Role and underlying mechanisms of the interstitial protein periostin in the diagnosis and treatment of malignant tumors (Review)

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Abstract. Invasion and metastasis are the major characteristics of malignant tumors and are complex processes involving multiple genes. Gene regulation is a precise, large and complex biological control system, and its underlying mechanisms remain to be elucidated. Mesenchymal-specific genes are expressed primarily by mesenchymal cells, and the expression products of these genes are molecules with various structures and functions, including secreted proteins and extracellular matrix proteins. The periostin gene has been newly identified as a mesenchymal-specific gene and an extracellular-matrix secreted protein. Periostin is able to bind to various subtypes of integrin receptors on the surface of the cell membrane. This triggers relevant signal transduction pathways to alter the microenvironment of cancer cells in order to facilitate their survival, invasion, metastasis and angiogenesis as well as enhance the tolerance to hypoxia and chemicals. Therefore, periostin is associated with the grade of malignancy, level of invasion and prognosis of malignant tumors. The in-depth study of periostin may provide an effective marker for tumor diagnosis and prognosis, as well as a novel treatment target.

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1. Introduction

The two major characteristics of malignant tumors are invasion and metastasis. These characteristics involve complex processes that includes multiple genes. The underlying mechanisms of gene regulation are precise and complicated in their control and have yet to be fully resolved. At present, research view points are based on Paget's 'seed and soil hypothesis'. Previous studies have focused on the 'seed', cancer cells, and emphasized the impact of the molecular pathological changes of cancer cells on biological behaviors, including proliferation, invasion and metastasis (1-5). However, no specific biological markers that are able to predict the invasion and metastasis of tumors have been identified. The role of the 'soil', the tumor microenvironment, in the development of tumors has been the focus of a number of studies investigating the expression and function of relevant genes, developing a novel approach for the basic research of tumor development (6,7). Mesenchymal-specific genes bridge the 'seed' and 'soil' aspects of research and are also important in the tumor regulatory process (8,9).

The expression of mesenchymal-specific genes produces proteins with a variety of structures and functions, including secreted proteins and extracellular matrix (ECM) protein. Periostin, a newly identified mesenchymal-specific gene, was originally cloned from a mouse osteoblastic cell line (10). Previous studies revealed that the periostin gene was associated with the formation of bones (11) and teeth (12), as well as the maintenance of their structures. At present, studies on periostin mainly focus on two areas: i) The facilitation of the growth and development of heart valves and its involvement in the pathophysiological processes of various ischemic heart diseases, including myocardial infarction and heart failure (13); ii) the variations between the expression levels of periostin mRNA and protein in normal and tumor tissues, as this is implicated to be closely associated with the occurrence, development and prognosis of malignant tumors (14).

Periostin, also termed osteoblast-specific factor 2, is an ECM secreted protein that is able to improve the proliferation and differentiation of osteoblasts, and the aggregation and adhesion of periosteal osteoblast precursor cells (15). It is expressed in various normal human tissues that are not only

involved in numerous normal physiological processes, but are also closely associated with the pathological processes involved in the occurrence and development of cardiovascular diseases, asthma and tumors (16). Currently, the majority of studies indicate that the overexpression of periostin is associated with the malignancy grade of a cancer; however, other studies have reported that periostin may inhibit the invasion and metastasis of bladder cancer (17,18). Kanno *et al* (19) identified that periostin has the dual effect of promoting and inhibiting pancreatic cancer. Collectively, the results of these studies suggested that the variable biological effects of periostin are observed in distinct tissues, and further research is required to examine its complex and multifaceted functions (20). The current review focuses on the progression of periostin research for the diagnosis and treatment of malignant tumors, and its underlying mechanisms of action.

2. Structures and features of periostin

The human periostin gene is located on chromosome 13q13.3, with two isoforms identified through studies on human placenta and osteosarcoma cDNA libraries (10). One of the variants is a 779-amino acid protein with a molecular weight of 87 kDa and the other is an 836-amino acid protein with a molecular weight of 93.3 kDa (10). The mouse periostin gene is located on chromosome 3, and the coding region is 30 kbp in length, producing an 811-amino acid protein with a molecular weight of 90.2 kDa. Periostin is highly conserved, and has 89.2% protein sequence homology between humans and mice. Compared with other regions of periostin, the C-terminus is less conserved, with 85.5% sequence homology (10). Periostin also shares homology with the adhesion molecule of the insect embryonic central nervous system, fasciclin I (10). Periostin is in the same protein family as transforming growth factor β-induced, stabilin I and II, myelin basic protein-70 and algal-cell adhesion molecule (10).

Periostin has an N-terminal signal peptide, a cysteine-rich region, four internal homology domains and a carboxyl terminal region (21). There is a typical signal sequence at the N-terminus suggesting that it has the potential to be a secreted protein (21). The cysteine-rich region contains ~75 amino acids and may be associated with protein-protein interactions or protein polymerization (21). The four internal homology domains are homologous with the insect protein fasciclin I and contain the binding sites for integrin and glucosamine (21). This allows periostin to interact with integrin to mediate the epithelial-mesenchymal transition (EMT) (21). The EMT enables tumor cells to phenotypically resemble mesenchymal cells, thus mediating the migration and adhesion of cells and enabling tumor cells to acquire stronger metastasis potential (22-24). The C-terminus of periostin is hydrophilic and is able to undergo alternative splicing at the transcriptional level to form splice variants or isomers of periostin (25). Periostin has eight types of homologous isomers in human tissues that are considered to be associated with the occurrence of specific tumors (26).

3. Periostin in the diagnosis of malignant tumors

Periostin is highly expressed in multiple solid tumor tissues, including head and neck, lung, breast, colorectal, ovarian and liver cancer (27). Periostin protein is secreted from tumor cells and the surrounding stromal cells and this continuously destroys the surrounding matrix during the infiltration process of tumors (28), leading to the release of periostin into the blood circulation. Previous studies have identified that there is a high level of periostin expression in the blood serum of patients with head and neck, breast, colorectal and non-small cell lung carcinoma, and that the potential for infiltration and metastasis was higher in those with a raised level of serum periostin (29,30). Periostin is able to facilitate the survival, invasion and angiogenesis of tumor cells, and enhance their tolerance to hypoxia and chemicals, suggesting it has a close association with the grade of malignancy, metastasis and prognosis of malignant tumors (31,32). Following further study of periostin, it may present an ideal marker for the diagnosis and prognosis of tumors.

Kudo *et al* (33) demonstrated that periostin expression correlates with vascular endothelial growth factor C (VEGF-C) expression levels in tissue and serum from patients with head and neck squamous cell carcinoma (HNSCC). Periostin and periostin-induced upregulation of VEGF-C may promote lymphangiogenesis, and this has been reported to be mediated by Src and Akt activity (33). Periostin has the potential to be a marker for the prediction of malignant behaviors and a potential therapeutic target to obstruct lymphatic invasion and lymphangiogenesis in patients with HNSCC.

Wang *et al* (34) reported that periostin was frequently highly expressed in esophageal squamous cancers and was associated with lymphatic metastasis, tumor staging, vascular invasion and tumor node metastasis (TNM) staging. High levels of periostin expression are associated with the progression of tumors, angiogenesis and poor prognosis, indicating that it may be an independent prognostic factor for esophageal squamous cancer. Heidari *et al* (35) demonstrated that specific imaging of ECM periostin in esophageal squamous cell carcinoma is feasible using a targeted positron emission tomography tracer. Detection of periostin in the tumor microenvironment may aid early detection, post-surgical follow up, and *in situ* characterization of primary and metastatic lesions.

Soltermann *et al* (36) examined the expression levels of periostin in the tumor tissue sections of 533 patients with non-small cell lung carcinoma (NSCLC). The results revealed that periostin was expressed in epithelial and mesenchymal tumor tissues and that its expression levels exhibited a positive correlation with the size of tumor, the tumor staging and progression-free survival, as well as being elevated in male patients, and with a higher postoperative recurrence rate in patients with high levels of periostin expression in the tumor mesenchymal tissues (36). This previous study also indicated that the abnormal expression of periostin in patients with lung cancer serves an important role in the occurrence and development of the tumor, affecting patient prognosis (36).

Zhang *et al* (37) demonstrated that, compared with benign breast tumors and normal breast tissue, the levels of periostin mRNA and proteins were higher in breast cancer tissues and thisassociation was positively correlated with TNM stage. Puglisi *et al* (38) examined tumor tissue sections of 189 patients with breast cancer and revealed that periostin was mainly located in tumor mesenchymal tissues and the

cytoplasm of tumor cells. The expression level of periostin in the cytoplasm was associated with the size of the tumor, and its progesterone receptor and VEGF receptor status, suggesting periostin has an effect on the growth of tumors and angiogenesis (38). Contié *et al* (39) transplanted the MDA-B02 human breast cancer cell lineinto nude mice and identified that high levels of periostin were expressed mainly in the matrix of cells surrounding the tumor, compared with the breast cancer cells.

The expression level of periostin is abnormally increased in the tumor tissues and blood serum of patients with colorectal cancer (40). Using ELISA, Ben *et al* (40) revealed that the serum level of periostin in patients with colorectal cancer was significantly higher compared with healthy individuals and patients with colorectal polyps or colorectal adenoma, and that this was closely associated with distant metastasis, tumor staging and prognosis. This may be of clinical value in the determination of whether patients with colorectal cancer have a high risk of tumor invasion and metastasis. Using reverse transcription-polymerase chain reaction, it was also revealed that the expression of periostin mRNA was significantly increased in colorectal cancer tissues compared with normal tissues, but periostin mRNA was not detected in four cultured colon cancer cell lines suggesting that periostin was secreted by the surrounding matrix cells and not colorectal cancer cells (40). Kikuchi *et al* (6) used immunohistochemistry (IHC) and immunoelectron microscopy to detect periostin in the blood serum of patients with colon cancer, which was secreted by the fibroblasts that surroundcolon glands and tumor-associated fibroblasts. Li *et al* (41) performed IHC staining of periostin on tissue samples from 115 patients with colorectal cancer during the follow-up period, revealing positive periostin expression. The levels of periostin expression in colorectal cancer cells (59.13%, 68/115) were significantly higher compared withthe adjacent normal colon mucosa (0.47%, 11/109) (41). In colorectal cancer, the overexpression of periostin was positively correlated with tumor size, serosal invasion, differentiation, five-year survival rates, lymph node metastasis andclinical stage (41,42). Those with early-stage colorectal cancer and low periostin expression levels had higher survival rates compared with patients with advanced-stage colorectal cancer and high levels of periostin expression. These findings suggest that periostin may be important in the progression of various types of colorectal cancers.

A previous study examined the expression of periostin in intrahepatic cholangiocarcinoma using IHC, revealing that periostin was expressed only in the interstitial fibroblasts and not in cancer cells and immune cells (6). The survival time of patients with cholangiocarcinoma with a high level of periostin expression was shorter compared with those with low levels of periostin expression (6). The multivariate analysis revealed high expression level of periostin and lymphatic metastasis may be independent prognostic factors for cholangiocarcinoma (6). *In vitro* analysis of recombinant periostin also indicated that periostin is able to induce the proliferation and invasion of cholangiocarcinoma cells (43). Preoperative serum levels of periostin are of limited value for the diagnosis of benign and malignant hepatic disease, but may be used as an independent prognostic indicator for liver cancer (44).

4. Periostin in the treatment of malignant tumors

As aforementioned, the expression of periostin and changes to the extracellular matrix may alter the adhesion and migration of tumor cells, characteristics that are closely associated with the treatment of several types of malignant tumor (45). Periostin is able to facilitate the survival, migration and invasion of tumor cells, as well as promoting angiogenesis, enhancing the metastatic potential of tumors (46). Therefore, periostin may be a novel target for tumor treatment.

The periostin-integrin signaling pathway regulates the development of breast cancer and the tumor microenvironment at multiple levels, and the periostin-binding DNA aptamer is reported to be a potential target for inhibiting the development of breast cancer (45). Choi *et al* (46) demonstrated that recombinant periostin is able to stimulate the adhesion and invasion of the SK-OV-3 human ovarian adenocarcinoma cell line and induce the expression of matrix metalloproteinase-2. Zhu *et al* (47) constructed periostin expression vectors and inserted them into the OVCAR-3 and OV2008 ovarian cancer cell lines. The results revealed that the overexpression of periostin did not alter the *in vitro* growth speed of tumor cells, whereas it greatly enhanced the growth of peritoneal metastatic tumors in immunodeficient mice (47). This growth enhancement was primarily associated with increased angiogenesis and decreased tumor-cell apoptosis (47). Purified periostin has been reported to facilitate the *in vitro* adhesion, migration and invasion of ovarian cancer cells and human umbilical vein endothelial cells (HUVEC) (47). Gillan *et al* (14) identified that the purification of recombinant periostin facilitated the adhesion of ovarian epithelial cells where as antibodies against αvβ3 and αvβ5 inhibited this adhesion, suggesting that αvβ3 and αvβ5 are the receptors of periostin on the ovarian cancer cell membrane. It was hypothesized that periostin serves an important role in the angiogenesis and distant metastasis of ovarian cancer, which mayprovide a novel target for the treatment of ovarian cancer (14).

The 293T human renal epithelial cell line exhibits high levels of periostin expression and has increased migratory and invasive potential compared with normal cells (48). However, this effect may be blocked by αvβ5 antibody or an epidermal growth factor receptor (EGFR) kinase inhibitor, and cell movement and invasion mayalso be promoted by the increased expression of EMT associated genes (elastic protein genes and fibrin genes) and the activation of matrix metalloproteinase-9 (MMP-9) (48). It has been suggested that periostin may enhance the invasion and metastasis of cancer cells through integrin and the EGF signaling pathway, and periostin may be an effective therapeutic target for human epithelial renal cell cancer (48).

A previous study demonstrated that the expression of periostin increased and promoted the survival of A549 cells that were placed in a chemically-simulated hypoxic tumor microenvironment via activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway (49). Hong *et al* (50) constructed a plasmid vector that expressed periostin and inserted it into A549 cells. The expression of vimentin and neural-cadherin were induced and simultaneously the expression of epithelial-cadherin was inhibited suggesting that the enhancement of the epithelial-mesenchymal

transition may facilitate the proliferation and migration of A549 cells (50). This demonstrated that periostin was closely associated with the invasion and migration of NSCLC and it may be a potential therapeutic target for the treatment of NSCLC (29,50).

An *in vitro* study demonstrated that recombinant periostin induces the proliferation and invasion of cholangiocarcinoma cells (43). It has also been reported that the upregulation of periostin expression enhanced the invasion of prostatic cancer, suggesting that it may be a potential target for the treatment of primary and metastatic prostatic cancer (51). Tai *et al* (52) identified that periostin antibodies promote the apoptosis of cancer cells and enhance the efficacy of 5-fluorouracilin the treatment of colorectal cancer. Periostin serves an important role in the facilitation of cancer cell survival; therefore, periostin antibodies may be an effective therapeuticfor colorectal cancer (52).

5. Regulatory factors of periostin

Yang *et al* (53) demonstrated that histamine induced the production of periostin and collagen, by activating the H1 receptor-mediated extracellular signal-regulated kinase (ERK) 1/2 pathway. Tai *et al* (52) identified that, in colon cancer cells, transforming growth factor (TGF)-β1 induced the production of periostin. Fibroblast growth factor (FGF)-1 and angiotensin II enhanced the expression of periostin in pulmonary arterial smooth muscle cells (54). Bone morphogenetic protein, platelet-derived growth factors and acidic and basic FGF were all potential factors promoting pancreas stellate cells to secrete periostin (55). In a hypoxic environment, TGF-α and basic FGF are able to increase the expression of periostin in A549 lung cancer cells by activating the PI3K/Akt signaling pathway (49). In human ovarian cancer tissues, periostin was not expressed in the cancer cells, but in the cancer-associated mesenchymal cells (56). Lysophosphatidic acid (LPA) is able to induce the secretion of periostin by mesenchymal cells and periostin expression may be effectively inhibited using viral delivery of short hairpin RNA to silence LPA receptor 1 (46). In addition, previous studieshave demonstrated that Twist and interleukin-4 and -13 are also able to induce the expression and secretion of periostin (57,58). Fig. 1 summarizes the aforementioned regulatory factors of periostin.

6. Mechanisms underlying periostin action

The activation of relevant signaling pathways, including the EGFR pathway and PI3K/Akt pathway, is able to enhance the proliferation and migration of vascular endothelial cells, inhibit the apoptosis of endothelial cells, reduce damage to the cells in hypoxic and low nutrition environments and maintain normal cell functions (49,59). These processes are beneficial for the angiogenesis of tumor tissues and enhancement of tumor invasion, thus facilitating the formation of metastatic tumors. Due to the biological structures and features of periostin, it is able to bind to various subtypes of integrin receptor on the surface of the cell membrane, including αvβ3, αvβ5 and α6β4, and trigger relevant signal transduction pathways, including PI3-K/Akt and focal adhesion kinase (FAK) phosphorylation. Periostin may also bind to EGFR andthis serves an important role in the occurrence and development of tumors through the enhancement of tumor cell survival, angiogenesis, and the invasion and metastasis of tumors (15,49). The potential underlying mechanisms of periostin action are summarized in Fig. 2.

Periostin is able to bind to several cell surface receptors, and particularly interacts with integrin receptors on the cell surface. Integrin is a transmembrane receptor heterodimer that is involved in cell-cell and cell-ECM interactions, which promote the EMT, enhance the invasion of cells and inhibit ECM-integrin interaction via periostin-integrin interaction (56,59). This triggers relevant signaling transduction pathways, including the PI3-K/Akt signaling pathway, and may alter the microenvironment to favor cancer cell survival and growth (20). Baril *et al* (47,56) demonstrated that periostin facilitated the invasion of tumor cells by enhancing the activity of pancreatic cancer cells, and enhanced the survival of cancer cells under hypoxic conditions. At the molecular level, periostin is able to activate the PI3K/Akt signaling pathway by binding to integrin α6β4 receptor, thus promoting FAK phosphorylation rather than expression of MMP-9, to exert biological effects (56). Zhu *et al* (47) revealed that the interaction between periostin and ovarian cancer cells and HUVEC cells may facilitate the migration and invasion of ovarian cancer cells andthe adhesion and migration of HUVEC cells, as well as improving the angiogenesis of tumors, allowing the invasion and metastasis of tumors. Another previous study demonstrated that purified recombinant periostin is able to enhance the adhesion of ovarian epithelial cells, a process that is inhibited by αvβ3 and αvβ5 antibodies but not αvβ1 antibody. The selection of integrin occurred according to the distinct subtypes of integrin receptors on the cell membrane that are expressed in various cell types, suggesting that αvβ3 and αvβ5 are the receptors of periostin on the ovarian cancer cell membrane, and that periostin functions by binding to them (47,56). Yan *et al* (48) identified that periostin-transfected cells exhibited morphological changes and increased expression of the matrix markerselastic protein and fibrin. 293T cells, which express a high level of periostin, had stronger migratory and invasive potential compared with normal cells. However, this effect was able to be blocked by αvβ5 antibodies or EGFR kinase inhibitors, suggesting that periostin may improve the invasion and metastasis of tumor cells via the integrin and EGFR signaling pathways. The expression of EMT associated genes (elastic protein and fibrin genes) and activation of MMP-9 may also enhance the migratory and invasive potential of cancer cells (48,56).

Growth of new capillaries to provide nutrient substance and oxygen is essential when solid tumors grow to a diameter of 2-3 mm, and this requires the proliferation and migration of vascular endothelial cells and the formation of capillary lumens. It has been identified that VEGF and its receptor, fetal liver kinase-1/kinase insert domain receptor (Flk-1/KDR), serve an important role in this process (59). Tumor cells and mesenchymal cells secrete VEGF to act on the vascular endothelial cell receptors but VEGF also facilitates the adhesion and migration of endothelial cells by activating the receptors Flk-1/KDR and integrin αvβ3. Shao *et al* (59) identified that, in breast cancer, periostin upregulates the VEGF receptor Flk-1/KDR through the integrin αvβ3-FAK-mediatedsignaling

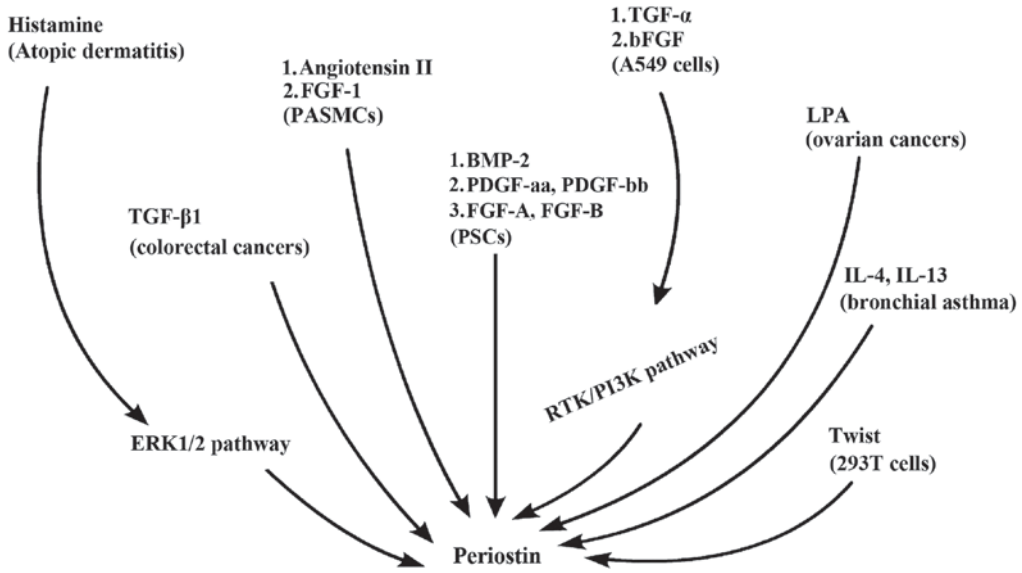

Figure 1. Regulatory factors of periostin. Previous studies in eight diseases have revealed more than twelve factors might regulate periostin. TGF, transforming growth factor; ERK1/2, extracellular signal-regulated kinase 1/2; FGF, fibroblast growth factor; PASMCs, pulmonary artery smooth muscle cells; BMP-2, bone morphogenetic protein 2; PDGF, platelet-derived growth factor; PSC, pancreatic stellate cells; LPA, lysophosphatidic acid; RTK/PI3K, receptor tyrosine kinase/phosphatidylinositol 3-kinase; IL, interleukin.

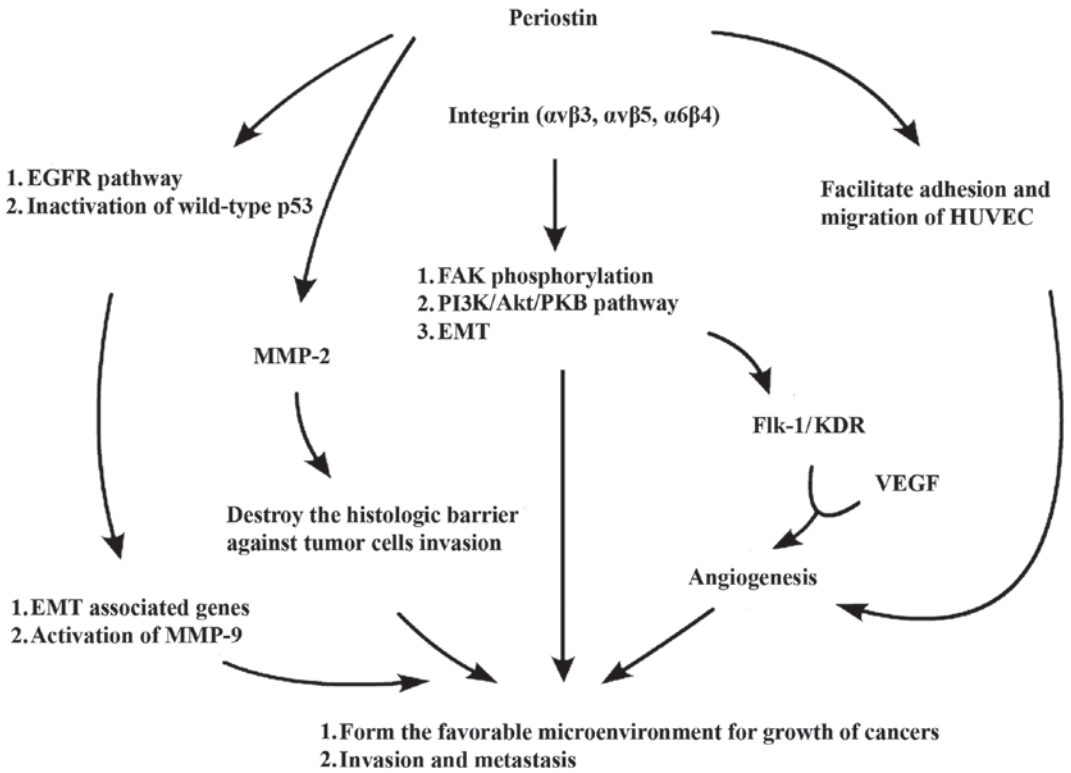

Figure 2. The potential mechanisms underlying periostin action. Studies have revealed more than four relevant signal transduction pathways are implicated in the formation of a favorable microenvironment for the growth, invasion and metastasis of cancer. EGFR, epidermal growth factor receptor; EMT, epithelial mesenchymal transition; MMP, matrix metalloproteinase; FAK, focal adhesion kinase; PI3K/Akt/PKB, phosphatidylinositol 3-kinase/protein kinase B; Flk-1/KDR, fetal liver kinase 1/kinase insert domain receptor; VEGF, vascular endothelial growth factor; HUVEC, human umbilical vein endothelial cells.

transduction pathway. This has an important impact on tumor angiogenesis and the growth of metastatic tumors (59). The regulation of growth in rectal cancer is implemented through the αvβ3-PI3 K/Akt signaling pathway; however in pancreatic cancer, this occurs through the α6β4-PI3K-Akt and FAK signaling pathways (59). Therefore, tumor cells secrete periostin in a paracrine manner, which allows it to bind to integrin receptors that facilitate the survival of endothelial cells and the formation of new blood vessels. Thus, periostin has an important role in the development of tumor vessels and the growth of metastatic tumors. Despite differing cell origins, the regulatory effects of periostin on signaling pathways are

generally consistent across various studies and all of these pathways are common angiogenesis regulators (59).

In human ovarian cancer tissues, periostin was not expressed in cancer cells, but in the cancer-associated mesenchymal cells. Recombinant periostin is able to stimulate the adhesion and invasion of SK-OV-3 human ovarian adenocarcinoma cells and induce cancer cells to express MMP-2, which may destroy the histological barrier of the basement membrane and extracellular matrix against tumor cell invasion, thus serving an important role in the invasion and metastasis of tumors (46).

Using three-dimensional tissue culture of esophageal squamous cancer cells, Michaylira *et al* (60) identified that periostin is a cell adhesion molecule that is highly expressed by tumor cells and may be a novel molecular marker for tumor invasion. Inhibition of the EGFR signaling transduction pathway and restoration of the function of wild type p53 weakened the effect of periostin suggesting an interdependent association exists between these two common genetic alterations and the functions of periostin (60).

Using *in situ* hybridization, Kikuchi *et al* (61) revealed that periostin was generated by gastric cancer-associated fibroblasts rather than cancer cells, and thismay form a favorable microenvironment for the growth of gastric cancers by activating ERK, thuspromoting the progression of tumors. Genome-wide analysis of gene expression identified significantly higher levels of periostin expression in stage II-IV gastric cancer tissuescompared with normal tissues. In parallel with the activation of ERK, periostin may enhance the *in vitro* growth of diffuse gastric cancer cell lines, including OCUM-2MLN and OCUM-12 (61).

7. Conclusion

Notable progress has been achieved on investigating the involvement of periostin in the occurrence and development of tumors. This hasprovided novel approaches for tumor research through providing a potentialdiagnostic marker and therapeutic target for tumors. Previous studies reveal that periostin is primarily produced by the mesenchymal cells surrounding cancer cells, and cancer cells may stimulate its expression and secretion by mesenchymal cells (8,12,49). This may occur through interactions with receptor molecules on the cell surface, including integrin (20), triggering relevant signaling transduction pathways that alter the microenvironment in favor of cancer cell survival and growth.

At present, there remain numerous problems that require addressing to elucidate the role of periostin in tumor development. These include: i) investigating the mechanisms underlying periostin action on the survival, invasion, angiogenesis and metastasis of tumor cells; ii) identifying the factors that regulate the expression of periostin by mesenchymal cells, and whether the regulatory factors of periostin differ in the varying types of cancer; iii) determining the receptor molecules that interact with periostin and the tumor factors that may be regulated to produce effects including facilitation of survival, invasion and angiogenesis of tumor cells and enhance tolerance to hypoxia and chemicals; iv) identifying the factors that cause periostin to exhibit varied effects among differing tumor cells and v) detecting whether multiple types of tumor cells express or secrete periostin individually. Continuous in-depth research may aid further understanding of the role of periostin in the occurrence and development of tumors, and provide novel evidence for the application of periostin in the clinical diagnosis and treatment of tumors.

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