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Matricellular proteins in drug delivery: therapeutic targets, active agents, and therapeutic localization

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Abstract

Extracellular matrix is composed by a complex array of molecules that together provide structural and functional support to cells. These properties are mainly mediated by the activity of collagenous and elastic fibers, proteoglycans, and proteins such as fibronectin and laminin. ECM composition is tissue-specific and could include matricellular proteins whose primary role is to modulate cell-matrix interactions. In adults, matricellular proteins are primarily expressed during injury, inflammation and disease. Particularly, they are closely associated with the progression and prognosis of cardiovascular and fibrotic diseases, and cancer. This review aims to provide an overview of the potential use of matricellular proteins in drug delivery including the generation of therapeutic agents based on the properties and structures of these proteins as well as their utility as biomarkers for specific diseases.

Graphical abstract

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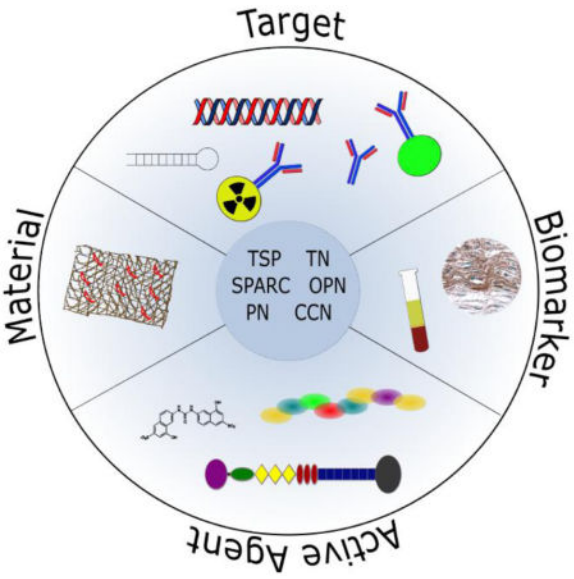

Keywords

Extracellular matrix; matricellular; cell-matrix interactions; angiogenesis; fibrosis

1. Introduction

Matricellular proteins constitute a class of molecules linked by their ability to function as modulators of cell-matrix interactions without serving primary roles as structural components (1). Originally, this genetically unrelated group consisted of several thrombospondin (TSP) family members, osteopontin (OPN), tenascin-C (TN-C), and secreted protein acidic and rich in cysteines (SPARC). More recently, the group has expanded to include additional proteins such as periostin, autotaxin, PEDF, fibulin-5 and other tenascins that contribute to its functional complexity. In fact, for some matricellular proteins there is now an appreciation for significant intracellular functions (2–7). Because of their ability to interact with both matricellular proteins and cell surface receptors, these proteins have been shown to influence ECM assembly (collagen secretion, fibrillogenesis) as well as numerous cell functions (adhesion, proliferation, migration). Despite the ability of the matricellular proteins to influence these significant processes, mice lacking one or more matricellular genes are, in most cases, viable and fertile and do not display remarkable phenotypes (8). These observations suggested that the matricellular proteins are dispensable during development. However, some matricellular proteins, including autotaxin and members of the CCN family, are necessary for development, and deletion is embryonic lethal (9, 10). In addition, their expression in adult tissues is usually low but is highly induced in various pathologies or injuries (11–14). Therefore, investigators have sought to establish functions in various disease and injury models. Such studies have expanded our understanding of the matricellular proteins and have suggested that they can be exploited in the context of developing therapeutic strategies, and many of those strategies have advanced to the clinic (Table 1) (15). Specifically, because they have diverse functions in many tissues, they can they can be used in multiple ways to enable effective drug delivery. Based

on their expression and contribution to various pathologies, matricellular proteins could serve as either targets for inhibition or as a basis for the development of therapeutic agents (15–19). In addition, their ability to interact with both cells and matrix makes them suitable for localized drug delivery. Finally, the presence of certain matricellular proteins, both in diseased tissue or in circulation, can indicate the state and progression of the disease and thus could be useful biomarkers for assessing clinical outcomes (Table 2). Therefore, several matricellular proteins have been suggested as diagnostic or predictive biomarkers for various diseases ranging from cardiovascular pathologies to cancer (20, 21).

2.1 Thrombospondins and drug delivery

Thrombospondins (TSP) are a family of secreted multifunctional ECM proteins with five members (TSP 1-5) (8). TSP-1 and -2 are synthesized as homotrimers with a molecular weight of 450,000. TSP-3, -4 and -5 are synthesized as homopentamers with molecular weights of each monomer ranging from 105,000 to160,000. TSP-1 and TSP-2 share a high degree of homology and display potent anti-angiogenic activity (22). However, they display distinct spatiotemporal expression patterns and functional diversity due to differences in their promoter regions (23). For example, both are implicated in wound healing but TSP-1, which is primarily released by platelets and secreted by monocytes/macrophages, plays a significant role in the early inflammatory phase. In contrast, TSP-2 is mainly secreted by fibroblasts and influences matrix remodeling. In addition to angiogenesis, TSPs have been implicated in many other processes including ECM synthesis and assembly, synaptogenesis, and inflammation (24–26). Despite the differences in structure and expression patterns, TSPs have been implicated in a variety of diseases including cancers, glaucoma, pulmonary and cardiovascular diseases, and kidney diseases (14, 27–30). Because of their significant roles in these conditions, both the overexpression and inhibitory targeting of TSPs have been pursued as therapeutic treatments (31–34).

The primary biological functions of TSP-1 are platelet aggregation, modulation of the inflammatory response, and the regulation of angiogenesis (35). Of these roles, the antiangiogenic effect is the most studied (36). In cancer, many oncogenic mutations result in the downregulation of TSP-1, which enable a proangiogenic phenotype (37). The restoration or induction of TSP-1 signaling in the tumor environment has the potential to restrict tumor growth by decreasing the tumor vasculature. This effect was observed in human skin carcinoma cells that were engineered to express TSP-1, the resulting tumors had greatly reduced vascularity and exhibited restricted growth (38). The effect was reversed with antisense inhibition of TSP-1. The inhibition of angiogenesis and restriction of tumor growth was also observed in cutaneous squamous cell carcinomas, breast carcinomas, and in human gliomas transfected to overexpress TSP-1 (39–41).

The initial attempt to create a therapy out of TSP-1’s antiangiogenic properties was with the isolation of antiangiogenic peptides from the larger TSP-1 protein (42). A recombinant protein composed of 3 type 1 repeats (TSR) from the antiangiogenic region of TSP-1was designed to avoid using the full length protein. 3TSR treatment was initially proven effective at inhibiting lung and pancreatic tumor growth (43, 44). Antiangiogenic treatment with 3TSR has also been used in combination with traditional cytotoxic chemotherapy. In an

advanced ovarian cancer model, treatment with 3TSR normalized the tumor vasculature and increased the efficacy of carboplatin delivered by either a maximum tolerated dose or metronomic dosing regimens (45). Similary, lexatumumab, a humanized antibody against TRAIL receptor DR5, was used in combination with 3TSR to attack tumor endothelial cells. The combination therapy was shown to be more effective than either drug as a monotherapy in treating a colon cancer model in mice (46). This synergy results from 3TSRs ability to upregulate DR5, and prime the tumor cells for treatment with the antibody (47).

In addition to 3TSR, individual peptides from TSP-1 were created and utilized for antiangiogenic chemotherapy (48). The two peptide mimetics, named ABT-510 and ABT-526, were shown to be effective at inhibiting angiogenesis and tumor growth in both mouse cancer models and naturally occurring cancers in dogs (48–50). An initial phase 1 study of ABT-510 in humans showed linear pharmokinetics across all doses, but continuous infusions resulted in pain at the injection site, which was minimized by bolus dosing (51). Further clinical trials investigated ABT-510 as a monotherapy for patients with advanced soft tissue sarcoma, renal cell carcinoma, and metastatic melanoma (52–54). In each case ABT-510 exhibit a good safety profile, but failed to produce clinical responses. ABT-510 was used in additional Phase 1 clinical trials in combination with 5-fluoruracil and leucovorin, or gemcitabine and cisplatin, for solid tumors, and with temozolomide and radiation as a treatment for glioblastoma (55–57). Each study noted a strong safety profile for ABT-510 as part of a combination therapy. Additional combination therapies are being examined in preclinical models to build on ABT-510s antiangiogenic capability (58, 59).

Like TSP-1, TSP-2 is antiangiogenic and a potent inhibitor of tumor growth (60). Cell-based techniques have been developed to provide local delivery of TSP-2, and could prove useful for cancer treatment, macular degeneration, or other diseases of aberrant angiogenesis (61). However, TSP-2 also plays a role in ECM assembly, wound healing, and the foreign body response (62–64). Wounds in TSP-2 null mice appear to heal faster, produce less scarring, and produce an irregular, highly vascularized, granulation tissue. Injection of polymer-based delivery vehicles loaded with antisense TSP-2 cDNA was able to reproduce the increased angiogenesis and irregular matrix remodeling observed in the null mice (65).

Implants in TSP-2 null mice induce an altered foreign body response that results in more vascularized capsules, when compared to WT controls. A gene-activated matrix that delivered anti-sense TSP-2 cDNA was able to induce local transfection and yield a vascularized capsule similar to TSP-2 null mice (66). Looser, more vascularized capsules could enable the use of implantable devices, like glucose sensors for diabetics. A reduced FBR would also be advantageous for vascular grafts, where adverse remodeling after implantation can lead to neointimal hyperplasia and restenosis. One potential solution, a vascular graft coated in gene delivery vehicles for TSP-2 siRNA, showed the ability to transfect adhered aortic smooth muscle cells and knockdown TSP-2 (67).

2.2 Osteopontin and drug delivery

OPN, also known as bone sialoprotein I (BSP-1 or BNSP) is a highly negatively charged, extracellular matrix protein that is heavily glycosylated and phosphorylated (68–70). Both the extensive presence of acidic amino acids and many phosphate groups contribute to its

negative charge. In addition to phosphorylation, OPN undergoes glycosylation and sulphation (71). Moreover, full length OPN can be modified via enzymatic digestions by thrombin and carboxypeptidase C that expose cryptic sequences and remove the C-terminal amino acids, respectively. Splice variants of OPN have also been described with expression patterns that appear to be cancer-specific (72). Coupled with the ability of OPN to interact with multiple receptors, the existence of multiple OPN isoforms contribute to its functional complexity. Even though OPN was first identified as a major constituent of bone with prominent roles in bone formation and calcification, it is now appreciated that it is a multifunctional molecule with critical roles in physiology and pathology that are primarily dependent on its spatiotemporal expression. Consistent with its extensive associations with numerous processes, OPN has been shown to be expressed in multiple cell types including fibroblasts, various bone cells, chondrocytes, immune and inflammatory cells, and vascular cells and it is associated with cell attachment via integrins, chemotaxis, and survival/apoptosis (68). In terms of physiological processes, OPN functions in bone mineralization and remodeling, angiogenesis, and immune and cardiovascular functions (68, 69, 73). OPN has also been linked to many pathological conditions such as skeletal disorders, cancer, rheumatoid arthritis, multiple sclerosis, atherosclerosis and heart disease (68, 73–80).

OPN has been shown to play a role in the epithelial to mesenchymal transition (EMT), a process where epithelial cells lose polarity and gain motility (18). In cancer, EMT generally precedes growth and metastasis, which makes OPN a likely biomarker for disease progression. In colon, prostate, pancreatic, head and neck, and metastatic breast cancers, expression of OPN is correlated with disease progression and decreased survival (81–86). Osteopontin is also strongly associated with metastasis, particularly with bone metastasis, which makes it a good biomarker for disease progression in many types of cancers (87, 88).

The role of OPN in the growth and metastasis of multiple cancers is well-known, and there have been multiple studies examining OPN as a therapeutic target (74, 89). The anticancer effects of dietary genistein (an isoflavone found in soy bean), resveratrol, curcumin, and thalidomide in animal cancer models was partially attributed to each compounds ability to decrease OPN (90–93). Posttrascriptional gene silencing using siRNA or shRNA has also been used to silence OPN expression in animal models of cancer. The technique has been used extensively in models of liver and gastric cancers, with knockdown of OPN resulting in decreased growth, invasion, and angiogenesis (21). Similar results were seen in vitro and in vivo with breast, oral, and endometrial cancer cell lines (94–96). As with other matricellular proteins, aptamers, small molecule inhibitors, and antibodies can also be used therapeutically (74, 97).

An alternate approach to treating cancer, via the inhibition of OPN, is by attempting to prevent metastasis. To examine this approach Yu et. al. used an orthotopic mouse breast cancer model that metastasized to the lungs (98). Two weeks after tumor inoculation, shRNA against OPN was delivered as an aerosol into the lungs of the mice. The shRNA decreased the levels of OPN in the lung tissue and prevented metastasis up to two months after application.

Outside of cancer, OPN has been associated with a variety of other diseases. A recent study of OPN as a biomarker for sepsis, determined that plasma OPN could serve as a prognostic biomarker for a variety of critically ill patients (99). This increase in plasma OPN was attributed to increased levels TNF-α and IL-1, which are increased in inflammation and stimulate the expression of OPN. Plasma OPN also correlated with disease severity in both alcoholic liver cirrhosis and hepatic fibrosis from hepatitis C virus infection (100, 101). Moreover, hydrodynamic intravenous injection of OPN siRNA reduced liver tissue injury in a murine model of concanavalin A (ConA)-induced fulminant hepatitis (102).

Osteopontin has also been shown to be upregulated during oxidative stress, making it a biomarker for vascular diseases (103–105). In a mouse stroke model, OPN increased after injury, reaching peak levels 5 days post-occlusion (106). In humans, OPN increased after stroke, and greater levels in plasma correlated with disability and decreased functional outcome (104, 107).

The use of OPN as a target or treatment for cardiac disease is complicated by the need to balance inflammation, angiogenesis, and fibrosis (19). However, in the CNS, OPN is neuroprotective when administered after an ischemic event (108). The neuroprotective effect is mediated via RGD motif and signaling via Akt and MAPK. As a therapy, both OPN peptide mimics and OPN containing gelatin nanoparticles were neuroprotective in a mouse MCAO stroke model after intranasal administration (109–111).

Outside of OPNs use as an active agent or therapeutic target, the adhesive capability of OPN, mediated by a variety of binding motifs, makes it a good candidate for integrative biomaterial coatings and implants (112). For example, surface treatment of positively charged polymer (p(HEMA-co-AEMA) with oriented OPN reduced the foreign body response in a mouse implant model (113). Mixtures of OPN and gelatin have shown improved integration in both tooth and bone repair (114, 115). The adhesive capacity can also be used to direct the cellular coating of biomaterial implants. Endothelial progenitor cells were shown to increase adhesion and spreading on a surface coated with OPN (116). Similarly, mesenchymal stem cells showed attachment, spreading, and motility on OPN coated hydroxyapatite and gold surfaces, which could be potentially useful as orthopedic implants (117). Finally, in a murine dorsal air sac assay the OPN-derived peptide SVVYGLR induced an angiogenic response similar to vascular endothelial growth factor (VEGF) (118).

2.3 Tenascins and drug delivery

Four molecules, TN-C, TN-R, TN-W, and TN-X make up the TN family. These large oligomeric proteins are homologous in structure and are made as homotrimers or hexamers that contain tandem epidermal growth factor and fibronectin type III repeats and a fibrinogen homology domain (119, 120). As a family, the tenascins have been shown to play roles in cancer, fibrosis, and the function of the central nervous system (CNS) (120, 121). However, more specialized roles in physiological and pathological conditions have been described for each member. TN-C is a hexameric protein with a molecular weight of 220,00 and is the most widely studied member of the family (122, 123). It has anti-adhesive properties that are mediated by its ability to interact with fibronectin. In addition, isoforms

of TN-C generated via alternative splicing have shown functional heterogeneity that includes effects on cell proliferation and migration. Thus far, TN-C has been implicated in various diseases including cancers and sarcomas, fibrosis, and cardiovascular disease (124–127). TN-R, TN-W, and TN-X exist in multiple isoforms and are less well studied with limited reports linking them to vascular calcification, Ehlers-Danlos syndrome, and CNS diseases (128–131).

In cancer, TN-C is produced by both the tumor and stromal cells in the primary tumor and as a part of the metastatic niche (119). TN-C supports the growth and metastasis of neoplasms by promoting proliferation, migration, angiogenesis, metastasis, and aiding in the EMT (132–134). In breast cancer, TN-C expression is correlated with disease progression and relapse by metastasis to the lung and is a potential biomarker for the disease (135, 136). Similarly, TN-C has also been noted as a biomarker for pancreatic, bladder, colorectal cancers, and glioma (137–141). Therapeutic inhibition of TN-C is a possible treatment strategy in these models as well, which was illustrated in a mouse breast cancer model when cells treated with shRNA against TN-C produced fewer metastases (135).

A great amount of research has been conducted on the relationship between TN-C and glioma. Expression of TN-C in glioma is associated with increased invasion, recurrence, and poor prognosis (142). Encouragingly, initial research using glioma cell lines showed that inhibition of TN-C using antibodies resulting in decreased proliferation and migration (143). As a result, one of the first studies of RNAi in humans was a study that injected dsRNA targeting TN-C into the brains of patients with recurrent gliomas (144). After positive results in the initial, 8 person, study, a larger 46 person trial was conducted (145). The results showed an improvement in survival and disease score, but the observed benefits were not definitively linked to therapeutic gene silencing. However, the study was a promising first step towards a new therapy for glioma, and there have been numerous advances in RNAi technology since the completion of the study.

Another way the overexpression of TN-C can be used to treat brain tumors is by using targeting ligands to localize toxins or radiotherapeutics. Using this strategy, an aptamer against TN-C was able to localize imaging agents to intracranial tumors, indicating potential as a therapeutic (146). An alternative to aptamers, antibodies against TN-C have been developed, tagged with radiolabels, and are able to specifically target intracranial tumors from i.v. administration (147, 148). One therapeutic modality, referred to as an avidin-biotin pretargeting system, used systemic administration of a biotinylated anti-tenascin antibody, followed by avidin administration and then subsequent administration of a biotinylated radioligand to provide radiotherapy (149).

Anti-TN-C antibodies were also used in intracranially delivered radiotherapy. Phase one safety studies showed good tolerability with few instances of hematologic toxicity of TN-C targeted radioligands administered into the resection cavity of patients with recurrent or newly diagnosed glioma (150, 151). Follow up studies evaluated new antibodies, radioligands, patient populations, and dosing methods, all with promising results for the intracranially delivered therapeutic (150, 152–155). The progression free survival achieved with the local administration of the targeted radiotherapy compared favorably with Gliadel,

a locally delivered chemotherapeutic (156). The ability of TN-C antibodies to target radiotherapies could conceivably be extended to larger drug delivery vehicles delivered intracranially (157, 158).

TN-C also plays a role in cardiovascular disease. After myocardial infarction, TN-C is transiently expressed at the border of the injury and is not expressed in the mature scar (14). Experiments in TN-C null mice have demonstrated that it promotes cell migration in the early phase, but may contribute to fibrosis at later stages (159, 160). This highlights the multifunctional role of TN-C in cardiac remodeling, which involves the recruitment of myofibroblasts, collagen fiber formation, and angiogenesis that promote repair, as well as the creation of a de-adhesive state, upregulation of MMPs, and enhancement of inflammation that contribute to fibrosis (19). As such, TN-C is a reported biomarker for a number of cardiovascular diseases, including: dilated cardiomyopathy, coronary plaque rupture, heart failure, and acute myocardial infarction (161–166). For cardiovascular imaging, a labeled TN-C antibody has been used to noninvasively detect remodeling in rats after infarction, and could potentially be used to look for left ventricular remodeling, which can lead to heart failure in humans (167).

In vascular disease, TN-C has been shown to accelerate neointimal formation (168, 169). The formation was reduced in TN-C-null mice, identifying a possible therapeutic target. Towards this end, PLGA microparticles have been fabricated to deliver an antisense oligonucleotide against TN-C and are able to reduce smooth muscle cell proliferation and migration (170). Tenascin-C is also found in atherosclerotic plaques, and a labeled TN-C antibody was able to successfully image them in rats (171). The characteristics that make TN-C deleterious for vascular grafts could make it advantageous for aneurysm treatment. This was evident in a study that implanted TN-C coated platinum coils into a rat aneurysm model and observed accelerated organization and decreased aneurysm volume (172).

Tenascin-C can also serve as a biomarker and potential therapeutic for inflammatory conditions. TN-C is expressed at sites of damage and inflammation in rheumatoid joints, and is required to maintain inflammation (173). A preclinical investigation of a TN-C targeting antibody conjugated to IL10 (F8-IL10), successfully inhibited the progression of arthritis in a mouse model and showed a good safety profile in monkeys (174). An update on the Phase 1b study of F8-IL10 noted early beneficial effects and no dose-limiting toxicities (175).

Early promising results have also been observed in the connection between Alzheimer’s disease and TN-C (176). TN-C was noticed to be upregulated in cultured microglial cells challenged with amyloid β peptide and in the brains of mouse that overexpress a mutated amyloid β. Crossbreeding the amyloid β overexpressing mouse into a TN-C null mouse resulted in a reduced amyloid β load and improved disease pathogenesis, indicating an exciting new possible therapy.

While TN-C is the most studied member of the tenascin family, TN-W also plays a role in the progression of cancer (134). TN-W is present in many solid tumors, including colon and breast cancers, and functions in the same manner as TN-C, but its presence in healthy tissues is more restricted (177). Further studies have shown that TN-W could be an effective

biomarker for glioma, melanomas, pancreas, kidney, and lung carcinomas, and warrants further study alongside TN-C as a biomarker and therapeutic target (20).

2.4 CCNs and drug delivery

CCN intercellular signaling proteins consist of six members that make the CCN family of extracellular matrix (ECM)-associated signaling proteins (178–182). Based on the first three members of this family (CYR61, CTGF, and NOV; now known as CCN1, CCN2, and CCN3, respectively) the acronym CCN was selected (183). WISP1, WISP2, and WISP3 were also added to the family as CCN4, CCN5, and CCN6. All the CCNs are characterized by having four conserved cysteine-rich domains. These include an insulin-like growth factor binding protein (IGFBP) domain (domain I), a Von Willebrand factor domain (domain II), a thrombospondin-homology domain (domain III), and a cysteine knot, heparin-binding domain (domain IV). Despite early studies suggesting that CCNs had growth factor-like activities, it is now well accepted that they are matricellular proteins with diverse functions. Importantly, consistent with the matricellular concept, CCN proteins are involved in the integration of signals between the extracellular matrix and the cell surface. Recent studies have also indicated that they play significant roles in several diseases and are considered valid candidates for either therapeutic targeting or development of therapeutics (184, 185). These include diseases related to chronic inflammation such as rheumatoid arthritis, atherosclerosis, diabetes-related pathologies, as well as hematological malignancies, and many cancers.

Expression of the CCN family of matricellular proteins is often correlated with increased vascular density, growth, and metastasis (179, 185). In fact, the increased presence of one or multiple members of the CCN family is associated with poor prognosis in breast, prostate, pancreatic, renal, bone, head and neck, and brain cancers (186–190). More specifically, CCN4 is upregulated in early stages of prostate cancer and correlated with higher circulating levels of the protein (191). CCN5 has been correlated with decreased progression free survival and overall survival in patients with astrocytomas (192). Additionally, CCN1 can be used as a biomarker to predict poor prognosis in patients with esophageal squamous cell carcinoma (193).

The overexpression of the CCN family during the growth and metastasis of cancer presents an opportunity for therapeutic intervention (184). Pancreatic, ovarian, and prostate cancer xenografts showed less growth and metastatic ability in vivo after transfection with RNA inhibitors against CCN1 or CCN2 (187, 194–196). siRNA against CCN1 was also effective at slowing the growth of an orthotopic glioma model when injected intratumorally (197). In addition to CCN1 and CCN2, CCN4 inhibition using antibodies was able to slow the growth and metastasis of a prostate cancer xenograft in vivo (191). In contract, the addition of CCN3, 5, and 6 can negatively affect proliferation of cancer xenografts (198–202).

Outside of cancer, CCN2 plays a prominent role in, and can be used as a biomarker for, many fibrotic diseases (184, 203). In scleroderma, CCN2 is correlated with severity of the disease in both plasma and tissue samples (204). Similarly, CCN2 in plasma also correlates with risk and mortality for patients with diabetic retinopathy (205, 206).

A strong relationship between CCN2 and multiple types of fibrotic disease has inspired the development of multiple therapeutic inhibitors (207, 208). Therapeutic gene silencing using siRNA has been shown to reduce the expression of CCN2 in vitro and in rodent models, and that the reduction in expression correlates with reduced fibrosis (209–211). Antisense oligonucleotides have also been used in rodent models with similar effects (212, 213).

Therapeutic antibodies against CCN2 have also been developed, and one, FibroGens's FG-3019, is currently undergoing clinical trials for the treatment of fibrotic diseases in humans (184, 208, 214). A phase 1 study of FG-3019 in patients with diabetic nephropathy showed good tolerability and a reduction in albuminuria (215, 216). In the Duchenne muscular dystrophy mouse model, FG-3019 was able to improve muscular strength and reduce impairment and fibrosis (217). An aptamer is also being developed to inhibit CCN2 signaling (218).

CCN proteins themselves, because of their effects on adhesion, angiogenesis and inflammation, can also serve as therapeutics. CCN1 in particular has a potent ability to modulate inflammation (219). Vascular graft remodeling, a process driven by inflammation, was improved in a sheep model with a decellularized graft coated with CCN1 that showed enhanced endothelialization (220, 221). CCN1 also reduced immune infiltration and disease score in a mouse model of myocarditis (222).

2.5 SPARC and drug delivery

SPARC, also known as osteonectin, has a molecular weight of 40,000 and is composed of four domains that include a calcium-binding region at the amino terminus, a cysteine-rich domain, a hydrophilic domain, and a helix-loop-helix structural motif (EF hand) at the carboxy terminus (223, 224). In addition to binding calcium and promoting mineral crystal formation, SPARC interacts with collagen and participates in the activation of latent TGF-β (223). It is made by multiple cell types including fibroblasts, endothelial cells, osteoblasts and macrophages and has been shown to influence cell adhesion and morphology as well as proliferation. In addition, SPARC plays important roles in tissue remodeling, wound healing, and fibrosis. Various studies have also linked SPARC expression to different types of cancer, diabetes, glaucoma, and fibrotic disorders (225–231).

The role of SPARC in the pathophysiology of cancer is complicated by its many functions. SPARC can abrogate focal adhesions and lead to migration and metastasis (232). However, it can also bind and interact with growth factors to promote cell cycle arrest and reduce angiogenesis (233). This dichotomy is borne out in the literature, summarized nicely by Podhajcer et.al., where SPARC is noted to be highly expressed in a wide range of very aggressive human tumors, but is also noted to be antitumorigenic in many other models (234). Using glioblastoma as an example, SPARC expression has been correlated with increased migration and poor prognosis in humans (235, 236). However, when SPARC expression was inhibited using shRNA, a human cell line showed increased growth and tumorigenic potential (237). The multiple roles played by SPARC in the tumoral environment complicate its use as a biomarker and as a target for therapeutic inhibition.

The high expression of SPARC in the tumor environment, regardless of its function, could be used to localize other therapeutic molecules. The high levels of tumoral SPARC was proposed as one mechanism for the efficacy of nanoparticulate albumin bound paclitaxel (nab-paclitaxel), owing to the capacity of SPARC to bind albumin, and in a Phase III trial of nab-paclitaxel in metastatic pancreatic, SPARC had positive association with efficacy (238, 239). However, in a mouse pancreatic cancer model, this binding effect was found to be saturable at low doses and not responsible for efficacy of the nab-paclitaxel (240). The effect of SPARC expression on nab-paclitaxel efficacy in vivo is likely muted by the abundance of albumin in serum, and the pharmacokinetics of the nab-paclitaxel. More specific targeting of SPARC, using a high affinity antibody linked to a nanoparticle, was able to increase the detection of tumor and metastases using CT and fluorescent imaging in mice. SPARC can also be used as a target antigen to direct immunotherapy, providing therapeutic localization while avoiding inhibition (241).

Outside of cancer, SPARC is highly involved in fibrosis, mediated by its role in the organization of collagen and ECM assembly as well as TGF-β activity (1). In humans, SPARC expression is increased in pulmonary, renal, hepatic, and dermal fibrosis (230). Experiments in SPARC-null mice illustrated that in the absence of SPARC, fibrosis was decreased (230, 242). In wild type mice, SPARC gene silencing using siRNA has been examined as a method to reduce fibrosis. For example, the injection or instillation of siRNA against SPARC reduced the expression of SPARC in situ and reduced the extent of fibrosis in both skin a lung fibrosis models (243). A nanoparticle system based on hydroxyapatite was developed to deliver SPARC siRNA more efficiently to fibroblasts that drive fibrosis (244).

In a biomaterial based approach, SPARC-derived components susceptible to enzymatic cleavage have been incorporated into hydrogels to enhance their degradation in response to plasmin, matrix metalloproteinase 1 (MMP-1), and MMP-2 (245). Incorporation of such degradation sensitive sites allows for the tuned response of the hydrogel system, and enables tissue specific delivery.

2.6 Periostin and drug delivery

Periostin, also known as osteoblast-specific factor-2, has a molecular weight of 90,000 and contains a fasciclin domain (FAS1 domain), which is involved in cell adhesion (246, 247). It shares structural homology with FAS1, which is an axon guidance protein, and transforming growth factor (TGF)-β-induced protein, βig-h3. Consistent with the presence of a fasciclin domain, periostin promotes adhesion as well as spreading of various cell types (248). Isoforms of periostin also exist due to alternative splicing and have been linked to cancers (249). In addition, periostin has been associated with numerous pathological conditions including asthma, skin disorders, polycystic kidney disease, and cardiovascular disease (247, 250–254).

Periostin, like many of the other matricellular proteins, is expressed at low levels in healthy tissue but is upregulated in pathology and during tissue repair, and neoplasia (14). One pathological condition where periostin is significantly upregulated is asthma, as a result of fibrosis in the lungs (246). Specifically, periostin is associated with eosinophilic, TH2 driven

asthma, which responds well to corticosteroid treatment (255). Serum levels of periostin can serve as a biomarker for this subtype of asthma and, when confirmed, patients can be given the appropriate therapy (256). Via a similar mechanism, periostin is a biomarker for idiopathic interstitial pneumonias with fibrosis (257).

The expression of periostin is increased in many cancers, including neuroblastoma, ovarian, breast, colon, pancreas, NSCLC, and head and neck cancers (258). In each of these cancers, the presence of periostin is associated with metastasis, progression, and poor survival. The therapeutic inhibition of periostin has been proposed as a method to reduce tumor growth and metastasis, and improve survival, particularly in gastric cancer and glioma (259, 260). This strategy was used successfully in an orthotopic breast cancer xenograft (261). After tumor inoculation, systemic injection of an inhibitory DNA aptamer, PNDA-3, reduced tumor growth and metastasis. Inhibition of tumor growth was also observed in an ovarian cancer model when periostin was inhibited by specific siRNA delivered using chitosan nanoparticles (262).

In development, periostin is responsible for ECM maturation in the heart (254). Similarly, in failing hearts, increased levels of periostin are associated with myocardial fibrosis (263). However, after a myocardial infarction, there is damaged tissue in the heart that needs to be repaired for proper function, and periostin, because of its ability to regulate fibrosis, angiogenesis, and proliferation, could promote the cardiac healing process (264). This hypothesis was tested in a rat myocardial infarct model, where delivery of periostin via injection or in a gelfoam matrix improved cardiac remodeling and reduced the infarct area after (265). The gelfoam matrix delivery system was evaluated again in a swine model of myocardial infarction (266). In this large animal model, delivery of periostin again resulted in increased cardiomyocyte cell cycle activity and increased angiogenesis at the infarct border. However, a similar study using gelfoam to deliver a periostin peptide described an increase in cardiac fibrosis in addition to improved cardiac function (267). The potentially limiting fibrosis observed in the swine model highlights the complexity encountered when delivering a multifunctional active agent with a complex signaling pathway. Clinical translation will rely on careful dosing and control over the pharmacokinetics to ensure improved healing without fibrosis.

2.7 Other Matricellular proteins and drug delivery

As mentioned in the introduction, the matricellular family of proteins has recently expanded with the addition of autotaxin, R-Spondin, PEDF, and fibulin-5. This diverse group of proteins has pleiotropic functions that include modulation of cell-matrix interactions and cell adhesion. Similar to the prototypical members of the matricellular family, studies have implicated these proteins in the pathophysiology of several diseases. In this section, we briefly describe these proteins, their functions, and their associations with specific diseases.

Autotaxin is an ecto-lysophospholipase involved in the generation of lysophosphatic acid and has been implicated in the regulation of proliferation, invasion, migration and angiogenesis (268). In addition, studies have implicated this protein in several diseases including idiopathic pulmonary fibrosis, liver cirrhosis, and several cancers (269–278). Because its structure has been elucidated and the active sites are defined, autotaxin has been

utilized in the development of small molecular weight drugs (270, 279). R-spondins are predominantly involved in Wnt signaling and play roles in gonadal and skeletal development (280, 281). They are considered matricellular because they contain type 1 TSP repeats and can interact with both ECM components and cell surface receptors. PEDF is a secreted protein with anti-angiogenic and neurotrophic activities (282). It has been implicated in a diverse set of diseases including Alzheimers, acute coronary syndrome, bone diseases, and tumors (283–286). From a therapeutic perspective, PEDF has been successful employed in the treatment of age-related macular degeneration (282). In addition, its ability to treat tumors due to its anti-angiogenic activity and its role in other angiogenic diseases has received attention (287, 288). Finally, fibulin-5 is a secreted protein that is intimately involved in the process of elastogenesis and plays a prominent role in development (289). Similar to other matricellular protein it has anti-angiogenic activity and has been suggested as a possible treatment in tumors (290).

3 Conclusion

The ability of matricellular proteins to regulate cell-cell and cell-matrix interactions during the progression of multiple disease states makes them targets for potential therapies, most notably in cardiovascular diseases and cancer. Many matricellular proteins, including TSP-1and 2, SPARC, OPN, and TN-C, are involved in the structure and remodeling of the myocardium following injury (14, 19). They are typically expressed at low levels, if at all, in healthy tissue, but are highly expressed after injury and during remodeling. Their role in the regulation of vascular growth factors, and the creation of a de-adhesive state, can lead to improper remodeling and tissue dysfunction. However, in the correct context, certain matricellular proteins can actually improve healing after injury. This dichotomy complicates their use as therapeutics and therapeutic targets in cardiovascular disease.

In addition to cardiovascular disease, matricellular proteins have a demonstrated role in the progression of cancer. The hallmarks of cancer, and the progression of healthy cells towards malignancy, arise as a result of the loss of homeostasis governing growth, proliferation, and death (291). In addition, the growth and metastasis of the resulting neoplasm requires the induction of angiogenesis, increased motility, and avoidance of immune detection. The extracellular matrix and matricellular proteins are potent modulators of each of those hallmarks, and their expression can be used to drive or suppress cancer progression (292). Their integral role in the tumoral microenvironment makes matricellular proteins useful as biomarkers, therapeutic targets, and active agents.

However, the multifunctional role of matricellular proteins within the environment complicates their use in the design of novel therapies. Each of the matricellular proteins has multiple functional regions that interact with many cell surface and ECM molecules to modulate cell-cell and cell-matrix interactions. In many cases, the exact nature of these interactions is unclear, and can result in a complicated network of signaling events. For example, TSP1 has known antiangiogenic properties, but is also highly expressed in certain high grade tumors (293, 294). This suggests that in certain cancers the ability of TSP-1 to promote motility, proliferation, and adhesion, outweigh the effects on angiogenesis (295).

The complicated roles of matricellular proteins present significant difficulties in designing therapies to inhibit or mimic their activities. Fortunately, TSP-1 also provides a positive example of isolating a single matrix protein property for the development of a therapeutic agent. By identifying the specific peptide regions responsible for TSP1's antiangiogenic activity, therapeutic peptides and small molecules can be designed to reduce angiogenesis in the clinic (34, 51). Similarly, elucidation of sites in these proteins that mediate their interactions with cells and matrix could lead to the development of small molecular weight inhibitors with highly specific activities. In addition to TSP1, the rest of the matricellular proteins discussed in this review highlight multiple opportunities for effective drug delivery, especially in cardiovascular disease and cancer. However, the continued development of therapies derived from matricellular proteins, will require more research to precisely define their mode of action, and allow for the identification and creation of powerful targets, agonists, and drug carriers.

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Table 1

Registered clinical trials of matricellular protein-based therapeutic agents

Family	Agent	Trial Design	Population	Study Phase	Enrollment (actual or estimated)	Trial Number
Thrombospondins	ABT-510	TSP-1 mimetic to treat advanced renal cell carcinoma	Patients with locally recurrent or metastatic renal cell carcinoma that is not amendable to curative resection	Phase II	103	NCT00073125
	ABT-510	TSP-1 mimetic to treat advanced or metastatic soft tissue carcinoma	Patients with locally advanced or metastatic soft tissue sarcoma not amenable to surgery, radiotherapy or combined modality therapy with curative intent	Phase II	88	NCT00061659
	ABT-510	TSP-1 mimetic plus combination chemotherapy in subjects with non-small cell lung cancer	Patients with Stage IIIB with pleural effusion or Stage IV NSCLC	Phase II	25	NCT00061646
	ABT-510	TSP-1 mimetic to treat patients with advanced head and neck cancer	Patients with squamous cell carcinoma of the head and neck that is not amenable to curative therapy, including radiation or surgery	Phase I, II	6	NCT00113334
	ABT-510	TSP-1 mimetic to treat subjects with refractory lymphoma	Patients with non-Hodgkin's Lymphoma (NHL) (excluding Burkitt's, Burkitt's type or HIV associated lymphoma) or Hodgkin's Lymphoma (HL) that is refractory to or has relapsed after standard therapy or for which there is no known effective treatment	Phase II	67	NCT00061672
	CVX-045	A Thrombospondin-1 Mimetic, Anti-Angiogenic Agent, In Patients With Advanced Solid Tumors	Patients with advanced solid tumors unresponsive to currently available therapies, or for which there is no standard therapy	Phase I	40	NCT00879554
Osteopontin	Osteopontin	Osteopontin addition to formula to increase infant growth, health, and immune function	Healthy infants 37–42 weeks of age.		320	NCT00970398
Tenascins	Neuradiab®	Combination therapy with Bevacizumab and Neuradiab (131I-labled anti tenascin mab)	Recurrent glioblastoma	Phase II	60	NCT00906516
	211At labled 81C6 (mab)	Astatine 211 labled anti-tenascin mab (At 211 Mab 81C6) delivered into the resection cavity	Recurrent primary and metastatic brain tumors	Phase I, II	12–24	NCT00003461
	I 131 Mab 81C6	Iodine 131 labled anti-tenascin mab infused into the resection cavity and followed by carmustine and irinotecan chemotherapy	Primary brain tumors after external beam radiation	Phase I, II	21	NCT00003484
	I 131 Mab 81C6	Iodine 131 labled anti-tenascin mab infused into the resection cavity	Primary or metastatic brain tumors, with or without previous radiotherapy	Phase I, II		NCT00002752
	I 131 Mab 81C6	Comparison of bolus injection and microinfusion of radiolabled anti-tenascin mab	Malignant primary brain tumors	Phase I, II	10	NCT00003478
	I 131 Mab 81C6	Intracystic delivery of radiolabled anti-tenascin mab	Recurrent cycstic glioma	Phase I	6	NCT00002753

Family	Agent	Trial Design	Population	Study Phase	Enrollment (actual or estimated)	Trial Number
	Neuradiab®	Randomized evaluation of radiolabled anti-tenascin mab in combination with radiation therapy (XRT) and temozolomide	Newly diagnosed glioblastoma multiforme	Phase III	9	NCT00615186
CCNs	FG-3019	Monoclonal antibody targeting CTGF for treatment of liver fibrosis	Chronic hepatitis B infection and liver fibrosis	Phase II	228	NCT01217632
	FG-3019	Monoclonal antibody targeting CTGF for treatment of advanced or metastatic pancreatic cancer	Stage III or IV adenocarcinoma of the pancreas	Phase I	50	NCT01181245
	FG-3019	Monoclonal antibody targeting CTGF for treatment of focal segmental glomerulosclerosis	Focal segmental glomerulosclerosis	Phase I	12	NCT00782561
	FG-3019	Monoclonal antibody targeting CTGF for treatment of diabetic nephropathy	Diabetic nephropathy and proteinuria (with ACE inhibitor or angiotensin II receptor antagonist therapy)	Phase I	36	NCT00754143
				Phase II	34	NCT00913393
	FG-3019	Monoclonal antibody targeting CTGF for treatment of idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis	Phase II	136	NCT01890265
				Phase II	42	NCT01262001
				Phase I	27	NCT00074698
	FG-3019	Monoclonal antibody targeting CTGF as neoadjuvant chemotherapy for advanced pancreatic cancer	Pancreatic ductal adenocarcinoma	Phase II	40	NCT02210559
	FG-3019	Monoclonal antibody targeting CTGF for treatment of incipient nephropathy	Type 1 or type 2 diabetes and incipient nephropathy	Phase I	20	NCT00102297
	Pravastatin	Small molecule targeting Rho/ROCK/ CTGF pathway for treatment of radio-induced fibrosis	Cutaneous and subcutaneous radio-induced fibrosis	Phase II	55	NCT01268202
Sparc	Nab-paclitaxel	Albumin bound nanoparticles proposed to target elevated SPARC in tumor microenvironment	SPARC positive patients with resectable/resectable borderline pancreatic cancer	Pilot	15	NCT01442974
PEDF	AdGVPEDF.11D	Adenoviral vector containg the gene to encode PEDF	Neovascular age-related macular degeneration (AMD)	Phase I		NCT00109499

Selected clinical trials from the U.S. National Institutes of Health database, ClinicalTrials.gov

Table 2

Registered clinical trials based on matricellular proteins as biomarkers

Family	Model	Trial Design	Status	Trial Number
Thrombospondins (TSPs)	Intracerebral Hemorrhage	Determine the predictive effect of TSP1 levels (plasma) in patients with acute intracerebral hemorrhage	Completed	NCT02465671
	Diabetes	Expression of TSP1 (blood and vitreous) in diabetes	Completed	NCT01809093
Osteopontin	Coronary Artery Disease (CAD)	OPN and other proteins as biomarkers (plasma) for CAD severity	Completed	NCT02159235
(OPN)	Osteoarthritis	Expression of OPN and other proteins (synovial fluid) in osteoarthritis and correlation to inflammatory markers	Recruiting	NCT01993342
	Head, Neck, Lung Cancers	OPN and other proteins as biomarkers (serum, tumor) for head, neck, and lung cancers	Recruiting	NCT00568490
	Mesothelioma	OPN and other proteins as biomarkers (serum) for malignant pleural mesothelioma	Completed	NCT02029105
CCN	Transitional Cell Carcinoma	Expression of CCN1/CYR61 in urinary tract transitional cell carcinomas	Pending	NCT01189838
	Non-small Cell Lung Cancer	CCN1/CYR61 as a transcript biomarker (salivary) for non-small cell lung cancer detection	Recruiting	NCT02294578
	Proliferative Retinopathy	CCN1/CYR61 as a biomarker (vitreous) for different stages of proliferative diabetic retinopathy	Completed	NCT01920984
	Atrial Fibrillation	CTGF as a biomarker (plasma) for recurrence of atrial fibrillation after surgical maze procedure	Completed	NCT00542659
	Kidney Disease	CTGF as a biomarker (urinary and serum) for chronic allograft nephropathy	Completed	NCT00056784
SPARC	Triple Negative Metastatic Breast Cancer	SPARC expression in breast tumors as a prediction for progression-free survival post chemotherapy	Completed	NCT00479674
	Non-Small Cell Lung Cancer	SPARC expression and correlation with overall survival post chemotherapy	Completed	NCT00540514
Periostin	Chronic Kidney Disease	Periostin as a biomarker (urinary) for renal pathology and chronic kidney disease	Completed	NCT02493101
	Bone Fragility	Periostin as a biomarker (serum) for cortical porosity in hyperparathyroidism patients	Recruiting	NCT02524041
	Asthma	Periostin as a biomarker (serum) for “allergic” vs. “non-allergic” asthma	Completed	NCT01618318
	Periodontal Disease	Periostin as a biomarker (gingival crevicular fluid (GCF), saliva, serum) for susceptibility and/or progression of periodontal disease	Completed	NCT01180920
Autotaxin	Intrahepatic cholestasis of pregnancy	Determine the diagnostic accuracy of autotaxin as a biomarker for cholestasis and differentiate ICP from of liver disorders	Recruiting	NCT02480478
PEDF	Diabetes mellitus	Measure levels and isoforms of PEDF and TSP-1 to determine correlation with diabetic retinopathy severity	Completed	NCT01809093

Selected clinical trials from the U.S. National Institutes of Health database, ClinicalTrials.gov