, compensating for transcriptional dysfunctions linked to the presence of mutant Huntingtin and preventing the continuous replenishing of damaged muscle fibers with new centrally nucleated satellite cells, in which the formation of Huntingtin aggregates has not yet occurred [41]. This supports the view that the soluble forms of the mutant Huntingtin would be more harmful than its aggregates.

Many drugs targeting oxidative stress and mitochondrial dysfunctions have shown to ameliorate HD symptomatology [44]. For example, treating R6/2 mice with bezafibrate, an agonist of PPARs, restored the mRNA levels of PGC-1α. This brought about various beneficial effects, such as an improvement of mitochondrial shape and alignment, an appropriate redistribution of type I and type II muscle fibers, an increased muscular strength and performances and an extension of the life span [45]. Coenzyme Q10, a component of the electron transport chain, raised an initial enthusiasm for its ability to alleviate muscle dysfunction by promoting aerobic respiration and scavenging toxic reactive oxidative species [46][47][48]. Unfortunately, further large-scale studies, carried out on HD patients [49] and HD mouse models [50], demonstrated that coenzyme Q10 does not provide significant benefits in HD. Furthermore, creatine and eicosapentaenoic acid improved muscle performances by reducing mitochondrial damages in HD patients, but failed to rescue neuromuscular and cognitive functions [51][52]. Molecules aimed at reducing inflammation attracted a lot of interest, such as Laquinimod that plays an immunomodulatory role [53] and improved motor function and striatal neuropathology in R6/2 HD mice [54].

Antibody blockage of Semaphorin 4D, a transmembrane signaling protein that acts as immunomodulatory agent, displayed beneficial effects on YAC128 HD mice [55]. Molecules that inhibit TNF-α signaling have been also considered for their anti-inflammatory effects, but they exhibited limited ability to alleviate HD symptoms [56]. Currently, only two drugs achieved approval for treatment of HD, namely, the Tetrabenazine and its deuterated variant Deutetrabenazine, which showed better tolerability. These two molecules block the dopamine pathway by inhibiting vesicular monoamine transporter (VMAT) type 2. However, the therapeutic relevance of these two drugs is limited to the treatment of chorea and other motor dysfunction, as they are not able to block or slow down the HD progression [57][58][59][60]. It is now clear that the only therapeutic strategies that could really block the HD progression must be aimed at eliminating or at least reducing the levels of mutant Huntingtin. Indeed, drugs that facilitate the removal of the mutant Huntingtin misfolded variants, by promoting proteasome activity and macroautophagy, showed beneficial effects [61]. The efficacy of a vaccination based on the immunogenicity of three non-overlapping peptides identified within the amino acid sequence of the Huntingtin exon 1 was tested in preliminary studies [62][63]. Reduction of mutant Huntingtin aggregation and toxicity was also observed in cell culture and animal models of HD treated with different recombinant antibodies directed against Huntingtin [56]. Inhibition of Huntingtin mRNA translation has been successfully obtained with non-coding RNAs, such as small interfering RNAs, short hairpin RNAs, microRNAs, as well as with small molecules, such as coumarin derivatives [64]. Further therapeutic approaches likely to be developed in the next future are based on the CRISPR/Cas9 gene editing that could be employed to excise the abnormal CAG repeats or to introduce missense mutations, in order to render mutant Huntingtin innocuous [64].

At this time, the most promising therapeutic application is based on antisense oligonucleotides (ASOs) that are short single-stranded synthetic DNA oligomers composed of 8–50 nucleotides that bind mRNAs through Watson–Crick base pairing. The DNA-RNA double strands meet three different fates: degradation by endogenous enzymes, such as ribonuclease H, inhibition of mRNA translation or modulation of mRNA splicing [65]. For HD treatment, two categories of ASOs were developed, one that targets both, wild-type and mutant Huntingtin mRNAs, and the other that selectively targets mutant Huntingtin mRNA. This latter offers the advantage of maintaining adequate levels of wild-type Huntingtin that are needed for many cellular functions [64][66]. Therapeutic agents targeting RNA or DNA must be delivered to the cells, a particularly challenging task, especially for the central nervous system that can be reached by crossing the blood-brain barrier. From this point of view, skeletal muscle represents a more accessible tissue that can be targeted by any kind of drugs more easily. As a matter of fact, different studies demonstrated that rescue of the muscular function may mitigate the effects of a systemic disease, such as HD, even if the underlying molecular mechanisms of the disease are not targeted [41][45]. This can be explained considering that muscle releases myokines that produce beneficial effects for many organs, including the brain, and therefore, its correct function may have positive widespread repercussions.

3. Conclusions

The high expression levels of Huntingtin in skeletal muscle render this tissue heavily involved in the pathophysiology of the HD. The occurring of soluble and non-soluble oligomeric forms of mutant Huntingtin causes mitochondrial dysfunction, related to loss of energy homeostasis, oxidative stress, inflammation and apoptosis. In addition, it probably impairs the effciency of the protein quality control systems, such as ubiquitin-proteasome system and macroautophagy, further exacerbating damages driven by the accumulation of mutated Huntingtin aggregates (see Figure 1). Mutant Huntingtin promotes these pathologic events by triggering a profound alteration of the transcriptome, which has widespread repercussions. Moreover, it is very likely that the mutant Huntingtin establishes aberrant interactions with mitochondria, autophagosome and proteasome, altering their physiologic functions, as demonstrated in other tissues. Very few studies have been focused on defects of the protein quality control systems in HD skeletal muscle, but there are many clues suggesting that impairment of these processes may play an important role in muscle dysfunction, so that it would be very useful to investigate this aspect further. In the light of these considerations, preventing the accumulation of misfolded forms of mutant Huntingtin, by stimulating macroautophagy and/or proteasome-driven protein degradation, could represent a rational therapeutic approach.

Interestingly, many pathologic events occurring in HD skeletal muscle, such as mitochondrial dysfunction, oxidative stress, inflammation and reduced eciency of the protein quality control systems, also characterize the natural aging process, leading to loss of muscle mass and strength, called sarcopenia. From this point of view, the HD muscle phenotype resembles that of a precociously aged muscle. This suggests that some therapeutic interventions that are beneficial for sarcopenia can be introduced in the treatment of HD.

There are two still open issues: the first one is whether muscle dysfunction is a primary defect, or a consequence of nerve degeneration. The second one is the reason for which the detrimental effects driven by the expression of mutant Huntingtin are more severe for some organs than others, although Huntingtin and its pathological variants are expressed

at similar levels in many organs, such as liver, lung, kidney, testis, beside brain and skeletal muscle. Further studies are needed to obtain a deeper comprehension of these aspects.

References

1. Li, W.; Serpell, L.C.; Carter, W.J.; Rubinsztein, D.C.; Huntington, J.A. Expression and characterization of full-length human huntingtin, an elongated HEAT repeat protein. J. Biol. Chem. 2006, 281, 15916–15922.
2. Tartari, M.; Gissi, C.; Lo Sardo, V.; Zuccato, C.; Picardi, E.; Pesole, G.; Cattaneo, E. Phylogenetic comparison of huntingtin homologues reveals the appearance of a primitive PolyQ in sea urchin. Mol. Biol. Evol. 2008, 25, 330–338.
3. Duyao, M.P.; Auerbach, A.B.; Ryan, A.; Persichetti, F.; Barnes, G.T.; McNeil, S.M.; Ge, P.; Vonsattel, J.P.; Gusella, J.F.; Joyner, A.L.; et al. Inactivation of the mouse Huntington's disease gene homolog Hdh. Science 1995, 269, 407–410.
4. Nasir, J.; Floresco, S.B.; O'Kusky, J.R.; Diewert, V.M.; Richman, J.M.; Zeisler, J.; Borowski, A.; Marth, J.D.; Phillips, A.G.; Hayden, M.R. Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. Cell 1995, 81, 811–823.
5. Zeitlin, S.; Liu, J.P.; Chapman, D.L.; Papaioannou, V.E.; Efstratiadis, A. Increased apoptosis and early embryonic lethality in mice nullizygous for the huntington's disease gene homologue. Nat. Genet. 1995, 11, 155–163.
6. Shirasaki, D.I.; Greiner, E.R.; Al-Ramahi, I.; Gray, M.; Boontheung, P.; Geschwind, D.H.; Botas, J.; Coppola, G.; Horvath, S.; Loo, J.A.; et al. Network organization of the huntingtin proteomic interactome in mammalian brain. Neuron 2012, 75, 41–57.
7. Langfelder, P.; Cantle, J.P.; Chatzopoulou, D.; Wang, N.; Gao, F.; Al-Ramahi, I.; Lu, X.H.; Ramos, E.M.; El-Zein, K.; Zhao, Y.; et al. Integrated genomics and proteomics define huntingtin cag length-dependent networks in mice. Nat. Neurosci. 2016, 19, 623–633.
8. Saudou, F.; Humbert, S. The biology of Huntingtin. Neuron 2016, 89, 910–926.
9. MacDonald, M.E.; Barnes, G.; Srinidhi, J.; Duyao, M.P.; Ambrose, C.M.; Myers, R.H.; Gray, J.; Conneally, P.M.; Young, A.; Penney, J.; et al. Gametic but not somatic instability of CAG repeat length in Huntington's disease. J. Med. Genet. 1993, 30, 982–986.
10. Gusella, J.F.; MacDonald, M.E. Molecular genetics: Unmasking polyglutamine triggers in neurodegenerative disease. Nat. Rev. Neurosci. 2000, 1, 109–115.
11. Orr, H.T.; Zoghbi, H.Y. Trinucleotide repeat disorders. Annu. Rev. Neurosci. 2007, 30, 575–621.
12. Kremer, B.; Goldberg, P.; Andrew, S.E.; Theilmann, J.; Telenius, H.; Zeisler, J.; Squitieri, F.; Lin, B.; Bassett, A.; Almqvist, E.; et al. A worldwide study of the Huntington's disease mutation: The sensitivity and specificity of measuring CAG repeats. N. Engl. J. Med. 1994, 330, 1401–1406.
13. Ross, C.A.; Aylward, E.H.; Wild, E.J.; Langbehn, D.R.; Long, J.D.; Warner, J.H.; Scahill, R.I.; Leavitt, B.R.; Stout, J.C.; Paulsen, J.S.; et al. Huntington disease: Natural history, biomarkers and prospects for therapeutics. Nat. Rev. Neurol. 2014, 10, 204–216.
14. Lieberman, A.P.; Shakkottai, V.G.; Albin, R.L. Polyglutamine repeats in neurodegenerative diseases. Annu. Rev. Pathol. Mech. Dis. 2019, 14, 1–27.
15. Wanker, E.E.; Ast, A.; Schindler, F.; Trepte, P.; Schnoegl, S. The pathobiology of perturbed mutant huntingtin protein–protein interactions in Huntington's disease. J. Neurochem. 2019, 151, 507–519.
16. Arrasate, M.; Mitra, S.; Schweitzer, E.S.; Segal, M.R.; Finkbeiner, S. Inclusion body formation reduces levels of mutant Huntingtin and the risk of neuronal death. Nature 2004, 431, 805–810.
17. Mende-Mueller, L.M.; Toneff, T.; Hwang, S.R.; Chesselet, M.F.; Hook, V.Y.H. Tissue-specific proteolysis of Huntingtin (Htt) in human brain: Evidence of enhanced levels of N-and C-terminal Htt fragments in Huntington's disease striatum. J. Neurosci. 2001, 21, 1830–1837.
18. Wellington, C.L.; Ellerby, L.M.; Gutekunst, C.A.; Rogers, D.; Warby, S.; Graham, R.K.; Loubser, O.; Van Raamsdonk, J.; Singaraja, R.; Yang, Y.Z.; et al. Caspase cleavage of mutant Huntingtin precedes neurodegeneration in Huntington's disease. J. Neurosci. 2002, 22, 7862–7872.
19. Wang, C.E.; Tydlacka, S.; Orr, A.L.; Yang, S.H.; Graham, R.K.; Hayden, M.R.; Li, S.; Chan, A.W.S.; Li, X.J. Accumulation of N-terminal mutant huntingtin in mouse and monkey models implicated as a pathogenic mechanism in huntington's disease. Hum. Mol. Genet. 2008, 17, 2738–2751.

20. Miller, J.P.; Holcomb, J.; Al-Ramahi, I.; de Haro, M.; Gafni, J.; Zhang, N.; Kim, E.; Sanhueza, M.; Torcassi, C.; Kwak, S.; et al. Matrix metalloproteinases are modifiers of huntingtin proteolysis and toxicity in huntington's disease. Neuron 2010, 67, 199–212.

21. Steffan, J.S.; Kazantsev, A.; Spasic-Boskovic, O.; Greenwald, M.; Zhu, Y.Z.; Gohler, H.; Wanker, E.E.; Bates, G.P.; Housman, D.E.; Thompson, L.M. The huntington's disease protein interacts with P53 and CREB-binding protein and represses transcription. Proc. Natl. Acad. Sci. USA 2000, 97, 6763–6768.

22. Warby, S.C.; Doty, C.N.; Graham, R.K.; Carroll, J.B.; Yang, Y.Z.; Singaraja, R.R.; Overall, C.M.; Hayden, M.R. Activated caspase-6 and caspase-6-cleaved fragments of huntingtin specifically colocalize in the nucleus. Hum. Mol. Genet. 2008, 17, 2390–2404.

23. Vonsattel, J.P.G.; DiFiglia, M. Huntington disease. J. Neuropathol. Exp. Neurol. 1998, 57, 369–384.

24. Cruickshank, T.; Reyes, A.; Peñailillo, L.; Thompson, J.; Ziman, M. Factors that contribute to balance and mobility impairments in individuals with Huntington's disease. Basal Ganglia 2014, 4, 67–70.

25. Strong, T.V.; Tagle, D.A.; Valdes, J.M.; Elmer, L.W.; Boehm, K.; Swaroop, M.; Kaatz, K.W.; Collins, F.S.; Albin, R.L. Widespread expression of the human and rat Huntington's disease gene in brain and nonneural tissues. Nat. Genet. 1993, 5, 259–265.

26. Sharp, A.H.; Loev, S.J.; Schilling, G.; Li, S.H.; Li, X.J.; Bao, J.; Wagster, M.V.; Kotzuk, J.A.; Steiner, J.P.; Lo, A.; et al. Widespread expression of Huntington's disease gene (IT15) protein product. Neuron 1995, 14, 1065–1074.

27. Trottier, Y.; Devys, D.; Imbert, G.; Saudou, F.; An, I.; Lutz, Y.; Weber, C.; Agid, Y.; Hirsch, E.C.; Mandel, J.L. Cellular localization of the Huntington's disease protein and discrimination of the normal and mutated form. Nat. Genet. 1995, 10, 104–110.

28. Sathasivam, K.; Hobbs, C.; Turmaine, M.; Mangiarini, L.; Mahal, A.; Bertaux, F.; Wanker, E.E.; Doherty, P.; Davies, S.W.; Bates, G.P. Formation of polyglutamine inclusions in non-CNS tissue. Hum. Mol. Genet. 1999, 8, 813–822.

29. Luthi-Carter, R.; Hanson, S.A.; Strand, A.D.; Bergstrom, D.A.; Chun, W.; Peters, N.L.; Woods, A.M.; Chan, E.Y.; Kooperberg, C.; Krainc, D.; et al. Dysregulation of gene expression in the R6/2 model of polyglutamine disease: Parallel changes in muscle and brain. Hum. Mol. Genet. 2002, 11, 1911–1926.

30. Sassone, J.; Colciago, C.; Cislaghi, G.; Silani, V.; Ciammola, A. Huntington's disease: The current state of research with peripheral tissues. Exp. Neurol. 2009, 219, 385–397.

31. Ciammola, A.; Sassone, J.; Alberti, L.; Meola, G.; Mancinelli, E.; Russo, M.A.; Squitieri, F.; Silani, V. Increased apoptosis, huntingtin inclusions and altered differentiation in muscle cell cultures from Huntington's disease subjects. Cell Death Differ. 2006, 13, 2068–2078.

32. Almeida, S.; Sarmento-Ribeiro, A.B.; Januário, C.; Rego, A.C.; Oliveira, C.R. Evidence of apoptosis and mitochondrial abnormalities in peripheral blood cells of Huntington's disease patients. Biochem. Biophys. Res. Commun. 2008, 374, 599–603.

33. Kosinski, C.M.; Schlangen, C.; Gellerich, F.N.; Gizatullina, Z.; Deschauer, M.; Schiefer, J.; Young, A.B.; Landwehrmeyer, G.B.; Toyka, K.V.; Sellhaus, B.; et al. Myopathy as a first symptom of Huntington's disease in a marathon runner. Mov. Disord. 2007, 22, 1637–1640.

34. Busse, M.E.; Hughes, G.; Wiles, C.M.; Rosser, A.E. Use of hand-held dynamometry in the evaluation of lower limb muscle strength in people with Huntington's disease. J. Neurol. 2008, 255, 1534–1540.

35. Hamilton, J.M.; Wolfson, T.; Peavy, G.M.; Jacobson, M.W.; Corey-Bloom, J. Rate and correlates of weight change in Huntington's disease. J. Neurol. Neurosurg. Psychiatry 2004, 75, 209–212.

36. Turner, C.; Cooper, J.M.; Schapira, A.H.V. Clinical correlates of mitochondrial function in Huntington's disease muscle. Mov. Disord. 2007, 22, 1715–1721.

37. Carroll, J.B.; Bates, G.P.; Steffan, J.; Saft, C.; Tabrizi, S.J. Treating the whole body in Huntington's disease. Lancet Neurol. 2015, 14, 1135–1142.

38. Van der Burg, J.M.; Björkqvist, M.; Brundin, P. Beyond the brain: Widespread pathology in Huntington's disease. Lancet Neurol. 2009, 8, 765–774.

39. Dickey, A.S.; La Spada, A.R. Therapy development in huntington disease: From current strategies to emerging opportunities. Am. J. Med. Genet. Part A 2018, 176, 842–861.

40. Dash, D.; Mestre, T.A. Therapeutic update on Huntington's disease: Symptomatic treatments and emerging disease-modifying therapies. Neurotherapeutics 2020.

41. Bondulich, M.K.; Jolinon, N.; Osborne, G.F.; Smith, E.J.; Rattray, I.; Neueder, A.; Sathasivam, K.; Ahmed, M.; Ali, N.; Benjamin, A.C.; et al. Myostatin inhibition prevents skeletal muscle pathophysiology in Huntington's disease mice. Sci.

Rep. 2017, 7, 14275–14288.

42. Lee, S.J.; McPherron, A.C. Regulation of myostatin activity and muscle growth. Proc. Natl. Acad. Sci. USA 2001, 98, 9306–9311.
43. McPherron, A.C.; Lawler, A.M.; Lee, S.J. Regulation of skeletal muscle mass in mice by a new TGF-β superfamily member. Nature 1997, 387, 83–90.
44. Fão, L.; Rego, A.C. Mitochondrial and redox-based therapeutic strategies in Huntington's disease. Antioxid. Redox Sign. 2020, 1–24.
45. Vainshtein, A.; Sandri, M. Signaling pathways that control muscle mass. Int. J. Mol. Sci. 2020, 21, 4759.
46. Matthews, R.T.; Yang, L.; Browne, S.; Baik, M.; Beal, M.F. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc. Natl. Acad. Sci. USA 1998, 95, 8892–8897.
47. Schilling, G.; Coonfield, M.L.; Ross, C.A.; Borchelt, D.R. Coenzyme Q10 and remacemide hydrochloride ameliorate motor deficits in a Huntington's disease transgenic mouse model. Neurosci. Lett. 2001, 315, 149–153.
48. Smith, K.M.; Matson, S.; Matson, W.R.; Cormier, K.; Del Signore, S.J.; Hagerty, S.W.; Stack, E.C.; Ryu, H.; Ferrante, R.J. Dose ranging and efficacy study of high-dose coenzyme Q10 formulations in Huntington's disease mice. Biochim. Biophys. Acta Mol. Basis Dis. 2006, 1762, 616–626.
49. McGarry, A.; McDermott, M.; Kieburtz, K.; DeBlieck, E.A.; Beal, F.; Marder, K.; Ross, C.; Shoulson, I.; Gilbert, P.; Mallonee, W.M.; et al. A randomized, double-blind, placebo-controlled trial of coenzyme Q10 in Huntington disease. Neurology 2017, 88, 152–159.
50. Menalled, L.B.; Patry, M.; Ragland, N.; Lowden, P.A.S.; Goodman, J.; Minnich, J.; Zahasky, B.; Park, L.; Leeds, J.; Howland, D.; et al. Comprehensive behavioral testing in the R6/2 mouse model of Huntington's disease shows no benefit from CoQ10 or minocycline. PLoS ONE 2010, 5.
51. Verbessem, P.; Lemiere, J.; Eijnde, B.O.; Swinnen, S.; Vanhees, L.; Van Leemputte, M.; Hespel, P.; Dom, R. Creatine supplementation in Huntington's disease: A placebo-controlled pilot trial. Neurology 2003, 61, 925–930.
52. Puri, B.K.; Leavitt, B.R.; Hayden, M.R.; Ross, C.A.; Rosenblatt, A.; Greenamyre, J.T.; Hersch, S.; Vaddadi, K.S.; Sword, A.; Horrobin, D.F.; et al. Ethyl-EPA in Huntington disease: A double-blind, randomized, placebo-controlled trial. Neurology 2005, 65, 286–292.
53. Dobson, L.; Träger, U.; Farmer, R.; Hayardeny, L.; Loupe, P.; Hayden, M.R.; Tabrizi, S.J. Laquinimod Dampens hyperactive cytokine production in Huntington's disease patient myeloid cells. J. Neurochem. 2016, 137, 782–794.
54. Ellrichmann, G.; Blusch, A.; Fatoba, O.; Brunner, J.; Hayardeny, L.; Hayden, M.; Sehr, D.; Winklhofer, K.F.; Saft, C.; Gold, R. Laquinimod treatment in the R6/2 mouse model. Sci. Rep. 2017, 7, 1–13.
55. Southwell, A.L.; Franciosi, S.; Villanueva, E.B.; Xie, Y.; Winter, L.A.; Veeraraghavan, J.; Jonason, A.; Felczak, B.; Zhang, W.; Kovalik, V.; et al. Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease. Neurobiol. Dis. 2015, 76, 46–56.
56. Fatoba, O.; Ohtake, Y.; Itokazu, T.; Yamashita, T. Immunotherapies in Huntington's disease and α-synucleinopathies. Front. Immunol. 2020, 11, 1–17.
57. Wang, H.; Chen, X.; Li, Y.; Tang, T.S.; Bezprozvanny, I. Tetrabenazine is neuroprotective in Huntington's disease mice. Mol. Neurodegener. 2010, 5, 18.
58. Coppen, E.M.; Roos, R.A.C. Current pharmacological approaches to reduce chorea in Huntington's disease. Drugs 2017, 77, 29–46.
59. De Tommaso, M.; Serpino, C.; Sciruicchio, V. Management of Huntington's disease: Role of tetrabenazine. Ther. Clin. Risk Manag. 2011, 7, 123–129.
60. Claassen, D.O.; Carroll, B.; De Boer, L.M.; Wu, E.; Ayyagari, R.; Gandhi, S.; Stamler, D. Indirect tolerability comparison of deutetrabenazine and tetrabenazine for Huntington disease. J. Clin. Mov. Disord. 2017, 4, 3.
61. Shacham, T.; Sharma, N.; Lederkremer, G.Z. Protein misfolding and ER stress in Huntington's disease. Front. Mol. Biosci. 2019, 6, 20.
62. Ramsingh, A.I.; Manley, K.; Rong, Y.; Reilly, A.; Messer, A. Transcriptional dysregulation of inflammatory/immune pathways after active vaccination against Huntington′s disease. Hum. Mol. Genet. 2015, 24, 6186–6197.
63. Miller, T.W.; Shirley, T.L.; Wolfgang, W.J.; Kang, X.; Messer, A. DNA vaccination against mutant huntingtin ameliorates the HDR6/2 diabetic phenotype. Mol. Ther. 2003, 7, 572–579.
64. Shannon, K.M. Recent Advances in the treatment of Huntington's disease: Targeting DNA and RNA. CNS Drugs 2020, 34, 219–228.

65. Bennett, C.F.; Baker, B.F.; Pham, N.; Swayze, E.; Geary, R.S. Pharmacology of antisense drugs. Annu. Rev. Pharmacol. Toxicol. 2017, 57, 81–105.
66. Smith, A.V.; Tabrizi, S.J. Therapeutic antisense targeting of huntingtin. DNA Cell Biol. 2020, 39, 154–158.