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Teneurins and Alzheimer's disease: A suggestive role for a unique family of proteins ☆

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ABSTRACT

Alzheimer's disease is a debilitating age-related disorder characterized by distinct pathological hallmarks, such as progressive memory loss and cognitive impairment. During the last few years, several cellular signaling pathways have been associated with the pathogenesis of Alzheimer's disease, such as Notch, mTOR and Wnt. However, the potential factors that modulate these pathways and novel molecular mechanisms that might account for the pathogenesis of Alzheimer's disease or for therapy against this disease are still matters of intense research. Teneurins are members of a unique protein system that has recently been proposed as a novel and highly conserved regulatory signaling system in the vertebrate brain, so far related with neurite outgrowth and neuronal matching. The similitude in structure and function of teneurins with other cellular signaling pathways, suggests that they may play a critical role in Alzheimer's disease, either through the modulation of transcription factors due to the nuclear translocation of the teneurins intracellular domain, or through the activity of the corticotrophin releasing factor (CRF)-like peptide sequence, called teneurin C-terminal associated peptide. Moreover, the presence of Ca^{2+}-binding motifs within teneurins structure and the Zic2-mediated Wnt/β-catenin signaling modulation, allows hypothesize a potential crosslink between teneurins and the Wnt signaling pathway, particularly. Herein, we aim to highlight the main characteristics of teneurins and propose, based on current knowledge of this family of proteins, an interesting review of their potential involvement in Alzheimer's disease.

Introduction

With the increased aging of the human population, age-related diseases, such as Alzheimer's (AD) and Parkinson's disease, are believed to become a critical subject for world health [1,2]. Neuronal network failure, as a result of several molecular alterations within neurons that take place during the neurodegenerative process [3–5], have become of primary concern regarding neurodegenerative disorders [6,7]. Since the work of Eriksson et al. [8] regarding human adult neurogenesis, several studies have been devoted to exploring the feasibility of this process as part of therapeutical approaches against a variety of pathologies affecting the central nervous system (CNS). Moreover, it has become evident that knowledge associated with neuronal development, including neuronal network functionality and neuronal recovery, are dependent on our understanding of the cellular signaling pathways that might be involved in a whole range of neuronal responses to physiological or pathological conditions [9]. In the present work, we will present the main aspects of teneurins, a novel family of transmembrane proteins, and their close relationship, so far identified, with critical aspects of neuronal development and synapse establishment. Furthermore, at the end of the manuscript, we will discuss the emerging similarities and potential crosslinks between teneurins functions and some critical cellular signaling pathways, particularly Wnt. We believe that the information herein presented is suggestive of the potential involvement of teneurins in AD, setting a starting point to approach this new family of proteins in order to elucidate its potential therapeutic value in neurodegeneration and AD in particular.

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Hypothesis

Role of cell adhesion molecules (CAMs) in the CNS

The ability to establish functional synapses between cells is determined by the presence of proteolytic complexes in both the pre- and post-synaptic membranes. These components define the complexity of the neuronal network, and evolve during embryonic development to sustain cognitive functions during adulthood [10]. Importantly, synaptic transmission is dependent on the formation of asymmetric intercellular junctions with three clearly differentiable compartments: the pre-synaptic membrane, synaptic cleft, and post-synaptic membrane [11,12]. The synaptic cleft is not an empty space, but rather it is populated with synaptic material constituted in part by synaptic cell adhesion molecules (CAMs) [13]. Neurexins, neuroligins, N-cadherin, synaptic cell adhesion molecule-1 (SynCAM-1), and the ephrinB-receptor system are some of the main representatives of this family of proteins [14] (Fig. 1). Interestingly, the importance of CAMs in the CNS has increased enormously during the last decade. Indeed, several authors have described that the interaction of structural proteins, such as CAMs, and intracellular proteins play a fundamental role not only in synapse establishment and maintenance, but also in synaptic plasticity, a critical process that links synaptic proteome variations with physiological alterations, such as cognitive impairment [15–17]. In this regard, of most relevance are several studies that have demonstrated the interplay between different families of proteins and their processing at the synaptic terminals with the expression of glutamate and AMPA receptors, evidencing the critical balance of protein processing to ensure synaptic functionality [16,18–21].

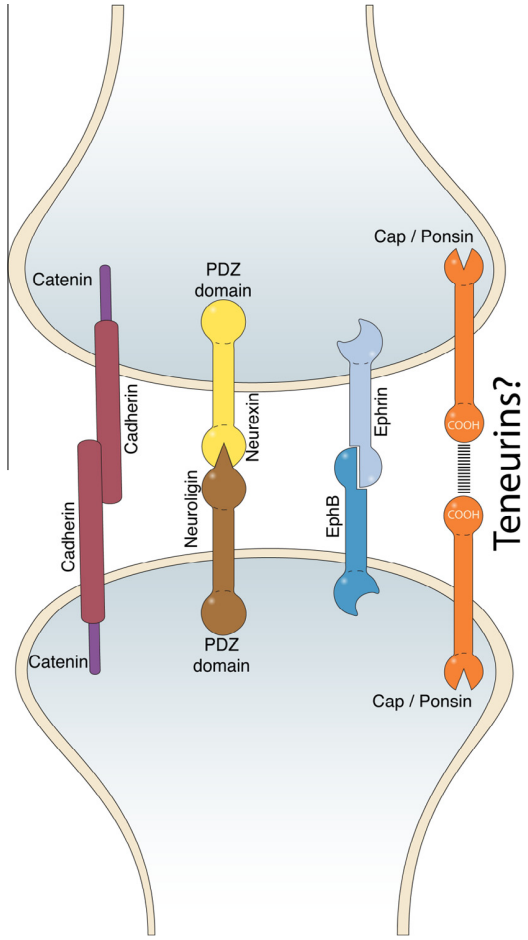

Fig. 1. Synaptic cell adhesion molecules (CAMs). Synapses are complex structures that require the expression of several proteins to function properly. Among these proteins, some specific cell adhesion molecules play a relevant role for the establishment and maintenance of synapses. Furthermore, it has been demonstrated that the proteolytic cleavage of some of these proteins might act as secondary messengers within cells, inducing the modulation of several cellular processes. Teneurins have emerged as a new critically important class of proteins capable of conducting neuronal matching during CNS development. Based on current knowledge, the function of this family of proteins remains to be addressed.

More recently it has been reported that CAMs might act as important regulators of transcription, providing additional support to the increased relevance of these kinds of proteins in the CNS. For instance, PS1 (presenilin 1)/γ-secretase can cleave both full-length E-cadherin and a transmembrane C-terminal fragment, which acts as a key regulator of the Wnt signaling pathway [22]. In the same way, it has been demonstrated that under pathological conditions these proteins could also be affected, altering their functionality. Indeed, N-cadherin is down-regulated by amyloid-β peptide (Aβ), one of the most relevant neurotoxic elements in AD, making synapses more susceptible to disease-related toxicity, and increasing Aβ production via interaction with the PS1 complex [23]. Furthermore, it has been reported that the Neuroligin–Neurexin interaction, fundamental for synapse stability, is also a target of Aβ, resulting in alteration of the pre- and post-synaptic structures [24]. On the other hand, the expression of integrin proteins has been reported to be increased in neurons surrounding plaques and tangles, suggesting a critical role in Aβ neurotoxicity in AD [25]. Recently, teneurins have been described as relevant synaptic adhesion molecules with a critical role in neuronal matching and synapse organization [26–28]. Moreover, the interactions that have been evidenced between teneurins and other cell adhesion molecules allows hypothesize that teneurins might play an interesting role as modulators of synapse formation and function [29–31].

Teneurins as regulators of neurogenesis

Teneurins are a family of transmembrane glycoproteins, described originally in *Drosophila* [32,33]. They were discovered independently in the 90's by two laboratories, and until today, four members have been described, namely *Ten*-m1 to *Ten*-m4. Teneurins are high molecular weight proteins with their C-terminals oriented to the extracellular media [34]. Although teneurins are transmembrane proteins, they exhibit an elevated number of functional domains, particularly at the extracellular domain, some of them being exclusive for this family of proteins [33]. Teneurins have been shown to be highly expressed in the CNS of several organisms, including mice, rats and humans [35,36]. They have been implicated in several biological processes, such as gene transcriptional regulation, neurite outgrowth, axon fasciculation and cell adhesion [32,33,37–39]. Indeed, recent studies have demonstrated that *Ten*-m1 and m2 are mainly expressed in the CNS (Table 1), and their expression levels are dependent on the stage of CNS development and brain region, e.g. *Ten*-m2 is localized mainly in the hippocampus, while *Ten*-m1 is present in the olfactory bulb, with a significantly lower expression in the hippocampus. Moreover, and as mentioned previously, Hong et al. [26] recently demonstrated that teneurins are involved in the olfactory synaptic partner matching during brain development, while Mosca et al. [27] further showed that teneurins were involved in neuromuscular synapse organization. Both studies suggest that the differential expression pattern of this protein family accounts for the specificity required for the organization and restructuring of complex neuronal networks. Indeed, the several active domains present in the extracellular fraction of this family of proteins, such as the epidermal growth factor (EGF)-, NHL-, and YD (tyrosine, aspartate)-domains, and the interactions between them, has been

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Table 1
Localization and function of Teneurins in the CNS.

Name	Localization	Function	References
Ten-m1	Visual system and tectofugal pathway, olfactory bulb mitral cells, subpopulations in the hippocampus and piriform cortex, retinal ganglion cells, inner nuclear layer adjacent to the inner plexiform Layer I and in large neurons found within the rotund nucleus, and the neurons of the stratum griseum centre of the optic cellularis and throughout the cerebellum	The predominant neuronal expression suggests a major function in brain development and as a cell signaling transducer	[37]
Ten-m2	In different neuronal groups, in the hippocampus (dentate gyrus) and piriformis posterior medial cortex in chicken, granular layer, Purkinje cells, and the molecular layer of the cerebellum	Induces gene inhibition; Mediates axon guidance and heterophilic cell–cell adhesion	[37,40,41]
Ten-m3	In interconnected regions of the visual pathway: retina, dLGN and visual cortex both in soma and in neuronal axons expression going from high to low from the ventral to dorsal retina	Involved in maintenance of neural development, axonal guidance and homophilic cell adhesión. Plays important roles in the visual pathway by regulating the formation in ipsilateral retinal mapping to both the dorsal lateral geniculate nucleus (dLGN) and the superior colliculus (SC)	[42]
Ten-m4	Nervous systems, visual system, adipose tissue, spinal cord and mesenchymal tissues (cartilage)	Involved in maintenance of neural development, and as a cell signaling transducer	[36,37]

described as critical for the guidance, recognition and stabilization of the cell–cell adhesion [28]. On the other hand, the anchorage of teneurins to the actin-based cytoskeleton through the polyproline domain (teneurin intracellular fraction)-CAP/ponsin binding, will explain in part the alterations in the structure, organization and physiology of the synapses when teneurins are poorly expressed or depleted [27].

Interestingly, it has been proposed that teneurin-teneurin interaction and the selective cleavage of teneurins, with the release of the extra- and intracellular domains, might induce teneurin-mediated transcriptional regulation [36]. When cleaved, the intracellular domain can translocate to the nucleus, suggesting teneurins activity as transcription factors through interaction with the Methyl-CpG Binding Domain Protein 1 (MBD-1) and the transcription factor Zic [29,35,36]. In the same way, several studies have suggested that the proteolytic cleavage of the teneurins extracellular C-terminal domain will release a bioactive Teneurins C-terminal associated peptide (TCAP), which is able to induce a receptor-mediated cell response. Interestingly, exon 31 of ten-1, which encodes for TCAP1, is highly expressed in limbic regions, including major cell groups of the hippocampus and dentate gyrus [30,34,43]. Several studies have shown that TCAP1 exerts a wide range of neuronal effects, including: increased activity of the endogenous antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT) activity [43]; regulation of BDNF [38]; modulation of cAMP; accumulation and attenuation of CRF-induced c-Fos immunoreactivity in the hippocampus and amygdala [30,44]; promotion of neurite growth by direct modulation of cytoskeletal protein synthesis [32,45]; and modulation of dendritic spine density in hippocampal neurons [30]. Although these functional roles are poorly understood, Wang et al. [34] showed that these unique proteins possess a wide range of functional domains that are likely to interact with several elements of the extracellular matrix on the cell surface, or with calcium and SH3-mediated signaling mechanisms on the intracellular component. In this regard, recent work by Südhof and coworkers [31] suggests that the interaction of teneurins with other CAMs, or CAM-related fragments, is able to affect teneurins binding capacity, affecting the stability of the synapses.

Importantly, factors that can induce the cleavage between both domains (extra and intracellular) are largely unknown. However, the mechanism responsible for the release of the intracellular domain has been proposed to be similar to several known transmembrane signaling molecules, such as Notch-1 and APP [40]. Indeed, it is likely that the Teneurins/TCAP system may represent a novel and a highly conserved regulatory signaling system in the vertebrate brain.

Although the mechanisms that participate in teneurins expression regulation are mainly unknown, it has been proposed that, considering its role during embryo development, the family of homeobox transcription factors (Hox genes) may be at the basis of the regulation of teneurins expression [46]. The HoxD and EMX2 genes are the most representative genes of the homeobox cluster that have been associated with teneurins expression. HoxD and EMX2 knock-out mice have demonstrated reduced levels of different teneurins family members, with the concomitant malformation or alteration of specific organs [47–49]. In the same way, a link between some members of the fibroblast growth factor family (FGF) and teneurins have also been demonstrated, particularly the relationship between FGF8 and *Ten*-m2 [50].

Involvement of teneurins in AD-related signaling pathways

The structure of teneurins is currently under investigation, but parts of its functional domains have already been characterized. Importantly, the interplay between the members of this family and several cellular processes are still a matter of intense research [28,40]. Moreover, the effects derived from teneurins and/or from the nuclear translocation-dependent activity of the teneurins intracellular domain on different cellular signaling pathways are poorly understood, but might be of considerable interest, particularly in pathologies which may benefit from teneurins activities, such as neurodegenerative disorders, such as AD (Fig. 2).

AD, which ranges from a mild cognitive impairment to severe memory and cognitive impairment [51], is mainly characterized by the formation of neurofibrillary tangles (NFTs), constituted by the hyperphosphorylated microtubule-associated protein *tau* [52,53], and senile plaques, a complex extracellular structure defined by the accumulation of a 4 kD protein with a β-pleated sheet configuration known as amyloid-β peptide (Aβ) [54,55]. These pathological changes induce critical alterations of specific brain areas, including the temporal and parietal cortex, the hippocampus and the amygdala, and the frontotemporal association cortex [56,57]; and the major symptoms of AD (memory loss and cognitive impairment) perfectly reflects the damage to the complex neuronal network of these areas [56,58]. The hippocampus is the most critically brain areas involved in memory and cognition [59]. Considering that teneurins are capable to induce cytoskeleton reorganization through presynaptic or postsynaptic modifications on microtubule-binding protein (Futsch) and/or α-spectrin [27], there is possible to suggest that teneurins might be involved with the cytoskeleton alteration observed in some neurodegenerative disorders, such as AD.

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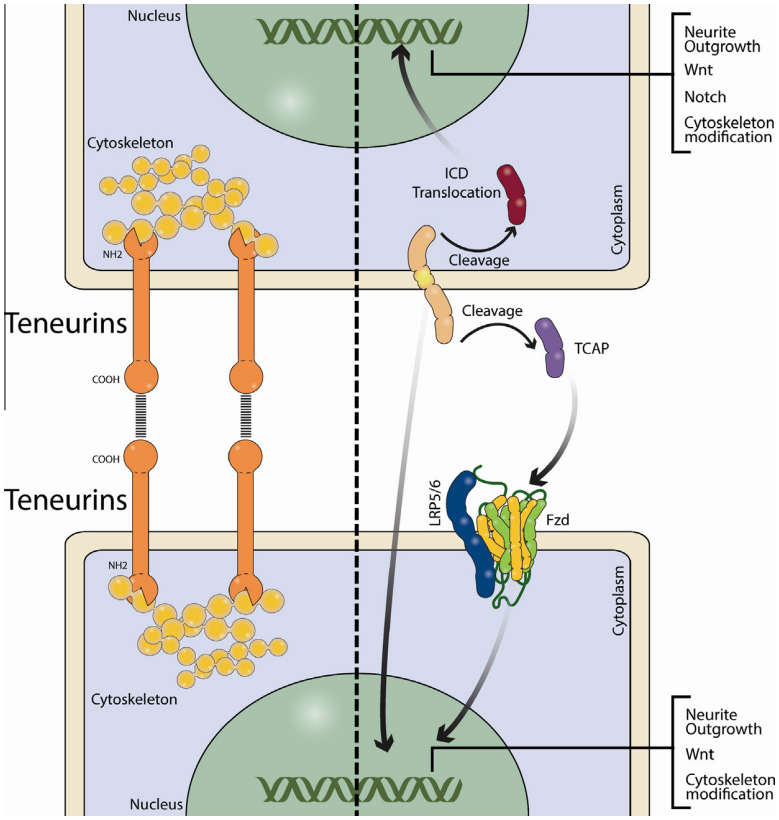

Fig. 2. Teneurins: cellular localization and hypothetical cleavage-induced signaling. Teneurins have been described as a well-conserved transmembrane protein family. One of the remarkable aspects of teneurins is that their terminal-COOH is oriented to the extracellular region of the cell, contrary to the vast majority of transmembrane proteins. Although several domains have been identified within these proteins, such as epidermal growth factor-(EGF), Ca^{2+}- and poly-prolines (Pn)-binding domains, their function remains largely unknown. It is possible that some of them, released by means of appropriate protein cleavage, are able to interact with different cellular signaling reactive elements. Left: Transmembrane localization of teneurins, anchored to the cytoskeleton through Pn domains. Right: Suggested teneurins cleavage-derived effects, through the release of the intracellular domain (ICD) which could translocate to the nucleus, similar to Notch, inducing DNA transcription of target elements; or the release of extracellular fragments, such as the teneurin c-terminal associated peptide (TCAP), which could also translocate to the nucleus or interact through a ligand-receptor mechanism with additional cellular elements, inducing target gene transcription. *Abbreviations:* LRP5/6: low density lipoprotein receptor-related protein 5/6; Fzd: Frizzled receptor.

Although the key pathogenic events, such as increased Aβ levels, have been well established, the molecular mechanisms causing such alterations as well as the cellular pathways involved in neuronal degeneration and dementia are not yet fully understood [9]. Precisely, at least in part, the complexity of AD lies in the several cellular signaling pathways that have been associated with it and the crosstalk usually established between them. These cellular signaling pathways are mainly related to neuronal survival, cellular proliferation and differentiation, and cell death. Of these pathways, *Wnt* [60–63] and Notch [64] signaling have been frequently associated with neuronal proliferation and survival. Moreover, several *Wnt* and Notch deficient models have demonstrated critical age-related deficits in neuronal development, cognitive dysfunction, and spatial navigation [9,62,63,65,66]. On the other hand, the Ca^{2+}, mTOR and FoxO pathways have been associated with cell senescence and with the apoptotic cascade triggered after neuronal insult [9,67,68].

Considering the current available knowledge regarding *Wnt* signaling pathways and teneurins, several critical observations suggest that these two components might be closely related, not only during normal CNS development, but also during pathological conditions [69,70]. Indeed, *Wnt* signaling plays a major role in several aspects that also seem to be associated with teneurins, such as neurogenesis, cytoskeletal arrangement and dendritic spine density [9,71]. Moreover, some of the already described regulatory factors for teneurins expression have also been related to the regulatory activity of *Wnt* genes [72]. On the other hand, the fact that teneurins express Ca^{2+}-binding motifs makes them vulnerable to the deleterious effects of increased intracellular Ca^{2+} levels, a mechanism that should further connect teneurins with the *Wnt* pathway [73]. All these aspects allow us to hypothesize that teneurins might play an unexpected role in AD, considering the critical function that these proteins exhibit during the development and maintenance of the neuronal network. Moreover, teneurins might interact directly and/or indirectly with the *Wnt* signaling pathway, perhaps, acting as a canonical *Wnt* agonist or antagonist, taking into consideration recent studies suggesting that the teneurins intracellular domain might suppress *Wnt*/β-catenin signaling through Zic2 activation [35,74,75]. In addition, because of the Ca^{2+} sensitive domains, the non-canonical *Wnt*/Ca^{2+} pathway might also be involved in the teneurin-mediated effects and could imply a direct crosstalk between them. Likewise, it is important to remember that the activity of teneurins may be exerted not only by the IC domain, but also by the extracellular TCAP, which has been demonstrated to have teneurin-independent activity and important roles in several neuronal processes, closely related with the activity of several cellular signaling pathways, such as *Wnt* [45,76].

Conclusion

Research focused on AD has provided new perspectives regarding the mechanisms related to the early phases of the disease, and

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how these mechanisms interact between them to establish a highly complex network of cellular signaling pathways which ultimately culminate in neuronal damage and loss. Although several molecules have demonstrated neuroprotective effects against Aβ-induced damage, no effective therapy is currently available. Adult neurogenesis has emerged as a promising research field, not only for the treatment of AD, but also for several neurological conditions that will benefit from neuronal repopulation. In this regard, different efforts have been made to preserve, increase and stimulate neuronal progenitor cells [6,77,78]. The *Wnt* signaling pathway has emerged as one of the potential pathways capable of modulating adult neurogenesis [77]; however, it is not only important to achieve an increased number of fully developed neurons, but also to ensure its appropriate incorporation into the neuronal network, providing healthy functional synapses to replace the deficits that develop during the neurodegenerative process [62,79]. The role that CAMs seem to play during this process is out of discussion; however, our current knowledge regarding teneurins allows hypothesize that this family of proteins might play an unexpected role in this process and subsequently in AD, considering the critical function that these proteins exhibit during the development and maintenance of the neuronal network, and mediating, at least in part, adult neurogenesis, similar to what have been demonstrated during CNS development. Indeed, hippocampal neurogenesis is dependent on the ability of neurons to recognize and form key inter-neuronal synapses; a key hallmark of teneurins activity. In the same way, so far, teneurins seem to exert their actions by both acting as adhesion proteins and also as a signaling system able to establish a complex network of interactions with several cellular signaling pathways that participate in normal aging and neurodegeneration. Particularly, along with the similar functions observed for teneurins and the Wnt signaling pathway, the presence of Ca^{2+}-binding motifs and the Zic2-mediated Wnt/β-catenin signaling modulation offers further support to the hypothesis of a relevant role and a close relation between teneurins and the Wnt signaling pathway and the processes under its control.

Of course, our knowledge is still very limited, and we are not able to fully understand the full range of effects derived from teneurins activity [69]. In the same way, the mechanisms related to teneurins cleavage are still completely unknown, and even when it is possible to suggest that an APP or Notch γ-secretase-like processing might be involved, it is extremely necessary to address if this mechanism verified *in vivo*. So far, research seems to suggest that teneurins might be important players not only during neuronal development, but also during neurodegeneration. Thus, new research focused on addressing and evaluating the roles of teneurins, as well as teneurins proteolytic end-products, should be seriously considered and it might provide new insights regarding AD and other neurodegenerative disorders.

Conflict of interest

The authors declare that there are no conflicts of interest.

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References

[1] Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. Nature 2008;451(7179):716–9.
[2] Zlokovic BV. Neurodegeneration and the neurovascular unit. Nat Med 2010;16(12):1370–1.
[3] Salmon DP, Bondi MW. Neuropsychological assessment of dementia. Annu Rev Psychol 2009;60:257–82.
[4] Perl DP. Neuropathology of Alzheimer's disease. Mt Sinai J Med 2010;77(1):32–42.
[5] Manji H, Kato T, Di Prospero NA, et al. Impaired mitochondrial function in psychiatric disorders. Nat Rev Neurosci 2012;13(5):293–307.
[6] Bredesen DE, Rao RV, Mehlen P. Cell death in the nervous system. Nature 2006;443(7113):796–802.
[7] Rubinsztein DC. The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 2006;443(7113):780–6.
[8] Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. Neurogenesis in the adult human hippocampus. Nat Med 1998;4(11):1313–7.
[9] Godoy JA, Rios JA, Zolezzi JM, Braidy N, Inestrosa NC. Signaling pathway cross talk in Alzheimer's disease. Cell Commun Signal 2014;12:23.
[10] Fields RD, Itoh K. Neural cell adhesion molecules in activity-dependent development and synaptic plasticity. Trends Neurosci 1996;19(11):473–80.
[11] Gray EG. Electron microscopy of synaptic contacts on dendrite spines of the cerebral cortex. Nature 1959;183(4675):1592–3.
[12] Guillery RW. Early electron microscopic observations of synaptic structures in the cerebral cortex: a view of the contributions made by George Gray (1924–1999). Trends Neurosci 2000;23(12):594–8.
[13] Dalva MB, McClelland AC, Kayser MS. Cell adhesion molecules: signaling functions at the synapse. Nat Rev Neurosci 2007;8(3):206–20.
[14] Sindi IA, Tannenberg RK, Dodd PR. A role for the neurexin–neuroligin complex in Alzheimer's disease. Neurobiol Aging 2014;35(4):746–56.
[15] Südhof TC, Malenka RC. Understanding synapses: past, present, and future. Neuron 2008;60(3):469–76.
[16] Südhof TC. Neuroligins and neurexins link synaptic function to cognitive disease. Nature 2008;455:903–11 (7215).
[17] Bingol B, Sheng M. Deconstruction for reconstruction: the role of proteolysis in neural plasticity and disease. Neuron 2011;69(1):22–32.
[18] Lu X, Wyszynski M, Sheng M, Baudry M. Proteolysis of glutamate receptor-interacting protein by calpain in rat brain: implications for synaptic plasticity. J Neurochem 2001;77(6):1553–60.
[19] Lee SH, Liu L, Wang YT, Sheng M. Clathrin adaptor AP2 and NSF interact with overlapping sites of GluR2 and play distinct roles in AMPA receptor trafficking and hippocampal LTD. Neuron 2002;36(4):661–74.
[20] Li Z, Jo J, Jia JM, et al. Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. Cell 2010;141(5):859–71.
[21] Li Z, Sheng M. Caspases in synaptic plasticity. Mol Brain 2012;5:15.
[22] Marambaud P, Shioi J, Serban G, et al. A presenilin-1/gamma-secretase cleavage releases the E-cadherin intracellular domain and regulates disassembly of adherens junctions. EMBO J 2002;21(8):1948–56.
[23] Andreyeva A, Nieweg K, Horstmann K, et al. C-terminal fragment of N-cadherin accelerates synapse destabilization by amyloid-β. Brain 2012;135(Pt. 7):2140–54.
[24] Dinamarca M, Ríos JA, Inestrosa NC. Postsynaptic receptors for amyloid-β oligomers as mediators of neuronal damage in Alzheimer's disease. Front Physiol 2012;3:464.
[25] Wright S, Malinin NL, Powell KA, Yednock T, Rydel RE, Griswold-Prenner I. Alpha2beta1 and alphaVbeta1 integrin signaling pathways mediate amyloid-beta-induced neurotoxicity. Neurobiol Aging 2007;28(2):226–37.
[26] Hong W, Mosca TJ, Luo L. Teneurins instruct synaptic partner matching in an olfactory map. Nature 2012;484(7393):201–7.
[27] Mosca TJ, Hong W, Dani VS, Favaloro V, Luo L. Trans-synaptic Teneurin signalling in neuromuscular synapse organization and target choice. Nature 2012;484(7393):237–41.
[28] Beckmann J, Schubert R, Chiquet-Ehrismann R, Müller DJ. Deciphering teneurin domains that facilitate cellular recognition, cell–cell adhesion, and neurite outgrowth using atomic force microscopy-based single-cell force spectroscopy. Nano Lett 2013;13(6):2937–46.
[29] Nunes SM, Ferralli J, Choi K, Brown-Luedi M, Minet AD, Chiquet-Ehrismann R. The intracellular domain of teneurin-1 interacts with MBD1 and CAP/ponsin resulting in subcellular codistribution and translocation to the nuclear matrix. Exp Cell Res 2005;305(1):122–32.
[30] Tan LA, Al Chawaf A, Vaccarino FJ, Boutros PC, Lovejoy DA. Teneurin C-terminal associated peptide (TCAP)-1 modulates dendritic morphology in hippocampal neurons and decreases anxiety-like behaviors in rats. Physiol Behav 2011;104(2):199–204.
[31] Boucard AA, Maxeiner S, Südhof TC. Latrophilins function as heterophilic cell-adhesion molecules by binding to teneurins: regulation by alternative splicing. J Biol Chem 2014;289(1):387–402 (This is the first article that describes Teneurins like cell adhesion molecules in neurons).
[32] Al Chawaf A, Amant K, Belsham D, Lovejoy DA. Regulation of neurite growth in immortalized mouse hypothalamic neurons and rat hippocampal primary cultures by teneurin C-terminal-associated peptide-1. Neuroscience 2007;144(4):1241–54.

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[33] Kenzelmann D, Chiquet-Ehrismann R, Tucker RP. Teneurins, a transmembrane protein family involved in cell communication during neuronal development. Cell Mol Life Sci 2007;64(12):1452–6.
[34] Wang L, Rotzinger S, Al Chawaf A. Teneurin proteins possess a carboxy terminal sequence with neuromodulatory activity. Brain Res Mol Brain Res 2005;133(2):253–65.
[35] Bagutti C, Forro G, Ferralli J, Rubin B, Chiquet-Ehrismann R. The intracellular domain of teneurin-2 has a nuclear function and represses zic-1-mediated transcription. J Cell Sci 2003;116(Pt. 14):2957–66.
[36] Tucker RP, Kenzelmann D, Trzebiatowska A, Chiquet-Ehrismann R. Teneurins: transmembrane proteins with fundamental roles in development. Int J Biochem Cell Biol 2007;39(2):292–7.
[37] Kenzelmann D, Chiquet-Ehrismann R, Leachman NT, Tucker RP. Teneurin-1 is expressed in interconnected regions of the developing brain and is processed in vivo. BMC Dev Biol 2008;8:30.
[38] Ng T, Chand D, Song L, et al. Identification of a novel brain derived neurotrophic factor (BDNF)-inhibitory factor: regulation of BDNF by teneurin C-terminal associated peptide (TCAP)-1 in immortalized embryonic mouse hypothalamic cells. Regul Pept 2012;174(1–3):79–89.
[39] Almeida RG, Lyons DA. On the resemblance of synapse formation and CNS myelination. Neuroscience 2013 (pii:S0306-4522(13)00758-6).
[40] Young TR, Leamey CA. Teneurins: important regulators of neural circuitry. Int J Biochem Cell Biol 2009;41(5):990–3.
[41] Zhou XH, Brandau O, Feng K, Oohashi T, Ninomiya Y, Rauch U. The murine Ten-m/Odz genes show distinct but overlapping expression patterns during development and in adult brain. Gene Exp Patterns 2003;3(4):397–405.
[42] Leamey CA, Merlin S, Lattouf P, et al. Ten_m3 regulates eye-specific patterning in the mammalian visual pathway and is required for binocular vision. PLoS Biol 2007;5(9):e241.
[43] Trubiani G, Al Chawaf A, Belsham DD, Barsyte-Lovejoy D, Lovejoy DA. Teneurin carboxy (C)-terminal associated peptide-1 inhibits alkalosis-associated necrotic neuronal death by stimulating superoxide dismutase and catalase activity in immortalized mouse hypothalamic cells. Brain Res 2007;1176:27–36.
[44] Chen Y, Xu M, De Almeida R, Lovejoy DA. Teneurin C-terminal associated peptides (TCAP): modulators of corticotropin-releasing factor (CRF) physiology and behavior. Front Neurosci 2013;7:166.
[45] Chand D, Song L, DeLannoy L, et al. C-Terminal region of teneurin-1 co-localizes with dystroglycan and modulates cytoskeletal organization through an extracellular signal-regulated kinase-dependent stathmin- and filamin A-mediated mechanism in hippocampal cells. Neuroscience 2012;219:255–70.
[46] Shah N, Sukumar S. The Hox genes and their roles in oncogenesis. Nat Rev Cancer 2010;10(5):361–71.
[47] Cobb J, Duboule D. Comparative analysis of genes downstream of the HoxD cluster in developing digits and external genitalia. Development 2005;132(13):3055–67.
[48] Li H, Bishop KM, O'Leary DD. Potential target genes of EMX2 include Odz/ten-m and other gene families with implications for cortical patterning. Mol Cell Neurosci 2006;33(2):136–49.
[49] Beckmann J, Vitobello A, Ferralli J, Brož DK, Rijli FM, Chiquet-Ehrismann R. Human teneurin-1 is a direct target of the homeobox transcription factor EMX2 at a novel alternate promoter. BMC Dev Biol 2011;11:35.
[50] Tucker RP, Chiquet-Ehrismann R, Chevron MP, Martin D, Hall RJ, Rubin BP. Teneurin-2 is expressed in tissues that regulate limb and somite pattern formation and is induced *in vitro* and *in situ* by FGF8. Dev Dyn 2001;220(1):27–39.
[51] Selkoe DJ. Alzheimer's disease. Cold Spring Harbor Perspect Biol 2011;3(7) (pii a004457).
[52] Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein, tau, is a major antigenic component of paired helical filaments in Alzheimer's disease. Proc Natl Acad Sci 1986;83(11):4044–8.
[53] Mandelkow EM, Mandelkow E. Biochemistry and cell biology of tau protein in neurofibrillary degeneration. Cold Spring Harbor Perspect Med 2011;2(7):a006247.
[54] Kang J, Lemaire HG, Unterbeck A, et al. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature 1987;325(6106):733–6.
[55] Masters CL, Selkoe DJ. Biochemistry of amyloid β-protein and amyloid deposits in Alzheimer disease. Cold Spring Harbor Perspect Med 2011;2(6):a006262.
[56] Smits LL, Tijms BM, Benedictus MR, et al. Regional atrophy is associated with impairment in distinct cognitive domains in Alzheimer's disease. Alzheimers Dement 2013(5 Suppl.) (pii: S1552-5260(13)02494-1).
[57] Wenk GL. Neuropathologic changes in Alzheimer's disease. J Clin Psychiatry 2003;9:7–10.
[58] Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol 2007;8(2):101–12.
[59] Shaerzadeh F, Motamedi F, Minai-Tehrani D, Khodagholi F. Monitoring of neuronal loss in the hippocampus of Aβ-injected rat: autophagy, mitophagy, and mitochondrial biogenesis stand against apoptosis. Neuromolecular Med 2013;16(1):175–90.
[60] Cerpa W, Godoy JA, Alfaro I, et al. Wnt-7a modulates the synaptic vesicle cycle and synaptic transmission in hippocampal neurons. J Biol Chem 2008;283(9):5918–27.
[61] Varela-Nallar L, Grabowski CP, Alfaro IE, Alvarez AR, Inestrosa NC. Role of the Wnt receptor Frizzled-1 in presynaptic differentiation and function. Neural Dev 2009;4:41.
[62] Inestrosa N, Arenas E. Emerging roles of Wnts in the adult nervous system. Nat Rev Neurosci 2010;11(2):77–86.
[63] Oliva CA, Vargas JY, Inestrosa NC. Wnt signaling: role in LTP, neural networks and memory. Ageing Res Rev 2013;12(3):786–800.
[64] Woo HN, Park JS, Gwon AR, Arumugam TV, Jo DG. Alzheimer disease and Notch signaling. Biochem Biophys Res Commun 2009;390(4):1093–7.
[65] Toledo EM, Colombres M, Inestrosa NC. Wnt signaling in neuroprotection and stem cell differentiation. Prog Neurobiol 2008;86(3):281–96.
[66] Tanveer R, Gowran A, Noonan J, Keating SE, Bowie AG, Campbell VA. The endocannabinoid, anandamide, augments Notch-1 signaling in cultured cortical neurons exposed to amyloid-β and in the cortex of aged rats. J Biol Chem 2012;287(41):34709–21.
[67] Zolezzi JM, Silva-Alvarez C, Ordenes D, et al. Peroxisome proliferator-activated receptor (PPAR) γ and PPARα agonists modulate mitochondrial fusion-fission dynamics: relevance to reactive oxygen species (ROS)-related neurodegenerative disorders? PLoS ONE 2013;8(5):e64019.
[68] Godoy JA, Allard C, Arrázola MS, Zolezzi JM, Inestrosa NC. SIRT1 protects dendrites, mitochondria and synapses from Aß oligomers in hippocampal neurons. J Alzheimers Dis Parkinsonism 2013. http://dx.doi.org/10.1007/s12035-014-8645-5.
[69] Ziegler A, Corvalán A, Roa I, Brañes JA, Wollscheid B. Teneurin protein family: an emerging role in human tumorigenesis and drug resistance. Cancer Lett 2012;326(1):1–7.
[70] Allodi I, Hedlund E. Directed midbrain and spinal cord neurogenesis from pluripotent stem cells to model development and disease in a dish. Front Neurosci 2014;8:109.
[71] Ciani L, Krylova O, Smalley MJ, Dale TC, Salinas PC. A divergent canonical WNT-signaling pathway regulates microtubule dynamics: dishevelled signals locally to stabilize microtubules. J Cell Biol 2004;164(2):243–53.
[72] Storm EE, Garel S, Borello U, et al. Dose-dependent functions of Fgf8 in regulating telencephalic patterning centers. Development 2006;133(9):1831–44.
[73] Inestrosa NC, Varela-Nallar L. Wnt signaling in the nervous system and in Alzheimer's disease. J Mol Cell Biol 2014;6(1):64–74.
[74] Pourebrahim R, Houtmeyers R, Ghogomu S, et al. Transcription factor Zic2 inhibits Wnt/β-catenin protein signaling. J Biol Chem 2011;286(43):37732–40.
[75] Baumgartner S, Martin D, Hagios C, Chiquet-Ehrismann R. Ten-m, a Drosophila gene related to tenascin, is a new pair-rule gene. EMBO J 1994;13(16):3728–40.
[76] Chand D, Casatti CA, de Lannoy L, et al. C-terminal processing of the teneurin proteins: independent actions of a teneurin C-terminal associated peptide in hippocampal cells. Mol Cell Neurosci 2013;52:38–50.
[77] Varela-Nallar L, Inestrosa NC. Wnt signaling in the regulation of adult hippocampal neurogenesis. Front Cell Neurosci 2013;7:100.
[78] Murai K, Qu Q, Sun G, et al. Nuclear receptor TLX stimulates hippocampal neurogenesis and enhances learning and memory in a transgenic mouse model. Proc Natl Acad Sci USA 2014 (pii(25):201406779).
[79] Ciani L, Salinas PC. WNTs in the vertebrate nervous system: from patterning to neuronal connectivity. Nat Rev Neurosci 2005;6(5):351–62.

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