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Mini-review

Teneurin protein family: An emerging role in human tumorigenesis and drug resistance

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ABSTRACT

Using a chemoproteomic strategy, we recently demonstrated the expression of teneurin-2, a transmembrane glycoprotein, in the majority of malignant mesothelioma cell lines. This finding was unexpected since no formally organized evidence existed to implicate teneurins in human malignancy. For this reason, here we provide a comprehensive review on the expression of teneurins in human tumors and cell lines. Current evidence supports the aberrant expression of teneurins in various tumor types, their involvement in cancer-related regulatory networks, and their potential participation in drug resistance. Structural attributes of teneurins could enable the detection of shedded forms in body fluids for clinical applications.

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1. Introduction

Teneurins belong to a family of highly conserved pair-rule proteins that play essential roles in embryonal development in a wide range of animal species [1–3]. In vertebrates, four teneurins have been identified which are encoded by distinct genes (ODZ1 through ODZ4). Teneurins show high conservation among species and significant homology between the different family members. All teneurins are large type II transmembrane glycoproteins with their amino terminus directed toward the inside of the cell and with typical molecular weights around 300 kDa. The extracellular portion is highly conserved among species and has been shown to engage in teneurin dimerization through interaction of adjacent tenascin-like EGF repeats [4]. A conserved cysteine stretch probably plays a role in protein folding, while a series of tyrosine and aspartic acid (YD) repeats has been shown to have heparin-binding properties and is likely rich in N-linked glycosylation sites [5]. The intracellular portion is also conserved and contains motifs proposed to bind Ca^{2+}, putative tyrosine phosphorylation sites, and proline-rich stretches potentially involved in interactions with the cytoskeleton [6]. Structural and functional aspects of teneurins have been reviewed in detail elsewhere [3,7].

Animal studies revealed that expression of teneurins is highly regulated during embryogenesis, where they play fundamental roles in the development of the central nervous system. In chicken embryos, teneurin-1 and teneurin-2 are expressed in the developing visual system, where they localize to neuronal cell bodies and axonal tracts [8]. Teneurin-2 and teneurin-4 were also detected in developing limbs, each with differential localization patterns [9,10]. In mice, teneurin-2 was localized to the granular layer, Purkinje cells and the molecular layer of the developing cerebellum [11], and the expression of all teneurins was shown to occur in specific spatial and temporal patterns in the developing cortex and thalamus [12]. In adult organisms, teneurin-2 is consistently expressed in the brain and the central nervous system throughout different species [11,13]. Besides their predominant neural

Abbreviations: Zic1, zinc finger of the cerebellum-1; MBD-1, methyl-CpG binding domain protein 1; TCAP, teneurin-C-terminus associated peptide; CHOP, CCAAT enhancer-binding protein homologous protein; Emx2, empty spiracles homeobox-2; BRCA1, breast and ovarian cancer susceptibility protein 1; FGF8, fibroblast growth factor-8; IgH, immunoglobulin heavy chain; HELUs, breast hyperplastic enlarged lobular units; HBV, hepatitis B virus; MALT, mucosa-associated lymphoid tissue lymphoma; cHL, classic Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; 5-AzaCy, 5-aza-2′-deoxycytidine.

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distribution, teneurin mRNAs have been detected in other adult organs such as the testes and thymus, but at significantly lower levels [14], (searchable expression profiles at BioGPS, www.biogps.org).

2. Teneurin function

Current evidence suggests that teneurins are predominantly involved in neural development, regulating the establishment of proper connectivity within the nervous system [7]. Various transfection studies demonstrated that teneurins can promote neurite outgrowth and cell adhesion [8,15]. Knockdown of ten-1 in *Caenorhabditis elegans* lead to defects in migration of gonadal and neuronal cells, axon pathfinding and fasciculation [15], while targeted deletion of teneurin-3 in mice caused a marked visual phenotype with impaired binocular vision [16].

Despite the strong evidence linking teneurins to the development of the nervous system, less is known about the molecular mechanisms involved in teneurin function. Several protein cleavage sites exist along the teneurin amino-acid backbone both in the intracellular and extracellular domains. Internal cleavage close to the plasma membrane was shown to release the intracellular domain of teneurin-2, which then translocated to the nucleus to apparently act as a transcription factor able to repress Zic-1 mediated transcription [17]. Consistent with a role in transcriptional regulation, the cleaved intracellular domain of teneurin-1 can interact with the methylation-dependent transcriptional repressor MBD-1 (methyl-CpG binding domain protein 1) as part of a specific signaling pathway [6]. On the other hand, teneurin-2 carries a potential furin cleavage site outside the plasma membrane, which is susceptible to cleavage *in vitro* [8]. Release of the extracellular domain has not been demonstrated *in vivo*, but could explain the staining of the extracellular matrix observed with some antibodies directed at avian teneurin-2 [9]. A third cleavage site located near the extracellular C-terminus of all teneurins can release a short bioactive neuropeptide (teneurin-C-terminus associated peptides, TCAPs) with roles in the induction of neurite outgrowth, upregulation of cytoskeletal proteins, and regulation of stress and anxiety in rats [18,19].

3. Teneurins in cancer: Available evidence

Lung tumors of the thoracic cavity require specific treatment regimes that depend on an accurate yet often difficult histological classification. Using a chemoproteomic strategy, we recently identified N-glycosylated cell surface protein markers displaying differential abundance levels between adenocarcinoma of the lung and malignant pleural mesothelioma [20,21]. Among the identified proteins, expression of the transmembrane glycoprotein teneurin-2 could be confirmed by validation on low density arrays in the majority of mesothelioma but not in lung adenocarcinoma cell lines. These data suggested that teneurin-2 might be useful for histologic discrimination of both tumor entities. As part of subsequent validation studies, we were surprised by the scarcity of information available on teneurins in human tissues and, in particular, in tumors or related models. Thus, here we performed an in-depth data search on teneurins with a special focus on cancer, which included published articles and publicly available databases for gene expression and proteomic profiles. Most data presented here was obtained by indirect means such as differential expression approaches, array technologies, or linkage analysis. A summary is provided in Table 1.

Within the recovered evidence, decreased expression of teneurin-2 was recurrently reported in different tumors and premalignant lesions. A microarray profiling of microdissected epithelial cells revealed significantly reduced teneurin-2 transcript levels (14.8-fold) in breast hyperplastic enlarged lobular units (HELUs) as compared to normal tissue [22]. These lesions are the earliest histologically identifiable potential precursors of breast cancer. In line with this findings, the ODZ2 gene was found to be disrupted by hepatitis B virus (HBV) insertional mutagenesis in livers of patients with chronic hepatitis, an early genetic change that could lead to hepatocarcinogenesis [23]. These findings were strengthened by analysis of hepatic tumors, where lack of teneurin-2 mRNA was found in one tumor and low levels in four of seven additional cases [23]. Similarly, a differential cDNA analysis revealed reduced teneurin-2 transcript levels in esophageal squamous cell carcinoma as compared to normal tissue [24], and findings were validated by RT-PCR on a set of cell lines and tissue samples.

Table 1
Summary of studies with direct implication of teneurins in human malignancies.

Tumor/lesion	Tissue analyzed	Teneurin reported	Transcript levels	Mechanism	Refs.
Breast hyperplastic enlarged lobular units (HELU)	Microdissected epithelial cells	Teneurin-2	Decreased compared to normal breast tissue	Unknown	[22]
Hepatocellular carcinoma	Tissue	Teneurin-2	Decreased or absent in 5/7 tumors compared to normal surrounding tissue	Unknown; could relate to HPV insertional gene mutagenesis	[23]
Esophageal squamous cell carcinoma	Esophageal normal and cancer cell lines	Teneurin-2	Decreased compared to normal esophageal epithelium	Unknown	[24]
Mucosa-associated lymphoid tissue (MALT) lymphomas	Tissue	Teneurin-2	Increased in 1/1 tumor compared to other lymphomas and normal lymph nodes	Gene translocation	[27]
Classic Hodgkin lymphoma (cHL)	Microdissected tumor cells	Teneurin-2	Increased compared to nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)	Unknown	[29]
Early-stage cervical cancer	Tissue	Teneurin-2	Upregulated in tumors without (N_0) compared to tumors with (N_{+}) lymph node metastasis	Unknown	[26]
Malignant pleural mesothelioma	Established and primary cell lines	Teneurin-2	Frequent expression[a]	Unknown	[20]
Ovarian carcinoma	Vincristine- sensitive and resistant cell lines	Teneurin-2	Highly overexpressed in vincristine-resistant cell line	Unknown, no apparent gene amplification	[35]
Renal carcinoma	Renal carcinoma cell lines	Teneurin-4	Decreased compared to non-tumorigenic epithelial cell line	Unknown, potentially epigenetic (histone modifications)	[47]
Breast carcinoma	Breast cancer cell line	Teneurin-4	Expressed	Gene translocation	[31]
Brain tumors	Tissue	Teneurin-4	Increased in tumors compared to normal brain tissue	Unknown	[34]

[a] Teneurin-2 protein was also detected by a proteomic approach in one cell line analyzed.

Although protein-based evidence is limited due to a lack of suitable affinity binders, strong staining for teneurin-2 was observed in normal squamous cells of the esophagus and in glandular cells of the stomach and small intestine using an antibody validated for recognition of Human Protein Atlas teneurin-2 antigens (http://www.proteinatlas.org/ENSG00000145934/summary). In contrast, 83% of stomach tumors had low or undetectable teneurin-2 staining, which suggests that ODZ2 gene expression might be generally reduced in cancers of the digestive system. Teneurin-2 mRNA levels also showed a gradual reduction with metastatic progression of prostate cancer (Gene Expression Omnibus, http://www.ncbi.nlm.nih.gov/geo/, accession GS1439, [25]), and were significantly higher in early-stage cervical cancer without lymph node involvement compared to cases with lymph node metastasis [26]. Lymph node involvement is a main prognostic factor for this patient group. Together, these data strongly suggest that loss or diminished teneurin-2 expression is not uncommon. It appears to be an early event in the initiation of some human tumors, and could relate to disease progression. Confirmation of these data in vertebrate teneurin knock-out models would be ideal, but teneurin silencing is associated with an elevated embryonic lethality and only teneurin-3 knock-out mice have been reported to date [16]. However, expression of intracellular teneurin-3 domains could not be excluded in this model and data on survival or the appearance of tumors was not provided.

A different line of evidence indicates that teneurin genes might also be affected by chromosomal translocation. In three mucosa-associated lymphoid tissue (MALT) lymphomas, a novel translocation affecting the IGH and ODZ2 genes was identified in tumors of the skin and the ocular adnexa [27]. These anatomical locations are highly reminiscent of the impairments in the visual system and the hypodermis described for some mouse and *C. elegans* teneurin mutants [16,28]. In one MALT tumor with sufficient material, a several-fold elevation of teneurin-2 mRNA could be confirmed. Increased teneurin-2 transcript levels were also reported in classic Hodgkin lymphoma (cHL) compared to the nodular lymphocyte-predominant subtype (NLPHL), but this profiling approach did not address the presence of translocations [29]. An additional translocation fusing the ODZ4 and the neuregulin-1 (NRG1) genes was detected in one breast cancer cell line [30], and the resulting γ-heregulin fusion protein was shown to act as a secreted autocrine growth factor through activation of the ErbB3-ErbB2 receptor complex [31]. However, γ-heregulin could not be detected in subsequent series of breast tumors and cell lines, indicating that this translocation is not a common genetic event in breast carcinogenesis [32,33].

In line with the augmented levels of teneurin transcripts associated with some of the above translocations, additional evidence seems to favor an oncogenic rather than a tumor suppressive role for teneurins in some tumor types. In fact, consistently elevated mRNA levels have been found for teneurin-4 in a microarray analysis of brain tumors including astrocytomas, oligodendriomas, and glioblastomas [34]. Although immune detection of teneurin-4 was attempted for validation, the interpretation of results was hampered by unspecific staining of necrotic tumor regions and blood vessels, which led to the hypothesis that teneurin-4 might also play a role in tumor angiogenesis. Importantly, teneurin-2 mRNA was overexpressed >250-fold in vincristine-resistant Skov-3 ovarian cancer cells [35]. The underlying mechanism was not addressed, but no concomitant alterations in ODZ2 gene copy numbers could be detected. This finding is highly significant considering recent data showing that *Drosophila* teneurins are essential for proper microtubule organization [36]. Thus, overexpression of teneurin-2 in vincristine-resistant cells might counter vincristine toxicity by the sequestration of free tubulin into microtubules. This effect on microtubule dynamics might also explain the potential role of teneurin-2 as a risk-modifier for breast cancer in patients carrying BRCA1 mutations [37]. BRCA1 was shown to inhibit centrosomal microtubule nucleation, and loss of BRCA1 has been associated with centrosome hyperactivity, supernumerary centrosomes, and decreased sensitivity to microtubule-targeted cytotoxic drugs [38,39]. Loss of BRCA1 and altered expression of teneurin-2 might thus affect a common microtubule-related pathway and potentiate in concert mechanisms driving hyperproliferation and the accumulation of chromosomal anomalies. These findings could place teneurins in the prognostic biomarker group related to the emergence of drug resistance and prediction of patient response to cytotoxic therapy.

Taken together, coincident results from different and independent sources show that some teneurins, most notably teneurin-2 and teneurin-4, show altered expression patterns in different tumors at the transcript level. Whether teneurins participate as tumor-suppressors or rather oncogenes remains to be determined and might depend on the tumor type. In fact, a meta-analysis performed on array profiles of >5000 human tissue samples and a transcription profiling including 950 cell line measurements (Gene Expression Atlas, http://www.ebi.ac.uk/gxa/, accessions E-MTAB-62 and E-MTAB-37, respectively)[40] showed that significant reductions as well as elevations of teneurin-2 and -4 mRNA can occur depending on the tumor type. In addition, based on the known functions of some teneurins in the maintenance of basal membrane integrity and as mediators of homophilic intercellular adhesion [41,42], similarities are evident with E-cadherin, another adhesion molecule altered in cancer. Loss of E-cadherin expression in tumors is associated with transition to malignant phenotypes and with an increased potential for metastatic spread [43]. However, E-cadherin overexpression can also occur. In this case, the presence of shedded, proteolytically cleaved E-cadherin ectodomains with oncogenic properties has been demonstrated [43]. Similar mechanisms could explain the apparently contradicting findings of reduced and augmented expression of teneurins in cancer.

4. Teneurin-4 and miR-708

Considering that teneurins-2 and -4 were the predominant family members identified in profiling of cancer tissues, some recently uncovered mechanisms involved in the control of teneurin expression should be discussed. In earlier work, Wang et al. demonstrated that the CAAT enhancer-binding protein homologous protein (CHOP) could induce expression of the teneurin-4 gene [44]. CHOP acts a transcription factor in response to stress of the endoplasmic reticulum (ER), and is involved in the induction of apoptosis under such conditions [45]. A recent search for microribonucleic acids (miRNAs) responsive to ER stress, identified miR-708 as a CHOP-induced miRNA [46]. It was further shown that miR-708 resides in the first intron of the ODZ4 gene, and that expression of teneurin-4 and miR-708 were correlated in adult mouse tissues, with particular enrichment in eyes and brain. It could be concluded that miR-708 and teneurin-4 are coregulated by CHOP. With regard to cancer, a recent microarray profiling revealed decreased levels of miR-708 in renal carcinoma cells, and validation by RT-PCR confirmed a significant reduction in miR-708 levels in ~75% of renal cancer tissues analyzed [47]. Importantly, exogenous miR-708 was shown to suppress tumor growth *in vitro* and lead to tumor regression in a mouse xenograft model. The authors further showed that the proapoptotic action of miR-708 was mediated in large part by direct targeting of the survivin transcript. In analogy to the findings in mouse tissues, renal tumors showed concordant downregulation of miR-708 and teneurin-4. These data provide first functional evidence on the importance of the ODZ4/miR-708 gene expression complex in cancer, and underscore the need to assess the impact of teneurin-4 expression on cancer-related cellular

mechanisms and patient prognosis. It is currently unknown whether analogous miRNAs could be encoded within other ODZ genes, but this issue should also be addressed.

5. Homeobox genes and control of teneurin expression

Considering their fundamental role in development, it is not surprising that expression of teneurins would be controlled by Homeobox transcriptions factors, the key regulators of embryonal morphogenesis and cell differentiation [48]. A previous study showed that deletion of the murine HoxD gene cluster causes a small but significant increase in ODZ4 mRNA in the developing limbs and genitals, and the authors proposed that ODZ4 might be a target for HoxD-mediated repression [49]. These results are consistent with the known role of some teneurins in the regulation of limb formation [9,50]. Disregulation of Hox genes has previously been reported in some solid tumors and can be oncogenic in leukemias [51]. More detailed evidence exists for EMX2, the human homologue of the *Drosophila* empty spiracles gene (*ems*). In *Drosophila* and mice, EMX2 controls the development of the fly head [52] and the cerebral cortex [53], respectively, and knockout studies have shown that it is essential for the development of the male and female reproductive systems [54]. EMX2 has been implicated in the regulation of gene expression of virtually all teneurins. In the first study to analyze teneurin-1 promoter elements in humans, EMX2 was shown to directly activate teneurin-1 gene expression by binding to a novel alternate promoter [55]. Similarly, expression of teneurin-4 was significantly reduced in the cortices of EMX2 knockout mice, and comparable decreases were observed for the remaining teneurin-2 and -3 transcripts [12]. Together, these data suggest that EMX2 can positively regulate teneurin gene expression, potentially by direct binding to teneurin regulatory sequences (Fig. 1A).

The functional link between teneurins and EMX2 could be relevant to cancer. Okamoto et al. reported significantly reduced expression of EMX2 in 71.8% of lung cancers as compared to their adjacent normal tissues [56]. The authors also showed that epigenetic mechanisms could control expression of EMX2 in lung cancer cell lines, and that exogenous EMX2 could suppress proliferation and enhance cisplatin-mediated cytotoxicity. In agreement with these data, low EMX2 expression was significantly associated with decreased overall and relapse-free survival in patients with lung adenocarcinoma [57]. Decreased levels of EMX2 have also been reported in endometrial tumors, where EMX2 mapped to a region of allelic deletion and was postulated to act as a tumor suppressor gene [58]. Considering this evidence, loss of EMX2 could lead to reduced expression of teneurins, which would place teneurins in the same category of potential tumor suppressor genes. Although data on the correlation of EMX2 and teneurin expression in tumors is lacking, we and others have found reduced or absent expression of teneurin-2 in lung adenocarcinoma [20], (GEO, accession GDS3627, [59]), which would agree with the reduced levels of EMX2 reported for these tumors [56,57].

6. Activation of teneurin-2 expression by FGF8

The regulatory activity exerted by FGF8 on teneurin-2 gene expression could also bare importance for cancer [9]. The expression of teneurin-2 and FGF8 coincide both spatially and temporarily during vertebrate limb development, and exogenous FGF8 was shown to induce teneurin-2 expression in primary limb bud cultures and explanted limbs [9,60]. The family of fibroblast growth factors and their receptors are profoundly involved in human carcinogenesis and their action is considered oncogenic [61]. Among others, aberrant signaling can result from amplification and overexpression of FGFs and mutation of FGF receptors. FGF8 is frequently overexpressed in breast and ovarian cancer to drive proliferation thorough an autocrine loop [62,63], and in a model of mouse mammary tumorigenesis, FGF8 was shown to cooperate with *Wnt-1* [64]. The latter is important since the *Drosophila* teneurin homolog, ten-m, was shown to initiate a signal transduction cascade which acted on downstream targets including the *Wnt-1* homolog, *wg*, whose activation was strictly dependent on ten-m [65]. Since FGF and Wnt signaling play crucial roles in cancer and cooperate in carcinogenic transformation, teneurin-2 could be involved in the interplay between these pathways acting as an oncogene. A tentative scheme for these interactions is summarized in Fig. 1B. This could be of particular relevance to hormonal cancers where FGF8 is highly expressed and has been associated with tumor growth and progression [66].

7. Epigenetic control of teneurin expression

Methylation of DNA is substantially altered in human tumors and is crucial for the aberrant expression of numerous cancer genes [67]. Using a high-resolution mapping technique for profiling of global DNA methylation, Tommasi et al. found significant methylation of the ODZ3 gene upstream region in breast ductal carcinomas *in situ* as compared to normal surrounding tissue [68]. These premalignant lesions often progress to invasive carcinoma. Similarly, CpG islands were found in proximity of an alternate first exon identified in the human teneurin-1 gene [55]. Although these results suggest an epigenetic control mechanism, neither study assessed whether DNA methylation could account for the silencing of teneurin genes. In contrast, analysis of data from two microarray profilings that included breast and ovarian cancer cell lines treated with the demethylating agent 5-aza-2′-deoxycytidine (5-AzaCy) did not show significant induction of teneurin-2 or -4 [69,70], and thus do not support a role for DNA methylation in the control of teneurin gene expression. In line with this finding, expression of miR-708 was induced by an inhibitor of histone deacetylases but not by 5-AzaCy in a non-tumorigenic epithelial cell line [47]. Since expression of miR-708 and teneurin-4 appears to occur concomitantly, these data point to an epigenetic control mechanism by histone modification rather than DNA methylation. It will be crucial to clarify the mechanism(s) responsible for teneurin expression to understand their contribution and regulation in human tumors.

8. Secreted teneurin forms as potential tumor biomarkers

In early reports, *Drosophila* ten-m was proposed to be a secreted protein based on the presence of an N-terminal secretory signal sequence, and on the recovery of a soluble protein from conditioned medium by immunoprecipitation [65]. Although the presence of a transmembrane domain was later demonstrated, the existence of secreted forms remains feasible based on the presence of multiple potential cleavage sites along the vertebrate teneurins [6,17]. Cleavage by a furin-type protease was indeed demonstrated for a recombinant teneurin-2 protein and led to secretion of cleavage products into the medium [8]. Proteolytic cleavage of avian teneurin-4 has also been suggested based on immunoblotting evidence of smaller protein subspecies [50]. Avian teneurin-4 bears a putative furin recognition site and multiple dibasic residues, all of which could mediate proteolytic processing. Immunohistochemical data has revealed staining compatible with localization of both teneurin-2 and teneurin-4 to the extracellular matrix in the chicken embryo [9,50]. Evidence for the existence of a secreted teneurin-4 form was further obtained in a recent proteomic profiling of human urine [71], where several teneurin-4 derived peptides

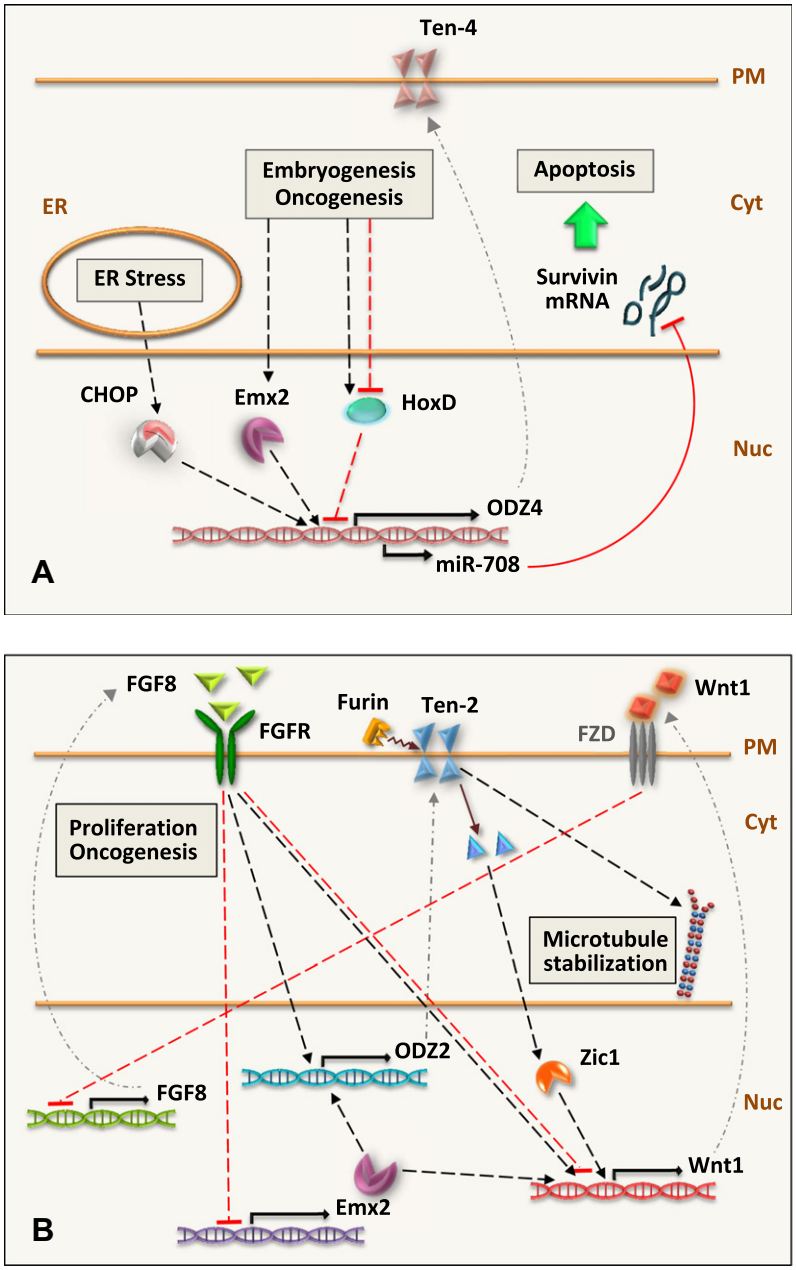

Fig. 1. Tentative model of regulatory pathways involved in teneurin-4 (A) and teneurin-2 (B) signaling. The evidence reviewed here suggests differences in the regulatory networks associated with teneurin-2 and teneurin-4 expression. (A) Homeobox genes can both induce or repress teneurin-4 expression. In cancer, reduced levels have been reported for EMX2 [57], while Hox genes can be either up- or downregulated in solid and hematologic tumors [51]. Stress of the endoplasmic reticulum, usually associated with a response to misfolded proteins, induces CHOP which in turn activates teneurin-4 gene expression. The concomitant transcription of miR-708 targets survivin mRNA for degradation, thus facilitating apoptosis. (B) Proposed interaction of Wnt and FGF pathways in the regulation of teneurin-2 expression. For FGF signaling, both positive and inhibitory effects have been reported on Wnt expression and mutual feedback loops appear to exist [75,76]. Expression of Wnt1 can be induced through the transcription factor Zic1 [65,77], which in turn was shown to associate in the nucleus with the cleaved intracellular domain of teneurin-2 [17]. Both teneurin-2 and Wnt signaling have been implicated in the regulation of microtubule dynamics, suggesting that additional interactions are likely between these two signaling pathways [36,78] (not shown). Current evidence points to a coordinated role of teneurin-2, FGF8 and Wnt-mediated signaling in promoting cell growth and differentiation. Dotted lines denote indirect inhibitory (red) and stimulatory (black) effects, solid lines correspond to direct interactions. *PM*, plasma membrane; *Cyt*, cytoplasm; *Nuc*, nucleus. The Wnt receptor Frizzled (*FZD*) was not discussed here but has a well-established role in Wnt signaling. For convenience, protein and gene names correspond to vertebrate species. The interplay of pathways presented here needs to be confirmed in a cancer-related model where regulatory mechanisms might differ.

could be identified. This finding could be of particular interest to patients with teneurin-expressing tumors such as mesothelioma, and might point to a potential role for teneurins as soluble blood or urine tumor biomarkers for disease detection and management. An analogous approach proved effective for detection of serum mesothelin, a tumor membrane protein cleaved by furin proteases and released into the blood stream [72]. Although serum mesothelin has evidenced high specificity, its sensitivity remains poor and better biomarkers are still required for improved diagnosis of mesothelioma.

9. Summary and outlook

The data surveyed here provides evidence from different sources for altered expression patterns of teneurin family genes in human tumors, and for their involvement in crucial

cancer-related regulatory networks and mechanisms associated with drug resistance. Since suitable affinity-based probes for direct testing of human teneurin protein levels are sparse and of questionable quality, most current data stems from transcript measurements. Statements about teneurin quantities are thus not possible, including the abundance levels on the cell surface that are crucial for actual function and for potential biomarker evaluation. Recent advances in proteomic technologies might be a way forward since mass-spectrometry-based strategies now enable identification and quantification of specific peptides from cells, tissues, and clinically interesting body fluids [73,74]. Such approaches have already revealed the presence of peptides derived from teneurins-2 and -4 in mesothelioma and human urine samples, respectively [20,71]. This should be a main outlook for validating the role of teneurins in human oncogenesis and drug resistance, and for the assessment of their clinical utility as prognostic and/or response predictive cancer biomarkers. As of now, sufficient evidence exists to substantiate a possible role of human teneurins in cancer initiation and progression, and in resistance to microtubule-targeting drugs. Our ongoing research is evaluating the expression and function of teneurins-2 and -4 in hormone-dependent cancers, and proteomic approaches will be included for quantitative determination of teneurin-derived peptides in serum and tumor tissues of suitably selected patients.

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