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Review Article

PRESENILIN, "A NEW GENE TARGET IN NEURODEGENERATIVE DISORDERS" A REVIEW

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ABSTRACT

Presenilins are multipass transmembrane proteins which are expressed in many tissues, including brain and they appear to be membrane bound and primarily expressed in endoplasmic reticulum. Ps1 and ps2 genes encode for 46 and 55KDa proteins. Numerous misense mutations in presenilins are associated with neurodegenerative disorders, a condition related both heart and brain may experience. β-catenin associated with partner proteins to regulate its cytoplasmic level. Ps1 is a member of partner proteins and involved in the regulation of β-catenin signal as well as other proteins. This β-catenin signal is connected with onset of familial alzheimers disease. Presenilin have a role in notch pathway so presenilin can also be targeted notch receptor. Alzheimers disease is transmitted as an autosomal dominant disorder and is characterized by an age onset. Mutations in ps1 and ps2 of these genes cause in 5-10% of cases of FAD. Ps2 homolog of ps1,reduces level of cytoplasmic β-catenin and inhibits β-catenin t-cell factor regulated transcription. These results indicate that ps1 plays a role as inhibitor of β-catenin signal which is connected with AD dysfunction. The finding of ps2 in heart and responsiveness to low glucose and hypoxia suggests that ps2 can be regulated by conditions of ischemia. This article reveals about the presenilin gene is a physiological importance in various neurogenerative disorders.

Keywords: Presenilin, Alzheimers disease, neurodegenerative disorders

INTRODUCTION

Presenilin genes encode polytopic transmembrane proteins, with eight transmembrane domains and a large cytoplasmic loop[1-2],which are processed by proteolytic cleavage and form high molecular weight complex[3] under physiological conditions. It has been involved in developmental morphogenesis, unfolded protein response & processing of selected proteins including β-APP.

Types of presenilins

PS_1 and PS_2 are 467 and 448 amino acid polypeptides[4].

Source of presenilin

Presenilins are initially located to endoplasmic reticulum and golgi compartments, but very recent work suggests a much wider localization other intracellular compartments with a small pool present at plasma membrane[5-6]. Ps 1 is being in many tissues ,both within CNS and in non-neuronal organs[7-8]. PS is maximally expressed in cardiac muscle, Skeletal muscle and pancreas1. PS is most abundant is dendrites of neurons[8].

Characteristic features of presenilins

Very low levels of haloproteins are detected in un-transfected cells and tissues. the major form existing in cells are the endoproteolytically derived N and C-terminal fragments. The half life of the haloprotein in brief (30-60min) and they undergo distinct phosphorylation[4]. Halo protein is actively catabolised possibly by at least two different proteolytic mechanisms. First mechanism Proteasome[9] ,second involves a series of heterogeneous Endoproteolytics cleavages near residue within loop domain by presenilins. This presenilins generates N&C-terminal fragments approximately 35 and 20kDa respectively[10-11].a)Intramembrane proteases b)Cleave substrates within their transmembrane domains[12].All intracellular proteases are conserved polytopic membrane proteins contains catalytic residues within the transmembrane domains[13]. Transmembrane domains include three families: a.presenilin type aspartyl proteases including presenilin dependent γ-secretase and signal peptide peptidase that is essential for generation of signal peptide derived HLA-E epitope in humans.[17-21].b.Site2-protease family zinc metalloprotease that cleave and activate sterol regulatory element binding proteins [22].c.The rhomboid serine proteases that use a catalytic triad to cleave transmembrane ligand substrate such as EGF ligand[23-24]. Presenilins have conserved aspartyl residue a feature of aspartyl proteases within PS transemenbrane domain 6&7 required for production amyloid β protein. Aspartyl protease transition state analog inhibitor directly bind PS_1 and PS_2 and serve as the active site of multi-component enzyme[25-26]. Ps $_1$ and PS_2 genes encode 46 and 55KDA proteins respectively about 80% homologous with eight transmembrane domains and a large hydrophilic loop facing to the cytoplasm[27]. They undergo endo-proteolysis within loop domain and resultant 30 kda N-terminal and 20 kda C-terminal fragments associate with each other in stable heteromeric components of a larger multimeric protein complex that appears as resident in endoplasmic reticulum, golgi complex [28]. The incorporation of PS proteins into a larger complex represents a rate limiting step in PS processing pathway, thus nce incorporated the endoproteolytic fragments remain together with a stable 1:1 stoichiometry and very long half-lives. Haloproteins monomers are fail to get incorporate into these complexes are rapidly degraded with half live of less than 1 hour via a proteosome dependent mechanism[29-30].

Functions of Presenilins

1. PS_1 role in protein and membrane trafficking[31].
2. Ablation of functional PS, expression causes aberrant processing of the β-APP with the failure of γ-secretase cleavage which results in accumulation of uncleaved α-secretasem, β-secretase stubs in a variety of intracellular loci including ER,Golgi,Lysosomes[32-33].
3. PS deficiency alters trafficking of proteolytic fragments of APP and APLP to subcellular compartments which contains γ-secretase and the PS play a direct role in APP processing by γ-secretase[34].
4. Other functions for PS_1 include roles in regulation of signal transduction during development in apoptosis and in cellular calcium ion hemostasis
5. PSS is regulator of the unfolded protein response[35-36]
6. Ps2 plays a role in cellular apoptosis[37-38].
7. Presenilins has an important role in neuronal development and regulating neuronal survival.
8. PS has potential role of presenilins in cell cycle and chromosome segregation[39].

Presenilin in alzheimer's disease.

Alzheimer's disease.

AD is a age related neurodegenerative disorder that arises when neurons in certain regions of the brain particularly those involved in memory, cognition are damaged and ultimately killed, probably as a consequence of abnormal production of amyloidogenic Aβ peptides[40]. The two abnormal microscopic structures called neurofibrillary tangles & senile plaques as the hall marks of AD[41]. Neurofibrillary tangles consist of aberrantly phosphorylated

fibrillary proteins aggregated within neuronal cytoplasm. Their presence signifies failure of the neuron to properly maintain its cytoskeleton, which is required to support the extraordinarily complex branching shape of its numerous processes. The development of tangles is a major & possibly the main mechanism is neuronal death in AD[42]. Senile plaques are more complex, & consists of extracellular deposits of amyloid material and are associated with swollen, distorted neuronal processes called dystrophic neuritis.Plaques start as innoculous deposits of non- aggregated putatively non-neuronal β-amyloid (diffuse plaques). Complex sugar polymer components(glycosamine glycans)are thought to be crucial in the assembly of these deposits. Alzheimers begin to damage the brain years befpre symptoms emerge , nerve cells that process, store & retrieve information have already begun to degenerate & die[43-45].

Symptoms of alzheimers disease.

1. Memory changes that disrupt daily life .
2. Challenges in planning or solving problems .
3. Difficulty completing familiar tasks .
4. Confusion to time & place .
5. Trouble understanding visual images and spatial relationships.
6. Misplacing things & losing abilty to retrace steps
7. New problems with words in speaking or writing .
8. Decreased or poor judgement .
9. With drawal from work or social activities.
10. Changes in mood & personality[41].

Role of presenilins in alzheimers disease.

Several point mutations in the gene coding for the novel proteins presenilin-1 β-app on chromosome 21 are sufficient to cause early on set autosomal familial dominantly inherited AD. Some mutations increase the production of β-amyloid while ,other favours the formation of long (42 Amino acids)forms of β-amyloid ,which aggregate more readily than (40 A.A) short forms[46]. The interaction of presenilins &β-app in the neuronal cell body is critical for organizing vesicular traffic. When this process interrupted the delivery of synaptic vesicles to pre synaptic terminals is impaired & neurotransmitter deficit may exceed neuronal loss[47-49].A common genetic polymorphism affecting gene for apolipoprotein E is firmly established as the major risk factor for the development of AD.This lipoprotein is involved in synaptic repair particularly in response to tissue injury .It has an important role in maintenance of neuronal structure & cholinergic function [50-51]. The marked increment in risk produced by single amino acid difference in the APOE –allelic protein makes it a potentially attractive therapeutic target. Autosomal genetic risk factors currently being investigated include a susceptibility locus on chromosome 12 , polymorphism of the very low density lipo-protein receptor genes as well as an intron mutation of presenilin gene[52-54] .The report that the HLA-A2 allele is assoiated with an earlier age on set suggests modulation of inflammation plays a role in development of disease. In addition, reported mutations in the mitochondrial genome, which can either be inherited or acquired, would contribute to oxidative damage plays a central role for development of AD[55-56].

Presenilin with partner protein β -catenin

β-catenin was detected in peripheral and interior cytoplasm. Co-localisation of ps1 and ß-catenin observed in ER and the proximity of plasma membrane[57-58]. Ps1 is membrane fraction indicate lower activity of proteolytic cleavage. anti β-catenin antibody indicated the presence of endogenous β-catenin in both cytoplasm and membrane fractions .these proteins associated with each other during immuno precipitation. Membrane associated β-catenin involved in cell adhesion and its soluble form in t-cell factor(Tcf) regulated transcription. Ps1 significantly reduced CRT(β-catenin response transcription) activity. CRT activity is regulated by the level of cytoplasmic β-catenin. The inhibition of cytoplasmic β-catenin by ps1 expression was restored by lithium chloride treatment known as an inhibitor of glycogen synthase kinase-3β(GSK -3β). PS-1,GSK-3β,β-catenin complex inhibits the β-catenin signaling cascade. PS-1 has ablity to bind gsk-3beta and mutant PS-1 facilitates phosphorylation of tau by GSK-3ß[59]. β-catenin is known to associate with partner proteins APC(The adenomatous polyposis cell)[60] to regulate it's cytoplasm level.The β-catenin signal may be tightly regulated by these partner proteins in response to extracellular stimuli. Ps1 is a member of these partner proteins. β-catenin signal may be connected with onset of alzheimers disease. Alternatively ps1 may interact with other proteins and induce neuronal death with formation of amyloid plaques and neuro fibrillary tangles[61-62].

β-catenin sigalling pathway

Formation of ps1: β-catenin complex lead to increased stability of β-catenin pathogenic mutant ps1 loses this stablistion effect and cause suppression of β-catenin signal[63].

Role of presenilins in heart failure

Under pathalogical conditions of heart failure, a lack of nutrients and oxygen flow to heart and would up regulate the ps2 expression and increase in ps levels[64]. The ps2 interact with at least three calcium binding proteins: calsenilin[67], calmynin[65], sorcin [66]. this sorcin serve as a modulator af the ryanodine receptor intracellular calcium channel. Cardiac rynodine receptor(r4r2) is the major sarcoplasmic reticulum calcium release channel in heart(68). Altered regulation of (r4r2) is the mechanism underlying a loss of cardiac excitation contraction coupling gain and arrhythmias. Treatment of cells with calcium ionophore does not alter the steady levels of sorcin or ps-2,but increases the binding between sorcin and PS-2[66]. By understanding these important mechanisms might provide a better treatment for heart failure. Ps2 responds to conditions of low glucose and low oxygen by up regulated expression ad responds to ischemia conditions which link the heart and brain pathophysiology[69].

Presenilin with notch receptor in cell fate

Notch receptor family includes 4 members in mammalians that are all anchored in the cell membranes as heterodimers and involved in cell-fate decision , patterning & cell polarity[70]. Notch ligands those of serrate or delta family, also contain a transmembrane domain and are anchored in the cell membranes. Notch signaling, resulting in expression of target genes via downstream transcription of observed CSL(c-promoter binding factor-1/suppressor of hair less/LAG-2) protein family[71-72].Proteolytic cleavage of notch &nuclear translocation of its intracellular domain has been considered to be crucial step in transduction of signal[73-74]. Presenilins have a role in notch pathway and required for intramembraneous notch proteolysis. Lacking ps1 activity, there is a dramatic reduction in notch -1 signalling fragment derived from intra membranes γ-secretase like cleavage of the notch-1 receptor, and a similar loss of APP γ- secretase cleavage also seen in these mammalian cells[75-82]. The ps proteins cleave the notch receptors at cell surface in a ligand-dependant manner is difficult to reconcile with the predominant localization of PS in intracellular ER,& GOLGI associated compartments and may facilitate notch &APP trafficking to cell surface[83]. First cleavage occurs in trans-golgi compartment and is performed by furin class serine proteases resulting the formation of notch heterodimer consisting of non-covalently associated extracellular and transmembrane fragments[84-86]. Ligand binding, second cleavage occurs just outside the transmembrane domains. Here ADAM protease cleaves notch ligand and that heterodimer dissociation & receptor inactivation may be triggered by reduced levels of extracellular calcium[87], therefore removal of notch extra cellular domain , and it is to be crucial step in ligand & induced activation of notch .this step apparently depends upon the endocytosis of notch[88-90]. Once the extracellular domain of notch has been removed,the remaining carboxy-terminal portion consisting of a short extracellular stalk,the transmembrane domain & complete extracellular domain is efficiently proteolysed in a presenilin dependent manner. Like removal of ectodomain of notch, the β-cleavage of APP generates a membrane anchored carboxy-terminal

derivative that may serve as an optimal substrate for intramembraneous ps-mediated proteolysis, providing a rational explanation for the involvement of PS- proteins in both notch &APP[90].

CONCLUSION

Presenilin is a novel gene, which is proteinaceous in nature, undergo mutations which increases the production of β-amyloid and account for majority of diseases viz, early onset of inherited AD, heart failure, CNS disorders etc. These type of physiological disorders which need chronic drug treatment. The future trend in medicine purely depend upon gene therapeutics, by targeting misleading gene encoding , disorders can be cured permanently without any side effects. Presenilin is a gene by targeting, we can treat number of physiological disorders.

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