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Review

Update on Huntington's disease: Advances in care and emerging therapeutic options

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ABSTRACT

Introduction: Huntington's disease (HD) is the most common hereditary neurodegenerative disorder. Despite the fact that both the gene and the mutation causing this monogenetic disorder were identified more than 20 years ago, disease-modifying therapies for HD have not yet been established.
Review: While intense preclinical research and large cohort studies in HD have laid foundations for tangible improvements in understanding HD and caring for HD patients, identifying targets for therapeutic interventions and developing novel therapeutic modalities (new chemical entities and advanced therapies using DNA and RNA molecules as therapeutic agents) continues to be an ongoing process. The authors review recent achievements in HD research and focus on approaches towards disease-modifying therapies, ranging from huntingtin-lowering strategies to improving huntingtin clearance that may be promoted by posttranslational HTT modifications.
Conclusion: The nature and number of upcoming clinical studies/trials in HD is a reason for hope for HD patients and their families.

1. Introduction

Huntington's disease (HD) is an autosomal dominant, progressive, neurodegenerative disorder for which symptomatic treatments but no disease-modifying therapies are available. Following identification, in 1993 of the huntingtin (*HTT*) gene located on the short arm of chromosome 4, it was widely expected that HD therapies ('cures') were around the corner [1]. More than 20 years later we know that the development of efficacious therapies, even for a monogenetic disorder such as HD, is more complex than was anticipated. However, today we can outline novel approaches with a demonstrated efficacy in HD animal models that provide rational foundations for clinical trials. HD is caused by a dynamic expansion of trinucleotide CAG repeats in *HTT* exon-1. The number of CAG repeats in the HD gene ranges from 6 to 35 in healthy individuals. People with 27–35 repeats (expandable range) may transmit, in particular males in their sperm, larger CAG repeat expansions to their offspring (i.e. into the pathological range of >35). Disease penetrance is reduced for those carrying 36 to 39 repeats, although it is thought to be complete in individuals with 40 repeats or more [1–3]. Most often, HD symptoms start between 30 and 50 years of age (the onset range of HD is 2–85 years) and progress slightly more quickly in women [4,5].

Huntingtin (HTT), a 350-kDa protein, is conserved among all vertebrates [6,7]. HTT is expressed ubiquitously, with its highest expression in the brain and testes [8,9]. Its subcellular localization is dynamic; HTT has been found to co-localize with organelles such as the nucleus, the endoplasmic reticulum, Golgi apparatus and endosomes [10,11]. Wild-type HTT appears to have numerous functions in the cell and has been shown to be involved in cell cycle progression, possibly coordinating spindle orientation which is an essential process in cell division [12]. HTT has also been detected in axonal processes and synapses where it is associated with microtubules, caveolae, synaptosomes and clathrin-coated vesicles [10,13]. More than 200 HTT interaction partners have been

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identified and can be classified based on their function as proteins that are involved in gene transcription, intracellular signaling, trafficking, endocytosis, and metabolism [7]. Although several interaction partners of HTT have been identified, this protein's primary function is not yet fully understood, and a polyQ mutation might lead either to a toxic gain-of-function or loss-of-function. HTT is ubiquitously expressed and it has become apparent that HD patients experience a wide array of peripheral organ dysfunction including HD-related cardiomyopathy [14–16] and skeletal muscle wasting [17]. Importantly, complete deletion of wild-type HTT in mice is lethal at day 6.5 of gestation [18,19]. Even animals that are heterozygous for HTT showed pathological defects in the brain and developed certain behavioral abnormalities [20–22].

HTT biological function seems to be highly regulated by post-translational modifications (PTMs), and many studies have shown that HTT might undergo phosphorylation, SUMOylation, ubiquitination, acetylation and palmitoylation [23]. It has been postulated that PTMs play a crucial role in HTT's protein–protein interactions. It has been hypothesized that HTT-associated PTMs are significantly altered by the presence of the HD mutation, which might potentially play a role in mHTT toxicity [23]. PTMs have been exploited therapeutically to enhance mHTT clearance, thus reducing its impact on HD pathogenesis. It was shown that acetylation of the lysine residue K444 in mHTT increases its clearance by directing to the autophagosomes [24]. Phosphorylation of mHTT at serine 431 and 432 alters both its toxicity and accumulation [25]. Consequently, these PTMs might alter the mHTT interaction network [26], thus leading to mHTT clearance, and are an attractive model for future HD treatments.

It has been well documented that mHTT can interact directly with histone acetyltransferases (HATs) such as CBP and PCAF by reducing their acetyltransferase activity and thus by leading to transcriptional deregulation. Hence, abnormal histone acetylation and chromatin remodeling might be a crucial process leading to transcriptional deregulation [27–29]. Consequently, different histone deacetylase (HDAC) inhibitors are currently being tested in pre- and clinical trials for efficacy as possible therapeutics in HD [30,31]. A recent study has shown that genetic inhibition of HDAC4 (a class IIa enzyme) significantly ameliorates many neurological features in HD mouse models by reducing cytoplasmic aggregate formation and rescues neuronal and corticostriatal synaptic function. Surprisingly, HDAC4 reduction had no effect on global transcriptional dysfunction and did not modulate nuclear mHTT aggregation [32], which was likely due to its cellular localization [33]. Moreover, it was shown that SAHA, a pan-HDAC inhibitor that was beneficial in pre-clinical studies earlier [34], could also down-regulate HDAC4 at the protein level [35,36]. Pharmacological approaches that facilitate the degradation of mHTT via activation of autophagy, the ubiquitin-proteasome system or molecular chaperones, are also being exploited [37]. Alternative molecular therapies include HDAC inhibitors, excitotoxicity suppressors, sirtuin activators and caspase inhibitors.

The availability of a predictive genetic test in HD allows for early identification of HD carriers and is vital for observational studies before the disease onset [38]. A complex observational study such as COHORT or REGISTRY resulted in better knowledge of the natural disease progression, while PREDICT and TRACK-HD have contributed to sensitive measurement methods that allow earlier diagnosis. This situation provides a perfect clinical setting where therapeutic approaches can be evaluated using a large number of participants; it is expected that important questions regarding the time frame for gene silencing therapy will be answered [39,40].

2. Looking for therapy targets in HD (Fig. 1)

2.1. Htt lowering

The proof-of-concept study came from a conditional, tet-regulated mouse model expressing a fragment of mutant HTT (mHTT) exon1. It was demonstrated that shutting down mHTT exon-1 after disease onset had occurred led to a reversal of behavioral deficits, neurodegenerative pathology, and mHTT aggregation [41]. In line with the development of RNA interference (RNAi) technology, targeting mutant HTT (mHTT) by siRNA directed towards *HTT* messenger RNA (mRNA) has become a rational and attractive therapeutic strategy. The first successful study conducted to reduce HTT mRNA levels was through RNAi [42]. Striatal injections of the adeno-associated virus (AAV) expressing short-hairpin RNA (shRNA) were used to lower mHTT transcript levels, thus leading to an aggregate reduction and motor deficit improvement in the HD mouse model [42]. However, developing nucleic acid-based drugs is challenging and an ideal clinical approach for gene silencing would combine the simplicity of single-stranded antisense oligonucleotides with the efficiency of RNAi. Recently, ss-siRNAs (single-stranded siRNAs) have been shown to be potent (>100-fold more than unmodified RNA) and allele-selective (>30-fold) inhibitors of m*HTT* expression in cells derived from HD patients. Strategic placement of mismatched bases mimics microRNA recognition and optimizes discrimination between mutant and wild-type alleles. Single-stranded siRNAs require the Argonaute protein and function through the RNAi pathway. Intraventricular infusion of ss-siRNAs produced selective silencing of the m*HTT* allele throughout the brain in mice. These data demonstrated that chemically modified ss-siRNAs function through the RNAi pathway and provide allele-selective compounds for clinical development [43]. An alternative approach for selective silencing of the mutant allele is based on single nucleotide

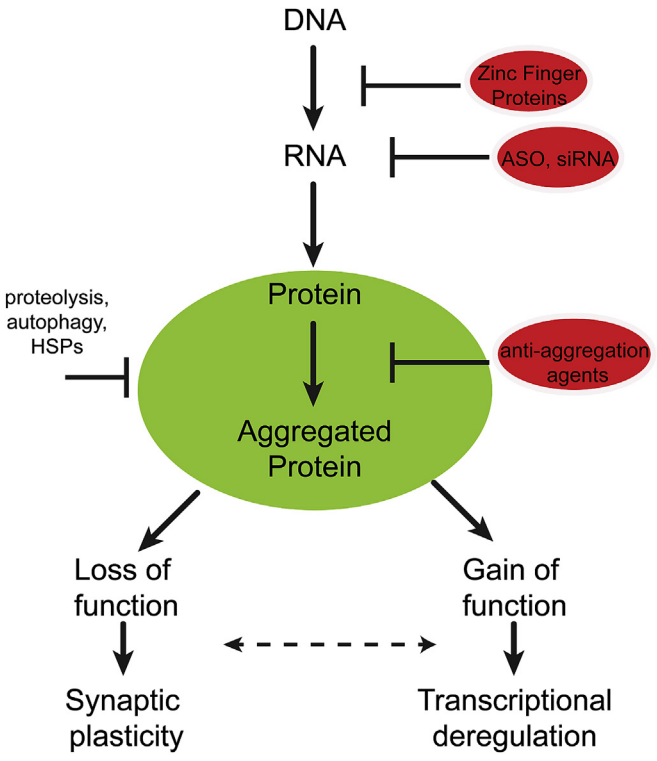

Fig. 1. Target hubs for future therapies in HD.