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# Abnormal Isoform-Induced Scaffolding by Mutant Huntingtin as Interacting Proteins in Transcriptional Creation of Abnormal Networks of Assembly in Huntington's Disease

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**Abstract**

Conditional activation and propagation of neuronal injury are accumulative and result from isoform network abnormalities mediated by the creation of a mutant huntingtin molecule in Huntington's disease. Further considerations of putative functions of the huntingtin molecule attest to a propagation of pathologic effects within neurons and axons that is primarily determined by the specific length of the polyglutamine tract that inherently lengthens. Proposed mechanisms in the creation of the mutant huntingtin are integral phenomena to subsequent involvement of neurons as created by isoforms of the scaffolding dysfunctionalities that result both from selective enzymatic cleavage and of subsequent protein-protein interactions involving in particular transcriptional dysregulation. In such context, transcriptional abnormalities bridge the dual phenomena of etiologic cause and of pathogenic propagation in neuronal injury in patients suffering from Huntington's disease.

**Keywords:** Huntingtin; Polyglutamine; Brain-Derived Neurotrophic Factor; Astrocytes; PGC1alpha; NRF-1; Tfam; Repressor Element-1 Transcription Factor/Neuron-Restrictive Silencing Factor; polyQ;

## Introduction

The complexity of transcriptional dysregulation evidences the central scaffolding functionalities of the large Huntingtin (HTT) protein moiety in a manner that further confirms the crucial roles subserved by huntingtin in nuclear-cytoplasm shuttle mechanisms of various transcriptionally enhancing and suppressive agonists. Caspase-6 is recognized as important and is implicated early in Huntingon's disease (HD) [1]. Bioenergetic dysfunction contributes to striatal cell and primary cortical degeneration of neurons in this disease [2].

Compound pathways attest to the network formulations in the creation of systems of transcriptional regulation and also of transport mechanisms within the neuron and also its axonal elongation. Molecular pathways should be studied at multiple levels, including neural stem/progenitor cells [3]. Proteostasis requires specific conformation, concentration and location to render functional huntingtin in a non-aggregated form [4]. It is further proposed that systems of elongated polyglutamine Q tract would evolve as parameters of re-distribution that permit various role models for the expanding polyglutamine tract in the mutant huntingtin molecule. HTT CAG-expansion has an impact on age at death but does not affect duration of disease, implicating different time courses in multiple cell types [5].

## Anticipation

HD is due to meiotically unstable CAG-repeats in the mutated gene on chromosome 4p16.3 that encodes the mutated huntingtin; transmission is autosomal dominant [6]. Anticipation further collaborates with the inclined dimensions of transcriptional dysregulation in a manner that is suggestive of disequilibrium further defined in terms of increasing molecular size of huntingtin. Age of onset of disease is principally determined by the length of the CAG repeat expansion in exon 1 of the HTT gene [7]. It is significant that the axonal kinesin and dyneim transport mechanisms are facets of the neurotrophin transport via antero-grade and retrograde transport of ions, vesicles and neurotrophins/neurotransmitters along axons in general. HTT induces synaptic dysfunction due to involvement of the neurotransmitter release mechanisms [8].

## Non-Neural Cell Autonomy

The further proposed roles of other cell types besides neurons as proposed in the non-neural cell autonomous theory indeed indicates a particularly activated role for microglia and of astrocytes in neuroprotection or neuro-injury in patients with Huntington's disease. Astrocytes may be a primary component in pathogenesis, and may constitute a potential primary therapeutic target [9]. Parallel or concomitant dysfunctions are apparent in neurons in view especially of the multi-functionalities of the normal Huntington protein and in terms especially of transcriptional modalities of neuronal pro-survival. In fact, a pro-apoptotic series of roles of mutant huntingtin is evident in neurons that further implicate in selective manner pro-caspase-9.

Beyond the dimensional or global implications of an expanding polyglutamine tract within the mutant huntingtin molecule, it is




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significant to note the presence of polyglutamine tracts within normal transcription factors themselves. Transcriptional dysregulation in HD is poorly understood, and the role of inflammation and abnormal developmental processes in particular may be implicated [10]. Sense and antisense Repeat-Associated Non-ATG (RAN) translation proteins also accumulate in HD brains and include polyAla, polySer, polyLeu and polyCys; these relate to neuronal loss regions, microglial activation and apoptosis [11]. Realization of misfolded protein aggregates is a centrally operative series of dimensional neuronal mechanistic steps within both the nucleus and cytoplasm of these cells. Indeed, the corticostriatal tracts are evidential sites for protein molecular aggregates within especially the axons in the white matter of patients with Huntington's disease and further support a direct mechanistic and physical role in abnormal axonal transport. Differential expressions of 31 proteins by 2D-DIGE implicated unfolded protein binding, negative regulation of neuronal apoptosis and response to superoxides [12].

## Networks and Neuronal Cell Death

Neuronal cell death is therefore an eventual end-result of a particularly compounding series of network change that promotes the redistribution of pathologic effect secondary to the centrally operative scaffolding functionalities of the huntingtin and mutant huntingtin molecule. Links between peripheral biology and HD neuro-degeneration may offer the opportunity of modulating therapeutic intervention [13].

Performance attributes are particularly severe within the local and distributional effects resulting in lack of sufficient neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF). Indeed a deficiency in supply of BDNF is crucial to the creation of striatal pathology of neurons beyond the simple dynamics of transport or of synaptic dysfunctionality within the putamen and caudate nuclei. The origin of pathologic effect of mutant huntingin arises within nuclei that show both microscopic diffuse and also macroscopic aggregation of this protein as inclusion bodies. Marked elevation of urea found globally in the HD brain may lead to defective osmo regulation or nitrogen metabolism [14]. Skeletal muscle wasting probably is important in HD pathogenesis [15].

Pertinent to such considerations, the evolving transport mechanistic pathology is indicative of a serious upset in neuronal economy and of trophic effects within the individual neuron and also within whole system networks of such individual neurons. Mitochondrial lesions in HD may implicate complex assembly, fission and fusion, mitochondrial transport and degradation via autophagy, and also mitochondrial biogenesis and protein import [15]. The creation of a mouse polyQ database may accelerate research in neurodegeneration (17).

## Systems of Operative Enhancement and Injury

Acetyltransferase activity with the addition of acetyl groups to lysine side-chains of histone molecules is particularly relevant with regard to CREB-binding protein CBP/CREB complexes and this inherent property of CBP emphasizes the strong potentiality for histone deacetylase inhibitors as targets in rescuing neurons in Huntington's disease patients. A peroxisome proliferator-activated receptor gamma is crucial to neuroprotective mechanisms in neurodegeneration and HD and includes downstream targets such as PGC1alpha, NRF-1 and Tfam [18]. Transcellular propagation of misfolded protein aggregates of mutant HTT first follows accumulation in synaptic regions and also non-cell-autonomous induced pathology [19].

The physiologic roles of the normal Huntington molecule are related to attributes of large molecular size and also lack of functional groups or active domains. In such manner, the scaffold functional of the molecule further operates within the context of enhancing and detrimental effects of various protein interactions in the presence of mutant forms of huntingtin. Specificity transcription protein-1, of PG coactivator-1alpha (peroxisome proliferator activated receptor gamma coactivator 1alpha), nuclear hormone receptors, CBP, sumoylation of multi-varied network substrates, are all targets of mutant huntingtin. Repressor Element-1 Transcription Factor/ Neuron-Restrictive Silencing Factor (REST/NRSF) is a transcriptional repressor that accumulates intra-neuronally in Huntington's disease with repression of prosurvival genes such as BDNF. The myocyte enhancer factor 2D, on the other hand, is a transcriptional activator with prosurvival roles in neurons. In such context, the further activation of Transcription Factor (TFIID) complex and TAFII130 mediate active complex assembly as an essential aspect of Huntington's disease pathobiology.

## Dual Loss and Gain of Function

Overall considerations of gain of function are also allied in integral fashion with essential loss of function of the mutant huntingtin molecule in Huntington's disease patients. Such effects occur particularly in the medium-sized spiny neurons of the striatum, but also in certain cortical groups of neurons, and also the hippocampus. Mitochondrial loss due mainly to autophagy and membrane depolarization of these specific cytoplasmic organelles contribute to the neuronal group specific targets in Huntington's disease that elicit the exquisite site restrictive effects of mutant huntingtin molecule. Mitochondrial metal dyshomeostasis has been implicated in HD and also Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis and Friedreich's ataxia [20].

The spongiform changes in the striatum are associated with neuronal cell loss and such mechanistic pathways activate microglia within a setting of neuroinflammatory reactivities. A global innate response to toxic mutant huntingtin in HD gene carriers appears to develop and may also entail associated pathogenesis between peripheral and central immune responses [21]. The protein aggregates are themselves targets for such a phenomenon, particularly also with reference to protein enzymatic cleavage of the mutant huntingtin molecule. The toxic fragment hypothesis has been clearly formulated in terms of the amino-terminal and included polyglutamine Q tract of mutant huntingtin.

## Mitochondria

Therefore, mitochondrial defects in organelle biogenesis and uncoupled respiratory activity predispose to defective energy metabolism. Such context is centered particularly with release of cytochrome c oxidase and caspase-9, leading to pro-apoptosis and neuronal cell loss of the medium spiny neurons of the striatum.

Lack of BDNF is coupled with such pro-apoptosis. Oxidative stress inducing neuronal injury arises also secondary to mitochondrial loss of function and organelle damage.

Astrocytes are important contributors to such neuronal injury, especially in terms of failure to transport extracellular glutamate, thus predisposing to excitotoxicity of neurons. Drosophila models have allowed faithful recapitulation of pathologic lesions that include polyQ length-dependent formation of protein aggregate and progressive degeneration of neurons [22].

## Sequestration

In general terms, sequestration of transcriptional factors in particular and hence disordered transport between nucleus and cytoplasm constitutes an integral series of pathways compounded intimately with proteasome-induced degradation of molecular species. It is clear that the phenomena associated with essential presence of mutant huntingtin include the contextual propagation of pathobiologic upsets as network pathway creation and activation. Such nodal properties of mutant huntingtin would also be responsible for etiologic derivation of the mutant huntingtin molecule itself. Oxidative stress and neuroinflammation are principal mechanisms implicated in neurodegenerative diseases such as HD, involving the Jak2/STAT3 pathway and inhibition of NF-kB nuclear translocation on the one hand, and the major regulator of oxidative stress Nrf2/HO1 [23]. Increased TRPC5 [Ca (2+)$^{-}$ permeable transient receptor potential cation] glutathionylation promotes loss of striatal neurons in Huntington's disease [24].

## Transcriptional Dysregulation

Transcriptional assembly abnormalities and transport mechanistic disarray are hence key network abnormalities implicated in inherent manner to the presence of mutant huntingtin molecules. Such phenomena are related especially to the initial stages of intra-nuclear diffuse micro-aggregates of oligomers and of profibrils of mutant huntingtin. A primary consideration in Huntington's disease is the creation and propagation of multiple isoforms of the mutant huntingtin as induced by enzymatic cleavage at selective sites in the parent molecule. N-terminal fragments of mutant huntingtin have a strong propensity to form oligomers and aggregates through mechanisms that include gain of toxic functions [25]. In such context, the disease of polyglutamine tract expansion appears to predispose to such variable isoform creation in a manner that is inherently linked to the length of the polyglutamine tract itself in the mutant huntingtin molecule. Multiple molecular pathways are dysregulated in HD and are already altered in undifferentiated pluripotent cells [26].

## Protein Aggregation

Aggregation of misfolded molecular isoforms is an essential corollary to expanded polyglutamine tracts and such aggregation in the nucleus and particularly within the cytoplasm contributes directly to neuronal demise. Patterns of neuronal set susceptibility may be determined by mitochondrial injury in selective fashion and further delineate the phenotypic and clinical manifestations in Huntington's disease, especially the motoric involvements in the disease. Dendritic degeneration and pre-synaptic vesicle fusion abnormalities are other features of a disease process that propagates within the striatum and certain cortical neuronal subsets in a manner that entails abnormal transport mechanics both within individual neurons and neuronal networks, and especially within the anterograde transporting corticostriatal pathways.

A structural basis for the apparent transition between normal and pathogenic expanded polyQ repeats of huntingtin is unknown; both a "linear lattice" model of increased affinity of the anti-polyQ antibody MW1 increases with the number of glutamines, and a "structural toxic threshold" model involving a specific toxic conformation for expanded polyQ have been proposed [27]. A single prominent point of reference in Huntington's disease is hence the operative network propagation of the multiple isoforms of mutant huntingtin that relate also to the degree of stability of this molecular species. Ubiquitin in the cerebrospinal fluid increases with HD progression and CAG-age product score and this may aid in understanding disease pathology early in affected patients [28].

## Concluding Remarks

Compound performance attributes of isoform moieties of the mutant huntingtin molecule is a context for multi-pathway creation that aberrantly transforms scaffolding functionalities of the normal huntingtin molecule within a setting of a plethora of transcription dysregulations. The protein interactivities with other proteins attest to the progressiveness of a neuronal injury in terms of complex assembly constructs including molecular aggregation and the creation of enzymatically mediated multi-isoform creation and propagation. Performance dynamics are clearly implicated in terms of molecular stability and enzymatic cleavage within further contextual aggregation of mutant huntingtin moieties. Indicative of such phenomena is the manifestation of disease progression that is primarily accumulative and specifically propagating as network dynamics of misfolded molecular species.

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