Periostin: A Novel Prognostic and Therapeutic Target For Genitourinary Cancer?

Pier Vitale Nuzzo,[1,2] Giulia Buzzatti,[1,2] Francesco Ricci,[1,3] Alessandra Rubagotti,[1,2,3] Francesca Argellati,[1,3] Linda Zinoli,[1,2,3] Francesco Boccardo[1,2,3]

Abstract

Many of the cellular abnormalities present in solid tumors are structural in nature and involve the proteins of the extracellular matrix (ECM). Periostin is a protein produced and secreted by the fibroblasts as a component of the ECM where it is involved in regulating intercellular adhesion. The expression of periostin has an important physiological role during embryogenesis and growth, namely at the level of bone, dental, and cardiac tissues. Many studies indicate that periostin plays an important role for tumor progression in various types of cancer, such as colon, lung, head and neck, breast, ovarian, and prostate. To the best of our knowledge, a limited number of studies have investigated periostin expression in urogenital cancer, such as prostate, bladder, penile, and renal cancer, and no studies were performed in testis cancer. In this review article, we summarize the most recent knowledge of periostin, its genetic and protein structure, and the role of the different isoforms identified and sequenced so far. In particular, we focus our attention on the role of this protein in genitourinary tumors, trying to emphasize the role not only as a possible prognostic marker, but also as a possible target for the development of future anticancer therapies.

Clinical Genitourinary Cancer, Vol. 12, No. 5, 301-11 © 2014 Elsevier Inc. All rights reserved.
Keywords: Biomarker, Extracellular matrix protein, Genitourinary tumors, Isoform, POSTN protein

Introduction

Periostin, originally named as osteoblast-specific factor-2, was first identified in 1993 as a putative cell adhesion protein for pre-osteoblasts in a mouse osteoblastic MC3T3-E1 cell line.[1] This protein was then renamed periostin because of its preferential location in the periosteum and periodontal ligament.[2] Periostin is an extracellular matrix (ECM) protein involved in regulating intercellular adhesion via an interaction with other ECM proteins, such as fibronectin, tenascin-C, collagen V, and periostin itself.[3,4] More recent studies have revealed that periostin is an important regulator of bone and tooth formation and is essential for heart development and healing after acute myocardial infarction.[4-6] Periostin is also reexpressed in adult tissues under stress conditions, for instance in the heart under pressure or volume overload,[7] in the skeletal muscle after injury,[8] in the bone after fracture,[9] in pulmonary aortic smooth muscle cells in response to hypoxia,[10] and in chronic sinusitis.[11]

Periostin protein expression was observed in a wide variety of normal adult and fetal tissues, such as embryonic periosteum, placenta, periodontal ligaments, cardiac valves, adrenal glands, lung, testis, thyroid, stomach, vagina, ovary, colon, prostate, and breast.[1,12]

Recently, it has been reported that periostin is frequently overexpressed in various types of human cancer cell lines in vitro and human cancer tissues in vivo (including breast cancer, colon cancer, non–small-cell lung carcinoma, head and neck cancer, ovarian cancer, pancreatic ductal adenocarcinoma, melanoma, gastric cancer, oral squamous cell carcinoma [SCC], thymoma and neuroblastoma), underlining the putative role of this protein in tumor development.[13]

Although the role of this protein in the process of carcinogenesis remains to be clarified, it is known that its overexpression in cancer stroma and/or the epithelium of the neoplasms is usually associated with the most malignant phenotypes and the poorest outcomes.[13]

Pier Vitale Nuzzo and Giulia Buzzatti should be considered equally as first author.

[1]Academic Unit of Medical Oncology (Medical Oncology B), University of Genoa, School of Medicine, Genoa, Italy
[2]Department of Internal Medicine, University of Genoa, School of Medicine, Genoa, Italy
[3]IRCCS San Martino University Hospital - IST National Cancer Research Institute, Genoa, Italy

Submitted: Dec 6, 2013; Revised: Jan 29, 2014; Accepted: Feb 12, 2014; Epub: Feb 21, 2014

Address for correspondence: Francesco Boccardo, MD, IRCCS San Martino University Hospital—IST National Cancer Research Institute, Academic Unit of Medical Oncology (Medical Oncology B), Largo Rosanna Benzi 10, 16132 Genoa, Italy
Fax: +39010352753; e-mail contact: f.boccardo@unige.it

1558-7673/$ - see frontmatter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clgc.2014.02.005

Indeed, the matrix protein periostin was shown to be a marker and an inducer of epithelial–mesenchymal transition (EMT), a process that is responsible for the dissemination of primary tumor epithelial cells to the sites of metastasis and the dedifferentiation program that leads to increased malignant behavior of tumors.[14,15]

To the best of our knowledge, a limited number of studies have investigated the expression of periostin in urogenital cancers, such as prostate, bladder, penile, and renal cancer, and nobody so far has reported about periostin in testicular cancer. In prostate, renal, and penile cancer, the upregulation of periostin was usually associated with a more aggressive tumor behavior and advanced stage; conversely, in bladder cancer, high-grade urothelial carcinomas appear to be associated with the lowest levels of periostin; moreover, in vitro transfection of urothelial tumor cells with the periostin gene was shown to neutralize their invasive potential.[15]

In cancer, namely in urogenital tumors, the following crucial issues related to the role of periostin and function have not been fully elucidated: (1) whether the production and secretion of periostin occurs in tumor or stromal cells or in both compartments; (2) where periostin is located at the cell level in epithelial and stromal cells; and (3) whether, and should this be the case, under which conditions, periostin functions as a tumor promoter or as a tumor suppressor.

In this review, we will first summarize the current knowledge about the functional roles of periostin; we will then focus on findings related to the current understanding of the specific role of periostin in tumorigenesis, with a special focus on urogenital cancer; finally, current findings supporting the role of periostin as a prognostic marker and a putative target for anticancer therapy will be reviewed.

Literature Review

A systematic literature search was performed using the Medical Subject Headings function on PubMed, from 1993 to October 2013, using the key words, "periostin," "isoform," "neoplasm," "prostate neoplasm," "bladder neoplasm," "renal neoplasm," "testicular neoplasm," and "penile neoplasm." An independent search of the Cochrane electronic databases was also performed to ensure that no additional studies were overlooked. Our search strategy yielded 8 articles concerning prostate cancer (PCa), 4 articles concerning bladder neoplasms, 5 articles concerning renal cancer, and just 1 article relative to penile cancer. As previously mentioned, we were not able to find any article dealing with periostin and testicular cancer. We also identified a further 137 potentially relevant articles related to periostin and neoplasms in general, or relative to other tumor types, or with periostin isoforms. Only the most complete, recent, and updated reports were used if believed to fit in with the scopes of the present literature review.

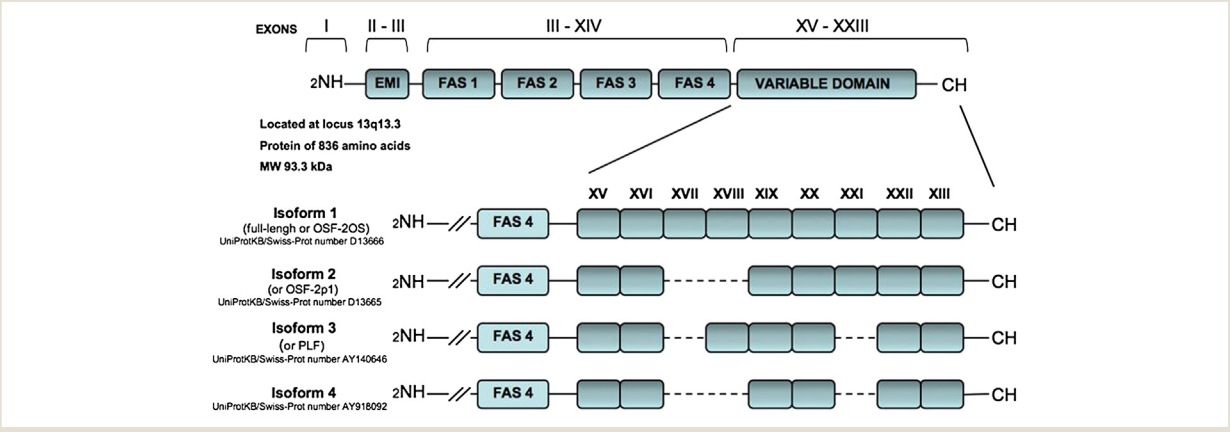
Structure of Periostin

The periostin gene has been cloned in humans and in several animal species (including mouse, rat, chicken, bovine, and xenopus). The gene is located at locus 13q13.3 in humans and 3C in mice.[16] The periostin gene in humans and mice has 23 exons, with a genomic footprint covering approximately 36 and 30 kilobases, respectively. The terminal exons in humans and mice are protein-coding. The length of the mouse periostin cDNA is 3187 base pair (bp), with an 18-bp 5′ untranslated region, a 733-bp 3′ untranslated region, and a 2436-bp open reading frame that encodes a protein of 811 amino acids with a molecular weight (MW) of 90.2 kDa (Fig. 1).[1]

The template of the 3D protein structure of periostin was obtained from the SWISS-MODEL Repository database (Fig. 2).[17,18]

The first 2 isolated human periostin cDNAs were screened from placental and osteosarcoma cDNA libraries using mouse periostin cDNA as a probe. The human placental periostin open reading frame encodes for a protein of 779 amino acids, with a MW of 87.0 kDa; the human osteosarcoma periostin open reading frame encodes for a protein of 836 amino acids with a MW of 93.3 kDa.[1] Periostin is highly conserved between human and mouse, with 89.2%

Figure 1 **Structure of Periostin and Its Isoforms. Periostin Protein Sequence Showing the Signal Sequence, the EMI Domain, the 4 FAS-1 Domains, and the Variable Domain With 9 Different Exons, Whose Combination Gives Rise to 4 Different Isoforms Sequenced and Annoted**



Abbreviations: EMI = EMILIN-like; FAS = fasciclin.