

## Review

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# Cancer: From Wild-Type to Mutant Huntingtin

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**Abstract.** Huntingtin (HTT) is a scaffold protein mostly known because it gives rise to the severe and incurable inherited neurological disorder Huntington's disease (HD) when mutated. The *Huntingtin* gene (*HTT*) carries a polymorphic trinucleotide expansion of CAGs in exon 1 that ranges from 9 to 35 in the non-HD affected population. However, if it exceeds 35 CAG repeats, the altered protein is referred to as mutant *HTT* and leads to the development of HD. Given the wide spectrum of severe symptoms developed by HD individuals, wild-type and mutant HTT have been mostly studied in the context of this disorder. However, HTT expression is ubiquitous and several peripheral symptoms in HD have been described, suggesting that HTT is of importance, not only in the central nervous system (CNS), but also in peripheral organs. Accordingly, HTT and mutant HTT may interfere with non-brain-related diseases. Correlative studies have highlighted a decreased cancer incidence in the HD population and both wild-type and mutant HTT have been implicated in tumor progression. In this review, we describe the current evidence linking wild-type and mutant HTT to cancer and discuss how CAG polymorphism, HTT function, and partners may influence carcinogenesis and metastatic progression.

**Keywords:** Huntington disease, huntingtin, cancer, CAG expansion, breast cancer, adhesion, metastasis

## INTRODUCTION

Huntingtin (HTT) is a large scaffold protein of 350 kDa, conserved from flies to mammals, that has been mostly studied in the context of Huntington's disease (HD), a rare inherited neurological disorder. HTT carries a polymorphic expansion of glutamine in its N-terminal sequence encoded by CAG repeats in its gene, *HTT* [1]. CAG repeats range from 9 to 35 CAGs in the non-HD population, with an average between 17 and 20 repeats (Fig. 1) [2]. When above 35 CAGs, it leads to the development of HD,

generally during adulthood, with a lower penetrance observed in carriers of 36 to 39 repeats [3–5]. Individuals carrying alleles with an intermediate number (between 27 and 35 CAGs) may display some aspects of the disease [6, 7].

HD symptoms, including motor, cognitive, and psychiatric disturbances, are severe and ultimately lead to dementia [8]. Thus, much effort has been focused on understanding the molecular mechanisms leading to HD in the central nervous system (CNS) and the function of HTT has been mostly described in cells of neuronal origin. HTT participates in numerous cellular functions essential for the physiology of the CNS, such as cell division, transcriptional regulation, and intracellular transport [9]. It is subjected to multiple post-translational modifications including

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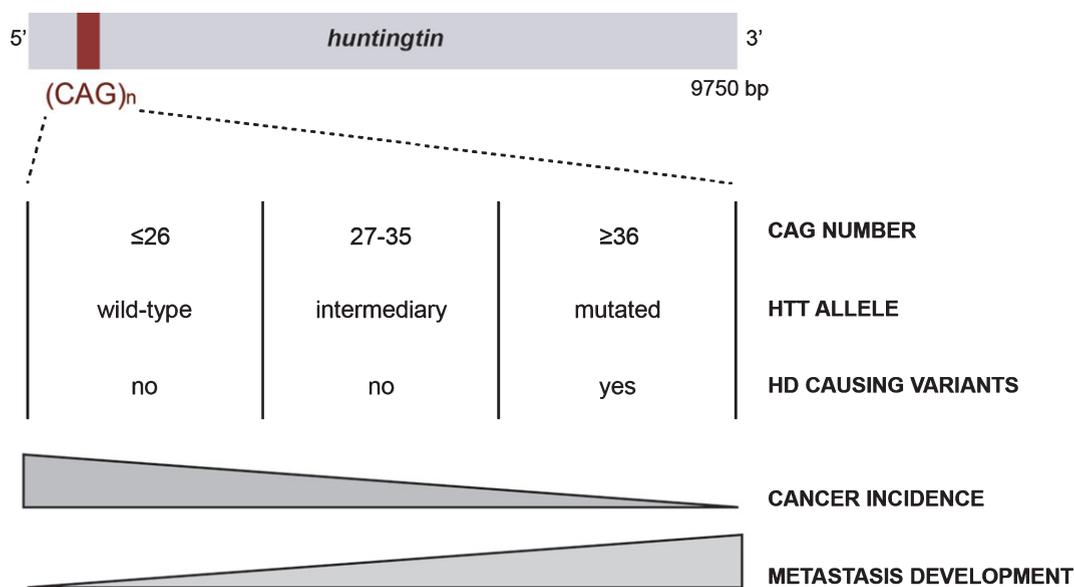


Fig. 1. The CAG polymorphism in *HTT* is associated with Huntington disease and cancer risk and evolution.

acetylation, sumoylation, ubiquitination, palmitoylation, and phosphorylation, which regulate its function and toxicity in HD [9]. However, HTT is widely expressed in the body and accumulating evidence suggests that it has a function in organs other than the brain [10, 11]. HD patients display peripheral symptoms, such as weight loss, muscular atrophy, cardiac failure, and osteoporosis [11], consistent with a role of HTT outside the CNS. Furthermore, some of these symptoms develop early during the disease and contribute to the mortality of HD patients. Several lines of evidence suggest that these peripheral manifestations are not dependent on cerebral dysfunction, but may be the consequence of mutant HTT expression in peripheral organs [11].

Our laboratory has shown that HTT is expressed in mammary tissue and regulates its morphogenesis and tumorigenesis [12–15]. We demonstrated that loss of HTT or the expression of mutant HTT is pro-metastatic in breast cancer. Additionally, we showed that wild-type HTT is involved in normal mammary gland development [12, 14, 15]. Moreover, we described an association between the size of CAG repeats in wild-type HTT and cancer prognosis [16], as well as decreased cancer incidence in the HD population [17]. In this review, we discuss the function of HTT during carcinogenesis, as well as the relationship between CAG repeats size and cancer incidence and prognosis. We also discuss several protein partners of HTT and signaling pathways in which HTT is

engaged that may mediate the effects of HTT during cancer progression.

### PARADOXICAL ASSOCIATION BETWEEN HD AND CANCER

The first study to examine the association between mutant HTT and cancer was published at the end of the last century [18]. Sorensen and Fenger investigated the leading causes of death in HD individuals and reported that only 5% were attributable to cancer. A few years later, Sorensen et al. reported a lower incidence of all cancers in HD individuals, except for those of the buccal cavity and the pharynx [19]. In 2012, Ji et al. described a similar decrease in the incidence of most cancer types in individuals with HD or other polyglutamine disorders [20]. In both studies, the authors did not have information concerning the length of CAG repeats or the clinicopathological characteristics of the cancer (grade, survival, metastasis) and suggested that HD and other polyglutamine disorders share common mechanisms leading to protection against cancer [20]. They proposed that HTT can act as a tumor suppressor by modulating the apoptosis of neoplastic cells. More recently, we confirmed the decreased risk of cancer in HD and spinocerebellar ataxia (SCA) patients [17].

Thus, long repeats could be protective against cancer, which may explain the advantage of germinal and somatic instability in *HTT* that leads to increased

CAG repeats size, even though it is detrimental with respect to HD [21, 22]. However, there are exceptions depending on the type of cancer. For example, decreased incidence of cancer in HD patients does not apply to digestive system related cancers [20] or skin cancers [17]. The patterns of expression, the functions and interactors of each protein, and/or the nature of the signaling pathways involved in the neurodegenerative processes may differentially influence the specificity of action in cancer.

Finally, in sharp contrast to the low risk of cancer in HD, one of our studies paradoxically suggests that pathological HD CAG expansions increase cancer severity once it develops (Fig. 1) [15]. Indeed, mutant HTT increases cancer growth and metastasis development in mouse and cellular models of HD through the accumulation of Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) (HER2 in human) at the cell membrane. Mutant HTT impairs HER2 recycling by interacting with dynamin 2, leading to its accumulation at the membrane and subsequent overactivation of signaling pathways involved in proliferation and metastasis. Thus, even though long CAG repeats correlate with a lower incidence of cancer, they may enhance the severity of specific subtypes of cancer once it is initiated.

### NON HD-PATHOLOGICAL CAG POLYMORPHISMS AND CANCER

The link between pathological HD CAG expansions and cancer risk and severity raises the question of whether CAG polymorphism is associated with cancer features and outcomes in a non-HD situation (in which the *HTT* CAG repeats is strictly below 36). We investigated the length of CAG repeats in the *HTT* gene in cohorts of cancer patients and found that it negatively correlated with ovarian cancer incidence in individuals that carry the cancer predisposition mutation in the *BRCA2* gene [16], consistent with the lower incidence of cancer in HD patients [17, 18, 20]. Moreover, cancer onset occurred earlier in individuals with *HTT* alleles with an intermediate number of CAG repeats than in those with <27 CAG repeats in *BRCA1* mutation carriers who developed breast cancer. Finally, the length of the CAG repeats in *HTT* appears to be an independent prognostic factor of metastasis development, specifically of the HER2 subtype, in good agreement with increased cancer aggressiveness by mutant HTT and the described molecular mechanism. This suggests

that there may be a linear relationship between the length of CAG repeats in *HTT* and cancer incidence and metastasis development rather than a threshold effect (Fig. 1). Long CAG repeats may protect against cancer whereas it enhances cancer progression once tumorigenesis has been initiated, even below the pathological threshold that results in HD.

The relationship between CAG polymorphism and disease has also been described for the androgen receptor. The androgen receptor gene carries a polymorphic CAG repeats in exon 1 and, as *HTT*, is associated with cancer risk and evolution, as well as with neurodegeneration [23]. Depending on its size, the CAG expansion in the androgen receptor is linked to an increased risk of prostate ( $\leq 21$  CAG repeats) or of breast cancers ( $\geq 21$  CAG) or to the development of spinal and bulbar muscular atrophy ( $>40$  CAG repeats) [23–25].

Finally, a functional relationship between CAG repeats and cancer cell death was recently described [26]. The authors identified a family of siRNA against CAG/CUG repeats which bind the open reading frames of several genes containing long complementary repeats. siCAG/CUG are highly toxic to cancer cells *in vitro* and efficient *in vivo* to decrease xenografted ovarian tumor progression in mice.

### WILD-TYPE HTT IS ANTI-METASTATIC IN BREAST CANCER

Breast cancer is a highly heterogeneous disease with many different histological and molecular subtypes showing different levels of differentiation, proliferation profiles, and outcomes [27–29]. We have used cellular and murine models, as well as the analysis of HTT expression in a large cohort of breast cancer patients, to show that HTT influences breast cancer differentiation and progression [14, 30]. HTT expression increases in human *in situ* carcinomas as compared to healthy tissue. In contrast, it decreases in invasive cells as compared to *in situ* carcinomas (Fig. 2). Indeed, loss of HTT is itself pro-metastatic in mice. We focused our attention on the phosphorylation of HTT at serine 421 (S421-P-HTT), which regulates its normal function and is neuroprotective in HD [31–36]. We found that it colocalizes at cell-cell junctions with zonula occludens 1 (ZO-1), a marker of tight junctions, and regulates its expression and localization. S421-P-HTT is much less abundant in human *in situ* tumors than healthy tissue and nearly absent from invasive cancer cells and

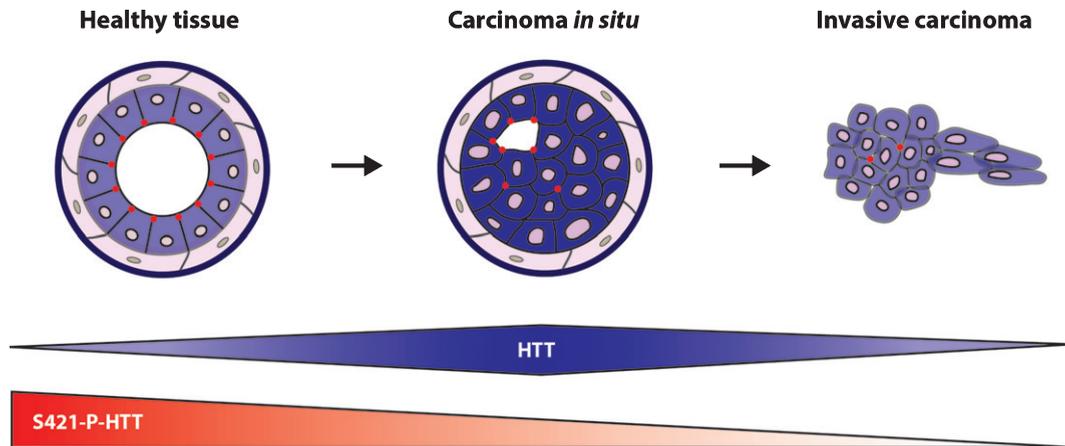


Fig. 2. HTT and S421-P-HTT during tumor progression. Schematic representation of HTT cellular localization and S421-P-HTT during mammary gland tumor progression. (from [30]).

colocalize at cell-cell junctions with ZO-1 (Fig. 2). HTT and ZO-1 expression positively correlate with the glandular differentiation stage of human carcinomas and are concomitantly downregulated in low-grade, poorly differentiated carcinomas associated with a poor prognosis.

Other studies have highlighted ZO-1 dysregulation in cancer. As for S421-P-HTT, the expression of ZO-1 is lower in tumoral tissue than in healthy mammary glands [37] and correlates with glandular differentiation of the carcinomas [38]. Furthermore, the loss of ZO-1 expression is linked to a poor prognosis and metastasis development [39]. Thus, HTT may modulate tumor differentiation, intercellular adhesion, and therefore metastasis progression, by regulating ZO-1. ZO-1 shares sequence homology with the tumor suppressor discs-large DLG protein in drosophila [40], suggesting that it may act as a tumor suppressor in mammals as well. Moreover, we observed nuclear localization of both S421-P-HTT and ZO-1 *in vitro* in mammary cell lines but we have been unable to detect S421-P-HTT within the cell nuclei in human biopsies. However, we observed ZO-1 localization in the nuclei of poorly differentiated basal carcinomas [14]. Nuclear ZO-1 localization has been previously shown to regulate cell proliferation through its interactor, ZONAB [41, 42]. HTT could therefore potentially act on ZO-1 through regulation of ZONAB.

### HUNTINGTIN MODULATES CELLULAR ADHESION AND DIFFERENTIATION

Several pathways are regulated by HTT, dysregulated in HD, and known to contribute to cancer

progression. Among these, several lines of evidence suggest that HTT modulates cellular adhesion and polarity, with an impact on differentiation. For example, HTT regulates the differentiation of mammary cells during development in healthy mammary glands [12]. In contrast, the differentiation process is affected in human HD-derived pluripotent stem cell lines [43, 44], consistent with the reported role of HTT as a positive transcriptional regulator of genes involved in neuronal maintenance, a function that is lost when HTT is mutated [45]. Thus, mutant HTT may have lost the ability to regulate cellular differentiation.

At the molecular level, HTT regulates proteins involved in cell adhesion and differentiation. It interacts with the metalloprotease ADAM10, thus allowing the proper cleavage of the neuronal cadherin, N-cadherin [46, 47]. The absence of HTT leads to decreased expression of N-cadherin and ZO-1 in zebrafish, altering homotypic interactions between neuroepithelial cells and neurulation [47]. Additionally, HTT favors N-cadherin recycling through RAB11, thus influencing the attachment of newly generated neurons to the fiber of radial glial cells during cortical development [48].

HTT has also been implicated in the regulation of components of adherence junctions. The mRNA levels for such proteins are reduced in embryonic stem cells and neurons with lower HTT levels [49]. In neurons, HTT interacts with the F-box protein  $\beta$ -TrcP and axin, which are part of the multisubunit  $\beta$ -catenin destruction complex [50–52]. By permitting  $\beta$ -catenin degradation through this interaction, HTT regulates the WNT signaling pathway, which itself

controls crucial aspects of cellular differentiation. Furthermore, loss of HTT from basal cells in healthy mammary tissue leads to the disruption of ZO-1 transport from the plasma membrane to the cytoplasm of luminal cells, leading to altered polarity [12]. In healthy and tumoral tissue, S421-P-HTT colocalizes with ZO-1 at the cell membrane and modulates its localization, as already discussed. As HTT phosphorylation at serine 421 is involved in microtubule-mediated vesicular transport to the cell membrane [34], it may regulate adhesion by transporting various components of intercellular complexes. Mutant HTT appears to act as a loss of function mutant, leading to decreased expression of ZO-1 and E-cadherin and increased metastatic capacity of tumoral cells [15]. The function of HTT in cellular adhesion may play a key role during embryonic neurogenesis, as neuronal adhesion and polarity are essential for the establishment of a functional network.

On a global scale, HTT expression appears to correlate with the stage of differentiation of normal and pathological tissues. HTT levels are higher in epithelial cell types, such as skin, squamous, and mammary cells, than in mesenchymal cell types, such as skin fibroblasts, mammary adipocytes, and stromal cells from the uterus [10]. HTT expression in breast cancer correlates with the differentiation stages of the tumoral tissue [14], being highly expressed in well-differentiated breast carcinomas and poorly expressed in poorly differentiated breast cancers, which are associated with a poor prognosis.

### **HTT-INTERACTING PROTEINS: PARTNERS IN CANCER?**

Since 2003, more than 350 interactors of HTT have been identified, whereas only few have been further validated by binding assays and co-localization experiments [53–58]. At the molecular level, most of these partners participate in one of the following pathways: intracellular dynamics, protein degradation, cytoskeletal dynamics, and gene expression. Obviously, proteins participating in such pathways could be involved in HTT-mediated effects during tumorigenesis. However, little is known on these interactions, except for the above-mentioned role of HTT on HER2 recycling and the maintenance of ZO-1 at junctions.

One pathway of particular interest is autophagy, a mechanism in which HTT acts as a scaffold protein [59, 60]. Autophagy prevents cancer development

and conversely, once cancer is established, increased autophagic flux often enables tumor cell survival and growth [61]. In fact, a role for autophagy at nearly every phase of the metastatic cascade has been identified [62]. Mutant HTT exon 1 protein is expressed in patients and knock-in HD mouse models as a result of incomplete HTT gene transcription [63, 64]. Interestingly, mutant HTT exon 1 protein expression causes cellular stress that activates autophagy [65, 66]. Thus, the activation of autophagy by mutant HTT expression in addition to a direct function for HTT in autophagy itself may be germane to a role for wild-type and mutant HTT in carcinogenesis and metastatic progression.

Also, studies have described a direct role for several HTT-interacting proteins in carcinogenesis. For example, the tumor suppressor P53 is mutated in many breast carcinomas [67]. Mutant HTT increases P53 expression, which has been shown to accumulate in murine and cellular HD models and postmortem brains of HD patients [68]. Thus, if this accumulation occurs as well in other cell types that do express mutant HTT, it may participate in the lower cancer incidence in the HD population [17, 19, 20], although this is yet to be established.

The HTT interacting protein 1, HIP1, an endocytic protein, is overexpressed in adenocarcinomas, such as breast, ovarian, colon, prostate, and lung cancers [69]. HIP1 acts as a pro-survival factor and its expression has been associated with metastatic progression and a poor prognosis for prostate cancer patients [69]. HIP1 is also associated with poor overall survival of acute myeloid leukemia patients [70]. Surprisingly, others found that HIP1 acts to suppress metastasis and regulates the epithelial-mesenchymal transition in lung cancer [71]. Moreover, HTT interacting protein 14, HIP14, is an oncogene that can induce tumor formation in mice [72]. Finally, expression of HAP1 (HTT associated protein 1) is lower in breast cancer than in healthy tissue and its overexpression decreases the migration velocity and invasive capacities of mammary tumoral cells [27, 73].

HTT may thus participate in the tumorigenic or anti-tumorigenic effects induced by its partners. This hypothesis could be tested by investigating the effect of HTT partners on tumorigenesis in the absence of HTT or in the presence of mutant HTT.

### **CONCLUSION**

Cancer and neurodegenerative disorders, which represent important health public issues, are two

research topics rarely associated. However, they clearly share dysregulated signaling pathways, as shown by the example of HTT that is a key regulator of the balance between cell survival and cell death under normal, neoplastic, and neurodegenerative conditions. The specificity of the cancer types that are regulated by HTT may depend on its expression levels which are heterogeneous across cell types as well as on the signaling pathways involved in the tumorigenic cascade. Unraveling the molecular mechanisms involved in both diseases will lead to a better comprehension of the function of a central scaffold protein such as HTT and of the association between CAG repeats length and cancers in polyglutamine disorders.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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