Myeloid-Derived Suppressor Cells as Key Players and Promising Therapy Targets in Prostate Cancer

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Prostate cancer (PC) is the second most often diagnosed malignancy in men and one of the major causes of cancer death worldwide. Despite genetic predispositions, environmental factors, including a high-fat diet, obesity, a sedentary lifestyle, infections of the prostate, and exposure to chemicals or ionizing radiation, play a crucial role in PC development. Moreover, due to a lack of, or insufficient T-cell infiltration and its immunosuppressive microenvironment, PC is frequently classified as a "cold" tumor. This is related to the absence of tumor-associated antigens, the lack of T-cell activation and their homing into the tumor bed, and the presence of immunological cells with regulatory functions, including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Treg), and tumor-associated macrophages (TAMs). All of them, by a variety of means, hamper anti-tumor immune response in the tumor microenvironment (TME), stimulating tumor growth and the formation of metastases. Therefore, they emerge as potential anti-cancer therapy targets. This article is focused on the function and role of MDSCs in the initiation and progression of PC. Clinical trials directly targeting this cell population or affecting its biological functions, thus limiting its pro-tumorigenic activity, are also presented.

Keywords: prostate cancer, myeloid-derived suppressor cells, immunosuppression, immunotherapy, anti-tumor immune response

PROSTATE CANCER—EPIDEMIOLOGY

Prostate cancer (PC) is the most common, after lung cancer, malignancy in men—in 2020, more than 1.4 million new cases of PC were diagnosed worldwide (1, 2). Advanced age, race, and ethnicities such as African descent and family history are well-established risk factors of PC (3–6). Additionally, a higher incidence of PC has been associated with a diet rich in saturated animal fat and red meat, low intake of fruits/vegetables, obesity, hyperglycemia, lack of physical activity, prostate inflammation, as well as exposure to chemicals or ionizing radiation (6–8). The most common genetic predispositions for PC development are related to aberrations of the *PTEN* tumor suppressor gene. Inactivation of *PTEN* by deletion or mutations is identified in ~20% of primary PC and as many as 50% of advanced castration-resistant tumors (9). The role of the immune system and prostatitis in PC development was also confirmed, indicating that inflammatory mediators may promote prostatic carcinogenesis *via* inhibition of apoptosis, promotion of cell proliferation, and

even loss of the tumor suppressor genes (10). Importantly, not only the local, prostate inflammation, but also systemic reaction associated with chronic inflammatory diseases, including asthma and allergies, are associated with the higher risk of PC (11).

Most of the patients develop a low-risk neoplasm (12); however, approximately 15% of men with localized PC present with high-risk tumors, which will progress, metastasize, and finally result in death (13). In men with advanced metastatic prostate cancer (mPC), hormonal–androgen deprivation therapy is a method of choice with a good response rate. In some patients, however, the mPC will evolve into metastatic castration-resistant prostate cancer (mCRPC) (14). While a radical prostatectomy may be beneficial for patients with high-risk PC (15), only multimodal treatment, including surgery, radiation, and systemic therapy, gives the best chance for a long-term progression-free outcome (13). Nowadays, immunotherapy options, including anti-PC vaccines, e.g., Sipuleucel-T (Provenge), and the use of immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1/PD-L1 monoclonal antibodies or antagonists) further improve the effectiveness of the PC treatment (16).

PC is often considered a "cold" tumor, meaning that due to the reduced or complete lack of T-cell infiltration, e.g., because of the missing tumor-associated antigens, lack of T-cell activation and their homing into the tumor bed, and local immunosuppression, it does not trigger a strong immune response. This term emphasizes the role of the immune system in PC progression (16, 17). Studies indicate that regulatory T cells (Tregs) and other cell populations, namely, myeloid-derived suppressor cells (MDSCs; attracted to TME by low-grade chronic inflammatory signals) and tumor-associated macrophages (TAMs) (17), are mainly responsible for the immunosuppression observed in PC (18). Among them, MDSCs emerge as potential therapeutic targets (19).

MYELOID-DERIVED SUPPRESSOR CELLS —THEIR ORIGIN AND ACTIVITY

The term "myeloid-derived suppressor cells" has been used in the literature since 2007; however, the history of these cells dates back to the early 20th century, when it was shown that cancer is often accompanied by extra-medullary hematopoiesis (EMH) and neutrophilia (20, 21). These immature leukocytes were further characterized by their suppressive activity and called myeloid suppressor cells (MSC) (22). This term was further changed to MDSCs (22), and although current, the progress in resolution techniques, including a high-dimensional single-cell analysis, has raised concerns regarding the development and activation state of MDSCs (23); it is still accepted that MDSCs represent a heterogeneous population of immature myeloid cells, promptly expanding during pathological conditions, including infection, inflammation, and cancer (24). With respect to their origin, MDSCs have been divided into two main subsets—monocytic (Mo-MDSCs) and granulocytic or polymorphonuclear (PMN-MDSCs). Recently, a third population of the so-called early-stage MDSCs (e-MDSCs) was also described (25). In cancer, the accumulation of MDCSs is inseparably related to the production of pro-inflammatory mediators by the tumor microenvironment (TME), which activate and drive their suppressive activity (26). The immunosuppressive mechanisms developed by MDSCs are diverse and may include arginase-1 (ARG1) and inducible nitric oxide synthase (iNOS) activity; secretion of TGFβ, IL-10, and cyclooxygenase-2 (COX-2); and depletion of tryptophan by indoleamine 2,3-dioxygenase (IDO) (27). Although the immunosuppressive nature and the induction of antigen-specific T-cell tolerance is common for all the MDSCs subsets (28), they differ in the mechanism of action. In this context, Mo-MDSCs suppress T-cell response in both an antigen-specific and an unspecific manner, utilizing the mechanisms associated with iNOS activity and production of nitric oxide (NO) (29, 30). In contrast, PMN-MDSCs suppress immune response primarily in an antigen-specific manner, using the STAT3-mediated mechanisms of NADPH-oxidase and ARG1 activities (31). PMN-MDSCs store ARG1 in the granules and release it to the extracellular milieu, leading to the local depletion of L-arginine, affecting T-cell functionality. Both MDSCs subsets release ROS, which are essential for their immunosuppressive activity, and for retaining their undifferentiated status. Numerous studies confirmed the interplay between chronic inflammatory factors and expansion of MDSCs (24, 32). The transcription factor STAT3 plays a central role in the generation and functioning of MDSCs (33–35). Various cytokines, including IL-6, IL-1β, IL-10, GM-CSF, and VEGF, secreted mainly in the TME by tumor cells (26), are involved in the activation of pSTAT3. Conversely, chronic inflammation is associated with the initiation and progression of the tumor (10). In this context, chemokines and their receptors, e.g., CCL2/CCL12-CCR2, CXCL5/2/1-CXCR2, CCL3/4/5-CCR5, CCL15-CCR1, and CXCL8-CXCR1/2, are relevant for a rapid progression of PC and the recruitment of MDSCs (36, 37). PC patients were shown to have higher MDSCs infiltration than those with a benign prostate hyperplasia (38). Therefore, the role of inflammation in the development and expansion of MDSCs, and hence in PC progression, is unquestionable.

EXPANSION OF MDSCs IN PC

Studies with the use of *PTEN* KO murine PC model documented that lack of this gene was associated with upregulated inflammatory response (enhanced production of CSF-1 and IL-1β), and an extensive MDSCs tumor infiltration (39). Another mechanism involved in the recruitment of MDSCs in PC could be linked to the Hippo–YAP signaling. This pathway, relevant for the regulation of cell proliferation and apoptosis, is often deregulated in human solid tumors and associated with enhanced cancer cell proliferation (40). In PC, the hyperactivated Hippo–YAP signaling causes the upregulation of CXCL5 in cancer cells, which promotes the MDSCs recruitment *via* the CXCL5–CXCR2 axis (41, 42). The

recruitment of MDSCs to the tumor mass may also benefit from the tumor-related hypoxia. This is supported by the observation that the hypoxia-targeted therapy may lead to a long-lasting decrease in the accumulation of MDSCs in the tumor (43). A significant role in the recruitment of MDSCs to PC has also been assigned to chromodomain helicase DNA-binding protein 1 (CHD1), an essential tumor suppressor (44). Its depletion was found in 29.7% of cases in African Americans, and 11.0% of European PC patients (45). It has been shown that CHD1 deficiency may recruit MDSCs *via* an IL-6-dependent mechanism (46). Interestingly, a positive correlation between CHD1 and CD15 expression (a surface marker of PMN-MDSCs) in PC was also documented (46).

A growing list of evidence suggests that miRNA carried by tumor-derived extracellular vesicles (TEVs) may also play a role in the generation of MDSCs in many types of cancer (47–49). Although there are no data confirming such a role of EV miRNA in PC, some miRNAs already shown as relevant in the induction of MDSCs in other cancers have also been considered for PC (50).
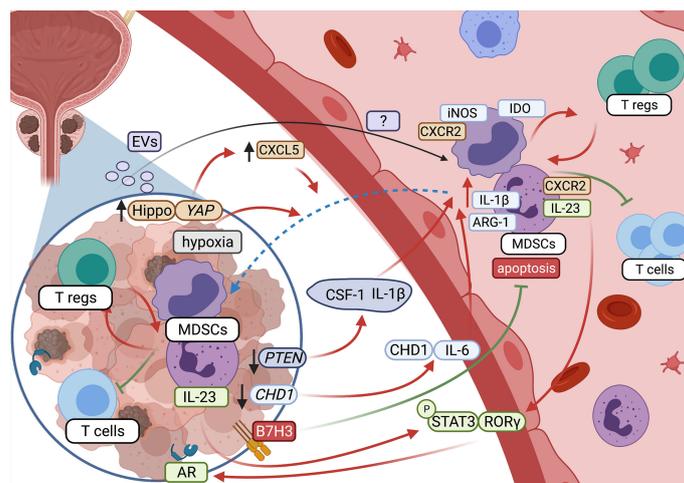
The crosstalk between MDSCs and the TME in PC is schematically presented in **Figure 1**.

ROLE OF MDSCs IN PC DEVELOPMENT AND PROGRESSION

In various cancers, the level of tumor-infiltrating MDSCs has been proposed as a prognostic marker (51, 52). In PC, however, such data are scarce and refer mainly to the *PTEN* mouse model (39). In contrast, there are observations that the MDSCs' blood level could be a useful parameter for monitoring the disease burden in PC, allowing researchers to distinguish between metastatic cancer, localized PC, and cancer-free men (53). Additionally, circulating MDSCs correlate well with PSA level and metastasis (33, 54). The pivotal role of MDSCs in the

development and progression of PC was further confirmed in randomized clinical studies showing that the increased level of MDSCs after the treatment is associated with the overall worse patients' survival (55, 56). Moreover, in a mouse model of PC, the lung infiltration by MDSCs was associated with the formation of lung metastases (57). However, what type of MDSCs subpopulation is pivotal and prevalent in PC remains controversial, mainly due to the lack of reproducibility and standardization of such research. The work showing MDSCs as a negative prognostic marker in mCRPC indicates only blood Mo-MDSCs as relevant (58). Furthermore, in patients with mCRPC, a positive correlation between Mo-MDSCs and Treg cells has been described (58), suggesting a mutual positive feedback loop (59). Generally, most of the studies in PC have focused on Mo-MDSCs rather than on PMN-MDSCs (55, 58, 60). Even early reports on circulating immunosuppressive cells in patients with PC were concentrated on CD14+HLA-DR$^{low/-}$ monocytes (54). This may result from the fact that Mo-MDSCs are more frequent in peripheral blood than PMN-MDSCs (61, 62). Another reason could be the fact that, in many studies, a cryopreserved material was used (63), affecting the recovery of PMN-MDSCs (64). Recently, Wen et al. documented infiltration of the primary prostate tumor by cells referred to as PMN-MDSCs (65); however, the markers used for their identification did not allow researchers to distinguish them from the population of tumor-associated neutrophils (TANs) (25). In this context, the phenotype definition of circulating blood PMN-MDSCs seems to be more reliable, but still, this should be further confirmed by functional tests that document the immunosuppressive nature of these cells (25).

Studies in PC showed that Mo-MDSCs and PMN-MDSCs are transcriptomically different (61), pointing out the ARG1 as typical for PMN-MDSCs (66) and iNOS or IDO for Mo-MDSCs (58, 60). Moreover, PMN-MDSCs can exert their immunosuppressive action also by the release of neutrophil elastase (NE), which was shown to stimulate the proliferation,

FIGURE 1 | Crosstalk between MDSCs and tumor microenvironment in prostate cancer (created with BioRender.com).

migration, and invasion of cancer cells both *in vitro* and *in vivo* in a mouse model of PC (67, 68).

It is proposed that, in PC, the tumor-infiltrating PMN-MDSCs express upregulated IL-1β and IL-23a (66). Although the IL-1β-restrained antitumor immunity was described before for other tumors (69), the secretion of IL-23 by PMN-MDSCs so far has been documented only for PC. In this context, it was shown that IL-23 preserves the androgen receptor's (AR) functionality, enabling survival and proliferation of PC in the androgen-deprived environment. The same mechanism is postulated as a driving force in the development of castration resistance (40). However, castration resistance may also be related to the secretion of IL-8 and subsequent tumor infiltration by PMN-MDSCs (66).

TARGETING MDSCs IN PC

Due to a lack of, or insufficient T-cell infiltration and immunosuppressive microenvironment in PC, there is a need to design new therapies that could "turn up the heat on the cold immune microenvironment" (17), to enhance the local anti-tumor immune response (16). Radiation *per se* has been found to activate the immune response (70); however, studies using the animal models of PC revealed that radiotherapy induces a rapid increase in the tumor-infiltrating MDSCs (71). Our previous studies showed that surgery or hormonal therapy alone did not reduce the level of circulating Mo-MDSCs in PC patients (62). In this context, in addition to the standard treatment, immunotherapy (72) or dietary strategies (73) are implemented, targeting cells with immunosuppressive potential, including MDSCs. One of the major challenges in targeting human MDSCs is their heterogeneous nature, e.g., differences in phenotype and mechanisms of suppression. A type of "universal" approach, covering the above aspects, may be the use of gemtuzumab ozogamicin, a calicheamicin-conjugated anti-CD33 humanized monoclonal antibody, already approved to treat a subset of patients with acute myeloid leukemia, which has also been highly effective against MDSCs in many solid tumors, including PC *in vitro* (61).

Clinically, MDSCs may be targeted by different approaches, including, e.g., inhibition of MDSCs expansion, MDSCs depletion, induction of their differentiation, functional inhibition, or multifactorial treatment. The clinical trials concerning all these potentially therapeutic strategies in PC have been described below **Table 1**.

Inhibition of MDSCs Expansion
Currently, there are three registered clinical trials, aiming at the inhibition of MDSCs expansion in PC. As mentioned, chemokines and their receptors are pivotal for the recruitment of MDSCs and the rapid progression of PC (36, 37); therefore, targeting the chemokine receptors or the use of chemokine inhibitors seems to be a promising form of immunotherapy in PC (74). One of the ongoing clinical trials (NCT03177187) seems to verify this hypothesis by using the CXCR2 antagonist

AZD5069 in combination with enzalutamide—the androgen receptor's antagonist in patients with mCRPC (75). An important additional factor associated with MDSCs expansion is VEGF (26); thus, administration of cabozantinib (a small-molecule inhibitor of tyrosine kinase receptor, including the VEFG pathway) followed by radical prostatectomy vs. prostatectomy alone (NCT03964337) is being tested in men with high-risk PC. Moreover, cabozantinib has already shown inhibitory effects on MDSCs (76). Another trial concerning dietary intervention, NCT03654638, is focused on soy bread, containing isoflavones, which were shown to reduce the level of pro-inflammatory cytokines and MDSCs (77).

MDSCs Depletion
MDSCs isolated from both mice and humans display elevated levels of STAT3, while inhibition of its pathway resulted in enhanced antitumor activity (28, 78). Circulating Mo-MDSCs maintain high levels of STAT3 until they reach the tumor, where hypoxia induces its rapid downregulation, causing differentiation of MDSCs to TAMs (79). STAT3 regulates the expression of the main factors of MDSCs activity, e.g., IDO, ARG1, IL-6, IL-10, IL-1β, and VEGF, among others, suggesting this pathway as an attractive therapeutic option (26). In this context, a fungal-derived pSTAT3 inhibitor, galiellalactone, was recently assessed for its ability to prevent PC-induced generation of MDSCs *in vitro* (53). In keeping with this, the clinical trial NCT03709550, aiming at testing decitabine (5-aza-2′-deoxycytidine), a hypomethylating agent with the ability to selectively deplete Mo-MDSCs, in mCRPC patients was implemented (80).

Inhibition of MDSCs Differentiation
Another therapeutic option involves a controlled differentiation of MDSCs towards the M1 anti-tumor macrophages with the use of curcumin (81). This approach will be considered in the recruiting clinical trial (NCT03769766). A similar approach will be used in the phase I clinical study in patients with biochemically recurrent PC, testing the effectiveness of the white button mushroom (WBM) extract containing β-glucan (NCT04519879). β-glucans, the most abundant carbohydrates found in yeast and mushrooms (82), may induce MDSCs differentiation to antigen-presenting cells, eliminating their suppressive abilities (83). The rationale for this concept was additionally grounded on the preclinical data showing that dietary WBM powder reduced not only the frequency of circulating MDSCs but also the level of prostate-specific antigen (PSA) (84).

Inhibition of MDSCs Induced Suppressive Circuits
There is also a possibility to inhibit some of the MDSCs-induced suppressive mechanisms operating in PC. One of such approaches is represented by a combination of abiraterone, a novel hormone therapy available for CRPC (85), and tildrakizumab (anti-IL-23 mAb) (NCT04458311), altering the production of IL-23 and therefore having a potential to target the MDSCs function specific for PC (41). In another clinical trial, a

TABLE 1 | Clinical trials targeting MDSCs in PC patients.

No.	Title	Condition or disease	Interventions	Mechanism of action	Trial number	Status
Inhibition of MDSC expansion						
1	Combination Study of AZD5069 and Enzalutamide. (ACE)	Metastatic Castration-Resistant Prostate Cancer	CXCR2 antagonist + enzalutamide	CXCR2 antagonist may block recruitment of MDSCs to the tumor (41)	NCT03177187	Recruiting
2	Immediate Prostatectomy vs. Cabozantinib Followed by Prostatectomy in Men with High-Risk Prostate Cancer (SPARC)	Prostate Cancer Prostate Cancer Adenocarcinoma Non-Metastatic	Cabozantinib (small molecule inhibitor of tyrosine kinase receptor) + Radical prostatectomy	Cabozantinib may reduce the tumor infiltration by MDSCs (76)	NCT03964337	Recruiting
3	Soy Bread Diet in Improving Immune Function in Participants With Prostate Cancer	Prostate Adenocarcinoma	Dietary intervention	Soy bread isoflavones may reduce pro-inflammatory cytokines and MDSCs level (77)	NCT03654638	Recruiting
MDSC depletion						
4	Enzalutamide and Decitabine in Treating Patients with Metastatic Castration Resistant Prostate Cancer	Metastatic Castration-Resistant Prostate Cancer	Decitabine (nucleic acid synthesis inhibitor)	Decitabine (5-aza-2′-deoxycytidine), a hypomethylating agent with the ability to selectively deplete Mo-MDSCs (80)	NCT03709550	Withdrawn
Stimulation of MDSC differentiation						
5	Trial of Curcumin to Prevent Progression of Low-risk Prostate Cancer Under Active Surveillance	Prostate Cancer	Curcumin	Curcumin may promote the differentiation of MDSCs (81)	NCT03769766	Recruiting
6	White Button Mushroom Soup for the Reduction of PSA in Patients with Biochemically Rec or Therapy Naive Fav Risk Prostate CA	Prostate Adenocarcinoma PSA Failure PSA Progression Recurrent Prostate Carcinoma Stage I Prostate Cancer stage IIA–C, III A, C	White Button Mushroom (WBM) Extract	WBM powder as a source of β-glucan may induce MDSC differentiation to antigen-presenting cells (83) and reduce the number of circulating MDSCs (84)	NCT04519879	Recruiting
Inhibition of MDSCs induced suppressive mechanisms						
7	Abiraterone Acetate in Combination with Tildrakizumab (ACTIon)	Metastatic Castration-Resistant Prostate Cancer	Abiraterone Acetate (selective inhibitor of CYP17) + Tildrakizumab (anti-IL-23)	Tildrakizumab (anti-IL-23 mAb), alters the production of IL-23 in PC, has the potential to affect castration resistance caused by MDSCs (41)	NCT04458311/ 2019-003485-40	Recruiting
8	A Trial of Ipatasertib in Combination with Atezolizumab (IceCAP)	Solid Tumor Glioblastoma Multiforme Prostate Cancer Metastatic	Ipatasertib (inhibitor of all three isoforms of protein kinase AKT) + Atezolizumab (anti-PD-L1)	Atezolizumab (anti-PD-L1 monoclonal antibodies)—a checkpoint inhibitor on MDSCs (86)	NCT03673787	Recruiting

(Continued)

TABLE 1 | Continued

No.	Title	Condition or disease	Interventions	Mechanism of action	Trial number	Status
9	A phase I/II basket trial evaluating a combination of Metronomic Oral Vinorelbine plus anti-PD-L1/anti-CTLA4 Immunotherapy in patients with advanced solid tumors.	Patients with locally advanced or metastatic solid tumors	Vinorelbine (cytostatic) Durvalumab (anti-PD-L1) + Tremelimumab (anti-CTLA-4)	Anti-PD-L1 and anti-CTLA-4 checkpoint inhibitors on MDSCs (86)	2017-001857-14	Ongoing
Multifactorial action: inhibition of MDSC expansion and blocking their suppressive activity						
10	A Phase 1b/2, Open-Label, Multicenter Study Assessing the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumor Activity of MEDI4736 in Combination with AZD9150 or AZD5069 in Patients with Advanced Solid Malignancies and Subsequently Comparing AZD9150 and AZD5069 Both as Monotherapy and in Combination with MEDI4736 as Second-Line Treatment in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck.	Part A: Advanced solid tumor Part B: Recurrent and/or spreading tumor of Head and Neck	MEDI4736 (Durvalumab- anti-PD-L1) + AZD9150 (Danvatirsen-STAT3 inhibitor) + AZD5069 (CXCR2 antagonist)	Combination of STAT3 inhibitor, selective CXCR2 antagonist, and PD-L1 inhibitor, where each of them has the potential to inhibit MDSCs activity (41, 60, 86)	2015-002525-19	Restarted or completed depending on the country
11	Phase II Trial of EP4 Receptor Antagonist in Advanced Solid Tumors	Prostate Cancer Non-Small Cell Lung Cancer Breast Cancer	Grapiprant + Gemcitabine	Gemcitabine may reduce the level of MDSCs (87), whereas grapiprant, a PGE2-receptor inhibitor, may block induction of MDSCs (88) and their suppressive effect (26)	NCT02538432	Withdrawn

combination of ipatasertib (inhibitor of all three isoforms of protein kinase AKT, which blocks the PI3K/AKT signaling pathway—a key driver of cancer cell growth and proliferation in PC), atezolizumab (anti-PD-L1 monoclonal antibodies)—a checkpoint inhibitor on MDSCs (86), and docetaxel (NCT03673787) will be tested in patients with mCRPC. Currently, in Europe, there is one registered clinical trial focused on blocking the MDSCs function in PC patients (no. 2017-001857-14). It tests the combination of vinorelbine, a cytostatic drug, and two checkpoint inhibitors, durvalumab and tremelimumab, which are anti-PD-L1 and anti-CTLA-4 mAb, respectively.

Multifactorial Intervention: Inhibition of MDSCs Expansion and Blocking Their Suppressive Activity

Combinations of both the inhibition of MDSCs expansion and blocking their suppressive activity provide the opportunity for multifactorial interventions with potential better therapeutic effectiveness. One of such trials tests the combination of STAT3 inhibitor (AZD9150), a selective CXCR2 antagonist (AZD5069), and the PD-L1 inhibitor (MEDI4736) (no. 2015-002525-19), where each can inhibit either MDSCs expansion or function. Another drug combination that is being tested is gemcitabine and RQ-00000007 (grapiprant), where gemcitabine inhibits MDSCs expansion (87), while grapiprant—an inhibitor of PGE2-receptor—reduces the differentiation, expansion, and suppressive activities of Mo-MDSCs (88), confirming its role in MDSCs functioning (26).

Potential New Targets

Despite a wide scope of the ongoing clinical research, there are other available potential therapeutic options targeting MDSCs in PC. One, yet unexplored route, concerns the angiotensin-converting enzyme (ACE)–angiotensin pathway, where the overexpression of ACE in monocytic cells was shown to reduce the generation of MDSCs (89), while angiotensin was able to reduce the tumor malignancy in PC (90). Nowadays, during the SARS-CoV-2 pandemic, this pathway, however, takes on a quite different significance. However, other forms of angiotensin may impact the biological properties of PC cells by modulating inflammatory reaction, or even genes, including downregulation of HIF1a and upregulation of CDH-1 (91) expression, both associated with MDSCs recruitment. Another potential approach involves estrogen, used previously in PC therapy (92). The combined therapy, linking activation of estrogen receptor β (ERβ) and the checkpoint inhibitor anti-PD-1 mAb, diminishes MDSCs infiltration in mouse models of colorectal and breast cancer (93). Interestingly, apoptosis and/or differentiation of PC cells may be promoted during the ERβ activation (94). Additionally, studies confirmed the benefits of ERβ activation in androgen-dependent CRPC, decreasing the viability of the tumor cells (95). Also, ARG1 is a potential therapeutic target in PC, and its inactivation through STAT3 inhibition was already confirmed (34). The ongoing clinical trials aiming at targeting MDSCs may be a trigger for more frequent

use of immunotherapy in combination with other forms of PC treatment.

CONCLUSION

Although the first observations reporting the negative role of MDSCs in antitumor responses in PC date back from the beginning of the 21st century, the last decade saw an upsurge of studies indicating their mechanisms of action and clinical relevance (96). Although several questions remain unanswered, the role of MDSCs in the development and progression of PC seems unquestionable, suggesting their potential as a therapeutic target. Hence, the implementation of the combination therapy, e.g., radiotherapy and immunotherapy, targeting both the tumor and MDSCs in PC seems crucial. Such therapy may increase the frequency of the abscopal response, which is a phenomenon associated with tumor shrinkage, occurring not only locally at the site of the treatment but also in other locations, where the tumor has already spread (97).

AUTHOR CONTRIBUTIONS

IS wrote the draft version of the manuscript. JB revised and edited the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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