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Review Article

Mast Cells as a Potential Prognostic Marker in Prostate Cancer

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Despite years of intensive investigation that has been made in understanding prostate cancer, it remains one of the major men's health issues and the leading cause of death worldwide. It is now ascertained that prostate cancer emerges from multiple spontaneous and/or inherited alterations that induce changes in expression patterns of genes and proteins that function in complex networks controlling critical cellular events. It is now accepted that several innate and adaptive immune cells, including T- and B-lymphocytes, macrophages, natural killer cells, dendritic cells, neutrophils, eosinophils, and mast cells (MCs), infiltrate the prostate cancer. All of these cells are irregularly scattered within the tumor and loaded with an assorted array of cytokines, chemokines, and inflammatory and cytotoxic mediators. This complex framework reflects the diversity in tumor biology and tumor-host interactions. MCs are well-established effector cells in Immunoglobulin-E (Ig-E) associated immune responses and potent effector cells of the innate immune system; however, their clinical significance in prostate cancer is still debated. Here, these controversies are summarized, focusing on the implications of these findings in understanding the roles of MCs in primary prostate cancer.

1. Introduction

Human carcinogenesis is a dynamical process that depends on a high number of variables and its regulation can be presented through multiple *spatial* and *temporal* scales [1–4]. Despite the advances in our genomic and cellular knowledge [5], prostate cancer remains one of the major public health problems throughout the world [6, 7]. It is important that it is recently gaining recognition being highly heterogeneous and therefore encompassing a wide range of clinical behaviors. It is evident that prostate cancer is underpinned by a complex array of gene alterations that affect molecular, cellular, and supracellular processes [5, 8–10]. It is also ascertained that solid tumors, including prostate cancer, are commonly infiltrated by a high number of innate and adaptive immune cells [11–16]. All of them are variably scattered within the tumor and loaded with an assorted array of cytokines, chemokines, and inflammatory and cytotoxic mediators [17–19]. This complex network reflects the diversity in tumor biology and tumor-host interactions. It has been recognized that inflammation plays a role in the development and progression of solid tumors although it still remains unclear whether aggressive disease caused increased inflammation or inflammation caused aggressive disease [20, 21]. Prostate cancer is infiltrated by T- and B-lymphocytes, macrophages, natural killer cells, dendritic cells (DCs), neutrophils, eosinophils, and mast cells (MCs) [22]. MCs (MCs) are recognized as important effectors in Immunoglobulin-E (Ig-E) associated immune responses, and potent effector cells of the innate immune system [23–25]. While in allergies or parasitic infections the role of MCs has been recognized for years, in cancer remain conflicting data showing a supporting or an inhibitory role [26–31]. In some tumor settings MCs have a protective role, exerted by their proinflammatory mediators [32], while in other tumors MCs may directly influence the advancement of the cancer cells [33] by stimulating the neovascularity,

tissue remodeling, and modulation of the host immune response. In prostate cancer no conclusive data on MCs function are available and the complex roles of these cells remain poorly understood [29]. Here, these controversies are summarized, focusing on the implications of these findings in understanding the role of MCs in primary prostate cancer.

2. Prostate Cancer: A Complex Dynamical Disease

Prostate cancer is a complex disease. Cancer progression involves both genetic and behavioral changes in cancer cells and these changes are in part driven by the surrounding microenvironment. Prostate cancer represents one of the most common public health problems throughout the world and prevalent cancer in aged men [34]. In developed countries, it is the second most frequently diagnosed cancer, and the third most common cause of cancer-related death in male population [6]. The main risk factors are age, ethnic origin, and a positive family history [35–37]. Higher incidences of prostate cancer occur in men from North America, Oceania, and Western countries, whereas men from Asia and North Africa have a much lower incidence rate [35]. Prostate cancer is usually diagnosed as local or advanced disease, and treatments range from "watchful waiting," active surveillance to radical treatment (i.e., radical prostatectomy or radiotherapy) or androgen deprivation [38–43].

Prostate cancer clinical phenotypes range from indolent or clinically insignificant to locally aggressive or metastatic. A large number of gene expression profiling studies have been carried out in an attempt to establish a "molecular staging system," but the identification of genetic markers that predict aggressive disease has not yet been clinically demonstrated [39, 44]. Molecular associations with prostate cancer phenotypes continue to be fragmentary and, in some cases, have been poorly substantiated by follow-up investigations [5, 10]. Apart from age and ethnic origin, a positive family history is now considered the strongest known risk factor [45, 46]. High-risk families, in which multiple men are affected likely, reflect the contributions of several genes some that are rare and highly penetrant, while others are more common and weakly penetrant [47]. It is now recognized that association of candidate genetic markers with this multifactorial malignancy is more difficult than the identification of susceptibility genes for other cancers including breast, ovary, and colorectal cancers. A number of reasons may explain such a difficulty: (a) prostate cancer has been frequently diagnosed at a late age, thus often making it impossible to obtain DNA samples from living affected men for more than one generation; (b) the presence within high-risk pedigrees of phenocopies, associated with the lack of distinguishing features between hereditary and sporadic forms; and (c) the genetic heterogeneity of this complex disease along with the accompanying difficulty of developing appropriate statistical transmission models taking into account simultaneously multiple susceptibility genes, frequently showing moderate or low penetrance [45]. The observed trends in mortality from prostate cancer remain less clear cut [48, 49]. In the prostate-specific antigen (PSA) era, the active surveillance remains a powerful solution to the problem of overdiagnosis and treatment associated with screening for prostate cancer [40]. The disparity between reported incidence and mortality rates leads to the conclusion that only a small number of diagnosed low-risk prostate cancers will progress to life-threatening disease during the lifetime of the patient. Hussain et al. [50] reported that the decrease in prostate cancer mortality was greater amongst men aged 55–74 years than in those aged ≥75 years. Early treatment of prostate cancer has benefited from important advances in surgical and radiotherapeutic strategies, with, as principal aim, the combination of a better survival and the reduction of the potential adverse effects that alter quality of life. A better definition of the characteristics of the tumors in terms of progression regarding various parameters, that is, clinical stage, PSA serum value, tumor differentiation, has resulted, despite the heterogeneity of the disease, in the determination of subgroups of tumors with different prognosis, which would lead to an improved therapeutic strategy. Recently, Thalgott et al. [51] explored circulating tumor cell (CTCs) counts in different stages of prostate cancer in association with tumor burden, metastatic pattern, and conventional serum biomarkers. They found that CTCs counts are applicable as a prognostic molecular marker, especially in metastatic castration resistant patients harboring bone metastases with or without visceral metastases. It is indubitable that although prostate cancer patients have a higher risk for dying from various causes other than prostate cancer, including external causes and heart failure [52], the real risk of the single patient remains still unidentifiable. This is mainly because prostate cancer is the unique solid cancer whose diagnosis is not provided and fully identifiable by imaging techniques [53], but only "suspected" due to changes in PSA serum values prior to biopsy. Historically used biomarkers such as prostatic acid phosphatase (PAP), PSA, and its precursor have, however, not stood to the challenge of sensitivity and specificity [54]. At present, there is a need to re-evaluate the approach to diagnose and monitor prostate cancer. For this reason, it is compulsory to investigate new aspects of the complex process underlying the prostate cancer and search new predictive and prognostic biomarkers.

3. Mast Cells: A Heterogeneous Cell Population

Histopathological examination reveals that likely other than solid tumors, prostate cancer is associated with diverse immune cell infiltrates and that in the cancer context, epithelial cells (i.e., resident cells) coexist with extracellular matrix components and nonneoplastic cell types, including fibroblasts, myofibroblasts, endothelial cells, autonomic nerve fibers, and associated ganglia, which collectively form the tumor stroma [55–57]. Several lines of evidence support the concept that tumor stromal cells are not merely a scaffold, but they rather influence growth, survival, and invasiveness of cancer cells, dynamically contributing to the tumor microenvironment, together with various innate and

adaptive immune cells [55, 58]. Among the innate immune cells, MCs infiltration has been often observed around human tumors [59].

MCs (MCs) have a rather unique position among cells of the immune response. They are potent effector cells of the innate immune system, and they have both beneficial and detrimental functions for the host [25]. They are also implicated in proinflammatory responses to allergens but can also contribute to protection against pathogens. Paul Ehrlich first described MCs in his doctoral thesis in 1878. He called them "mastzellen" (maestung—a root of the English word mastication; the active form "measten" is still in use) because of their metachromatic staining of proteoglycan, rounded nucleus, and protease-rich cytoplasmic granules [60, 61]. Ehrlich noted the tendency of MCs to be associated with blood vessels, nerves, and glandular ducts. Human MCs derive from circulating $CD34^+$, KIT^+ progenitor cells distinct from the basophil and monocyte lineages [25, 62]. The MC progenitors leave the bone marrow at an immature stage, enter the circulation as agranular mononuclear leukocytes, and are recruited into peripheral tissues by chemokines secreted by tissue stromal cells [62]. In tissues, several growth factors and cytokines present in the local microenvironment promote the terminal differentiation of MC progenitors into mature MCs, which are characterized by a high content of cytoplasmic secretory granules filled with various neutral proteases [61–64]. Early immunohistochemical studies of human tissues using specific antibodies raised against the proteases tryptase and chymase provided the first evidence for the existence of three MCs phenotypes: MC_{TC} cells contain tryptase, chymase, carboxypeptidase, and a cathepsin G-like proteinase, MC_T cells contain only tryptase, and MC_C cells contain chymase and carboxypeptidase, but not tryptase [61, 65–68]. They all contain histamine. It is known that histamine can produce powerful physiologic effects and its actions are mediated through specific receptors located on target cells labeled as H1, H2, H3, and H4 receptors. H1 actions include increased vascular permeability, bronchial and intestinal smooth muscle contraction, increased nasal mucus production, increased heart bit rate and cardiac output, and flushing and T-cell neutrophil and eosinophil mediated chemotaxis [69]. H2-mediated actions include increased gastric acid secretion, airway mucus production, and also inhibition of neutrophil and eosinophil influx into a tissue [70]. H3 receptors have been found in the brain and H4 receptors can act as chemoattractants for bone marrow derived MCs and modulation of calcium influx [71]. MCs-derived mediators are of three basic types and include (a) preformed mediators stored in secretory granules, which can be released into the extracellular environment within seconds after MC activation, (b) newly synthesized lipid mediators, and (c) cytokines and chemokines. Interestingly, Stoyanov et al. [72] reported that the proliferation rate of the human alveolar basal adenocarcinoma A549/LLC cell line was markedly increased by MCs and histamine. Histamine proliferating activity was mediated through H1, H2, and H4 receptors and caused the extracellular signal-regulated kinase phosphorylation [72]. In 2007, Ramos-Jiménez et al. [73] reported that androgen-independent prostate cancer cells DU-145 express a number of G protein-coupled receptors, including histamine H1 receptors. Tumor necrosis factor-alpha (TNF-α) was the first cytokine clearly associated with normal MCs in 1990 [74]. Other MC products include interleukins (IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-18, IL-2), chemokines (macrophage inflammatory protein alpha, MIP-1), hematopoietic factors (granulocyte macrophage colony stimulating factor, GM-CSF), stem cell factor (SCF), growth factors (transforming growth factor beta, (TGF-β), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), several metalloproteinases, chondroitin sulfates, cathepsin, and peroxidase. These products may be released when MCs are activated via IgE- or IgG-dependent mechanisms and may also be produced under other circumstances such as in response to stimulation by bacterial products through Toll-like receptors (TLRs) [75]. It is known that MC_T expressed IL-5 and IL-6 and are commonly found in connective tissues, skin, and peritoneal cavity, while MC_{TC} expressed IL-4 and usually are found in mucosa of the gut and lung [76]. Hauswirth et al. reported that the ectonucleotide pyrophosphatase/phosphodiesterases 3 ectoenzyme (E-NPP3 = CD203c) is an activation-linked cell surface antigen that is expressed on blood basophils and their progenitors and less abundantly on normal MCs [77]. CD203c is, however, found constitutively overexpressed on neoplastic MCs in patients with systemic mastocytosis, a neoplastic disease of MCs and their progenitors [77]. Additionally, CD203c is upregulated on MCs upon crosslinking of IgE receptors [77–79].

The growth of MCs is mainly influenced by stem cell factor (SCF), which is produced by stromal cells, endothelial cells, and fibroblasts [80]. SCF participates in each stage of growth and differentiation of MCs including differentiation, proliferation, chemotaxis, adhesion, and survival [81]. It has been suggested that this global influence of SCF results in the ubiquitous presence of MCs [82]. There are numerous growth and differentiation factors other than SCF, which have been shown to affect MC functions including several of the type 2 helper T cell cytokines [83]. It is likely that the two main human MCs subsets (i.e., MC_T and MC_C) can interconvert, depending on the local environment, as has been demonstrated in experimental models.

It has been recognized for long time that MCs elicit allergic symptoms, but it is now widely accepted that they are multifunctional effector cells of the innate and adaptive immune system [24, 27, 84–86]. MCs have been found to modulate adaptive type 2 immunity in different ways [87]. Several *in vitro* experiments have demonstrated that the expression of MHC class II and costimulatory molecules can be induced on mouse and human MCs but that there is no evidence that MCs have a crucial role as antigen-presenting cells (APCs) for the activation of $CD4^+$ T-lymphocytes *in vivo*. However, MCs might induce the recruitment of migrating DCs and modify the quality of those DCs to induce T_H2 cell differentiation. MCs and IgE have long been associated with the pathogenesis of the acute manifestations of the immediate hypersensitivity reaction, the pathophysiologic hallmark of allergic rhinitis, allergic asthma, and anaphylaxis [23, 88, 89]. The central role of MCs in these disorders is now widely

accepted [90]. Additionally, MCs are considered to be critical effectors in many human inflammatory diseases [91, 92], and the core of different diseases including liver hepatitis [93], rheumatoid arthritis [94], arteriosclerosis [95], chronic graft-versus-host disease [96], and ischemic heart disease [97]. It has been shown that any alteration in cell programs that determines a requirement for MC degranulation may have a considerable impact on disease severity. It should be underlined that MCs are found in almost all of the major organs of the human body, and in a large number of sites that come into contact with the external environment, including the skin, respiratory system, and digestive tract [98]. These main accumulations in sites where foreign material attempts host invasion suggest that MCs are one of the first cell populations to initiate defense mechanisms [98]. A local or systemic increase in the number of MCs has been, however, detected in various neoplastic diseases [99–102].

4. Mast Cells and the Prostate Cancer

It has been shown that reactive stroma initiates during early prostate cancer development and is associated with prostate cancer progression [103, 104]. The cancer microenvironment includes fibroblasts and myofibroblasts, extracellular matrix, and preexistent and newly forming vessels, as well as innate and adaptive immune cells. While we are able to produce a sketchy picture of the function of lymphoid cells or macrophages, understanding other participants is scarce or lacking. One of such forgotten cells of cancer-stromal interaction is the MC. This cell was recognized to infiltrate the interface between developing tumors and healthy issues as early as 1891 by Westphal using early metachromatic staining techniques on primary tumors [105]. He recognized that MCs aggregated in the tissue adjacent to cancer cells rather than in the tumor itself. Potential MC effects on tumor growth can be categorized as direct effects on tumor cells, such as MC-mediated cytotoxicity, or indirect effects such as MC-directed angiogenesis, tissue remodeling of the neighboring environment, and immune cell recruitment. Data on MC function in developing tumors largely resulted from experimental models of cancer [106, 107], with complementary, correlative studies in human patients [108]. As such, it is important to note that important differences exist between human and mouse MC subsets. In mice, MCs are broadly distinguished as the short-lived mucosal or long-lived connective tissue subtypes based on (a) their location, (b) their complement of proteases, and (c) their growth factor requirements.

MCs are recognized as an early and persistent infiltrating cell type in many human cancers, often entering before significant tumor growth and angiogenesis have occurred. It has been shown that they accumulate in and around adenomatous polyps [109] and skin epithelial dysplasia prior to tumor development and they have been observed around many aggressive human tumors, particularly malignant melanoma [110], breast carcinoma [111], gynecological malignancies [112], and colorectal carcinoma [113–115].

In prostate cancer, MCs have been only recently indicated as potential independent prognostic marker and MC targeting associated with castration suggested as a potential therapy [116]. Johansson et al. explore the role of MCs in relation to clinicopathological variables in men and during the formation of castrate-resistant tumors and identified for the first time that MCs are an independent prognostic variable [116]. Remarkably, MC function was related to the local tumor microenvironment (i.e., peritumoral and intratumoral MCs are differently related to prognosis). This could explain the contradictory findings regarding MC function in prostate cancer by different researchers [117, 118]. Nonomura et al. evaluated MC infiltration in 104 patients with prostate cancer who underwent needle biopsy of the prostate [117]. The MC count was higher around cancer foci in patients with the higher Gleason scores than in those with the lower Gleason scores. Additionally, the MC number correlated with the clinical stage ($P < 0.001$). PSA-free survival of patients with higher MC counts was better than that in patients with lower MC counts ($P < 0.001$). Multivariate analysis revealed that MC count was a significant prognostic factor ($P < 0.005$). Nonomura et al. concluded that the number of MCs infiltrating around cancer foci in prostate biopsy specimens is a valid prognostic factor of prostate cancer. Sari et al. investigated 27 specimens of prostate cancer histochemically stained with the toluidine blue and graded using the Gleason grading system [119]. The difference within and around the tissue was significant ($P < 0.001$) and there was a close negative correlation between the mean MC count within the tumor and Gleason grade ($r = -0.56$, $P = 0.002$) but not between the mean MC count around the tumor tissue and Gleason grade ($r = -0.18$, $P = 0.35$). The present results suggest that some MCs aggregate around prostatic carcinoma tissue, differing from previous results [120] in that there was a significant difference ($P < 0.001$) in the number of MCs within and around the tumor. There was also a negative correlation between Gleason grade and the MC count within the tumor tissue. The significance of the decrease in MCs in the tumor in advanced stages of disease has been explained by the degranulation of MCs as the tumor grows; MC degranulation is a common feature in later stages of tumor proliferation [121]. Recently, similar natural killer and MC infiltration was also seen in preinvasive cancerous epithelial structures [122]. Fleischmann et al. investigated the prognostic significance of MC in a prostate cancer tissue microarray of more than 2300 patients undergoing radical prostatectomy [118]. They found a strong association of high MC counts with low Gleason scores, early tumor stage, and low risk for PSA recurrence. Aydin et al. investigated the utility of MCs in evaluating benign and malignant prostate lesions, and ascertained variations in the numbers of MCs with the Gleason grade [123]. The study group consisted of 57 benign prostatic hyperplasia (BPH) patients and 47 prostate cancer patients. MCs were more frequently observed in the fibromuscular area than in the adenomatous area in BPH cases. The intratumoral mean MC density was 5.46 ± 5.11 in BPH cases. In the prostate cancer group, the intratumoral mean MC number was 0.34 ± 0.57 within the tumor and 4.88 ± 3.78 in the periphery of the tumor. The intratumoral

mean MC density of the intratumoral region was statistically significantly lower than in the peritumoral region ($P = 0.0001$). The difference between BPH and the intratumoral region was also found significant ($P = 0.0001$). However, there was no statistically significant difference between BPH and the peritumoral region ($P = 0.762$). Twenty-five (53.19%) of the prostate cancer investigated were Gleason 7, while 22 (46.80%) were Gleason <7 tumors. There was no statistical difference between Gleason score groups ($P = 0.452$), and there was no interaction between the score groups and the intraperitumoral regions ($P = 0.355$) [123]. Although the protective mechanism of MCs to counteract tumor growth remains unclear in human tumors [119], it has recently been suggested [119, 124] that the MCs aggregation around prostate cancer is a protective mechanism against the tumor. Nevertheless, previous studies on prostatic biopsies associated high MC densities with favorable tumor characteristics and good prognosis [119]. A likely explanation for these discrepant findings may come from the observation that prostate cancer is a multifocal disease; each prostate tumor is, in fact, usually characterized by multiple neoplastic foci with heterogeneous characteristics.

Inflammation is associated with the development of carcinoma, and, therefore, it is imperative to identify and study the causes of prostatitis to improve our understanding of this disease and its role in prostate cancer. Using the aromatase overexpressing (AROM+) transgenic mouse, which provides a novel model to examine the effect of altered aromatase activity, Ellem et al. [125] found that MCs were significantly increased at puberty and preceded chronic inflammation, which emerged by 40 weeks of age and was characterized by increased MCs, macrophages, neutrophils, and T lymphocytes. The expression of key inflammatory mediators, however, was also significantly altered, and premalignant prostatic intraepithelial neoplasia lesions emerged by 52 weeks of age. Taken together, these data link estrogens to prostatitis and premalignancy in the prostate, further implicating a role for estrogen in prostate cancer [125]. The role of MCs in the pathogenesis of BPH was also investigated by Papadoukakis et al. who evaluated MCs number and distribution in adult Wistar rats (100 days old) treated with citral transdermally for 1 month [126]. Transdermal citral application resulted in a significant increase of MC numbers in the stroma of the rat ventral prostate. Furthermore, these MCs were larger, contained a significant number of intracytoplasmic granules, and degranulated. This finding confirms a role for MCs in the pathogenesis of BPH.

Recently, Pittoni et al. analyzed the role of MCs in transgenic mouse prostate tumors and showed that MCs exert different functions according to the tumor subtype [127]. They confirm that MCs are essential players in the initial stages of prostate cancer progression, by supplying matrix metalloprotease 9 (MMP-9) in the microenvironment but become dispensable at post-epithelial-to-mesenchymal transition stages. Furthermore, they provided the first evidence that MC inactivation may end up with the paradoxical occurrence of fatal neuroendocrine tumor variants, an observation that must be taken into account before proposing future MC-targeted antitumor therapies.

5. Conclusions

MCs are granulocytic immune cells best known for their role in allergy and anaphylaxis, with important functions in innate immunity against bacteria, viruses, and parasites. Since their first description in the late 19th century, MCs were found aggregated around and within many types of solid cancers, but only in recent years the multiple functions operated by MCs in fostering angiogenesis, tissue remodeling, and immunomodulation in human and murine cancer have emerged. MCs may exert pro- or antitumoral roles, depending on tumor type, on microenvironmental signals, and on neighboring interacting cells [128]. It has been demonstrated that the infiltration of MCs at the tumor site can enhance tumorigenesis, although these findings are still debated. Tumor-infiltrating MCs express multiple proinflammatory factors and increase IL-17 expression in tumor. Additionally, it is believed that MCs may impact upon the growth of tumors by multiple mechanisms, including angiogenesis [129]. Several studies have demonstrated that early angiogenic activity is dependent upon MCs and is an essential part of neoplastic development, with MCs mediating this activity by releasing heparin, VEGF, and IL-8. The study of the role of MCs in prostate tumorigenesis is complicated by the multifocality of the prostate cancer, in which several tumor foci with different molecular and proliferative characteristics may appear and coevolve within the same organ. A fundamental question remains whether and how MCs contribute to the development of immune privilege within the tumor microenvironment. It is now indubitable that a major point linking MCs to cancer is the capacity of these cells to synthesize and release potent angiogenic cytokines. It has also demonstrated that not only MCs stimulate tumor angiogenesis but also they promote lymphangiogenesis in different solid tumors [111, 130]. Ma et al. demonstrated that both tumor cells and pancreatic stromal cells (PSCs) stimulated MC activation [131]. Conversely, MC-derived interleukin- (IL-) 13 and tryptase stimulated PSCs proliferation. In prostate cancer, MCs have been recently indicated as novel independent prognostic markers, although previous studies on prostatic biopsies associated high MC densities with favorable tumor characteristics and good prognosis. An explanation for these appearing to be a discrepant finding remains the observation that prostate cancer is a multifocal and heterogeneous disease. It has been ascertained that innate and adaptive immune cells commonly infiltrate solid tumors. Inflammation plays a major role in tumor progression. Overlooked in many studies of tumor inflammation, MCs are found in most tumor types. Considering their ability to secrete a wide variety of effector molecules, it is likely that MCs play an important role in many tumors, including prostate cancer. Some studies have shown that MCs are important proangiogenic effectors and inducers of the tumoral growth. MCs are, however, also known to be able to secrete a variety of molecules with antitumor effects. It has been suggested that the use of MC depletion/modulation therapies must be tailored toward each specific tumor [108]. The term "biomarker" in oncological sciences refers to a large range of markers, including biochemical markers,

cellular markers, cytokine markers, genetic markers, physiological results, radiological measurements, physical signs, and pathological assessment [132]. It has intuitive appeal to hypothesize that biomarkers with prognostic and/or predictive value are those intimately connected to the pathogenesis of human cancer [133]. These include biomarker division into *diagnostic (screening) biomarkers* for early detection, *prognostic biomarkers* for estimation of disease outcome, *predictive biomarkers* for adjuvant treatment stratification, and *surveillance biomarkers* for monitoring progression disease and treatment response [134]. Several proteins and genetic markers have been described in an attempt to refine prognostic information and predict the benefit derived from systemic treatment [135, 136]. The infiltrated host immune cell classification combined with some other biomarkers may have a prognostic value for tumor invasion and metastasis [15, 137–139]. Further studies of MC function in different tumor types and subtypes should help us develop effective antitumor strategies utilizing manipulation of the number and function of MCs.

Authors' Contribution

Gianluigi Taverna and Fabio Grizzi contributed equally to the paper.

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