Austin Alzheimer's and Parkinson's Disease

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Mini Review

Arguments for Caveolin-1 Knockout Mice as an Alzheimer's Disease Model

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Received: March 18, 2016; **Accepted:** June 02, 2016; **Published:** June 04, 2016

Abstract

Neurodegenerative diseases, such as Alzheimer's Disease, are now acknowledged to be multifactorial pathologies, explaining the failure to come up with specific targeted treatments. New pathogenic links should be addressed in order to integrate the molecular interactions into a comprehensive mechanism. Caveolin-1 is a scaffolding membrane protein of caveolae – membrane microdomains involved in cell signaling, senescence and cell growth. Increased caveolin-1 expression was related to inducement of senescence and was also reported in the aged brain. However, cav-1 KO mice express AD- like alterations in hippocampus and neurologic abnormalities and incongruent reports in AD patients or AD models in this review we present the involvement of caveolin-1 in aging, with emphasis on aging brain and propose several mechanisms of interaction between caveolin-1 and amyloid precursor protein, the main pathogenic link of Alzheimer's disease. Also, in view of reports of synaptic plasticity deficits upon Cav-1 KO and its involvement in post-injury reactive neuronal plasticity, we propose Cav-1 to be neuroprotective and increased as a compensatory mechanism, rather than a direct measurement of aging process.

Keywords: Amyloid precursor protein; Caveolin-1; Alzheimer's disease; Cav-1 knockout mouse; Aging brain

Introduction

"Neurodegeneration" is a term which can be translated into "loss of neurons" accompanied by clinical features related to cognition and affect. However, high variability in terms of histopathologic changes found in patients with the same clinical diagnostic led to a thorough investigation of molecular causes. The limit between "normal" aging and neurodegeneration was even more so difficult delineate from the perspective of "cognition reserve" – the ability of some subjects to counteract neuronal or synaptic loss by "using pre-existing cognitive processing approaches or by enlisting compensatory approaches" [1]. The most frequent causes of neurodegeneration are vascular dementia, Alzheimer's and Parkinson's diseases, each with its own molecular hallmarks. Alzheimer's disease diagnostic criteria include extraneuronal amyloid plaques and intraneuronal hyperphosphorylated tau tangles, but other molecular factors may contribute [2]. Parkinsons's disease is characterized by progressive loss of dopaminergic neurons, with yet unknown, but apparently multifactorial molecular basis [3]. Vascular dementia is also a multifactorial entity [4]. However, molecular research results reported a considerable overlapping between these entities, with two important consequences: 1) the need for a more accurate diagnostic, which led to search of new biomarkers; 2) new disease models emerged. Animal models still hold an important role for mechanism elucidation, as they allow assessment of apparently non-related effects of the molecular defect imposed on the animal. Classical

neurodegeneration mouse models include, among others, transgenic animals for mutated amyloid precursor protein, mutated tau protein, mutated presenilin enzyme, injection of neurotoxins in the corpus striatum, ligation of carotid arteries. Caveolin-1 is a membrane protein responsible for scaffolding a membrane microdomain called "caveola" (pl. caveolae). Caveolae are considered signaling nodes and caveolin-1 over expression was related to cellular aging [5]. Caveolin-1 knockout mouse is a well established model for endothelial dysfunction [6]. In this review we will present this animal as a potential AD- like disease model, with arguments related to stem cells, amyloid precursor protein and metabolic and signaling particularities in neurons.

The concept of brain aging

"Brain aging" concept referred at the beginning to a progressively deteriorating performance. Studies on aged animals [7] from more than three decades ago reported neuronal loss with aging, along with a decreased volume of gray matter. Later reports challenged previous data, showing preserved neuronal number, despite cortex thinning in human brain [8], and were soon followed by confirming studies on animals [9-12]. Modern imagistic methods, from computer tomography analysis in the early 80's [13] to MRI and fluorodeoxigluocose PET analyses [14,15], demonstrated that brain atrophy does occur with age, in healthy, non-demented elderly. The modifications affect both grey and white matter, but the loss is rather functional than cellular, more like defective circuitry, rather than neuronal loss. Cell preservation in aging was reported even in areas susceptible to dementia, such as frontal and medial temporal cortex, in which thinning is not always indicative of disease. Rather, instead of neuronal loss, a 3D

neuronal network loosening would account for frontal and temporal neocortical thinning [16]. A decrease in dendritic branching in animal [17] and human prefrontal cortex [18-20] supports this hypothesis. Surprisingly, hippocampal neurons, related to

Citation: Dudau M, Frumosu M, Codrici E, Tanase C and Ana-Maria E. Arguments for Caveolin-1 Knockout Mice as an Alzheimer's Disease Model. Austin Alzheimers J Parkinsons Dis. 2016; 3(1): 1028.

neurogenesis and learning, do not alter their dendritic length, nor reduce their spine density in aged humans [21] or rats [22]. MRI data showed that white matter reduction is also constant in the aged human brain, possibly as an indicator of a defective myelination, strongly correlated hypertension and stroke [23]. However, is still under debate whether the presence of white matter lacunae yielded is significantly related to cognitive impairment [24]. Aging is characterized by a reduced neurogenesis, due to altered neurotrophin signaling,

Activation of senescence programmers within the niche, imbalanced growth factor signaling. Although brain resides in a protected environment, isolate by the blood-brain barrier, there are evidence of blood-born aging factors to cross the blood brain barrier to negatively influence the neurogenesis [25]. Brain aging is also a "decrease in homeostatic reserve" [26] which affects, at different rates, different cell types that share a homeostatic balance. Cellular abilities to limit and buffer Reactive Oxygen Species (ROS), to sustain a protective response to cytotoxic stimuli, or to limit vicious circles such as inflammatory environments are diminished. DNA damage (some ROS-related), mitochondrial aging and decreased ATP reserves [27] and affected cellular calcium removal systems [28] add to neuronal vulnerability. Thus, understanding the aging process of nervous tissue is a more challenging task due to a more complex regulation, signaling and intercellular interactions [4].

Caveolin-1 in aging brain

Caveolins 1, 2 and 3, the scaffolding proteins of caveolae, have been related to cellular senescence for more than ten years [29], changes in their expression were interpreted either as determinants, either as effectors of the aging process. Main function of caveolin-1 has been as proposed to be of signaling node, therefore cav-1, its family members (caveolins 2 and 3) and associated proteins (cavins) would select which signals are to be transmitted into cells. New data revealed that cav-1 is involved in the regulation of many cellular processes relevant to cell biology such as growth, migration, control of mitochondrial antioxidant levels and senescence [30]. Senescent cells express increased levels of caveolins [31] and *in vitro* over expression of cav-1 induced an early senescence in different cell types [32-34]. Contradictory, cav-1 KO animal models showed reduced lifespan [35], paradox that was attributed to cav-1 function as tumor suppressor [36,37]. Cho et al. proposed the "Gate theory of aging", when "gatekeeper molecules at the membrane level would play the prime role in determining the senescent phenotype"; caveolae and caveolins are suitable for this role due to their regulation of cell signaling, calcium storage and quantization of cross-talk between signaling cascades [29]. Plasma membrane composition also changes with age, including the cholesterol composition. Such changes could influence the expression and distribution of caveolins in caveolae. Different tissues age differently in terms of caveolins expression: cardiac muscle shows increased cav-1 in the fractions of membrane forming caveolae [38], unlike smooth muscle, which does not change levels of cav-1 and cavin-1 [39]; aged endothelial cells increase their levels of cav-1 [40]. Brain and nervous tissue have their own particularities in term of aging and caveolin content. Aged mice increase their cav-1 expression in the hippocampus, similar to cav-1 expression in hippocampal tissue in patients with Alzheimer's disease [41]. Cerebellum does not change expression of cav-1 with age or pathology. Down regulation of hippocampal caveolin-1 was related to reduce synaptic plasticity in aging and its increased expression could be interpreted as a compensatory mechanism [42]. Cav-1 is expressed in neurons, mostly in pyramidal neurons of the frontal motor cortex, but also in parietal cortices, CA1 layer, stratum oriens and stratum radiatum of hippocampus [43]. The protein is also present in glial cells, although no caveolae have been identified in either cell type. Over expressing cav-1 in neurons led to a decrease in primary neurite outgrowth and branching, but an increase in neurite density [44]. In glutamatergic neurons, cav-1 interacts with glutamate receptors. Treatment with glutamate, kainate and AMPA increased the expression of caveolin-1, suggesting that "activation of ionotropic receptors regulates neuronal expression of caveolin" [45].

Caveolin-1 knockout mouse model

After identification of caveolin-1 as the prime component of [46], a knockout mouse model was generated for the study of the protein function *in vivo*. Surprisingly, cav-1KO mice were viable but showed evidence of hyperproliferative and vascular abnormalities, consistent with the wide distribution of caveolae in endothelial cells throughout the body. First roles attributed to cav-1 were stabilization of caveolin-2 to caveolae, mediator for caveolar endocytosis of specific ligands, negative regulator of cell proliferation and eNOS activity inhibition in endothelial cells [47].

Although viable, aged cav-1-deficient mice display significantly lower body weights and were resistant to diet- induced obesity, as compared with wild-type controls mice, even on a high fat diet. Serum profiles of these animals showed normal insulin, glucose, and cholesterol levels, but severely elevated triglyceride and free fatty acid levels, especially in the post-prandial state [6]. They have, however drastically reduced insulin receptor protein levels (>90%), without any changes in insulin receptor mRNA levels [48]. This mouse model is also characterized by alterations in other signaling pathways than nitric oxide and insulin, such as Extracellular-Signal Regulated Kinase (ERK), calcium signaling [45], modified balance of pro-and anti- inflammatory cytokines [49]. Cav-1 KO mice have reduced brain weight and develop a number of neurological phenotypes, with motor and behavioral abnormalities, including muscle weakness, clasping, reduced activity, abnormal spinning and gait abnormalities, without neuronal loss [50]. This finding could be related to previously report synaptic loss, sharing the same mechanisms at neuronal plate. Also, as a membrane protein, cav-1 loss could count for less myelinization, which is basically a glial cell membrane enwrapping around the axons.

Cav-1 and neurogenesis

An interesting approach regarding cav-1 involvement in nervous tissue homeostasis was reported starting from Neuronal Precursor Cells (NPC) from dentate gyrus and subventricular zone. Cav-1 KO mice showed increased number of newly formed neuroblasts than wild type of matching age, while *in vitro* knockdown of Cav-1 promoted oligodendroglial differentiation of NPCs via β- catenin expression [51]. In turn, cav-1 promoted differentiation of NPCs towards astroglial line [52]. Another cav-1 related way to modulate NPC proliferation was recently reported by Samarasinghe et al. A non-transcriptional glucocorticoid signaling pathway that operates via lipid-raft associated glucocorticoid receptors requires cav-1 to

alter NPCs proliferative capacity [53]. Cav-1 mediated signaling via GR could impact on development of NPCs by "regulating the degradation of cell cycle regulators or migration of differentiated cells derived from NPSCs to their final position in the cortex" [53].

Caveolin-1 in neurodegeneration and Alzheimer's disease

Although most data reported until several years back associated increased cav-1 with ageing, more and more results stated a neuroprotective role of cav-1. Starting with the cav-1 KO phenotype, to reports of synaptic plasticity deficits upon cav-1 KO [42] and involvement in post-injury reactive neuronal plasticity [44], cav-1 seems to be neuroprotective. From this perspective, the increase of cav-1 in brain of aged animals or brains of AD patients could be interpreted as a compensatory mechanism and not a direct measurement of aging process. Caveolin-1 and amyloid precursor protein – putative mechanisms of cooperation APP is a transmembrane protein, which can be metabolized in two ways: a physiologic one, generating soluble neurotrophic fragments and a pathologic one, generating insoluble amyloid beta peptides (Aβ) that aggregate in the extracellular matrix, forming senile plaques in the AD brain. Membrane regions of high cholesterol content, such as caveolae, favor the pathologic pathway and generation of Aβ. It has been demonstrated that APP localizes preferentially in cholesterol rich- membrane microdomains [43]. Cav-1 KO mouse model exhibits AD characteristics, such as elevated Aβ deposition in the hippocampus, cerebrovascular changes and increased astrogliosis, with early onset [54].

From literature data, several *mechanisms* can be put forth, through which amyloid precursor protein expression or processing can be modified by cav-1:

1- Cav-1 presents a Cav Scaffolding Domain (CSD), which can interact with other membrane proteins, including APP, thus facilitating its proteolysis [41].

2- APP is preferentially expressed in cholesterol –rich domains, such as caveolae [43] and its amyloidogenic processing is favored by hypercholesterolemia [55]. Disruption of caveolae by cav-1 KO may redirect APP traffic towards lipid rafts (also cholesterol enriched) leading to increased extracellular Aβ peptides deposition. Furthermore, both enzymes involved in amyloidogenic processing are located in lipid

rafts: β secretase compartmentalizes in non-caveolar lipid rafts [56] and γ secretase in detergent-resistant membranes [57].

3- Over-expressed cav-1 in β-secretase expressing cells resulted in decreased Aβ production, suggesting a protective role by cav-1 [54].

4- Caveolae and cav-1 act as signaling nodes, regulating activation of various kinases. In turn, APP has eight phosphorylation sites in the Cterminal domain, potentially affected by the modification of cav-1 expression. Phospho-Thr668 is essential for its binding to Fe65 and its nuclear translocation possibly followed by induction of glycogen synthase kinase 3β and tau phosphorylation [58].

5- Loss of cav-1 may alter phosphorylation of other proteins involved in APP trafficking: Mint1/X11α is one of four neuronal trafficking adaptors that interact with APP. Srcrelated tyrosine phosphorylation of Mint1 regulates the destination of APP, restricting its distribution to distal neurites [59].

Conclusion

Neurodegeneration is a multifactorial process, not necessarily related to a pathological process. Conversely, pathological alterations may be present, without any clinical signs. Although there are numerous and well characterized animal models to study the most frequent neurodegenerative diseases, other models may unravel new pathogenic links. Caveolin-1 knockout mouse is emerging as a novel, non-mutational model, which, due to is endothelial dysfunctions, could be related to vascular dementia. However, recent data regarding amyloid precursor protein processing in these mice, may argue also in favor of Alzheimer disease model, providing a multifactorial dementia model.

Acknowledgment

This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation CNCS- UEFISCDI, project number PN-II-RU-TE 2014-4-1534.

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Citation: Dudau M, Frumosu M, Codrici E, Tanase C and Ana-Maria E. Arguments for Caveolin-1 Knockout Mice as an Alzheimer's Disease Model. Austin Alzheimers J Parkinsons Dis. 2016; 3(1): 1028.