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Huntington's disease is a multi-system disorder

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Huntington's disease (HD) is one of the most common non-curable rare diseases and is characterized by choreic movements, psychiatric symptoms, and slowly progressive dementia. HD is inherited as an autosomal dominant disorder with complete penetrance. Although brain pathology has become a hallmark of HD, there is a critical mass of new studies suggesting peripheral tissue pathology as an important factor in disease progression. In particular, recently published studies about skeletal muscle malfunction and HD-related cardiomyopathy in HD mouse models strongly suggest their important roles, leading to upcoming preclinical and clinical trials. One might conclude that therapeutic approaches in HD should not be restricted only to the brain pathology but instead major efforts should also be made to understand the cross-talk between diseased tissues like the CNS-Heart or CNS-skeletal muscle axes.

Keywords: cardiomyopathy, Huntington's disease, neurodegeneration, peripheral tissue pathology, skeletal muscle atrophy, triplet repeat disorder

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Introduction

Huntington's disease (HD) belongs to a triplet repeat family of disorders and is caused by the expansion of a CAG trinucleotide within the N-terminal part of the huntingtin gene (*HTT*) on chromosome 4 (for a recent review, see).[1] This mutation leads to an extra-long tract of glutamines within the huntingtin protein (HTT) that causes the huntingtin protein to aggregate.[2] HTT is ubiquitously expressed and it has been found to be involved in many critical cellular processes.[3,4] In mice, HTT deletion is embryonically lethal at E 6.5 and leads to defects in all germ layers.[5] In HD, there is a hypothesis suggesting that small mutant HTT fragments that are being generated during disease progression by a proteolysis or mis-splicing process might account for the tissue pathologies. A recent study has shown that aberrant splicing of *HTT* exon 1 to exon 2 could be responsible for the production of a toxic N-terminal fragment that could be translated into a mutated exon 1 HTT protein in a CAG-dependent manner.[6] Importantly, the short polyadenylated mRNA that is produced through an abnormal splicing of exon 1 HTT has been found to be expressed in many peripheral tissues like heart, skeletal muscle, kidney, and liver, and expression levels in these tissues are similar to that in brain tissue.[6] Thus, one might conclude that a combined (tissue-independent) mechanism is leading to the production of toxic small HTT fragments that ultimately causes organ dysfunction. Indeed, in recent years, multiple studies have indicated a wide array of peripheral organ pathologies, including severe metabolic phenotype, weight loss, HD-related cardiomyopathy, and skeletal muscle wasting (for recent reviews, see).[7,8] Therefore, despite the fact that HD is still recognized principally as a neurological disease, peripheral pathologies, including heart failure and skeletal muscle malfunction, might significantly contribute to the overall progression of HD.

HD-related cardiomyopathy

There are multiple epidemiological studies that have demonstrated clearly that HD patients exhibit a high rate of cardiac events leading to heart failure (see[8] for a review). In addition, a couple of proof of concept studies showed that restricted over-expression of a polyQ peptide or mutant exon 1 HTT, only in cardiomyocytes, caused a severe cardiac dysfunction leading to a reduced lifespan in mice[9] and flies,[10] respectively. Recent studies in HD

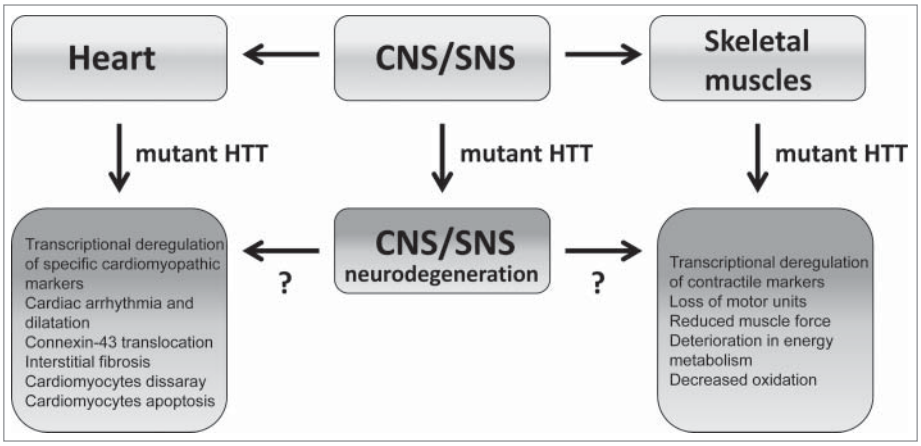

Figure 1. A summary of HD-striated muscle pathology in preclinical settings. CNS (Central Nervous System); SNS (Sympathetic Nervous System).

mouse models showed that HD-related cardiomyopathy is characterized by early changes in Connexin-43 localization at gap junctions, followed by a significant deregulation of hypertrophic markers and cardiomyocyte apoptosis in pre-symptomatic animals. These changes might lead to the profound arrhythmia and overall change in cardiac function that have been described in symptomatic animals.[11] Importantly, these changes were identified prior to a major brain pathology and cognitive deficiency in HD mouse models. During disease progression, these early changes were accompanied by a re-expression of foetal genes and a moderate degree of interstitial fibrosis in the symptomatic animals, resulting in an altered heart physiology and contractile dysfunction. Hence, one might conclude that some of the early changes identified in pre-symptomatic animals might be determined by intrinsic mutant HTT function.[11] However, at this stage of research, there is still no definitive answer to the fundamental question of whether heart failure in HD is caused exclusively by a widespread pathology of the Central Nervous System/Sympathetic nervous system (CNS/SNS) dysfunction or whether it is due to an intrinsic unknown function of mutant HTT in the heart (**Figure. 1**). Moreover, HD-related cardiomyopathy is also characterized by a partial response to the β-adrenergenic stimulation of HD hearts. A chronic treatment with isoproterenol, which is a potent β-adrenoreceptor agonist, did not change the overall gross morphology of the R6/2 murine hearts and some of the hypertrophic signals were attenuated in the symptomatic HD animals.[12] Interestingly, HD-related cardiomyopathy is not characterized by mutant HTT aggregates, since a quantitative methodology failed to identify aggregate load, even at the end stage of disease in HD mouse models.[11] Nonetheless, it is still possible that mutant HTT forms a specific type of aggregate that has not been identified due to technical limitations.

HD-related skeletal muscle atrophy

In HD skeletal muscles, in contrast to the heart, mutant HTT aggregates are apparent, but only in HD symptomatic animals.[13] This is accompanied by a progressive deficiency in the contractile characteristics of the hind limb muscles tibialis anterior (TA) and extensor digitorum longus (EDL), followed by a significant loss of motor units in the R6/2 mouse model of HD. In addition, these functional muscle impairments are accompanied by an aberrant deregulation of contractile protein transcripts and their upstream transcriptional regulators. One may conclude that these changes result in a significant reduction in muscle force, due to an energy imbalance and decreased oxidation in both fast and slow types of skeletal muscles.[13]

Interestingly, HD-related skeletal muscle weakness has been directly correlated to the re-expression of the HDAC4-DACH2-myogenin axis.[13] These results clearly identified skeletal muscle dysfunction as a key pathological feature of HD (**Fig. 1**). The function of HDAC4 in skeletal muscles has been well described (see[14] for a review). Moreover, HDAC4 overexpression has been already linked to disease progression in an amyotrophic lateral sclerosis (ALS) mouse model.[15] In clinical settings, HDAC4 up-regulation was also positively correlated with ALS disease progression.[16] Similarly, an amplified level of HDAC4 has been found in a spinal muscular atrophy (SMA) mouse model and in SMA patients.[17] Since, skeletal muscle atrophy has been established as a major symptom of HD, it is expected that genetic reduction of HDAC4 in skeletal muscle could be a contributing factor to the overall improvement of HD phenotypes.[18,19] In summary, recent studies highlighted a major regulatory role of HDAC4 in muscle remodelling in neurodegenerative diseases.

Conclusions

Recent preclinical studies have revealed striated muscle pathology as a potential major component of HD progression. It is still an open question as to whether HD-related cardiomyopathy and skeletal muscle malfunction are secondary events to CNS/SNS dysfunction or are partially caused by an intrinsic function of HTT in these tissues (**Fig. 1**). Despite this, it has been clearly shown that improvement of muscle function leads to a lifespan extension in HD mouse models.[20] Therefore, this makes striated muscle a valid target for future therapies and emphasizes peripheral components as an important part of HD disease progression. There is an urgent need to understand the mechanisms leading to HD-related striated muscle pathology, in preclinical and clinical settings, to be able to shape future therapeutic strategies in HD. While CNS dysfunction is a prime target in ongoing therapeutic studies, it might be necessary to use more systemic approaches to cure or delay HD symptoms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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