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Activity and Functions of Tumor-associated Macrophages in Prostate Carcinogenesis

Matteo Santoni [a,*], *Liang Cheng* [b], *Alessandro Conti* [c], *Cinzia Mariani* [a], *Antonio Lopez-Beltran* [d], *Rodolfo Montironi* [e], *Nicola Battelli* [a]

[a] *Oncology Unit, Macerata Hospital, Macerata, Italy;* [b] *Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA;* [c] *Azienda Ospedaliera dell'Alto Adige, Bressanone/Brissen Hospital, Bressanone/Brissen, Italy;* [d] *Department of Surgery, Cordoba University Medical School, Cordoba, Spain;* [e] *Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy*

Article info

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Abstract

Context: Tumor-associated macrophages (TAMs) constitute a heterogenous population and are highly represented in prostate cancer (PCa) primary tumor and metastases. Under various stimuli, macrophages can polarize into antitumoral M1 or protumoral M2 phenotypes.

Objective: In this review, we will focus on the activity and functions of TAMs and associated molecules in PCa carcinogenesis, thus underling their potential as therapeutic targets in these patients.

Evidence acquisition: To identify relevant studies, we performed a review of citations from PubMed from January 1966 to August 2017. The search was conducted by combining the words "macrophages" or "inflammation" to "prostate cancer." Data from ongoing trials were reported from clinicaltrials.gov.

Evidence synthesis: TAMs and related molecules are implicated in PCa cell growth, survival, and migration. Furthermore, they are involved in PCa angiogenesis and in the development of bone metastases. Moreover, TAMs can regulate the expression of programmed cell death-1 and its ligand programmed death-ligand 1, thus representing an ideal candidate for targeted approaches in PCa patients. Based on these evidences, several TAM-centered strategies have been proposed and are in the course of investigation in PCa patients. These approaches include TAM *re-education* from M2 to M1 phenotype, the depletion of their number, and their use as vehicles for gene therapy.

Conclusions: The pivotal role exerted by TAMs in PCa carcinogenesis and progression will open the way to the design of TAM-centered therapeutic approaches in these patients. This will represent a crucial step forward in increasing the efficacy of immunotherapy in patients with PCa.

* Corresponding author. Oncology Unit, Macerata Hospital, via Santa Lucia 2, 62100, Macerata, Italy. Tel. +3907332571; Fax: +3907332573783.
E-mail address: mattymo@alice.it (M. Santoni).

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1. Introduction

Prostate cancer (PCa) is a leading cause of cancer-related death worldwide, with 180 890 new cases and 26 120 deaths in the USA in 2016 [1]. Several risk factors for the onset of PCa have been identified, with age, race, and positive family history firmly established as key factors associated with an increased risk of this disease [2]. However, the variety of potential risk factors [2] and their heterogeneous impact on the different stages of PCa reflect the complexity of prostate carcinogenesis, a multifactorial and multistep process that underlies a wide spectrum of protumor modifications in PCa microenvironment [3–5]. These changes include: (1) wide simultaneous genomic rearrangements resulting into double-strand DNA breaks, a phenomenon named "chromoplexy" [6], (2) the de novo monoclonal seeding of daughter metastases and the transfer of distinct tumor clones among different metastatic sites [7], (3) metabolic alterations in tumor cells, including the Warburg effect and the increased protein, DNA, and de novo fatty acid synthesis [8,9], (4) the transdifferentiation from an epithelial-like to a neuroendocrine-like phenotype, which promotes tumor cell proliferation and invasion [10], (5) the creation of a proinflammatory enviroment, which supports PCa carcinogenesis and progression [11]. Understanding the leading mechanisms underlying PCa carcinogenesis in a single patient will represent a fundamental step in the route to personalized diagnosis and therapy in PCa patients [12].

Inflammation is fundamental in PCa carcinogenesis, being implicated in tumor growth, angiogenesis, metastatic spread, and progression to castration-resistant prostate cancer (CRPC) [12–14]. Tumor-associated macrophages (TAMs), a major leukocyte population originating from circulating blood monocytes, are highly represented in PCa primary tumor and metastases (Fig. 1). In response to various stimuli, prostate macrophages polarize into classically activated antitumor M1, which produce high levels of inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, and alternatively activated tumor-promoting M2 subtypes, which produce anti-inflammatory cytokines such as IL-10 [15] (Fig. 2). M1 and M2 phenotypes constitute the extremes of a wide polarization spectrum characterized by differences in the expression of receptors, cytokines, and chemokines and in their effector functions [15]. In human cancer, macrophages have been identified by using antibodies directed against CD68, while CD163 is highly expressed by M2 subpopulation [16,17] (Fig. 1).

In this review, we will focus on the activity and functions of TAMs and associated molecules in PCa carcinogenesis, thus underling their potential as therapeutic targets in these patients.

2. Inflammation in PCa pathogenesis and progression

In 1975, Brosman and his colleagues [18] first investigated the presence of immunologic alterations in patients with PCa. They observed that monocyte chemotactic response as well as the ability to develop a delayed cutaneous hypersensitivity response was reduced in PCa patients compared with healthy controls, and this alteration was directly correlated the tumor stage [18].

Successively, the contribution of inflammation in PCa development and progression has been extensively clarified. Inflammation of periprostatic white adipose tissue has been recently associated with high Gleason grade [19]. Acute and chronic inflammation has been correlated with the accumulation of immune cells in the prostatic tissue, mainly $CD8^+$ T

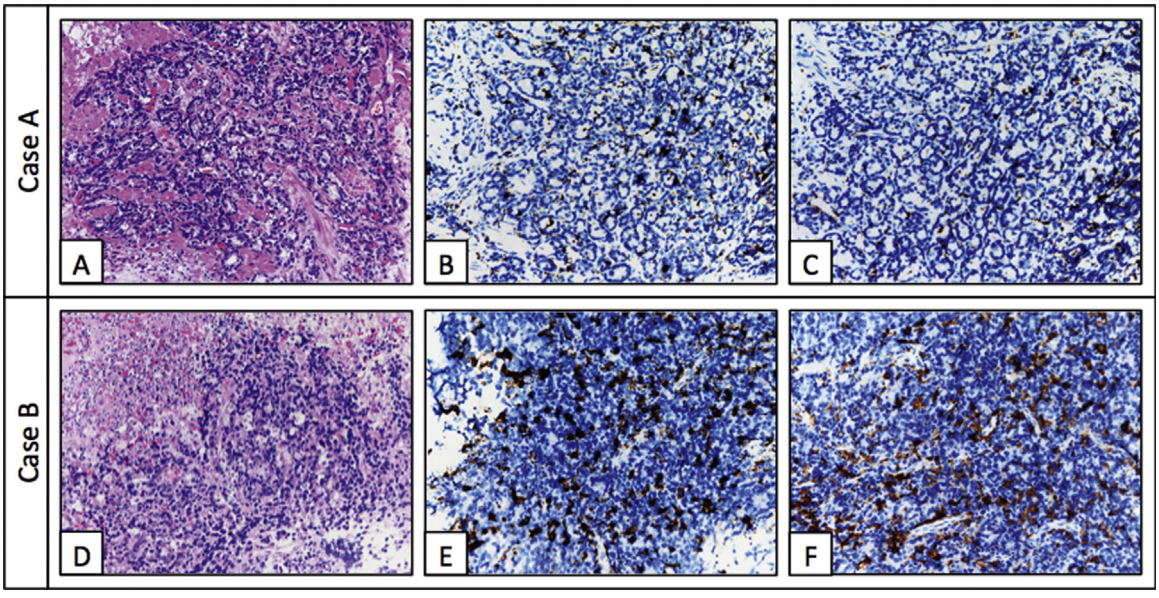

Fig. 1 – Presence of macrophages in prostate cancer samples as demostranted by positivity to macrophage markers CD68 and CD163. (A–C) Case A: (A) high-grade prostate cancer, (B) CD68 positivity, and (C) CD163 positivity. (D–F) Case B: (D) castration-resistant prostate cancer, (E) CD68 positivity, and (F) CD163 positivity.

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