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Hypothesis

Upregulated Chaperone-Mediated Autophagy May Perform a Key Role in Reduced Cancer Incidence in Huntington's Disease

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Abstract. Incidence of cancer is markedly reduced in patients with the hereditary neurodegenerative polyglutamine (polyQ) diseases. We have very poor knowledge of the underlying molecular mechanisms, but the expanded polyQ sequence is assumed to play a central role, because it is common to the respective disease related proteins. The inhibition seems to take place in all kinds of cells, because the lower cancer frequency applies to nearly all types of tumors and is not related with the characteristic pathological changes in specific brain tissues. Further, the cancer repressing mechanisms appear to be active early in life including in pre-symptomatic and early phase polyQ patients. Autophagy plays a central role in clearing proteins with expanded polyQ tracts, and autophagy modulation has been demonstrated and particularly investigated in Huntington's disease (HD). Macroautophagy may be dysfunctional due to defects in several steps of the process, whereas increased chaperone-mediated autophagy (CMA) has been shown in HD patients, cell and animal models. Recently, CMA is assumed to play a key role in prevention of cellular transformation of normal cells into cancer cells. Investigations of normal cells from HD and other polyQ carriers could therefore add further insight into the protective mechanisms of CMA in tumorigenesis, and be important for development of autophagy based strategies to prevent malignant processes leading to cancer and neurodegeneration.

Keywords: Polyglutamine disease, huntingtin, reduced cancer risk, chaperone-mediated autophagy

INTRODUCTION

It has for a long time been known that patients with neurodegenerative disorders have some protection against cancer diseases. Results from a meta-analysis of 50 epidemiological studies showed a lower co-occurrence of cancer in neurodegenerative disorders including Alzheimer's disease, Parkinson's disease. and, particularly pronounced, in Huntington's disease (HD) [1]. HD belongs to the polyglutamine (polyQ) diseases which are hereditary late onset neurodegenerative diseases that all have CAG repeat expansion mutations in otherwise unrelated genes resulting in expression of mutant proteins with an expanded polyQ sequence. In addition to HD, this group also includes Kennedy's disease, dentatorubral-pallidoluysian atrophy, and spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, and 17. The

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mutant proteins are ubiquitously expressed, and misfolding and aggregation leads to dysfunction and cell death mainly in brain neurons; however, peripheral cell dysfunction is also occurring. The toxicity of the mutant proteins is associated with aggregated as well as soluble forms which are highly challenging the protein clearance mechanisms. Degradation of the wild type and mutant forms of the proteins take place via proteasomes and lysosomes working in complex interactions [2].

The relationship between having a polyQ disease and reduced risk of cancer was first described in 1999 by Sørensen et al. from a study of HD patients identified from the Danish Huntington's disease registry [3]. The occurrence of cancer was determined from the files of the Danish Cancer Registry and compared with national incidence rates for various categories of tumors. A significantly lower incidence of cancer diseases was found. The standardized cancer incidence ratio for the HD patients was 0.6 with a 95% confidence interval of 0.5–0.8, and the lower incidence was seen for cancer of almost all types. The incidence of cancer was not lower among their healthy relatives, indicating that the inhibitory effect was linked to cellular pathological processes due to the HD mutation. These results were confirmed in a Swedish study, which besides HD also included other polyQ diseases [4]. The cancer incidence was found to be lower in all groups of polyQ diseases. Interestingly, this tendency was even more pronounced in mutation carriers before a clinical diagnosis of the neurological disease. Also this study reports that the lowered rate of cancer applies to nearly all types of cancer, and that the cancer incidence in relatives, here unaffected parents, was similar to that found in the general population. PolyQ patients that developed cancer diseases had, however, a median survival time that did not differ from cancer patients generally. A lower cancer incidence among polyQ patients has subsequently been confirmed in different populations [5, 6]. Recently, a study of 6540 subjects obtained from the European Huntington's disease network, REGISTRY, confirmed the significant lower cancer incidence ratio in this HD population [7].

These results clearly suggest impeding of tumorigenesis in carriers of a polyQ mutation. We have still deficient understanding of this at the molecular level, but the expanded polyQ sequence is assumed to play a central role because it is common to the otherwise different proteins. It is remarkable that the cancer inhibitory mechanisms seem to take place in all kinds of cells because the lower frequency of cancer applies to a wide range of cancer diseases and does not seem to be related with the most pronounced pathological changes and cell death in specific brain tissues. Further, the cancer repressing mechanisms appear to be active early in life in pre-symptomatic carriers and early phase polyQ patients [4].

Autophagy plays a central role in clearing the proteins with expanded polyQ tracts, and autophagy modulation has been demonstrated in polyQ diseases and particularly investigated in HD [8–10]. Recently, a specific form of autophagy, chaperone-mediated autophagy (CMA), has been shown to play a key role in prevention of cellular transformation of normal cells into cancer cells [11]. Taken together these observations lead to the here presented hypothesis:

Activation of chaperone-mediated autophagy in cells from HD gene carriers protects them from carcinogenesis.

AUTOPHAGY

Three types of autophagy, microautophagy, macroautophagy, and CMA, are essential for degrading cytoplasmic proteins including removal of misfolded and aggregated proteins and are constitutively active at different levels in healthy mammalian cells. Best characterized thus far are macroautophagy and CMA that target cytosolic components to the lysosomes for degradation and can crosstalk in most cell types. Definitions and autophagy processes have been described in detail by Galluzzi et al. [12]. Macroautophagy is characteristic by formation of double-membrane vesicles, autophagosomes, bringing proteins to the lysosomes by fusion. CMA is a selective form of autophagy that allows removal of specific proteins containing a KFERQ-like motif recognized by the chaperone Hsc70. This protein/chaperone complex associates with the lysosomal membrane protein receptor LAMP-2A for transport into the lysosome. CMA is activated by several stress factors including starvation, oxidative stress and the presence of misfolded proteins. A multitude of soluble cytosolic proteins are known to be CMA substrates, including huntingtin (HTT) [9], and CMA participates in several processes related to cancer and neurodegenerative diseases. It may exhibit a biphasic response where activation occurs early in pathogenesis as a protective mechanism followed by a decline that may contribute to disease progression

[13]. Importantly, different types of autophagy can coexist and cross-talk in the same cell dependent on the status and need of the cell [14, 15].

HD AND THE ROLE OF HTT IN AUTOPHAGY

The autosomal dominantly inherited HD is the most intensely studied of the polyQ diseases. It is caused by a trinucleotide (CAG) repeat expansion in exon1 of the *HTT* gene encoding the ubiquitously expressed HTT protein [16]. Complete penetrance of HD is observed for CAG repeat sizes of >40. The mean age of disease onset is 40 years, but dysfunction of specific neurons in the brain, particularly in basal ganglia and cerebral cortex, can be detected up to 10–15 years before a clinical diagnosis. This is usually based on the presence of chorea, dystonia, and other motor signs, but is often preceded by signs of cognitive and psychiatric diseases [17]. The patients also present symptoms in peripheral organs and tissues. Weight loss, cardiac failure, and skeletal-muscle wasting are additional occurrences [18, 19].

Wild type HTT is a large protein,>3000 amino acids, which is expressed throughout the body from embryonic development and throughout life. It localizes to the nucleus as well as to cytoplasmic compartments. It adapts various conformations depending on its interacting partners, and multiple post-translational modifications regulate HTT function and activity [20]. The HTT protein is involved in numerous cellular processes including different pathways that modulate autophagy. It seems to have a key function in promoting macroautophagy by interaction with the cargo receptor SQSTM1/p62 and with the autophagy initiation kinase ULK1 and bringing together components in macroautophagy [21]. Normal length polyQ domains, inclusive the HTT polyQ tract, interact with beclin1 considered to be a key initiator of macroautophagy in mammalian cells [22]. Further, due to the Atg11-like C-terminal domain, HTT is considered to function as a scaffold for selective macroautophagy [23, 24].

Mutant HTT (mHTT), carrying the expanded polyglutamine tract in the N-terminal of the protein, accumulates over time and exists in all cells in soluble as well as in aggregated forms. The toxicity of the different forms and the cascade of cellular events leading to degeneration and death of neuronal cells are still being debated [20]. PolyQ containing fragments of different lengths, arisen by calpain and caspase cleavage, play a crucial role in the molecular pathogenesis. Cell and animal HD models expressing just an N-terminal fragment of mHTT show molecular and symptomatic changes characteristic for HD with a dependence on the fragment length [25]. Mutant HTT is cleared through the ubiquitin/proteasome system (UPS) and autophagy. UPS has been proposed to be impaired, but the results are conflicting [26, 27]. Macroautophagy has been found to be dysfunctional; although the number of autophagosomes is increased several defective steps in their formation result in empty autophagosomes and blocked fusion with the lysosomes, reviewed by Martin et al. [28].

The conditions for CMA activity are present as HTT contains functional KFERQ-like CMA targeting motifs of which one, 99-KVRVN-103, has been shown to mediate interaction of HTT fragments with Hsc70. In the very N-terminal part of the HTT fragment a 14-LKSFQ-18 motif has similar properties after phosphorylation and acetylation [29, 30]. Several stress factors which could contribute to activation of CMA occur in cells with mHTT, e.g., oxidative stress is pronounced [10]. Actually, increased CMA activity has been reported in several HD cell and mice models. CMA appears to target truncated amino-terminal HTT fragments preferentially; studies of cell models have shown that HTT fragments with an expanded polyQ have a stronger interaction with LAMP-2A and Hsc70 than wtHTT fragments [8, 9].

Important and central to the hypothesis is the cross-talk between macroautophagy and CMA. Thus, blockage of macroautophagy can lead to compensatory upregulation of CMA [15, 31]. By studying HD mouse and cell models Koga et al. just found a compensatory upregulation of CMA in response to macroautophagic dysfunction in early stages of HD [8]. It was brought about by increase in Hsc70 and LAMP-2A. The mRNA level of LAMP-2A was higher in all the studied cell types. Although the extend of upregulation was cell type dependent these observations demonstrate it to be universally occurring in both neuronal and non-neuronal cell types containing mHTT fragments.

CMA has been found to decrease with age in several cell types and tissues mainly due to reduced levels of LAMP-2A, although it may depend on the model used [11, 13, 32]. It is possible that as long as CMA functions at a significant high level HD gene carriers can degrade mHTT before it causes fatal toxicity, but an age dependent decline of autophagy may contribute to the pathological manifestations of HD and

probably also to a reduced cancer protective effect with age.

ANTI-TUMOR FUNCTION OF CMA

The complex role of autophagy in cancer biology has been eagerly studied through the last decade but is still far from being fully clarified. In particular has macroautophagy been investigated, but also CMA has gained increasing interest. *In vitro* and *in vivo* studies have shown that CMA plays different roles depending on the different stages of tumorigenesis, inhibiting malignant cell transformation in normal cells but promoting cell growth in tumor cells. Arias and Cuervo have recently reviewed the anti-oncogenic versus pro-oncogenic effects of CMA [33], and it has also been demonstrated to occur in a subtype of cancer in HD [34]. In relation to the here presented hypothesis, focusing on the early stages of cancer development in HD, it is a very important finding that CMA can prevent cellular transformation of normal cells into cancer cells. Gomes et al. showed that CMA serves as a defense mechanism against malignant transformation of normal cells by studying MYC (myelocytomatosis viral oncogene homolog) driven transformation of fibroblasts [35]. The defense mechanism was due to CMA activation which indirectly controls MYC levels. Thus, CMA activation decreases the level of the pro-oncogene protein CIP2A which stabilizes MYC in human malignancies. Furthermore, the levels of the proto-oncogenic protein MDM2 and the tumor-associated protein TCTP can also be controlled by CMA [36, 37]. The role of CMA in cell cycle control and anti-tumor function has recently been reviewed and discussed by Andrade-Tomaz et al. [38].

CMA may also play an active role in blocking development of cancer. Results from experiments done to find strategies for elimination of cancer cells support this. Mutations in the tumor suppressor gene *TP53* are by far the most common occurring in cancer cells. By studying dormant, non-proliferating cancer cells Vakifahmetoglu-Norberg et al. found that degradation of mutant p53 in contract to wild-type p53 occurs via the lysosomes and involving CMA [39]. They showed that an Hsc70 recognition motif is exposed on the surface of mutant p53 indicating that it co-localize to the cytoplasm and interact with Hsc70 which promotes degradation through CMA. Overall, a variety of mechanisms relevant for the anti-oncogenic effect of CMA have now been supported [33].

CONCLUSION

A large number of genes and molecular pathways have been proposed to be involved in the inverse comorbidity of neurodegenerative diseases and cancer. DNA reparation, immune signal transduction, and mitochondrial activity are some of the mentioned possible processes. A large number of questions also arise regarding the cellular mechanisms that could be involved in HD gene carriers' resistance to cancer. As early as in the first publication of lower incidence of cancer among HD patients the authors proposed that the modified HTT could increase the rate of apoptosis in pre-neoplastic cells [3]. This was followed up by Ehrnhoefer et al. who suggested that upregulation of p53 found in mHTT containing neuronal and peripheral cells lowers the apoptotic threshold [40]. In a new publication, the authors analyzed gene networks associated with HD, apoptosis, and cancer and identified genes pointing on apoptosis along with lipid metabolism dysregulation and cell homeostasis as key processes [41]. In cell and mouse models Murmann et al. investigated the effects of trinucleotide repeat (TNR) siRNA in cancer cell and found the siCAG repeat to be the most toxic suggesting that RNA interference could be involved in neurodegeneration as well as cancer suppression mechanisms [42]. Various proposals thus exist to explain anti-cancer mechanisms in HD.

Based on the here described observations and experiments regarding autophagy it is reasonable to suggest that expression of mHTT in cells throughout the body causes stress that activates CMA which then plays a key role in blocking malignant transformation of normal cells in HD carriers. CMA could likewise play a role in the reduced cancer incidence among other polyQ disease patients. CMA has been shown to be involved in degradation of mutant proteins in cells expressing SCA proteins [43, 44], but the activity of CMA in pre-symptomatic and in early phase SCA patients needs to be investigated.

To clarify the molecular mechanisms involved, including the interplay between the different types of autophagy, further investigations in relevant models are important. The molecular observations of the effect of polyQ expanded sequences on autophagy have so far been obtained from *in vitro* studies, e.g., from transfected cell culture models under special

culture conditions and/or from cell and animal models expressing mHTT/mHtt fragments of different length; usually with polyQ length >100 which is not typical for HD patients. In terms of choosing a polyQ disease mouse model it would be important to study the role of CMA activation in early phase of tumorigenesis in cells from different tissues/organs. With respect to cell models, cells obtained from polyQ mutation carriers, e.g., cultured skin fibroblasts or induced pluripotent stem cells, could be particularly useful for clarification of the mechanisms. Cells could be obtained from carriers of different polyQ diseases, from individuals with different length of the CAG repeat sequence, from different age/ stages of diseases, and from different families to investigate the role of the genetic background. These kinds of studies would bring further insight into the mechanisms protecting HD cells from tumorigenesis and contribute to the clarification of the multifaceted biology of the transformation of normal cells into cancer cells. They would equally improve our knowledge of the role of CMA in the molecular pathology of HD. Finally, they are important because modulation of autophagy processes has been proposed as treatment for both polyQ and cancer diseases.

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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