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Matricellular proteins and survival in patients with pancreatic cancer: A systematic review

Sirio Fiorino [a, *], Maria Letizia Bacchi-Reggiani [b], Chiara Birtolo [c], Giorgia Acquaviva [d], Michela Visani [d], Adele Fornelli [e], Michele Masetti [f], Andrea Tura [g], Stefano Sbrignadello [g], Fabio Grizzi [h], Federica Patrinicola [h], Matteo Zanello [f], Laura Mastrangelo [f], Raffaele Lombardi [f], Claudia Benini [f], Luca Di Tommaso [i], Arrigo Bondi [e], Francesco Monetti [j], Elena Siopis [j], Paolo Emilio Orlandi [j], Michele Imbriani [j], Carlo Fabbri [k], Silvia Giovanelli [k], Andrea Domanico [c], Esterita Accogli [c], Salomone Di Saverio [l], Daniela Grifoni [m], Vincenzo Cennamo [k], Paolo Leandri [l], Elio Jovine [f], Dario de Biase [m, **]

[a] Internal Medicine Unit C, Azienda USL-Maggiore Hospital, Largo Nigrisoli 3, Bologna, Italy
[b] Department of Medicine (Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale), Cardiology Unit, Policlinico S. Orsola-Malpighi, University of Bologna, via Massarenti 9, Bologna, Italy
[c] Internal Medicine Unit A, Azienda USL-Maggiore Hospital, Largo Nigrisoli 3, Bologna, Italy
[d] Department of Medicine (Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale), University of Bologna, Azienda USL di Bologna, Largo Nigrisoli 3, Bologna, Italy
[e] Anatomic Pathology Unit, Azienda USL-Maggiore Hospital, Largo Nigrisoli 3, Bologna, Italy
[f] Surgery Unit, Azienda USL-Maggiore Hospital, Largo Nigrisoli 3, Bologna, Italy
[g] CNR Institute of Neuroscience, Via Giuseppe Moruzzi 1, Padova, Italy
[h] Department of Immunology and Inflammation, Humanitas Clinical and Research Center, Via Manzoni 56, Rozzano, Milano, Italy
[i] Department of Pathology, Humanitas Clinical and Research Center, Via Manzoni 56, Rozzano, Milano, Italy
[j] Radiology Unit, Azienda USL-Maggiore Hospital, Largo Nigrisoli 3, Bologna, Italy
[k] Unit of Gastroenterology and Digestive Endoscopy, Azienda USL-Maggiore Hospital, Largo Nigrisoli 3, Bologna, Italy
[l] Surgical Emergency Unit, Azienda USL-Maggiore Hospital, Largo Nigrisoli 3, Bologna, Italy
[m] Department of Pharmacy and Biotechnology, University of Bologna, via San Donato 15, Bologna, Italy

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ABSTRACT

Extracellular matrix (ECM) plays a fundamental role in tissue architecture and homeostasis and modulates cell functions through a complex interaction between cell surface receptors, hormones, several bioeffector molecules, and structural proteins like collagen. These components are secreted into ECM and all together contribute to regulate several cellular activities including differentiation, apoptosis, proliferation, and migration. The so-called “matricellular” proteins (MPs) have recently emerged as important regulators of ECM functions.

The aim of our review is to consider all different types of MPs family assessing the potential relationship between MPs and survival in patients with pancreatic ductal adenocarcinoma (PDAC).

A systematic computer-based search of published articles, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement issued in 2009 was conducted through Ovid interface, and literature review was performed in May 2017. The search text words were identified by means of controlled vocabulary, such as the National Library of Medicine's MESH (Medical Subject Headings) and Keywords.

Collected data showed an important role of MPs in carcinogenesis and in PDAC prognosis even though the underlying mechanisms are still largely unknown and data are not univocal. Therefore, a better understanding of MPs role in regulation of ECM homeostasis and remodeling of specific organ niches

* Corresponding author. U.O.S.D. di Medicina Interna C, Ospedale Maggiore Largo Nigrisoli (Bologna), 40133 Bologna, Italy.
** Corresponding author.
E-mail addresses: sirio.fiorino@ausl.bologna.it (S. Fiorino), dario.debiase@unibo.it (D. de Biase).

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may suggest potential novel extracellular targets for the development of efficacious therapeutic strategies.

Introduction

Pancreatic adenocarcinoma (PDAC) is the most frequent and lethal form of pancreatic cancer accounting for almost 90% of pancreatic tumors [1]. It represents the fourth cause of cancer-related death in the most developed countries [2] with an overall five-years survival rate lower than 5% [3]. However, remarkable differences in PDAC incidence exist among different geographical areas and ethnicities [4]. The aggressive biological behavior, frequent advanced stages at the time of diagnosis, early metastatic dissemination and the lack of effective systemic therapies result in a low survival rates. Understanding the underlying epidemiological, pathogenic and biological factors of PDAC is fundamental for the development of novel therapies. Many studies focused on genetic alterations, molecular events, and the precursor lesions associated with PDAC development and progression [5–7]; however, its prognosis remains unfortunately unchanged [8]. Therefore, additional factors might contribute to the aggressive biological behavior of this neoplasm [9]. Extracellular matrix (ECM) represents a dynamic niche in cancer development [10–13]. It is a complex three-dimensional network with peculiar physical, biochemical, and biomechanical properties that contributes to preserve cellular, tissue and organ homeostasis [14–16]. ECM plays a fundamental role as a regulator factor for cellular differentiation, apoptosis, proliferation and migration [17]. Physiologically, tightly regulated interplay exists between mammalian cells and ECM [18], involving soluble factors, such as cytokines, chemokines, costimulatory molecules, additional biological mediators (oxidants and prostaglandins) [19] and physical stimuli (microenvironment stiffness and tensional/compression forces) [10,20] (Fig. 1). Recent data suggest that ECM alterations promote tumor development and progression by directly inducing cellular transformation and metastasis [21,22]. Furthermore, ECM changes may deregulate behavior of stromal cells determining tumor-associated inflammation and angiogenesis and promoting a pro-neoplastic microenvironment [23]. Among the factors potentially responsible of this process, tissue stiffness modifications seem to be one of the most important [24]. PDAC has a very complex structure, including epithelial, mesenchymal, endothelial and hematopoietic cells embedded in a dense desmoplastic stroma. This framework represents the bulk of the cancer mass [25]. To date, mechanisms involved in the cancer initiation and progression are not completely understood [26]. Chronic inflammation seems to have a considerable impact on carcinogenesis [27] by promoting the deposition of an altered ECM tissue with qualitatively and quantitatively-modified proteins in comparison with those detectable in normal parenchyma [28]. These events lead to modifications on tissues' structure inducing an increasing stiffness [29]. This condition is characterized by a progressive elevation of tensional resistance stresses and compression forces [30] in the intracellular and extracellular compartments causing a perturbation of their homeostasis [31]. Therefore, tissue stiffness is now recognized as a risk factor for cancer development in different organs [32].

ECM consists of structural (collagens, proteoglycans and glycoproteins) and non-structural (matricellular) proteins [12,33]. Matricellular proteins (MPs) are variably secreted into ECM of tissues and promote its remodeling (Figs. 2–4). This process occurs in different stages of embryological development and wound healing after tissue damage [22]. In addition, MPs, even in soluble form, are detectable in neoplastic stroma in a higher amount compared to normal tissue; MPs may bind serum growth factors and cellular receptors inducing modification of cellular functions [34–36], such as proliferation, differentiation, apoptosis, survival, stromal adhesion and ability to migrate [13,37]. MPs levels detected in serum and/or tissues have been recently associated with the survival rate of patients with different cancers [38–43]. However, no definitive conclusions have been obtained concerning the prognostic value of MPs family components in patients with PDAC and more detailed evaluations are needed. Only few reports [44,45] have been published to assess the correlation between the expression of MPs, included in the Secreted Protein Acidic and Rich in Cysteine (SPARC) family, and the outcome of patients with PDAC. We performed a systematic review and considered all members of MPs family according to the review by Joanne Murphy-Ullrich [46]. A list of these proteins is shown in Supplementary Tables 1–3 and includes the following members: Autotaxin, CCN1, CCN2/CTFG and CCN3 (where CCN indicates the first elements of a Cystein-rich Protein Family: Cysteine-rich 61 or CCN1, Connective Tissue Growth Factor or CCN2/CTFG and NOV or nephroblastoma overexpressed/CCN3) [47], Fibulin-5, Osteopontin, Periostin, Pigment Epithelium Derived Factor (PEDF), Plasminogen Activator Inhibitor Factor-1 (PAIF-1), R-Spondin, SPARCs, Small Leucine Rich Proteoglicans (SLRP), Tenascin-C, Tenascin-R, Tenascin-X, Tenascin-W, Thrombospondin-1, Thrombospondin-2, Thrombospondin-4, Thrombospondin-5.

Materials and methods

Search strategy and selection of studies

A systematic computer-based search of published articles, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement, issued in 2009 [48], was conducted through Ovid interface, to identify relevant studies on the association between serum/tissue MPs and survival in patients with PDAC. The literature review was performed in May 2017. The following electronic databases were used: MEDLINE (1950 to April 2017) and the Cochrane Library (until the first quarter of 2017) for all relevant articles. A professional librarian provided a support in the search strategy and in the search terms, which were identified by means of a controlled vocabulary like the National Library of Medicine's MESH (Medical Subject Headings) and Keywords. The used MESH terms and keywords were: “pancreatic cancer” OR “pancreatic tumor” OR “pancreatic malignancy” OR “pancreatic neoplasm” OR “pancreatic carcinoma” OR “pancreatic adenocarcinoma” AND “Autotaxin” OR “CCN1, CCN2/CTFG, CCN3” OR “Fibulin-5” OR “Galectin-1” OR “Galectin-2” OR “Galectin-3” OR “Osteopontin” OR “PAIF-1” OR “Periostin” OR “PEDF” OR “R-Spondin” OR “SLRP” OR “SPARCs” OR “Tenascin-C” OR “Tenascin-R” OR “Tenascin-X” OR “Tenascin-W” OR “Thrombospondin-1” OR “Thrombospondin-2” OR “Thrombospondin-4” OR “Thrombospondin-5” AND “survival” OR “prognosis” OR “outcome”. The inclusion criteria for our analysis were:

1) Studies considering data from all published case-series, case-control-, hospital-based-, population-based case-control and