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Periostin and cancer

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Keywords: periostin, cancer, mesenchymal proteins, treatment

Citation: A. Kreatsoula, M. Trapali, Periostin and cancer. Review Clin. Pharmacol. Pharmacokinet. 2021, 35 1, 5-14.

<https://doi.org/10.5281/zenodo.10029698>

Received: 21 December 2020

Accepted: 02 March 2021

Republished: 21 October 2023

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S u m m a r y: *Periostin belongs to the family of mesenchymal proteins. Mesenchymal proteins are a family of non-structural proteins of the extracellular matrix that regulate a variety of biological processes in physiological and pathological conditions. Many components of this family such as periostin (POSTN), osteopontin (SPP1) have been shown to regulate in various stages of carcinogenesis, such as proliferation, invasion, remodeling of the extracellular matrix, and spread to pre-metastatic sites in distant organs. Mesenchymal proteins can be produced by cancer cells themselves or by tumor-related cells, and their synthesis can be influenced by intrinsic or exogenous tumor factors. In this paper, we will focus on the role of periostin, in the development and progression of cancer. Tumors in which their expression changes under the influence of periostin (tumors of the colon, breast, pancreas, glioma, stomach, lung, liver, leukemia and other tumors) and the usefulness of periostin as a biomarker will be analyzed. Finally, the usefulness of periostin as a therapeutic target for the cure of various cancers will be analyzed, for future directions for research and therapeutic approaches that target periostin.*

INTRODUCTION

Periostin is overexpressed in various cancers in humans, such as cancer of the ovary, colon, pancreas, thyroid, oral squamous cell carcinoma etc. Overexpression of periostin has been associated with increased tumor aggression and poor survival in most tumors. This is because

periostin promotes increased cell survival, angiogenesis, invasion, metastasis, and epithelial-mesenchymal transition of cancer cells through binding to integrins. Integrins, which often express changes in cancer cells, cause interactions between cells and extracellular substance (ECM) and alter cellular behaviors that promote various conditions (1).

In recent years, many studies have described the role of periostin in the oncogenesis process. The precise mechanisms responsible for the effect of periostin on cancer progression and metastasis are still under intense investigation. Many studies have confirmed an increase in the expression of periostin that accompanies the formation of metastasis. The formation of metastasis requires the proteolytic action of the tumor on the cells, the degradation of the ECM, the migration capacity and the stimulation of angiogenesis (1).

Periostin has been shown to bind to the integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_6\beta_4$, promoting uptake of the epidermal growth factor receptor (EGFR) and activation of the Akt/PKB and FAK signaling pathways (central regulator of survival and proliferation). Periostin-activated signaling pathways promote cell survival, angiogenesis, and resistance to hypoxia-induced cell death (1).

Cancer cells secrete transformative growth factor- β (TGF β 3), which is a known promoter of invasion and metastasis, and creates a cancer stem cell support cell (CSCs) with periostin in the extracellular matrix. Periostin acts as a mediator of TGF pre-metastatic activity by increasing the Wnt signaling pathway in the CSC through the FAS1 domain. This further promotes the self-renewal of cancer stem cells, as well as the formation of metastatic deposits. In addition, periostin enhances angiogenesis in a paracrine manner through the FAS1 domain, enhancing vascular endothelial growth factor (VEGF) receptor expression in endothelial cells, via the FIK-1 / KDR signaling pathway induced by $\alpha_v\beta_3$ -FAK (1). Periostin probably exerts its pro-oncogenic effect through its binding to cell membrane integrins and the subsequent activation of intracellular pathways that determine an improved permeability, such as acting on the fibrillogenesis of ECM (2).

Given that alterations in the ECM components of the tumor microenvironment have a significant

impact on cancer invasion, it is likely that periostin promotes an ECM reorganization that supports invasion and metastasis. It is believed that one of the main mechanisms responsible for the invasion and metastasis of cancer is the process of epithelial-mesenchymal transition (EMT). EMT is characterized by a loss of expression of epithelial cell markers such as E-cadherin, and an increased expression of mesenchymal cell markers such as vimentin, fibronectin, N-catherin, alpha-smooth muscle alpha (α -SMA) as well as the increased activity of uterine metalloproteinases MMPs (MMP-2, MMP-3 and MMP-9), associated with the penetrating phenotype. As a result, cancer cells acquire the ability to migrate and invade the surrounding layer. As shown in many studies, EMT can initiate signaling pathways activated by tyrosine and serine-threonine kinase activity receptors (e.g., PI3K, EGFR, and c-KIT, which activate the ras-raf-MEK-MAPK pathway). Numerous reports have shown that periostin is one of the major factors influencing the regulation of the intracellular pathway associated with phosphatidylinositol 3-kinase (PI3K) and B protein kinase (Akt/PKB) which is a serine/threonine kinase important role in the regulatory mechanisms involved in EMT, with invasion and metastasis processes (2).

In the first step of the PI3K/AKT signaling pathway, the tyrosine kinase activity receptor was activated by binding to the ligand, which activates PI3K, which converts phosphatidylinositol 4,5-diphosphate (PIP2) to phosphatidylinositol 3,5-phosphoryphosphate (PIP3). PIP3 contributes to the uptake of Akt kinase into the cell membrane, where it is activated due to the phosphorylation of threonine and serine residues. Activated Akt enhances tumor survival in cells by inhibiting apoptosis while promoting cell proliferation and regulating the ability of cells to migrate and invade. In addition, PI3K and Akt have been shown to be involved in the stimulation of EMT in breast cancer cells, either immediately after activation by TGF-b or indirectly, upon activation by epidermal growth factor (EGF) or platelet receptors growth factor (PDGF) (2).

Periostin has been shown to be not only an EMT marker, but is an inducer of this phenomenon. Researchers have shown ectopic expression of periostin in oncogenic but not metastatic 293T cells, which can induce epithelial-mesenchymal transition (EMT) and

promote invasion and metastasis *in vivo*. The overall regulation of periostin expression was accompanied by an increase in vimentin, fibronectin and MMP-9, while the expression of E-cadherin and N-cadherin was unchanged. The pathway of periostin signaling in 293T cells appears to require interaction with $\alpha_v\beta_5$ integrin and EGFR uptake. In addition, increased phosphorylation of Akt and Snail by periostin is involved in the regulation of E-cadherin and the invasion of prostate cancer cells. These data suggest that periostin may play an important role in cancer progression (2).

LUNG CANCER

Lung cancer is a common cause of cancer deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for just over 80% of all lung cancers. Less than 10% of patients with stage IV NSCLC survive five years after diagnosis, while the five-year survival rate of people with stage IA is as high as 80%. Treatment, including surgery, chemotherapy and radiotherapy, does not improve the prognosis satisfactorily. NSCLC treatment strategies change with the development of therapies that target specific molecules, in particular epidermal growth factor receptor (EGF) receptor tyrosine kinase inhibitors, lymphoid regenerative kinase inhibitors, and immune system inhibitors. The prognosis for NSCLC depends on factors such as the patient's overall health, stage and pathological type of NSCLC. Although the prognosis for NSCLC has improved, new prognostic indicators and treatment strategies are needed. Periostin is overexpressed in lung cancer tissues and is associated with prognosis (3).

Several studies show that overexpression of periostin or elevated serum periostin is associated with poor patient outcome. Studies show an association between high serum periostin and poor prognosis in NSCLC. However, its involvement in the development of the NSCLC is not fully understood (4).

Interestingly, five of the eight isoforms of periostin were detectable in non-small cell lung cancer (NSCL) and the corresponding normal lung tissues. Serum protein periostin levels appeared to be significantly higher in patients with NSCLC than in patients with healthy lungs and patients with benign lung disease. Cox regression analysis further showed that serum periostin is an independent prognostic factor in

patients with NSCLC. In addition, the expression of periostin can be induced by transforming growth factor α (TGF- α) and basic fibroblast growth factor (bFGF) under the stress of chemical mimetic hypoxia in NSCLC A549 cells and that periostin promotes A5 cell survival of the activation of the AKT signal pathway. Periostin can also promote the epithelial-mesenchymal transition to lung cancer by activating the p38/ERK pathway and suppressing the expression of microRNA-381 targeting both Snail and Twist. In addition, periostin is significantly increased in cisplatin-resistant A549 cells compared to stem cells, and periostin overexpression makes A549 cells more resistant to cisplatin-induced apoptosis by activating STAT3 and overexpression of Survivin or baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) (5).

BREAST CANCER

Periostin is highly expressed in breast tumors and can enhance the growth of cancer cells by promoting angiogenesis by increasing VEGF-2 expression. Research has shown that periostin is highly expressed in CAFs of breast cancer cells in mice as well as in metastatic lungs. Consequently, periostin deficiency significantly inhibits the metastatic growth of breast cancer cells in the lungs, but does not show a significant inhibitory effect on the growth of primary tumors. Overexpression of periostin has also been shown to promote tumor growth and subsequent metastasis of breast cancer cells to the lungs of mice. Analysis of the survival databases of breast cancer patients showed that high expression of periostin predicts a reduced chance of surviving without distant metastasis to ER-negative breast cancer and a significantly higher risk of recurrence, especially in primary breast cancer. In addition, chemotherapy regulates the expression of tumor-specific variants of periostin in breast tumors, and the fall of periostin inhibits the growth and invasion of mesenchymal tumor cells during chemotherapy. The expression of periostin was observed mainly in CAFs and its level in CAFs of invasive pore breast cancer is significantly higher than that of pore cancer *in situ*.

Serum periostin has been found to be detectable in early breast cancer and high serum periostin levels are associated with the specific mortality of breast cancer patients. Serum periostin levels are significantly increased in mice and in patients with bone metastases from breast

cancer. Interestingly, the intact form of periostin in serum was thought to aid in the detection of breast cancer metastasis formation in the experimental bone metastasis model. Periostin was identified as a marker enriched in breast cancer-derived exosomes using proteomic analysis. Breast cancer is characterized by high expression of periostin in epithelial cancer cells compared to normal tissue. Increased expression of periostin has been associated with poor free development and overall survival. Their studies revealed that high expression of periostin in cancer stem cells was associated with reduced survival without recurrence in baseline but not in lumbar breast cancer. In addition to cancer cells, periostin is also present in cancer-related fibroblasts (CAFs). In this case, the higher levels of periostin detected in CAF are associated with the degree of tumor malignancy, suggesting that CAF-secreted periostin could be a key element in the development of breast cancer (5).

COLON CANCER

Research has shown that periostin is overexpressed in more than 80% of human colon cancers, and its level is even higher in the corresponding liver metastatic tumors. In addition, periostin enhances the metastatic development of colon cancer by promoting cell survival and angiogenesis via the AKT signaling pathway. Another study further confirmed the increase in periostin expression in primary colon cancer and liver metastases. ELISA analysis showed that serum periostin levels in patients with colon cancer are significantly higher than in healthy volunteers and patients with benign colon polyps or adenomas (5).

Higher preoperative levels of periostin in serum colon cancer are thought to be associated with distant metastasis, advanced disease, and poor prognosis. Interestingly, the expression levels of stromal periostin in the tumor, instead of the expression of epithelial periostin, can be used to predict independent prognosis of colon cancer independently. In addition, periostin derived from colon fibroblasts significantly promotes colorectal cell proliferation, invasion, and chemical resistance (5).

LIVER CANCER

Studies have shown that periostin is strongly induced in the liver of mice with a variety of diseases, including acute and chronic hepatitis, hepatic fibrosis and non-alcoholic steatopathy (NASH), indicating that periostin is a major inflammatory factor in various diseases. A high level of periostin was also observed in the regeneration of the liver of mice after partial 2/3 hepatectomy and a significantly increased level of plasma periostin in hepatocarcinoma patients undergoing liver tumor resection. Immunohistochemical analysis of tissue microarrays revealed that periostin expression is upregulated in hepatocellular carcinoma (HCC) tissues compared to the corresponding normal tissues. Higher expression of periostin is associated with positive microvascular invasion, more frequent multiple tumors, advanced disease, and poor prognosis. A study related to the angiogenesis of hepatocellular carcinoma showed that sulfatase-2 (SULF2) -induced angiogenesis of HCC is dependent on periostin and that the fall of periostin in HCC cells reduces the growth of SULF2-induced. In addition, the expression of periostin in HCC cells is significantly increased after hypoxic treatment and periostin is attributed to arsenic trioxide resistance in hypoxic HCC cells (5).

KIDNEY CANCER

Renal cell carcinoma (RCC) represents the major renal tumors that are highly metastatic. They are heterogeneous tumors and are subdivided into twelve different subtypes where clear renal cell carcinoma (ccRCC) represents the major subtype. The extracellular matrix (ECM) is composed of renal cell carcinomas (RCCs), mainly different fibrous collagens, fibronectin, and basement membrane components such as laminin, collagen IV, and heparin sulfate proteoglycan. Little is known about the role of these components of ECM in the behavior of RCC cells (6). Periostin is an ECM protein that is involved in a variety of biological processes, including oncogenesis, by interacting with other ECM proteins or by binding to other cellular integrins. An increase in periostin was observed in high-grade RCC tumors and was significantly associated with poor overall survival. However, the relationship between periostin metastasis and RCC, as well as the underlying mechanism, is not clearly defined.

Overexpression of periostin induced by lens viruses that activate the FAK/JNK signaling pathway through interaction with $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, further increasing MMP activity and promoting RCC cell migration invasion (7).

According to previous studies in other cancers, periostin has also been implicated in motility and invasion of renal cell carcinoma. These data, combined with a report that extracellular periostin could enhance the attachment of A498 cells and ccRCC, suggest that periostin plays a critical role in the multi-stage process of cancer metastasis. Basement membrane and ECM invasion are necessary for RCC metastasis, which depends on the degradation of these components primarily by the MMP. Thus, overexpression of periostin significantly increased the enzyme activity of MMP-2 and MMP-9, which may contribute to the migration and invasion of RCC cells (7).

Binding to integrins and subsequent activation of the intracellular pathways is an important mechanism by which periostin exerts its pro-oncogenic effect. Multiple integrins, including $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_6\beta_4$, and $\alpha_5\beta_1$ have been reported to interact with periostin in different cell types. The results showed that the antibody against $\alpha_v\beta_3$ or $\alpha_v\beta_5$ blocked the restriction-activated activity of MMP, migration and invasion capabilities of RCC cells, indicating that either $\alpha_v\beta_3$ integrin or $\alpha_v\beta_5$ is involved in the effect of RCC restriction. These integrins mediate the functions of periostin in epithelial ovarian carcinoma, which are expressed in RCC. Meanwhile, the antibody against $\alpha_v\beta_3$ or $\alpha_v\beta_5$ inhibit the prostaglandin-induced phosphorylation of FAK, which is a tyrosine kinase always activated by integrin signaling. Similar to overexpression of periostin, exogenous periostin also promoted cell migration and invasion, and induced phosphorylation of FAK, which was inhibited by the antibody against $\alpha_v\beta_3$ or $\alpha_v\beta_5$. These results confirmed the interaction between periostin and integrin (7).

FAK is a tyrosine kinase and is one of the most prominent components of integrin signaling. Integrin activates FAK causing modulatory changes and automatic phosphorylation of FAK. Periostin could not significantly improve cell migration and invasion when FAK was reduced. These data indicated that an integrin ($\alpha_v\beta_3/\alpha_v\beta_5$) / FAK pathway is required to promote migration and RCC invasion. FAK contributes to the development of cancer through different pathways of molecular signaling. For example,

the extracellular regulated kinase (ERK) pathway is necessary for FAK to maintain cell growth or motility, at least some tumor cells, from the death-receptor complex. FAK also regulates cell invasion through JNK signaling and matrix degradation induced by MMP. Although FAK may mediate cell migration and invasion through different signaling pathways, JNK activity has been shown to be involved in both, while periostin has induced cell migration and invasion of RCC cells. FAK or JNK inhibitor attenuated MMP levels, which were enhanced by periostin, suggesting that MMP-9 and MMP2 are subsequent POSTN/FAK/JNK signaling agents and that periostin may promote migration and invasion RCC by increasing MMP expression. In addition, periostin could induce EMT and cell invasion via PI3K/Akt signaling into prostate cancer cells. However, periostin-activated Akt was not observed in RCC cells, suggesting that periostin function depends on cell type (7).

PANCREATIC CANCER

In invasive pancreatic adenocarcinoma, periostin was observed mainly in the stromal lesion adjacent to invasive cancer cells, whereas in non-neoplastic pancreas, no positive periostin could be detected in pancreatic epithelial cells and peripheral pancreatic cells. Similarly, other studies have shown that periostin is primarily expressed in pancreatic cancer tumors. In addition, neoplastic-derived periostin is significantly associated with the depth of the invasion as well as with lymph node metastasis of pancreatic cancer. Periostin can promote pancreatic cancer cell invasion and enhance the survival of pancreatic cancer cells exposed to hypoxic conditions by activating the AKT pathway. However, one study found that periostin had a biphasic effect on pancreatic cancer cells: low concentrations (150 ng/ml) of periostin reduced cell migration and metastasis, and high concentrations (1.5 $\mu\text{g/ml}$) of periostin promote cell migration. Tumor-associated macrophages (TAMs) may secrete granulocin to activate liver stem cells in myofibroblasts, and then myofibroblasts secrete periostin and other agents to promote the formation of fibrous microenvironment to facilitate the development of cells of the pancreas in the liver (5).

GLIOMA

In glioma tissues periostin is expressed in both tumor cells and the tissue layer, but the layer shows higher expression than cancer cells.

In addition, the expression of stromal periostin is positively correlated with the degree of glioma and contributes to a poor prognosis by enhancing cell invasion and proliferation among high-grade glioma patients. Another study showed that periostin levels were directly related to the degree of glioma and relapse, and inversely related to survival time in adult human glioma.

Periostin promotes the migration and adhesion of glioma cells through interaction with the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, while the reduction of periostin significantly impairs the survival of stem cells in a foreign glioma graft. Researchers have found through studies that the content of periostin-containing glioma stem cells can uptake M2-type TAM via the $\alpha_v\beta_3$ integrin to enhance glioma growth. Decreasing glioma stem cell content impairs TAM uptake, inhibits tumor growth, and increases the survival of mice that have foreign grafts with glioma stem cells (GSCs). Another study showed that reduction of periostin inhibited the invasion of U-87 glioblastoma cells and EMT by reducing the expression of fibronectin and vimentin and in part by reducing the phosphorylation of Smad2, AKT and FAK (5).

OSTEOSARCOMA

Osteosarcoma accounts for about 20% of primary bone malignancies, which is the most common malignant primary bone tumor among children and adolescents. It usually tends to develop distant metastasis and eventually leads to death, especially in cases of lung metastasis. Approximately 20% of patients develop visible metastases with imaging at diagnosis and a quarter of patients have metastases during treatment. However, due to the lack of effective tumor biomarkers for early diagnosis and that any treatment for relapse is completely resistant to the recurrent tumor, the prognosis remains poor and most patients die in the advanced stages. Thus, the development of a new prognostic factor for the prediction of penetrating potential and the prognosis of osteosarcoma is very important (8).

Osteosarcoma often tends to develop distant metastases especially in the lungs and results in eventual death. There is ample evidence to support the importance of angiogenesis in the onset, development and aggression of osteosarcoma. VEGF is considered a primary mediator for both normal and pathological

angiogenesis and has been implicated in carcinogenesis and metastasis. Expression of VEGF in untreated osteosarcoma is prognostic for pulmonary metastasis and poor prognosis. Serum VEGF levels may be diagnostic, predictive, and prognostic in patients with primary osteosarcoma. In addition, the high preoperative expression of VEGF and the MVD mevalone pathway has a high prognostic value in relation to the recurrence of patients with osteosarcoma. Periostin plays an important role in stratigraphic invasion and tumor adhesion. However, its exact mechanism of action remains under investigation. Histopathological analysis of periostin expression shows that periostin is produced by cancer-related fibroblasts. Here, periostin can act as an adhesion protein, facilitating the interaction between cancer stem cells and the site. This protects the tumor stem cells from being detected and destroyed by the immune system and thus keeps them in an undifferentiated state. Periostin can also promote angiogenesis in tumor metastasis and facilitate the survival and proliferation of cancer cells after colonization into distant tissues. This is because periostin interacts with the mutant p53 oncogene to mediate invasion by inducing STAT1 signaling into the microenvironment of the esophageal tumor. In addition, periostin activates α_5 and β_1 integrins through a dependent PI3K/AKT signaling pathway in cholangiocarcinoma invasion. To prove these hypotheses, further research is needed to investigate possible molecular mechanisms. In conclusion, periostin is overexpressed in human osteosarcoma (9).

OTHER TYPES OF CANCER

Compared to normal gastric tissues, periostin is significantly overexpressed in gastric cancer tissues and metastatic lymph nodes. In gastric cancer tissues, higher expression of periostin was found in stromal myofibroblasts but not in cancer cells. Studies have further shown that cultured NIH3T3 cells that express periostin significantly promote the proliferation of gastric cancer cells by activating ERK. However, periostin deficiency impairs the growth of gastric cancer cells that have been inoculated into the gastric wall of mice. Periostin is also overexpressed in non-solid tumors.

The expression of periostin is significantly increased in the bone marrow of patients with acute B-cell lymphoblastic leukemia (B-ALL)

compared with healthy controls. Similarly, both mRNA and expression of the periostin protein are significantly increased in the bone marrow of mouse models after injection into human or mouse B-ALL cells. Interestingly, periostin was particularly expressed in bone marrow mesenchymal stem cells (BM-MSCs) but not in B-ALL cells. Furthermore, periostin promotes proliferation and colony formation in both human and mouse cell leukemia. Periostin-deficient mice injected with B-ALL cells show much lower leukemia loads than their wild-type counterparts (5).

The researchers showed that the strong expression of periostin observed in the tumor layer was associated with shorter progression-free survival. The high expression of periostin in the tumor is related to the Gleason score, the stage of the tumor and the degree of malignancy. High expression of periostin was associated with high expression of fibronectin and low expression of integrin $\alpha 4$ in prostate cancer patients resistant to metastatic castration (10, 11).

PERIOSTIN AS A BIOCHEMICAL MARKER

Periostin is a promising biomarker for diseases such as tumor, pulmonary fibrosis, inflammation and allergy. The advantage of periostin is its detection and quantification in human peripheral blood samples. This liquid biopsy could be performed with minimal penetration, which does not burden patients. The content of periostin in the peripheral blood indicates the presence of disturbed tissues, in which abnormally activated fibroblast cells are highly expressed and secrete periostin that is transported into the blood through blood vessels.

Normally, periostin is expressed in limited tissues such as the periodontal ligament, periosteum and heart valves. The protein periostin is mainly found in extracellular collagen bundles and in maternal cell space. On the other hand, in a pathological condition, the expression of periostin is induced in malignant tissues of patients. In tumor growth and development, periostin increases mainly in the microenvironment and in the stratified tissue that is rich in extracellular substance. Tumor stromal fibroblasts particularly express periostin and organize the architecture of the extracellular substance that surrounds the tumor. In pulmonary fibrosis in the lungs, liver and kidneys, proliferating activated fibroblasts express periostin and replace normal functional tissues

with dense connective tissues. In inflammation and allergy, inflammatory cytokines such as IL-4 and IL-13 cause the expression of periostin, which plays an important role in the pathogenesis of these diseases. Elevated levels of periostin in patients could be detected not only in tissue biopsy specimens, but also in peripheral blood using specific anti-periostin antibodies, because periostin secreted by disturbed tissues is transported to blood vessels and circulates in the cardiovascular system (20).

Basic research in peripheral blood has used ELISA for detection, while rapid detection methods, such as quantitative immunochromatography, are used in routine clinical practice. Anti-periostin antibodies could also be used in the clinical diagnosis of immuno-PET. Specific and high-affinity anti-periostin antibodies have been developed and used for immune detection, functional exclusion and molecular imaging. Immuno-PET could visualize the distribution of disturbed tissues in living patients with minimal invasiveness, which contributes to accurate surgical treatment as well as evaluation of treatment outcomes. Because clinical molecular imaging, such as immuno-PET, is an emerging method, periostin in disturbed tissues would be targeted as a useful biomarker for the diagnosis of the disease (20).

Thus the expression of periostin is deregulated in various pathological conditions such as inflammation, tissue repair and malignant transformation. High levels of periostin are usually associated with a more aggressive tumor behavior, an advanced stage, or a poor prognosis, suggesting that it could be a useful prognostic biomarker (11).

In ovarian cancer, periostin is expressed at high levels in the tumor layer and in cancer epithelial cells. In one study, high expression of periostin in the stratum correlated significantly with lower overall survival and progression-free survival. In contrast, high levels of periostin in cancer epithelial cells did not show significant prognostic value compared to patients with lower expression of periostin in cancer cells. However, in another study, patients with high periostin expression in the epithelial cells of the stratum corneum and the stratum corneum had the shortest overall survival and no progression-free survival (12).

High expression of periostin has also been detected in other cancers, including melanoma,

prostate cancer and squamous cell carcinoma of the mouth. In most cases, periostin plays a role that promotes tumor growth and development (5).

PERIOSTIN AS A THERAPEUTIC INDICATOR

Cancer is a multifactorial disease whose inherent biological characteristics determine the development, progression, metastasis of cancer, and its response to clinical treatment. Although cancer treatment achieves some therapeutic results, cancer remains one of the leading causes of death worldwide. According to a systematic worldwide analysis, there were 17.2 million cases of cancer and 8.9 million deaths due to cancer 92 in 2016. However, there is a desperate need to test more effective diagnostic and prognostic indicators for cancer (13). Periostin plays multiple roles in cancer progression, so targeting it can be an attractive therapeutic approach.

Several researchers have used benzyl-d (U) TP-modified DNA aptamers (PNDAs) directed against periostin to treat breast cancer tumors in a foreign mouse graft model. This strategy effectively prevented the growth of tumors and the spread of cells to other organs. The researchers, on the other hand, used an anti-POSTN antibody (PN1-Ab), targeting the conserved exon 17 of the POSTN gene, to treat mice in a lung metastasis model. Administration of this antibody significantly inhibited the growth of primary tumors as well as the number of lung metastases (14). Similar results were obtained using a monoclonal antibody (MZ-1) directed against anti-periostin in an *in vivo* model of ovarian cancer. In this case, *in vivo* administration of the antibody also caused a reduction in the number of metastases (15, 11). Periostin is associated with drug resistance to certain solid cancers. In 2015, a study found an association between the expression of periostin and resistance to chemotherapy with gene expression in a large group of patients with ovarian cancer (16). In addition, resistance to carboplatin and paclitaxel is enhanced in chemosensitive ovarian cells under the influence of recombinant periostin (17).

Reducing periostin can prevent cancer cells from multiplying and invading small cell lung cancer and improve sensitivity to chemotherapy (18). Although the mechanism of periostin resistance to drugs needs to be further investigated, targeting of periostin represents a

new therapeutic strategy for neutralizing chemoresistance (19).

CONCLUSION

The accumulated knowledge about the relationship between periostin and cancer over the last two decades shows that this mesenchymal protein plays an important role in the development and progression of cancer, in addition to its effects on the homeostasis of specialized tissues. The fact that periostin can regulate the characteristics of cancer suggests that this multifaceted protein may affect the diagnosis and prognosis of cancer and most importantly the development of therapies aimed at the function of prostaglandin. Future research should focus on consolidating some findings and exploring new ones, especially in the field of prognostic indicators and treatment.

While it is clear that periostin is overexpressed in many tumors and that this overexpression is often associated with poor prognosis, the data are probably not convincing enough to stratify different groups of patients in terms of clinical response. In this sense, quantification of periostin tumor levels in a large group of patients undergoing homogeneous treatment in well-controlled clinical trials will be necessary to confirm whether periostin tumor could be used as a reliable prognostic indicator. Standardization of immunohistochemistry techniques used to detect periostin in tumor tissues (for example, antibodies and quantification methods) will also be necessary to draw conclusions. Several laboratories have studied serum periostin levels and their association with weight and tumor prognosis. In this case, the results are more complex and there are no clear conclusions about the usefulness of serum periostin levels as a prognostic indicator. In addition, studies in larger groups could be needed to clarify this question.

Periostin has been shown to induce resistance to certain chemotherapeutic drugs in certain types of cancer cells. Whether this is true in the clinical setting has yet to be determined, again in the context of observational clinical trials. This correlation between periostin and resistance to anticancer drugs suggests that it may be necessary to design new combination therapies in certain types of cancer to bypass the effect of periostin. Obviously, more basic and translational

research is needed, especially in clinically relevant animal models (e.g., foreign grafts from the patient) before translation into the clinic. In addition, the relationship between periostin and the proteins involved in the phenotype that is resistant to many cancer drugs also needs to be studied in more detail.

One of the most important findings is the effect of periostin on the metastatic process, including various aspects such as epithelial-mesenchymal transition, cell migration and metastatic site. The idea that cancer cells or tumor stromal cells can remotely send a protein like periostin to prepare the metastatic site is really fascinating. Interestingly, current knowledge strongly supports this possibility. Thus, several studies in animal models have shown that periostin may be a determining factor in determining metastatic site. Because the consequences of this finding could have a major clinical impact, more research is needed on this issue. One of the unresolved questions is how periostin reaches the metastatic site. An interesting possibility is that periostin produced by tumor stromal cells or in some cases by the cancer cells themselves was sent to the metastatic site enclosed in circulating exosomes. In this case, intervention in the transfer process could be of therapeutic interest. The complete characterization of these extrapolates at the molecular level will be necessary to determine if these extrapolate have any potentially targeting characteristics. In addition, detection of circulating prostostine levels could predict the risk of metastasis to clinically localized tumors, which could be exploited for immediate stratification of patients.

Finally, we know little about the relationship between periostin and the immune system. Since periostin appears to play a role in maintaining the hematopoietic site, it is possible that it could also play a role in regulating immune cell activity in tumors. The accumulated knowledge about the relationship between periostin and cancer over the last two decades shows that this mesenchymal protein plays an important role in the development and progression of cancer, in addition to its effects on the homeostasis of specialized tissues. The fact that periostin can regulate the characteristics of cancer suggests that this multifaceted protein may influence the diagnosis and prognosis of cancer and, most importantly, the development of therapies that target the function of periostin. Future research should focus on consolidating some findings and

exploring new ones, especially in the field of prognostic indicators and treatment. While it is clear that periostin is overexpressed in many tumors and that this overexpression is often associated with poor prognosis, the data are probably not convincing enough to stratify different groups of patients in terms of clinical response. In this sense, quantification of periostin tumor levels in a large group of patients undergoing homogeneous treatment in well-controlled clinical trials will be necessary to confirm whether periostin tumor could be used as a reliable prognostic indicator. Standardization of immunohistochemistry techniques used to detect periostin in tumor tissues (for example, antibodies and quantification methods) will also be necessary to draw conclusions. Several laboratories have studied serum periostin levels and their association with weight and tumor prognosis. In this case, the results are more complex and there are no clear conclusions about the usefulness of serum periostin levels as a prognostic indicator. Again, studies in larger groups could be needed to clarify this question.

Conflicts of Interest: The author declares no conflicts of interest regarding the publication of this paper.

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