Journal of Molecular and Genetic Medicine

Ziani et al., J Mol Genet Med 2015, 9:4
DOI: 10.4172/1747-0862.1000193

Opinion Open Access

Cancer-associated Fibroblasts and Modulation of the Antitumor Immune Response

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Received date: December 12, 2015; **Accepted date:** December 20, 2015; **Published date:** December 27, 2015

Description

During tumor progression, tumor cells proliferate under adverse host conditions and use several survival strategies to block the action of key regulators of the immune response and circumvent anti-tumor defenses. Consequently, the current development of new immunotherapeutic strategies aimed at inducing or optimizing the immune response directed against the tumor and opened the way to new treatments of cancers. Besides the several known classical strategies used by tumor cells to escape to immune surveillance, it should be noted that the evasion of immunosurveillance by tumor cells is also under the control of the tumor microenvironment complexity and plasticity [1,2].

Among the stromal cells, activated fibroblasts, termed cancer-associated fibroblasts (CAFs), play a critical role in the complex process of tumor-stroma interaction. CAFs, one of the prominent stromal cell population in most types of human carcinomas, are α-SMA (alpha-smooth muscle actin) positive, spindle-shaped cells, who closely resemble normal myofibroblasts but express specific markers (ie, FAP (fibroblast-associated protein), PDGFR-β (platelet-derived growth factor)) together with the fibroblastic marker FSP-1 (fibroblast specific protein 1) and vimentin (a mesenchymal marker). CAFs are also characterized by the absence of epithelial (cytokeratin, E-cadherin), endothelial (CD31) and fully differentiated smooth muscle (smoothelin) markers [3]. CAFs differentiate and proliferate in the tumor microenvironment in a transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF)-dependent manner from other cell types such as resident fibroblasts, mesenchymal stem cells, endothelial and epithelial cells [4,5]. In the tumor stroma, CAFs interact with tumor cells and secrete several factors such as extracellular matrix proteins (ie, collagen), matrix metallo-proteinases (MMPs), proteoglycans (ie, laminin, fibronectin), chemokines (ie, CXCL1, CXCL2, CXCL8, CXCL6, CXCL12/SDF1, CCL2 and CCL5), vascularisation promoting factors (ie, PDGF and VEGF) and other proteins which affect tumor cells proliferation, invasiveness, survival and stemness (ie, TGF-β, EGF, HGF, FGF, PGE2) [5]. Consequently, CAFs have been involved in tumor growth, angiogenesis, cancer stemness, extracellular matrix (ECM) remodelling, tissue invasion, metastasis and even chemoresistance [6,7].

During the past few years, these activated tumor-associated fibroblasts have also been involved in the modulation of the anti-tumor immune response by the secretion of immunosuppressive and pro-inflammatory factors (ie, TGF-β, IL-1β, IL6, IL10…), chemokines (ie, CXCL12, CCL2…) and chemical mediators (ie, PGE2…) in the tumor microenvironment. As such, CAFs can potentially affect both innate and adaptive antitumor immune response [8,9]. For example, the secretion of CXCL12/SDF1 and CCL2/MCP-1 by CAFs is potentially involved in macrophages attraction in the tumor microenvironment and in their differentiation into a M2 immunosuppressive phenotype [10]. CAF secretion of chemokines can also recruit immunosuppressive myeloid-derived suppressive cells (MDSC) population to the tumor [11]. The secretion of TGF-β by CAFs potentially affects dendritic cells biology by inhibiting their migration, maturation and antigen presentation capabilities, increases the numbers of regulatory T cells (Tregs) within the tumor microenvironment through the induction of FOXP3 expression [12] and interferes with cytotoxic T lymphocytes (CTL) function and frequency within the tumor [13]. The secretion of TGF-β by CAFs can also attenuate IFN-γ production by natural killer (NK) cells [14], as well as the expression of NK-activating receptors including NKG2D, NKp30 and NKp44 [12]. Similarly, the secretion of vascular endothelial growth factor (VEGF) by CAFs may affect dendritic function and increase the infiltration of Tregs and MDSC within the tumor [15]. Moreover, the secretion of prostaglandin E2 (PGE2) can decrease the expression of the activator receptor NKG2D on NK cells surface (which is also the case for indoleamine-2,3-dioxygenase (IDO) secretion by CAFs) [16] and induces FOXP3 expression in Tregs [17]. Nevertheless, further studies are clearly needed to fully elucidate the complex role of CAFs in the complex tumor immunosuppressive network.

Altogether, these findings highlight the action of CAFs on various levels of the antitumor immune response within the tumor microenvironment. Thus, combination therapy co-targeting CAFs and tumor cells or other immune check points (ie, PDL1, CTLA4) should represent a significant benefit in terms of tumor immunotherapy.

Acknowledgement

The authors are supported by the "Ligue Nationale contre le Cancer" (LNCC-Equipe Labélissée), the "Association pour la Recherche contre le Cancer" (ARC) and INSERM. L.Z. is supported by a PhD training fellowship from the "Ligue Nationale contre le Cancer" (LNCC).

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