



The Role of Periostin in Breast Cancer

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ABSTRACT

Periostin (POSTN), a member of the matricellular protein family, is a secreted adhesion-related protein produced in the periosteum and periodontal ligaments. Matricellular proteins are a nonstructural family of extracellular matrix (ECM) proteins that regulate a wide range of biological processes in both normal and pathological conditions. The studies have demonstrated the key roles of these ECM proteins in the tumor microenvironment. Furthermore, periostin is an essential regulator of bone and tooth formation and maintenance, as well as cardiac development. Also, periostin interacts with multiple cell-surface receptors, especially integrins, and triggers signals that promote tumor growth. According to recent studies, these signals are implicated in cancer cell survival, epithelial-mesenchymal transition (EMT), invasion, and metastasis. In this project, we will summarize the most current data regarding periostin, its structure and isoforms, expressions, functions, and regulation in cancerous tissues, and emphasis will also be placed on its association with breast cancer

Keywords:

Breast Cancer, Periostin, matricellular protein

Introduction

Periostin (POSTN) belongs to matricellular proteins, and since its first discovery in 1993, has become the subject of many studies in scientific research [1]. Matricellular proteins are a class of non-structural ECM proteins that are secreted into the extracellular environment and are expressed at low levels in most adult tissues. these proteins interact with cell-surface receptors and mediate cell and extracellular communications. Physiologically, periostin, a matricellular protein, regulates embryonic formation, tissue repair, ECM structure, formation and maintenance of bone and teeth [2], as well as other collagen-rich connective tissues subjected to mechanical stress, such as heart valves [3] and tendons [4]. In contrast, abnormal up-regulation of periostin expression has been observed in multiple pathological processes of various diseases, such as inflammatory diseases, fibrosis, and tumor progression [5,6].

Molecular structure of periostin

Periostin (POSTIN, OSF2) is a Extracellular matrix protein involved in wound healing consist 836 amino acid with a molecular weight of 93 kDa . Structurally, POSTN is a multimodular protein composed of a signal peptide, which is necessary for secretion, a small cysteine-rich module (EMI domain) probably involved in the formation of multimers through cysteine disulfide bonds [7], four fasciclin-like domains (FAS1) that interact with integrins ($\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha 6\beta 4$) [8] , and a hydrophilic C-terminal region known to interact with other ECM proteins such as collagens, fibronectin, tenascin C, or heparin [9,7]. Interesting, the FAS1 domains of human POSTN contain vitamin K-dependent γ -carboxyglutamic acid (Gla) residues [10], which are found in a small group of proteins called Gla-containing proteins. This group of particular proteins includes many coagulation and anticoagulation factors as well as bone-associated proteins such as osteocalcin (bone gamma-carboxyglutamate protein) and matrix-gla protein (MGP) [11]. These proteins suffer posttranslational modifications by γ -glutamyl carboxylase (a vitamin K-dependent enzyme) on specific glutamyl amino acid residues (Glu) to produce γ -carboxyglutamic amino acid residues (Gla) [12,13]. The main known function of γ -carboxyglutamic acid residues is their ability to bind divalent cations such as calcium. Hence, Gla-containing proteins play important roles in the regulation of coagulation cascade and bone homeostasis [14,15].

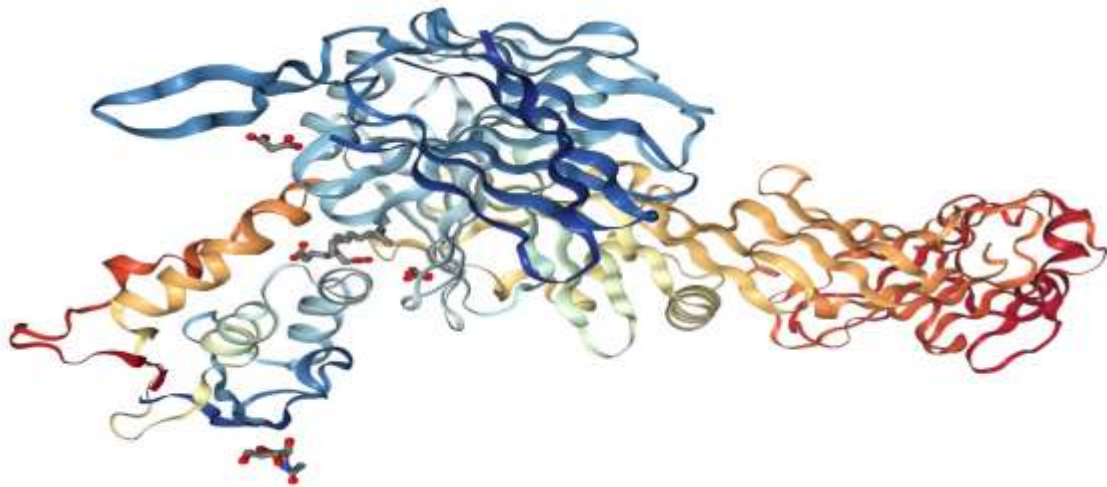


Fig. 1 Periostin Structure.

Expression and Function of POSTN in Normal Tissues

Periostin is preferentially expressed in the periosteum, hence its name. The periosteum is a specialized membrane, which covers the outer surface of bones and is responsible for growth in diameter of bone and for the cortical thickness. The activity of the periosteum is particularly elevated during the phases of embryonic development and body growth, although during the adult life, it also contributes to determinate bone diameter and, subsequently, bone strength [16, 17]. Interestingly, POSTN is also expressed in other connective tissues rich in collagens undergone to mechanical stress such as the periodontal ligament (a specialized structure of the teeth) [18], heart valves [19], and tendons [20]. During cardiac development, POSTN is highly expressed by embryonic fibroblasts [21] and pericardial cells that cover the embryonic heart [22], but not by cells of the cardiomyocyte lineages [23]. In the bone, POSTN mRNA has been detected by *in situ* hybridization in pre-osteoblast cells [24].

As described above, POSTN is able to interact with cells through its FAS1 domains and ECM proteins through its N-terminal EMI domain and C-terminal region. These properties make POSTN a key player in the regulation of cell behavior and organization of the ECM. POSTN has been shown to bind integrins $\alpha\beta3$ and $\alpha\beta5$ in osteoblasts and several types of normal and cancer cells where it elicits activation of FAK, PI3-Kinase, and AKT signaling pathways [25, 26]. The POSTN can act as a prosurvival protein in many cellular contexts. Periostin plays an important role in ECM structure and organization and particularly in collagen assembly. Collagen cross-linking is a natural process essential to provide stability to collagen-rich connective tissues. Two key elements in this process are BMP-1 and lysyl oxidase (LOX) [27]. Interestingly, POSTN binds BMP-1 and collagen I through its FAS1 domains and N-terminal EMI domain, respectively, and thus act as a key player in this process, serving as a scaffold for BMP-1 and collagens to accelerate collagen cross-linking [27]. The importance of POSTN in collagen cross-linking is also supported by POSTN knockout animal models. Thus, POSTN null mice exhibit aberrant collagen fibrillogenesis in the periosteum and a decrease in collagen cross-linking observed in skin, tendons, and heart [28]. Remarkably, POSTN has 28 glutamyl amino acid residues (Glu) that could be posttranslationally modified to generate γ -carboxyglutamic amino acid residues (Gla) [10]. The high number of potential Gla residues present in POSTN contrasts with the number of Gla residues contained in others Gla proteins of the bone such as osteocalcin and matrix Gla protein, which have 3 and 5 Gla residues, respectively. Coutu et al. studied the form of POSTN (carboxylated vs uncarboxylated) that was secreted by adipocytes, chondrocytes, and osteoblasts differentiated from mesenchymal stem cells. They found that undifferentiated human mesenchymal cells and also differentiated adipocytes and osteoblasts synthesized carboxylated POSTN while no POSTN was detected in cells undergone chondrogenic differentiation. Interestingly, carboxylated POSTN was detected in the conditioned medium of undifferentiated human mesenchymal cells and differentiated adipocytes but not in the conditioned medium derived from differentiated osteoblasts. In the latter case, POSTN was found to be abundantly deposited in bone nodules produced *in vitro*, indicating that osteoblasts are able to

produce carboxylated POSTN that is efficiently sequestered within the ECM in a calcium-dependent manner [10].

Definition of Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body .

Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Cancerous tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors [29].

There are two main categories of cancer:

- Hematologic (blood) cancers are cancers of the blood cells, including leukemia, lymphoma, and multiple myeloma.
- Solid tumor cancers are cancers of any of the other body organs or tissues. The most common solid tumors are breast, prostate, lung, and colorectal cancers.

Tumor periostin as a biomarker :

Periostin expression is deregulated in several pathologies such as inflammation, tissue repair, and malignant transformation [30]. In general, high POSTN levels are usually associated with a more aggressive tumor behavior, advanced stage or poor prognosis, suggesting that POSTN levels could be a useful prognostic biomarker.

Correlation between periostin expression levels and clinical parameters in solid tumors:

| Cancer | High expression in | Is associated with (1) | Reference |
|---------------|------------------------------------|-----------------------------|-----------|
| Breast cancer | Stroma and cancer epithelial cells | OS and PFS (poor prognosis) | [31, 32] |
| | Cancer-associated fibroblasts | OS (poor prognosis) | [33] |

(1) OS, overall survival; PFS, progression-free survival.

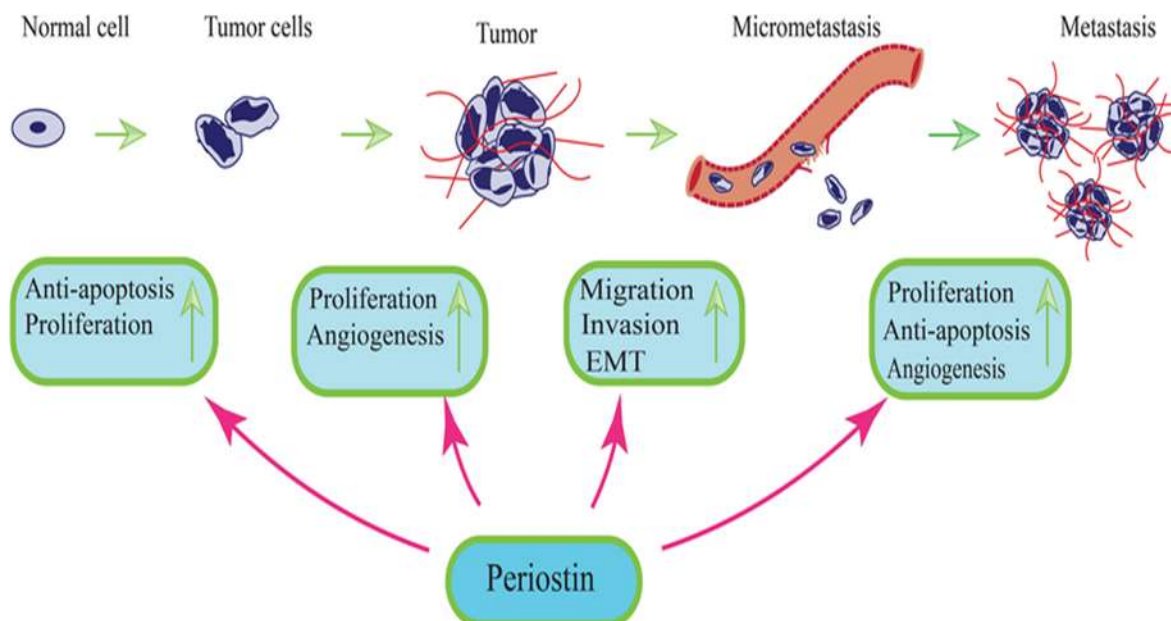


Fig. 2 Possible roles of periostin in tumorigenesis. Periostin could be involved in the transformation of normal cells into metastatic tumors by preventing apoptosis, and promoting cell proliferation, angiogenesis, migration, EMT, and invasion.

Definition of Breast Cancer :

Breast cancer is a cancer that develops due to uncontrollable changes in the function or growth of the cells forming breast tissue. These changes transform these cells into cancerous cells that have the ability to spread. Breast cancer can occur in both men and women, but it is more common in women [34].

The role of periostin in breast Cancer:

Breast cancer is characterized by high POSTN expression in cancer epithelial cells when compared with normal tissue. The elevated expression of POSTN has been associated with poor progression free and overall survival [32]. Lambert et al. studied the relationship between the expression of POSTN in cancer stem cells and the prognosis of the patients. Their studies revealed that high POSTN expression in these cells was associated with reduced relapse-free survival in basal-like type but not in breast cancers of the luminal type [31]. In addition to cancer cells, POSTN is also present in cancer-associated fibroblasts (CAFs). In this case, the higher levels of POSTN detected in CAF are associated with the malignancy grade of tumors, suggesting that POSTN secreted by CAFs could be a key element in breast cancer progression [33].

Conclusions:

The POSTN is a multifunctional matricellular protein secreted by tumor cells and CAFs. It is involved in collagen fibrillogenesis and cell adhesion. It binds to integrin receptors ($\alpha\beta3, \alpha\nu\beta5, \alpha6\beta4$) that are present on the surface of tumor cells and

vascular endothelium, which allows regulation of signaling pathways (PI3K-AKT,FAK). Thus, this protein may have an effect on cell proliferation, tumor growth and the formation of new blood and lymphatic vessels, which may be of crucial importance in the mechanism of metastasis and breast cancer progression.

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