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Transglutaminase Inhibition: A Possible Therapeutic Mechanism to Protect Cells from Death in Neurological Disorders

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Abstract

Transglutaminases are a family of Ca^{2+}-dependent enzymes which catalyze post-translational modifications of proteins. The main activity of these enzymes is the cross-linking of glutaminyl residues of a protein/peptide substrate to lysyl residues of a protein/peptide co-substrate. In addition to lysyl residues, other second nucleophilic co-substrates may include monoamines or polyamines (to form mono- or bi-substituted/crosslinked adducts) or –OH groups (to form ester linkages). In absence of co-substrates, the nucleophile may be water, resulting in the net deamidation of the glutaminyl residue. Transglutaminase activity has been suggested to be involved in molecular mechanisms responsible for both physiological or pathological processes. In particular, transglutaminase activity has been shown to be responsible for human autoimmune diseases, Celiac disease is just one of them. Interestingly, neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, supranuclear palsy, Huntington's disease and other polyglutamine diseases, are characterized in part by aberrant cerebral transglutaminase activity and by increased cross-linked proteins in affected brains. Here we describe the possible molecular mechanisms by which these enzymes could be responsible for such diseases and the possible use of transglutaminase inhibitors for patients with diseases characterized by aberrant transglutaminase activity.

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Commentary

Transglutaminases (TG; E.C. 2.3.2.13) are enzymes which catalyze irreversible post-translational modifications of proteins. Examples of TG-catalyzed reactions include: I) acyl transfer between the γ-carboxamide group of a protein/polypeptide glutaminyl residue and the γ-amino group of a protein/polypeptide lysyl residue; II) attachment of a polyamine to the γ-carboxamide of a glutaminyl residue; III) deamidation of the γ-carboxamide group of a protein/polypeptide glutaminyl residue [1, 2]. To date, at least eight different TG, distributed in the human body, have been identified. In the Nervous System several forms of TG are simultaneously expressed [3-5]. Moreover, several alternative splice variants of TGs, mostly in the 3'-end region, have been identified. In particular TG2, which is the best-studied enzyme of the TG family, shows at least five splice variants [6-8]. Some of these splice variants, interestingly, are differently expressed in neurological pathologies, such as Alzheimer's disease (AD) [9]. Up to now numerous scientific reports have suggest that TG activity is involved in the molecular mechanisms responsible for pathogenesis of neurodegenerative diseases, but, to date, however, definitive experimental findings about the role of these enzymes in the development of these human diseases have not yet been obtained. [10-12]. Protein aggregates in affected brain regions are histopathological hallmarks of many neurodegenerative diseases [13]. More than 20 years ago Selkoe et al. [14] suggested that TG activity might contribute to the formation of protein aggregates in AD brain. In support of this hypothesis, tau protein has been shown to be an excellent in vitro substrate of TGs [15, 16] and Nε-(γ-L-glutamyl)-L-lysine (GGEL) cross-links have been found in the neurofibrillary tangles and paired helical filaments of AD brains [17]. Interestingly, a recent work showed the presence of bis γ-glutamyl putrescine in human CSF, which was increased in Huntington's disease (HD) CSF [18]. This is an important evidence that protein/peptides crosslinking by polyamines does indeed occur in the brain, and that this is increased in HD brain. TG activity has been shown to induce also amyloid γ-protein oligomerization [19] and aggregation at physiologic levels [38]. By these molecular mechanisms, TGs could contribute to AD symptoms and progression [20]. Moreover, there is evidence that TGs also contribute to the formation of proteinaceous deposits in Parkinson's disease (PD) [21, 22], in supranuclear palsy [23, 24] and in HD, a neurodegenerative disease caused by a CAG expansion in the affected gene [25]. For example, expanded polyglutamine domains have been reported to be substrates of TG2 [26-28] and therefore aberrant TG activity could contribute to CAG-expansion diseases, including HD. However, although all these studies suggest the possible involvement of the TGs in the formation of deposits of protein aggregates in neurodegenerative diseases, they do not indicate whether aberrant TG activity per se directly determines the disease progression. For example, several experimental findings reported that TG2 activity in vitro leads to the formation of soluble aggregates of α-synuclein [29] or polyQ proteins [30, 31]. To date, as previously reported, at least ten human CAG-expansion diseases have been described [32-41] and in at least eight of them their neuropathology is caused by the expansion in the number of residues in the polyglutamine domain to a value beyond 35–40. Remarkably, the mutated proteins have no obvious similarities except for the expanded polyglutamine domain. In fact, in all cases except SCA 12, the mutation occurs in the coding region of the gene. However, in SCA12, the CAG triplet expansion occurs in the untranslated region at the 5' end of the PPP2R2B gene. It has been proposed that the toxicity results from overexpression of the brain specific regulatory subunit of protein phosphatase PP2A [38].

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