The regulatory role of cystatin C in autophagy and neurodegeneration

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Autophagy is a dynamic cellular process involved in the turnover of proteins, protein complexes, and organelles through lysosomal degradation. It is particularly important in neurons, which do not have a proliferative option for cellular repair. Autophagy has been shown to be suppressed in the striatum of a transgenic mouse model of Parkinson’s disease. Cystatin C is one of the potent regulators of autophagy. Changes in the expression and secretion of cystatin C in the brain have been shown in amyotrophic lateral sclerosis, Alzheimer’s and Parkinson’s diseases, and in some animal models of neurodegeneration, thus proving a protective function of cystatin C. It has been suggested that cystatin C plays the primary role in amyloidogenesis and shows promise as a therapeutic agent for neurodegenerative diseases (Alzheimer’s and Parkinson’s diseases). Cystatin C colocalizes with the amyloid β-protein in the brain during Alzheimer’s disease. Controlled expression of a cystatin C peptide has been proposed as a new approach to therapy for Alzheimer’s disease. In Parkinson’s disease, serum cystatin C levels can predict disease severity and cognitive dysfunction, although the exact involvement of cystatin C remains unclear. The aim: to study the role of cystatin C in neurodegeneration and evaluate the results in relation to the mechanism of autophagy. In our study on humans, a higher concentration of cystatin C was noted in cerebrospinal fluid than in serum; much lower concentrations were observed in other biological fluids (intraocular fluid, bile, and sweat). In elderly persons (61–80 years old compared to practically healthy people at 40–60 years of age), we revealed increased cystatin C levels both in serum and intraocular fluid. In an experiment on C57Bl/6J mice, cystatin C concentration was significantly higher in brain tissue than in the liver and spleen: an indication of an important function of this cysteine protease inhibitor in the brain. Using a transgenic mouse model of Parkinson’s disease (5 months old), we demonstrated a significant increase in osmotic susceptibility of brain lysosomes, depending on function of autophagy, while in a murine model of Alzheimer’s disease, this parameter did not differ from that in the appropriate control.

Key words: cystatin C; autophagy; neurodegeneration.

For citation: Korolenko T.A., Shintyapina A.B., Pupyshev A.B., Akopyan A.A., Russkikh G.S., Dikovskaya M.A., Vavilin V.A., Zavjalov E.L., Tikhonova M.A., Amstislavskaya T.G. The regulatory role of cystatin C in autophagy and neurodegeneration. Vavilovskii Zhurnal Genetiki i Selektsi = Vavilov Journal of Genetics and Breeding. 2019;23(4):390-397. DOI 10.18699/VJ19.507

Регуляторная роль цистатина С в аутофагии и нейропатологии

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Аутофагия – динамичный клеточный процесс, связанный с оборотом белков, белковых комплексов и органелл посредством мозаической деградации. Аутофагия особенно важна в нейронах, которые не имеют пролиферативного ресурса для клеточного восстановления. Одним из мощных регуляторов аутофагии является цистатин С. Изменения экспрессии и секреции цистатина С в головном мозге показаны при боковом амиотрофическом склерозе, болезни Альцгеймера и Паркинсона, а также на некоторых моделях нейродегенеративных заболеваний.
Introduction
The search for new markers of aging, neurodegenerative diseases, and atherosclerosis is important for modern medicine (Ciechanover, Kwon, 2015). Cystatins are known to be potent endogenous inhibitors of cysteine proteases of the papain superfamily and form equimolar, tight, and reversible complexes with human cysteine proteases (cathepsins B, H, K, L, and S) (Stoka et al., 2005; Korolenko et al., 2011, 2015).

Cystatin C is a known extracellular endogenous cysteine proteinase inhibitor, which has been studied more thoroughly than other cystatins (cystatin SN et al.) and has been evaluated as a possible marker of several pathological processes (tumor growth and metastasis) (Poteryaeva et al., 2000; Maxfield, 2014). Increased serum cystatin C concentration is well known as a possible marker of several pathological processes involved in such responses are poorly characterized and may contribute to secondary damage and/or regeneration in the central nervous system (Ling, Salvaterra, 2009; Harris, Rubinsztain, 2011). Increased levels of p62 (also called as sequestosome 1 (SQSTM1) and higher sensitivity to 7-oxyester-mediate lysosomal membrane damage was shown in macrophages isolated from cystatin C knockout (CysC−/−) mice (Li et al., 2016).

Cystatin C as a possible diagnostic marker of neurodegenerative diseases
Cystatin C has a broad spectrum of biological roles, including modulation of inflammatory response (Li et al., 2016). Using immunohistochemical methods in Alzheimer’s disease Zhong et al. (2013) have revealed that cystatin C co-localizes with amyloid-β in amyloid-laden vascular walls and in the senile plaque cores. These authors suggested that cystatin C revealed protection against neurodegeneration by inhibition of cysteine proteases (cathpsins B), suppression of amyloid-β aggregation and induction of autophagy (Zhong et al., 2013).

Low cystatin C level in cerebrospinal fluid of patients with Alzheimer disease and dementia confirmed this hypothesis. In elderly men (free of dementia at the baseline) low levels of serum cystatin C can precede clinical manifestation of Alzheimer’s disease and vascular dementia confirmed this hypothesis. In elderly men (free of dementia at the baseline) low levels of serum cystatin C can precede clinical manifestation of Alzheimer’s disease and vascular dementia confirmed this hypothesis. In elderly men (free of dementia at the baseline) low levels of serum cystatin C can precede clinical manifestation of Alzheimer’s disease and vascular dementia confirmed this hypothesis. In elderly men (free of dementia at the baseline) low levels of serum cystatin C can precede clinical manifestation of Alzheimer’s disease and vascular dementia confirmed this hypothesis. 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there are opposite points of view of researchers suggesting that brain amyloid-β level depends mainly on a balance between its formation from the amyloid precursor protein (APP) and its removal by proteolysis, with a significant role of several zinc-proteases including nephrilysin, the endothelin converting enzymes (ECE-1 and -2), and the insulin-degrading enzyme (Naivlaeva, Turner, 2017). Moreover, cathepsin B, as the most important cysteine protease, might be also anti-amyloidogenic, helping in amyloid-β clearance or, instead, might be involved in amyloid-β production (Zeronvnik, 2009).

Parkinson’s disease is characterized by a decreased motor activity resulting from the death of dopaminergic neurons in the substantia nigra. α-synuclein, located in presynaptic terminals of neurons, is considered as the main pathogenic protein in Parkinson’s disease; another strong pathogenic factor is oxidative stress (Hara et al., 2006; Huang et al., 2015). Dopamine can induce autophagic cell death with upregulation of α-synuclein in human neuroblastoma cells (Gomez-Santos et al., 2003).

An increased serum level of secreted cystatin C was demonstrated during the process of aging (Cuervo, Wong, 2014; Mathews, Levy, 2016) and in various diseases like tumors (Gashenko et al., 2013) or atherosclerosis (Korolenko et al., 2011, 2012, 2015). In biological fluids of healthy persons, the highest concentration of cystatin C in our study was noted in cerebrospinal fluid (CSF), with the following ranking of concentrations: CSF > saliva > serum > intraocular fluid > tear fluid > sweat > urine (Fig. 1).

Results similar to our data concerning cystatin C levels in CSF, saliva, and serum were obtained by other authors (Bjornstad et al., 2015). According to the data that we obtained in practically healthy persons, the concentration of cystatin C is increased in the serum and intraocular fluid of people aged 61–80 years (Fig. 2).

At early stage of Parkinson’s disease, increased serum cystatin C was associated with sleep-disordered breathing problems (Xiong et al., 2018). In CSF of patients with atrophic lateral sclerosis cystatin C level was significantly decreased, there was a correlation between cystatin C levels and G73A polymorphism in CST3 gene encoding cystatin C (Yamamoto-Watanabe et al., 2010). In the brain of patients with Alzheimer’s disease cystatin C revealed protective role as a strong endogenous inhibitor of cysteine proteases (cathepsin B), inducer of cellular autophagy related to amyloid-beta aggregation (one of the several pathways of protection) (Mathews, Levy, 2016).

Autophagy is a dynamic cellular process involved in the turnover of proteins, protein complexes, and organelles through lysosomal degradation (Chen, Klionsky, 2011). Autophagy is particularly important in neurons, which do not have a proliferative option for cellular repair (Lee, 2009; Son et al., 2012). Positive and some negative effects (like the “Janus-faced” role) of increased autophagy have been uncovered during development of neurodegeneration (Viscomi, D’Amelio, 2012; Wang, Hiesinger, 2012).

The regulatory role of cystatin C in autophagy and neurodegeneration

A common feature of neurodegenerative diseases is the accumulation of proteins prone to aggregation and protein inclusions, which are, on the one hand, the markers of these diseases and, on the other hand, the cellular tools for combating these diseases; one of the important therapeutic targets in this process is autophagy (Ciechanover, Kwon, 2015; Torra et al., 2018). Autophagy is weakened in various ways in these diseases and decreases with ageing. The removal of the accumulating toxic proteins and structures is carried out by the mechanisms of chaperone-mediated autophagy, macroautophagy, and mitophagy during interactions with the ubiquitin–proteasome system.

Changes in autophagy are involved in the development of various age-dependent degenerative disorders such as neurodegeneration (Tizon et al., 2010b), cancer (Gammoh et al., 2016), tissue atrophy, alcohol neurointoxication (Luo,
2014) and accelerated aging (Coria et al., 1987; Kovács et al., 2017). Decreased concentration of cystatin C in CSF was reported to have diagnostic significance in neurodegenerative diseases, such as amyotrophic lateral sclerosis, which is characterized by progressive motor neuron degeneration (Mathews, Levy, 2016). Low concentration of cystatin C was detected in the serum of patients with Alzheimer’s disease, correlating with conversion from mild cognitive disturbances to dementia; in CSF of patients with Alzheimer’s disease, the cystatin C level was found to be lower as compared to patients with dementia; therefore, it is possible that changes of cystatin C in CSF may serve as a biomarker of disease (Mathews, Levy, 2016). However, according to some data (Přikrylová Vranová et al., 2010) cystatin C level in CSF of patients with Parkinson’s disease was not changed significantly.

Many studies indicate that the weakening of autophagy and/or the incompleteness of protein degradation are important initiators of Parkinson’s disease (Wang, Hiesinger, 2012; Maxfield, 2014). *In vitro* studies have revealed that pharmacological induction of autophagy, for instance, by trehalose (Dehay et al., 2010) or by resveratrol (Wu et al., 2013), leads to an improvement in the molecular patterns of Parkinson’s disease. In general, it is believed that a decrease in autophagy and in recognition of the segregated material is the key factor of Parkinson’s disease, and possibly, activation of autophagy is a good therapeutic strategy against this disease.

Recently new pharmacological modulators of autophagy with a therapeutic potential were introduced (Galluzzi et al., 2017a, b). Among modulators of autophagy in brain cells for prevention of neurodegeneration (Cheung, Ip, 2011), various authors suggested activators of autophagy, like rapamycin (Malagelada et al., 2010), trehalose, valproate (Harris, Rubinsztein, 2011), and cystatin C (Watanabe et al., 2018).

According to our data obtained in an experimental study, the cystatin C level was significantly higher in the brain than in the liver or spleen of C57Bl/6J untreated mice (Fig. 3), indicating the significant role of this inhibitor in brain tissue. As demonstrated in our previous study on an experimental murine genetic model of Parkinson’s disease, autophagy (according to LC3-II expression) was decreased in the striatum and substantia nigra as compared to other regions of the brain, thus reflecting injury of motor neurons (Pupyshev et al., 2018). This model of Parkinson’s disease manifested increased osmotic susceptibility of lysosomes in the brain (according to a release of lysosomal enzyme β-galactosidase) (Fig. 4, a) in conjunction with secondary changes of their membranes as a result of dysfunction of lysosomes and intralysosomal accumulation of toxic material. In a model of Alzheimer’s disease, we did not notice the changes in the permeabilization of lysosomal membranes in brain tissue (Fig. 4, b). Stabilization of lysosomal membrane by a neuroprotector ceftriaxone (see Fig. 4, b) can be related to anti-inflammatory effect of this drug. In the pharmacological model of Alzheimer’s disease caused by the central administration of amyloid β in mice, amyloid β toxicity produced an almost 3-fold increase in LC3-II expression (as result of activation of autophagy related to neuroinflammatory process in the frontal cortex) (Fig. 5), and ceftriaxone significantly reduced the rate of autophagy, which apparently reflects the anti-inflammatory effect of ceftriaxone on the cerebral cortex and thereby weakening the autophagic response.

Regulation of autophagy is a complex process, depending on the cell types and diseases, including neurodegeneration (Kiriyama, Nochi, 2015; Zou et al., 2017). Current state of knowledge concerning transcriptional, post-transcriptional, and post-translational regulation of autophagy in yeast and mammals were discussed (Feng et al., 2015; Hwang et al., 2017). Novel pharmacological modulators of autophagy were revealed under recent investigations (Ha, Kim, 2016; Gao et al., 2017; Johnston et al., 2017). Several other approaches have been suggested for restoration of autophagy (Martini-Stoica et al., 2016). One of them is introduction of...
The absence of neurodegeneration in to 6 months of age (Huh et al., 1999). Earlier cystatin C knock­
out mice were found to be fertile and have no gross pathological abnormali­
ities or signs of neurodegeneration up to 6 months of age (Huh et al., 1999). The absence of neurodegeneration in
that study might be attributed to young age of mice (less than 6 m.o.) and strong compensatory mechanisms. Later cystatin C was shown to inhibit amyloid-beta deposition in Alzheimer’s disease mouse models (Mi et al., 2007). Moreover, induction of autophagy by cystatin C may be a mechanism that protects murine primary cortical neurons and neuronal cell lines (Lee et al., 2007; Maetzler et al., 2010; Tizon et al., 2010a). In the brain, multiple in vitro and in vivo findings have demonstrated cystatin C protective roles via pathways that depend upon the inhibition of endosomal-lysosomal pathway cysteine proteases (cathepsin B), via the induction of cellular autophagy, via the induction of cell proliferation, or via the inhibition of amyloid-β (Aβ) aggregation (Gauthier, Liu, 2016; Mathews, Levy, 2016).

There are some controversial results on the effect of certain drugs on serum cystatin C concentrations in humans for estimation of glomerular filtration rate (GFR) in patients with renal disease. Corticosteroids (prednisolone, repeated administration) can significantly increase serum cystatin C concentration from 1.24±0.40 mg/L at baseline to 1.61±0.80 mg/L at the end of a study period (p<0.05). This finding needs to be considered when interpreting cystatin C levels in patients with heart failure receiving corticosteroid therapy (Zhai et al., 2016).

An additional property of cystatin C (except as a protease inhibitor) that makes this protein clinically relevant is that it can form aggregates by the mechanism known as domain swapping, similar to that involved in the formation of amyloid β plaques in Alzheimer’s disease (Xu et al., 2011; Kaminskyy, Zhivotovsky, 2012). Secretion of IL-10 in response to inflammatory stimuli downregulates IRF-8 and consequently cystatin C synthesis in vivo. The serum concentration of cystatin C decreases in an IL-10-dependent manner in mice treated with the TLR9 agonist CpG (synthetic analog of bacterial DNA, activator of dendrite cells). Cystatin C synthesis is therefore more tightly regulated than hitherto recognized. The mechanisms underlying this regulation may be targeted to alter cystatin C production, with potential therapeutic benefits (Xu et al., 2005, 2011). Transcription factor – IFN regulatory factor 8 (IRF-8) is critical for cystatin C expression in primary dendritic cells. Only the cells with IRF-8 bound to the CST7 gene promoter express high levels of this inhibitor abundantly. Cystatin C can prevent formation of amyloid β plaques associated with Alzheimer’s disease and can itself form toxic aggregates. Cystatin C regulates NO secretion by macrophages and is a TGF-β antagonist.

New approaches to Parkinson’s disease treatment

According to data obtained by Chen et al. (2015), Hu et al. (2016), changes in the expression of cystatin C in Parkinson’s disease are related to mild cognitive dysfunc­
tion. Recently, it was shown that intracerebroventricular administration of cystatin C ameliorates amyotrophic lateral sclerosis-like disturbances in mice (Watanabe et al., 2018). Induction of autophagy by cystatin C was suggested as a potential mechanism of prevention of cerebral vasospasm during several neurological disturbances in an animal experiment (after subarachnoid hemorrhage in mice) (Liu et al., 2013). Possible mechanism of stimulation of autophagy by cystatin C is suggested via the mammalian target of rapamycin (mTOR) signaling pathway (Fig. 6).

It has been found that the injections of cystatin C into the s. nigra of A53T mutant alpha-synuclein transgenic mice revealed neuroprotective effect in vivo in Parkinson’s disease model with increased autophagy markers LC3B in different brain regions (Zou et al., 2017). Authors concluded, that neuroprotective effect of cystatin C in A53T transgenic mice was related to upregulating the autophagy and VEGF pathways. It presents a new approach to the treatment of Parkinson’s disease through neuronal-vascular protection mediated by cystatin C.

Conclusion

The roles of autophagy in the maintenance of cellular survival and in suppression of neurodegeneration have been evaluated in Alzheimer’s, Parkinson’s, and Huntington’s diseases, which are accompanied by the accumulation of amyloid β, α-synuclein, and huntingtin, respectively. Autophagy is down regulated in various ways in these diseases and decreases with ageing. Cystatin C is one of the potent regulators of autophagy. Changes in the expression and secretion of cystatin C in the brain have been shown in amyotrophic lateral sclerosis, Alzheimer’s and
PARKINSON’S DISEASE, AND IN SOME ANIMAL MODELS OF NEURODEGENERATION, THIS PROVING A PROTECTIVE FUNCTION OF CYSTATIN C. IT HAS BEEN SUGGESTED THAT Cystatin C PLAYS THE PRIMARY ROLE IN AMYLOIDODEGENSE. CONTROLLED EXPRESSION OF A Cystatin C PEPTIDE HAS BEEN PROPOSED AS A NEW APPROACH TO THERAPY FOR ALZHEIMER'S DISEASE. PROTECTIVE Cystatin C EFFECT IN VIVO (IN A53T TRANSGENIC MICE) WAS CONNECTED WITH UPRGULATION IN AUTOPHAGY AND VEGF PATHWAYS, OPENING A NEW APPROACH TO THE TREATMENT OF PARKINSON’S DISEASE THROUGH NEURALN- VASCULAR PROTECTION MEDIATED BY Cystatin C. ADMINISTRATION OF Cystatin C AS A REGULATOR OF AUTOPHAGY HOLS PROMISE AS ONE POSSIBLE APPROACH TO THE TREATMENT OF NEURODEGENERATIVE DISEASES.

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