Seminars in Cell & Developmental Biology 35 (2014) 173–179

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

The teneurins: New players in the generation of visual topography

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ARTICLE INFO

Article history:
Available online 22 August 2014

Keywords:
Axon guidance
Topography
Ten-m/Odz/Teneurin
Visual development
Synaptic matching

ABSTRACT

A functionally critical feature of the nervous system is the precision of its connectivity. An emerging molecular mediator of this process is the teneurin/ten-m/odz family of transmembrane proteins. A number of recent studies have provided compelling evidence that teneurins have homophilic adhesive properties which, together with their corresponding expression patterns in interconnected groups of neurons, enables them to promote appropriate patterns of connectivity. Particularly important roles have been demonstrated in the visual, olfactory and motor systems. This review attempts to relate new insights into the complex biology of these molecules to their roles in the establishment of functional neural circuits.

Contents

1. Introduction

The functioning of the nervous system is critically dependent on the integrity and precision of the connections of its constituent neurons. Interactions between intrinsic molecular signals expressed on the axons and their target cells have been shown to be central to the formation of these connections. This has been best characterised in the visual pathway where the Eph family of tyrosine kinase receptors and their ligands, the ephrins, have been shown to play key roles in the establishment of topographic maps in the visual system and elsewhere in the brain as reviewed in the accompanying papers in this issue. A key feature of their Eph-ephrin signalling system is the expression of the receptors and ligands in counter gradients across interconnected structures within the brain, which act to regulate connectivity *via* heterophilic and largely repulsive interactions. Their graded expression patterns contributed to their discovery as candidates for regulating topographic mapping [1] fulfilling many of the criteria first hypothesised by Sperry [2].

Over recent years, other families of molecules have also been shown to be important in the establishment of topographic maps. One of these is the teneurin family (Ten-m/Odz/Ten). Members of this family of type II transmembrane glycoproteins have recently been gaining prominence as key regulators of multiple aspects of neural connectivity, particularly in the visual system [3–10]. Of note, the teneurins have been shown to play particularly important roles in the guidance of uncrossed retinal axons, critical to the formation of functional binocular visual circuits. Recent work has demonstrated that the role of teneurins is in neural development not confined to axonal guidance: they have a complex biology which underlies their ability to also regulate dendritic morphology [10,11] and the formation and stabilisation of synapses [12–14]. This review will attempt to link recent advances in our

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http://dx.doi.org/10.1016/j.semcdb.2014.08.007
1084-9521/

understanding of their function with their multifaceted roles in the establishment of neuronal connectivity.

2. A brief history of the teneurins

The invertebrate homologue for this family was initially discovered in genetic screens performed in *Drosophila* by two independent laboratories and was subsequently named Odd Oz (Odz), after the oddless pair-rule like phenotype displayed by mutants [15] or Tenascin-like protein major (Ten-m), due to the presence of its Tenascin-type epidermal growth factor (EGF)-like repeats [16]. The teneurin term was proposed to reflect the original name, together with the strong expression of these molecules in the nervous system [17]. The teneurin/Ten-m nomenclature will be used here, with teneurin referring to the family and Ten-mX to individual genes/proteins (note within the literature the numerical designation is identical for all of the nomenclatures used, *e.g.*, teneurin-3, Ten-m3 and Odz3 are equivalent). Despite this history, it has been shown more recently that *Drosophila* Ten-m does not function as a pair-rule gene [18]. Evolutionarily, the teneurins are ancient molecules, with an ancestral teneurin discovered in a choanoflagellate, the predatory *M. brevicollis* [19]. The choanoflagellates are considered to be the living unicellular eukaryotes that are most closely related to animals (reviewed in [19]). Within choanoflagellates, the teneurin gene appears to have derived from horizontal gene transfer from prokaryotes, where its adhesive nature may have provided an advantage in trapping prey [19]. The presence and structure of teneurins is conserved across both vertebrate and invertebrate species. In most invertebrates, a single teneurin is present, with the exception of insects, where a gene duplication event has resulted in two homologues, Ten-a and Ten-m [19]. In vertebrates, there appear to have been two duplications, both separate from that which occurred in insects, resulting in four family members (Ten-m1–Ten-m4) in mouse, chicken, and human [19–21]. Within the gene family Ten-m1 and Ten-m4 are more closely-related to each other than to Ten-m2 and Ten-m3, and *vice versa*, presumably reflecting the pattern of gene duplications [19].

3. Structure and processing of the teneurins

In mammals, the teneurins comprise a family of 4 highly homologous type II transmembrane glycoproteins (Ten-m1-4). Each of the family members is quite large, around 300 kDa, and is composed of between 2500 and 2800 aa [17]. Teneurins are highly conserved between paralogues and across species (55–68% amino acid identity between mouse paralogues, and around 90% when vertebrate orthologues are compared). They comprise several distinct domains, each associated with different properties. At the N-terminal end is an intracellular domain (ICD) of 300–400 aa followed by a short (34 aa) hydrophobic region thought to serve as the transmembrane domain and then a large globular C-terminal extracellular domain (~2400 aa) [22,23]. Teneurins are hypothesised to exist as homodimers [23,24]. A schematic diagram illustrating the hypothesised structure, cleavage sites and major domains of the teneurins is provided in Fig. 1.

The teneurin ICD contains a number of conserved putative tyrosine phosphorylation sites, two EF-hand-like calcium-binding motifs, and two polyproline domains. These proline-rich stretches are characteristic of Src-homology 3 (SH3)-binding sites, and in chicken Ten-m1, have been shown to be required for specific protein interactions [25]. Consensus SH3 sequences are also present in Ten-m2 and Ten-m4, with a sequence which resembles known SH3 motifs also present in Ten-m3 [19]. A number of studies have reported the ability of the ICD to translocate into the nucleus

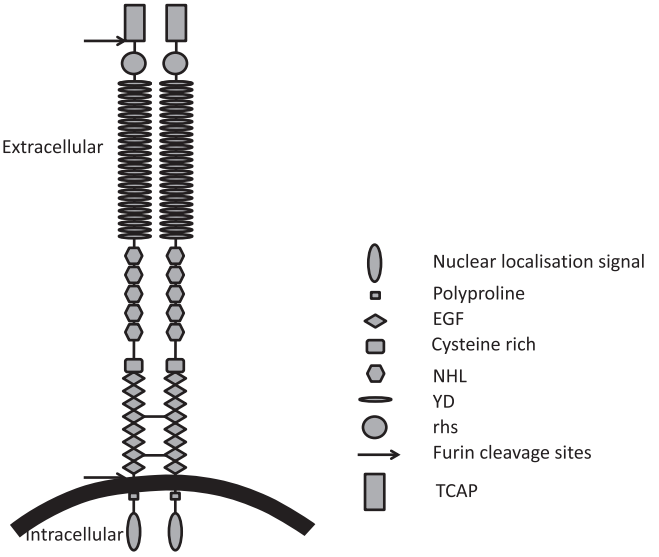

Fig. 1. Schematic diagram illustrating the hypothesised structure and major domains of teneurins. A pair of dimerised Ten-ms is shown. See text for details of domains. Note that not all features are common to all teneurins. An additional intramembrane cleavage site may be present to allow release of the intracellular domain. Based on [19,22–24].

[21,25,26]. When Ten-m1 and Ten-m2 were transfected *in vitro*, their ICDs became localised to distinct puncta within the nucleus [25]. Site-directed mutagenesis was used to demonstrate that Ten-m1 possesses a conserved nuclear localisation signal which is required for nuclear translocation of the ICD [21]. Immunostaining studies also support this, showing that antibodies to the extracellular domain of Ten-m1 only produce staining at the cell membrane, whereas antibodies to the ICD show labelling at both the cell membrane and nucleus [21,27], indicating that translocation occurs *in vivo*, at least for Ten-m1. A strong nuclear localisation signal was found to be present in Ten-m4 and a weaker one was also present in Ten-m3. No nuclear localisation signal, however, was found in the ICD of Ten-m2 [19]. This is surprising given previous *in vitro* studies which showed that binding of the extracellular domains triggered translocation of a tagged version of the ICD of Ten-m2 to the nucleus which was then able to regulate transcription of at least one target gene [26]. Details of the processing of the Ten-ms *in vivo* remain to be resolved. The mechanism for the release of the ICD has been proposed to be similar to the processing of several known transmembrane signalling molecules, such as Notch-1 and amyloid precursor protein (APP). These molecules use a mechanism known as regulated intramembrane proteolysis (RIP), which requires an initial cleavage of the extracellular domain prior to cleavage within the transmembrane region [reviewed in [28]. In addition to the proposed ability of the Ten-m family to regulate gene transcription, the ICDs have also been shown to mediate interactions with the actin cytoskeleton [25,29]. In the case of Ten-m1 this has been shown to occur *via* the cytoskeleton adaptor protein, CAP/ponsin [25].

Within the extracellular domain there is a linker region of around 200 aa which contains several dibasic residues, which may serve as proteolytic processing sites allowing this region to be shed [22]. A recent study has suggested that a potential cleavage site in this extracellular region is present in Ten-m2 and Ten-m3 but absent from Ten-m1 and Ten-m4 [19]. Following this is a series of eight Tenascin C-type EGF-like repeats. The presence of two conserved cysteine substitutions in EGF-like repeats 2 and 5 is thought to facilitate the formation of dimers. Immediately C-terminal to the EGF repeats there is a cysteine-rich region that may aid in the folding of the globular domains [23]. The distal two thirds of the teneurin molecules resemble the YD repeat proteins of bacteria