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REVIEW

Role of periostin and its antagonist PNDA-3 in gastric cancer metastasis

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Abstract

The extracellular matrix component periostin is a secreted protein that functions as both a cell attachment protein and an autocrine or paracrine factor that signals through the cell adhesion molecule integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. Periostin participates in normal physiological activities such as cardiac development, but is also involved in pathophysiological processes in vascular diseases, wound repair, bone formation, and tumor development. It is of increasing interest in tumor biology because it is frequently overexpressed in a variety of epithelial carcinomas and is functionally involved in multiple steps of metastasis progression. These include the maintenance of stemness, niche formation, EMT, the survival of tumor cells, and angiogenesis, all of which are indispensable for gastric cancer metastasis. Periostin has been reported to activate the PI-3K/AKT, Wnt, and FAK-mediated signaling pathways to promote metastasis. Therefore, periostin represents a potentially promising candidate for the inhibition of metastasis. In this review article, we summarize recent advances in knowledge concerning periostin, its antagonist PNDA-3, and their influence on such key processes in cancer metastasis as maintenance of stemness, niche formation, epithelial-to-mesenchymal transition, tumor cell survival, and angiogenesis. In particular, we focus our attention on the role of periostin in gastric cancer metastasis, speculate as to the usefulness of periostin as a therapeutic and diagnostic target for gastric cancer metastasis, and consider potential avenues for future research.

Key words: Periostin; Cancer; Tumorigenesis; Extracellular matrix; Epithelial-to-mesenchymal transition; Metastasis; Aptamer; PNDA-3

Core tip: Periostin is involved in various signaling pathways, mediates the critical steps of a wide variety of human tumors, and is associated with tumor growth, invasiveness, and metastasis. Although some authors have written reviews about periostin, they are often fragmented and not very comprehensive. The purpose of this review is to summarize the most recent knowledge of periostin and its antagonist, as well as their structure and the role they play in cancer metastasis, including the maintenance of stemness, niche formation, epithelial-to-mesenchymal transition, the survival of tumor cells and angiogenesis, and avenues for future research.

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INTRODUCTION

Gastric cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer death worldwide[1]. Metastases, rather than the primary tumor, are responsible for the majority of cancer deaths[2]. Gastric cancer metastasis is a very complex process involving epithelial-to-mesenchymal transition (EMT), extravasation, dissemination in the circulation, adhesion to and colonization of the distant site, angiogenesis, and survival. To complete this journey, gastric cancer cells use numerous strategies, all of which lead to a common ultimate goal: the dissemination of gastric cancer cells throughout the body and their survival to form secondary growths. These metastases are one of the greatest challenges to successful cancer therapy[3]. The prognosis for gastric cancer with concomitant liver metastasis is poor[4], with a 5-year survival rate as low as 0%-10% in unselected cases[5]. In 5.59% of gastric cancer patients, liver metastases are detected before or during surgery, while metastases occur in 21.75% following surgical treatment[6-11].

Gastric cancer metastasis is highly influenced by tumor microenvironment. For example, a change in nutrient availability or surrounding pH can influence tumor metastasis[12]. Extracellular matrix (ECM) proteins also play an important role in tumor cell metastasis by regulating stemness and the proliferation of cancer stem cells (CSCs)[13,14]. Therefore, an understanding of the roles played by ECM proteins present in the tumor microenvironment with regards to their influence on signaling pathways involved in cell-ECM interactions could aid the prevention and treatment of tumor metastasis.

The ECM protein periostin [formerly osteoblast specificity factor 2 (OSF2)] has been implicated in the process of gastric cancer metastasis[15]. Initially identified in the rat osteoblast cell line MC3T3-1, periostin contains 811 amino acid residues and is secreted by osteoblasts. It is also a member of the fasciclin family, and contains an NH_2-end signal peptide sequence, a cysteine domain structure, four homologous repeats (120-160 amino acids), and a hydrophilic COOH-terminal structural domain[16]. Research from Coutu *et al*[17] has shown that periostin is a member of a novel vitamin K-dependent γ-carboxylated protein family characterized by the presence of fasciclin domains. Periostin participates in normal physiological processes, including cardiac development, though it also has pathophysiological roles in vascular diseases[18], wound repair[19], bone formation[20], and tumor development[21].

Overexpression of periostin has been identified in various malignancies, including those of the pancreas[22-25], bile duct[26], lung[27], ovary[28], colon[29], breast[30,31], and the head and neck[32]. In contrast, periostin is a suppressor of bladder cancer metastasis, with mutational analysis revealing that the C-terminal region is responsible for this effect[33,34]. To date, the role of periostin in gastric cancer development has not been studied sufficiently[15,35]. Gastric cancers can be classified into two main histological groups, diffuse or intestinal[36], and these have distinct genetic and molecular backgrounds, morphologies, and clinical features[37]. The expression and function of periostin appears to differ between these two gastric cancer subtypes and so further research is needed to understand this phenomenon.

Periostin is highly expressed in gastric epithelial tumors and its function is indispensable for successful angiogenesis and metastasis[35,38]. Clinical studies have demonstrated that high periostin expression or elevated serological levels of periostin correlate with tumor metastasis and poor prognosis[39,40]. Periostin participates in and promotes tumor metastasis through multiple signaling pathways, suggesting that the development of periostin inhibitors could aid the prevention of gastric cancer metastasis.

Gastric cancer cells bind to periostin *via* the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$; however the epitope recognized by these integrins has not been formally identified. Orecchia *et al*[41] have explored whether particular periostin domains influence tumor growth and subsequent metastasis. They generated the monoclonal antibody OC-20 and used recombinant periostin fragments to characterize the epitope recognized by this antibody. Their study revealed that the epitope identified by monoclonal antibody OC-20 is also the binding site for the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, and is located in the second FAS1 domain of the protein. Additionally, the use of this antibody *in vivo* inhibits tumor growth and angiogenesis. The study also showed that the FAS1 domain of periostin plays an important role in tumor progression and subsequent metastasis. Further, the monoclonal antibody OC-20 could prove useful in further exploring the role of periostin in the metastasis of gastric cancer and may contribute to the design of novel anti-metastasis drugs.

EMT

EMT is critical in the development of tumor metastasis, facilitating the acquisition of invasive and metastatic potential by epithelial cells[42-45]. EMT was initially recognized as a key step of morphogenesis during embryonic development. Emerging evidence indicates that this important developmental program promotes tumor recurrence, drug resistance, and metastasis;

features associated with a poor clinical outcome for patients with gastric cancer. Periostin has been demonstrated to be both a marker of metastasis and a potent EMT inducer[46]. Analysis of periostin expression by histology strongly implicates cancer-associated fibroblasts as the primary source of periostin. Here, periostin facilitates gastric cancer cell invasion by promoting EMT and establishing a pre-metastatic niche[47]. It has also been shown to promote the migration of cells that have undergone EMT, thereby facilitating their colonization of distant tissues[48]. Therefore, a better understanding of the signaling pathways that influence EMT is essential for the development of novel targeted therapeutics. However, the mechanism by which periostin induces EMT in gastric tumor cells remains unclear, and this should be a major focus of future research.

STEMNESS

Periostin can both induce stemness in tumor cells and facilitate maintenance of this stemness during the initiation of the colonization process[49]. CSCs exhibit a phenotype similar to that of adult stem cells isolated from the same tissue, and share the properties of self-renewal and differentiation with normal stem cells[50]. CSCs were first discovered in hematological malignancies[51] and have more recently been identified in solid tumors[52,53]. Dieter *et al*[54] have described how tumor invasion is initiated by a small group of CSCs, suggesting that they are extremely important for metastasis. Recently, Vermeulen *et al*[55] revealed that Wnt signaling is important for maintaining stemness in both normal colon stem cells and in colon cancer cells. Here, the presence of Wnt activity allows for the identification of colon CSCs and facilitates screening of colon tumors for mutations. Further, this study found that particular cells close to the CSC maintain this high Wnt activity, and are capable of activating the Wnt pathway in more differentiated tumor cells, which then regain clonogenicity or tumorigenicity. Recently, an interaction between periostin and the Wnt pathway ligands Wnt1 and Wnt3A was identified in a CSC population, and new emerging evidence indicates that EMT may enhance the stemness of CSCs, which in turn facilitates metastasis[56]. More clearly defining the relationship between periostin and CSC stemness in gastric cancer will aid in elucidating the mechanisms underlying gastric cancer metastasis.

NICHE FORMATION

The role of periostin in promoting adhesion within the CSC niche is a key component of the metastatic process. Tumor cells colonizing distant tissues must successfully interact with the target tissue microenvironment to establish metastasis. The expression of certain ECM components is upregulated in CSCs, which protects tumor cells from detection and destruction by the immune system following implantation. Periostin has been characterized as a niche component capable of promoting the survival of stem cells by enhancing Wnt signaling and promoting metastasis[57]. The niche environment can also promote mutation and evolution of the CSC, thereby increasing cell survival and metastatic potential[58]. The pro-survival effect of periostin on tumor cells and human microvascular endothelial cells was discovered by simulating the stress environment encountered in metastatic tumors. Stress conditions such as low oxygen, nutritional deficiencies, and reduced adhesion are very common in metastatic tumors and fast growing tumor masses[59]. Malanchi *et al*[57] also described how tumor cells infiltrating the lung can induce the expression of periostin in the niche, thereby initiating the colonization process.

Periostin can be secreted by cells in niches supporting both normal stem cells and CSCs. Here, periostin can act as an adhesion protein by facilitating interaction between the CSC and the niche. This protects stem cells from being influenced by external differentiation factors and so maintains them in an undifferentiated state. CSCs therefore evade differentiation and apoptosis, preserving their ability to colonize distant sites. Within the niche, tumor cells enter a resting state and store energy for later proliferation. As they adapt to their new environment within colonized tissues, the proliferation process is activated.

ANGIOGENESIS

Periostin promotes angiogenesis in tumor metastases, thereby facilitating survival and proliferation of tumor cells following their colonization of distant tissues. Angiogenesis encompasses endothelial cell proliferation, migration, and tube formation, all of which are necessary for tumor growth. Periostin is secreted and signals through the cell adhesion molecules integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. In this pathway, periostin activates the PKB/AKT and FAK/Src signaling pathways, ultimately leading to increased angiogenesis, enhanced invasiveness and metastatic ability, and decreased apoptosis[39,60]. The induction of angiogenesis by periostin is partly achieved through upregulation of vascular endothelial growth factor (VEGF) receptor 2 (Flk-1/KDR) on endothelial cells by integrin signaling. VEGF and Flk-1/KDR have also been conclusively shown to be involved in the induction of angiogenesis during solid tumor development[61]. Periostin is differentially expressed in primary tumors and human colon cancer metastases, with studies showing that a high level of periostin expression is associated with metastatic colon tumor cells. Researchers have also identified elevated periostin expression in colon cancer cells inoculated into nude mice. Here, periostin promoted the growth of liver metastases, suggesting that periostin plays a significant role in the late stages of cancer progression.

In support of this, periostin secreted by tumor cells has been shown to induce angiogenesis *via* paracrine signaling during the development of metastases[59]. Additional support for this is provided by the suggestion that periostin is a hypoxia-response gene that mediates cross-talk between gastric cancer cells and endothelial cells under hypoxic conditions, at least partially through the regulation of VEGF expression[62].

CELL SURVIVAL

Metastatic growth is controlled by the dynamic balance between cancer cell proliferation and apoptosis[63]. Therefore, factors that facilitate cell survival or inhibit programmed cell death contribute to the success of metastatic colonization. Studies have shown that fewer apoptotic cells were present in metastatic tumors that originated from periostin-producing cells when compared with control cells *in vitro*[59]. Consistently, periostin activated the Akt/PKB pathway in colon cancer cells through integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, promoting cell survival[59]. To successfully establish at a metastatic site, tumor cells have to confront and overcome cellular stresses such as nutrient deprivation and hypoxia following their arrival. Interestingly, treatment of cells with an anti-periostin antibody potentiates the effects of 5-fluorouracil and augments apoptosis induced by chemotherapy in colon cancer cells[64]. Gastric and colon cells arise from the same progenitor cells during embryogenesis and share many characteristics. Therefore, periostin could be an effective target for the diagnosis and treatment of metastatic gastric cancer.

SOURCE OF PERIOSTIN

The source of periostin in tumors is a matter of controversy since periostin expression in most tumor cell lines is low. Interestingly, lower levels of periostin expression are detected in tumor cell lines when compared with similar tumor tissues, and periostin production by non-epithelial cells present in tumors of gastric origin has been demonstrated *via* analysis of publicly available microarray data sets[15]. Several independent studies have reported production of periostin by stromal cells[40,65], whereas others have detected periostin mRNA in the cytoplasm of cancer cells. In gastric cancer tissue, fibroblastic stromal cells present in a dense collagenous matrix show strong immunoreactivity for periostin[47]. Here, double-staining for α-SMA$^+$ and periostin in advanced invasive cancer showed that α-SMA$^+$ fibroblasts were embedded in the cancer stroma, which also contained abundant periostin. Furthermore, periostin mRNA was detected in fibroblastic stromal cells, but not in carcinoma cells, suggesting that periostin is produced by stromal myofibroblasts rather than by neoplastic cells in gastric cancer. An analysis of publicly available microarray data sets has subsequently revealed that no gastric cancer cell lines express periostin mRNA except YCC11[15]. Cells of this type harbor a unique, non-benign single-nucleotide variant in RPS6KA6, which could influence periostin expression *via* the activation of CREB, a known inducer of periostin expression[66]. These findings suggest that the stroma is an active participant in gastric cancer metastasis, and that focusing on the stroma in future research may help achieve a better understanding of the mechanisms underlying tumor progression and facilitate therapeutics based on stromal targets.

PERIOSTIN REGULATION

Periostin has been found to be potently upregulated by both bone morphogenetic protein-2 and transforming growth factor (TGF)-β[67,68]. In this context, it appears that periostin serves as an effector of the pro-metastatic activity of TGF-β during gastric cancer metastasis. Periostin has been revealed to be regulated by twist as well, with twist capable of binding the periostin promoter to upregulate periostin expression in cancer cells[69]. The hypoxia-responsive growth factors FGF-1 and angiotensin Ⅱ also increase periostin expression in pulmonary arterial smooth muscle cells by activating the PI3-K/Akt/p70S6K, Ras/MEK1/2/ERK1/2, and Ras/p38MAPK signaling pathways[70]. Further, periostin expression is regulated by IL-4 and IL-13 in lung fibroblasts, and by Wnt-3 in mouse mammary epithelial cells[71,72]. Pancreatic stellate cells are also stimulated to secrete periostin by FGF-A, FGF-B, PDGF-aa, and PDGF-bb. However, much data concerning periostin regulators is derived from studies of embryonic or adult processes. Further research is required to characterize the regulation of periostin under metastatic conditions. An understanding of the distinct mechanisms that regulate periostin in this context will enhance patient evaluation and facilitate the design of innovative therapeutic approaches to gastric cancer metastasis.

TRANSFORMING GROWTH FACTOR, BETA-INDUCED

Transforming growth factor, beta-induced (TGFBI) and periostin are both TGF-β-induced ECM proteins possessing FAS1 domains[73]. TGFBI mRNA expression shows a pattern complementary to that of its highly homologous relative, periostin[74]. TGFBI contains an N-terminal secretory signal peptide and a C-terminal RGD motif followed by a cysteine-rich domain and four internal homologous repeats that could serve as a bridge between cells expressing appropriate ligands[75,76]. TGFBI has been shown to play an important role in the invasion of colon and pancreatic cancers. TGFBI is also expressed in mesothelial cells, especially in those from patients with advanced gastric cancer. It has been suggested that expression of TGFBI

in peritoneal mesothelial cells during gastric cancer is both a novel marker of the metastatic behavior of gastric cancer and an important component of the process of peritoneal carcinomatosis[77]. These effects have been shown to result from interactions between the integrin receptors and the FAS1 domain of TGFBI[78]. Interestingly, although periostin and TGFBI share remarkable sequence and structural homology, the slight differences in their C-terminal domains may lead to differences in their effects at different stages of metastasis. TGFBI appears to promote colon cancer metastasis primarily during extravasation, which is an early stage of metastasis, by inducing dissociation of VE-cadherin junctions between endothelial cells through the activation of the integrin $\alpha_v\beta_5$-Src signaling pathway. Therefore, cancers over-expressing TGFBI may have an increased metastatic potential, leading to poor prognosis[75]. Periostin facilitates colon cancer metastasis by increasing cell survival at a later stage of cancer metastasis. Therefore, close examination of the C-terminal domains of periostin may enhance our understanding of gastric cancer metastasis.

NUCLEIC ACID APTAMERS

The potential use of aptamers in cancer therapy was recognized upon their development almost a quarter of a century ago[79]. PNDA-3 is a recently described modified nucleic acid that can specifically bind to the third or fourth FAS1 domain structure of periostin to inhibit its function. The development of targeted therapy has become a main focus of cancer treatment in recent years[80,81]. Aptamers have many potential advantages over other therapeutic tools, including enhanced stability, easy generation and modification, low immunogenicity, and low toxicity[82-85]. Aptamers often inhibit protein function following specific binding, and the lack of immunogenicity or toxicity, high penetrability, and easy clearance, make them attractive candidates to develop as inhibitors of tumor metastasis[86-88]. The production cost of RNA is lower than DNA and is difficult to be degraded, so the selected aptamer is more suitable for treatment *in vivo* and diagnosis *in vitro*. Scientists also combine aptamer with nanotechnology to develop a smartly-designed fluorescent probe (aptamer beacon) according to the character of high affinity and high specificity of the aptamer, to detect the content of target molecules through the intensity of the fluorescent signal. Aptamer is therefore a very promising antagonist molecule. Aptamers targeting cell-surface proteins have recently been developed as promising delivery vehicles, diagnostic tools, and treatment tools for targeting cancer[89,90].

Aptamers are used as aptamer-nanoparticle conjugates for smart drug delivery and in combination with nanoparticles for biomedical sensing and detection because of their outstanding properties. Aptamer-nanoparticle conjugates enable active controlled delivery of drugs that are incorporated in the nanoparticles when they are bind to a disease site because of the aptamer affinity to this site. Aptamers combined with nanoparticles are nanosystems well qualified for the development of new biomedical devices for analytical, imaging, drug delivery, and many other medical applications. In this way, nanoparticle-based bioimaging and smart drug delivery are enabled, especially by use of systematically developed aptamers for cancer-associated biomarkers.

Most anticancer pharmaceuticals have destructive effects on both gastric cancer cells and normal cells. Aptamers can facilitate cell-specific drug delivery in a selective way to sick gastric cancer cells because of their specific binding, which can not only enhance therapeutic effects, but also diminish adverse effects. Moreover, simultaneous *in vivo* detection and therapy for gastric cancer cells lowers the burden for gastric cancer patients. However, the widespread phenomenon of possible nonspecific accumulation of nanoparticles in the liver must be taken into account.

Problems and solutions

Although aptamers have a large number of advantages, it seems strange that they account for only a small part of modern therapeutic drugs. There main problems impeding the widespread application of aptamers in disease and approaches that could significantly expand the range of aptamer. The average time of aptamer decay in blood depends on conformational structure and oligonucleotide concentration. Since such a time is inappropriate for most therapeutic applications, some methods for protecting aptamers from degradation by nucleases have been developed. One of the methods used to generate nuclease-resistant aptamers is to perform SELEX with oligonucleotides containing modified nucleotides[79]. Furthermore, the removal of aptamers *in vivo via* renal filtration complicates their wide application. Most aptamers can be easily excreted by kidneys. Conjugation of aptamers with polyethylene glycol is the best solution to this problem. Additionally, aptamer generation usually requires purified target molecules. Some proteins are difficult to purify because of their chemical properties. Sometimes, aptamers generated against target proteins expressed in one kind of cells do not bind to the same proteins expressed in other kinds of cells as a result of post-translational modifications[91]. The modified SELEX protocol can be used to select aptamers recognizing cell-surface proteins[92,93]. Aptamers that recognize particular targets can also bind to molecules with a similar structure regardless of their high specificity. Aptamer cross-reactivity can be a barrier to their therapeutic application, since the possible side effects may be caused by aptamers interacting with other proteins; however, this problem can be settled by performing a SELEX negative selection step with

similar molecules in structure.

PNDA-3

PNDA-3 blocks the interaction between periostin and its cell surface receptor. Its use could therefore facilitate the effective diagnosis and treatment of tumor metastasis. PNDA-3 impairs the activation of signaling pathways that rely on ligand binding to integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. This produces a strong inhibitory effect on tumor cell adhesion, migration, and implantation in a mouse model. Importantly, the effect of PNDA-3 on the inhibition of tumor growth in this model is much higher *in vivo* than *in vitro*. This phenomenon could be explained by the role of periostin in the niche prior to colonization. Therefore, the presence of PNDA-3 in the tumor microenvironment affects the function of not only cancer cells, but also the surrounding endothelial and other tumor-related cells.

The effectiveness of periostin antagonism by PNDA-3 has been assessed *in vivo* using a tumor growth and metastasis model that employs metastatic 4T1 cells implanted into female BALB/c mice mammary fat pads. After 20 d, post-injection tumors in all mice showed a similar distribution, including the lymph nodes, liver, spleen, and lungs. However, large metastases (> 2 mm) were commonly found in the lung tissue of the control group, with few such metastases identified in the PNDA-3 treatment group. Use of a similar approach whereby gastric cancer cells are implanted into the stomach could enable the evaluation of PNDA's efficiency in reducing gastric cancer metastasis to the liver. Further investigations revealed an anti-angiogenic effect of PNDA-3, with microvascular density significantly reduced in the PNDA-3 treatment group. Therefore, the decreased activation of signaling pathways that rely on integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, such as the FAK/Src pathway, not only affects tumor metastasis itself, but also inhibits angiogenesis within metastases[94]. Employing PNDA-3 in a mouse model of gastric cancer could therefore aid in understanding how to control liver metastases of stomach cancer from the source.

To ascertain whether the specificity of PNDA-3 for periostin is constant *in vivo*, Cy3-labeled PNDA-3 was injected intravenously into tumor-bearing mice. Cy3-labeled PNDA-3 was detected in areas of metastatic tumor formation for a period of time, indicating that it could be used as a novel effective method for the diagnosis of gastric cancer metastasis. PNDA-3 could also impair metastasis by inhibiting the function of periostin, allowing it to function in both the treatment and prevention of gastric cancer metastasis.

CONCLUSION

Targeted therapies have become the key strategic focus in the development of cancer treatment in recent years. Nucleic acid aptamers are single-stranded DNA or RNA molecules designed to bind to proteins and regulate their activity and function. These aptamers represent an emerging class of targeted therapeutic molecules[95,96]. While the mutations that cause cancer change gene expression patterns first, the cell and tissue morphology changes occur later. Conventional methods of gastric cancer diagnosis are primarily focused on morphological abnormalities, and therefore cannot identify the early stages of gastric cancer. We have described how a modified DNA aptamer, PNDA-3, could be modified for *in vivo* use. PNDA-3 blocks the interaction between periostin and its cell surface receptors, reducing the activation of signaling pathways that rely on integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. This results in weaker FAK/Src signal pathway activity, potently inhibiting the maintenance of stemness, niche formation, EMT, and angiogenesis in cancer metastasis. These results suggest that molecules targeting periostin may be promising tools for the inhibition of cancer metastasis. The study of periostin may well be a promising direction for future research into the inhibition of gastric cancer metastasis.

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