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REVIEW ARTICLE

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MSCs and CAFs interactions in the prostate and bladder cancer microenvironment as the potential cause of tumour progression

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ABSTRACT

The tumour microenvironment (TME) is the broadly understood environment around the tumour. Cancer-associated fibroblasts (CAFs), Mesenchymal Stromal Cells (MSCs), and molecules synthesized by them are part of it. Both CAFs and MSCs can promote tumour progression by induction of an immunosuppressive, pro-inflammatory environment. Through indirect and direct cell-to-cell interactions they also have a pro-proliferative, pro-angiogenic, and pro-invasive effect on cancer cells. They can lead to aggressive cancer formation. At this stage, it is important to conduct research to modulate TME towards inhibition of cancer progression and preventing resistance to already introduced drugs. Moreover, it is extremely important to study these interactions in light of using MSCs in a drug-delivery strategy.

Key words: tumour microenvironment, cancer-associated fibroblasts, mesenchymal stromal cells

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Introduction

Considering the latest statistics, the frequency of cancer diagnosis in the world is constantly increasing. Cancers of the genitourinary system, which are asymptomatic or similar to inflammation, are diagnosed late, and therefore the prognosis is worse. They constitute a significant epidemiological and clinical problem. According to the latest Global Cancer Statistics (GLOBCAM 2020), prostate cancer is the second most common cancer and the fifth cause of death in the men population. Over 1.4 million new cases were reported in 2020. Moreover, it was recognized as the leading cause of cancer death in 48 countries out of 185 included in the study. Thus, bladder cancer is the 10th most frequently diagnosed cancer among both sexes, almost 600,000 new cases and over 200,000 deaths were reported in 2020. It is more common in men than women, making it the 6th most diagnosed and 9th most fatal cancer in this sex [1].

The tumour microenvironment (TME) is the broadly understood environment around the tumour. It is a breakdown of the tumour itself and its external components into its smallest part. Apart from cancer cells, it also includes all non-cancerous cells i.e. Mesenchymal Stromal Cells (MSCs), Cancer-associated Fibroblasts (CAFs), Immune and Inflammatory Cells, and many others [2]. Additionally, TME consists of proteins of the extracellular matrix (ECM), the blood vessels surrounding it, and soluble mediators synthesized by all cells in this environment. Cancer cells by secreting extracellular factors can control their microenvironment by inducing angiogenesis, proliferation, or immunotolerance, causing the progression of neoplastic disease and the spread of tumour cells [3]. At this stage, it is important to conduct research to modulate TME towards inhibition of cancer progression.

Currently, the ClinicalTrials.gov database reports only 10 TME-related clinical trials actively recruiting patients with bladder and prostate cancer.

Considering these results, it is extremely important to broaden the knowledge of TME in these cancers at the level of basic research, to be able to conduct more clinical trials in the future. Below is a short description of the knowledge gained on selected TME components.

Mesenchymal stromal cells in TME

Mesenchymal stromal cells are widely studied cells, and relatively easy to isolate and cultivate. They make up a small population of all cells in the organism. They are characterized by several unique properties, including the potential for multidirectional differentiation, and they play a supporting and regenerative role [4]. By secreting soluble extracellular factors, they take part in the regulation of angiogenesis, haematopoiesis, and immune response. The composition and effect of this secretome on surrounding cells are closely related to the origin of the MSCs and their environment [5]. They constitute a heterogeneous population of stromal cells which is confirmed by differences in the composition of surface markers and their regenerative abilities depending on the origin. They show different features in TME, which may result from different immunoregulation of individual types of MSCs [6]. In practice, this interlays into difficulties in distinguishing naive MSCs from CAFs, the phenotype of which may overlap depending on the type of tumour tissue [7]. One of the important properties of MSCs in the study of their influence on TME is their ability to migrate to inflammatory and hypoxic places. In response to such conditions, cells secrete chemokines such as CCL2, CCL15, CCL20, CCL25, CXCL1, and CXCL8. After their release, the MSCs are recruited to the secretory places due to the presence of specific receptors for the chemokines on their surface. Another mechanism responsible for the tropism of MSCs to TME is the secretion of many paracrine factors that degrade the ECM or the secretion of exosomes conducive to their further migration [8]. Exosomes are another component of TME, they are vesicles secreted by cells containing e.g. proteins or RNAs such as microRNA (miR). They are involved in the pathological mechanisms of the tumour, helping in the migration of MSCs as indicated above, but they can also affect communication in TME, e.g. by regulating IL-6, promoting the growth of cancer cells. What is more, miR from exosomes is involved in the main mechanisms supporting tumour growth by MSCs [8, 9]. Furthermore, the role of MSCs in promoting the epithelial-mesenchymal transition (EMT), a key phenomenon in cancer invasion, has been documented in the past few years. After remodelling the extracellular matrix, cells lose their polarity and begin to spread [2, 8]. It has also been shown that factors synthesized by cancer cells regulate the biological properties of MSCs transforming them into pro-inflammatory cells, thus promoting tumour growth [2]. While according to another study, MSCs can inhibit tumour cell proliferation by regulating AKT, and thus the Wnt pathway and this shows how much divergence can be met [10]. There is no doubt, however, that MSCs have a significant effect on cancer cells and *vice versa*. The MSCs present in TME can support and inhibit cancer progression. The research results are not unequivocal. The difference in results most likely stems from the nature and origin of the stromal or cancer cells used in the described experiments. Depending on that MSCs may have pro-inflammatory and anti-inflammatory properties. MSCs are a heterogeneous subset of stromal cells, as evidenced by differences in the composition of surface markers and their ability to differentiate. In the tumour microenvironment, they show different properties, which may result from different immunoregulation of individual types of MSCs or components of a particular TME [2, 8].

Some of the mechanisms of promoting and inhibiting cancer progression are presented in Figure 1.

MSCs in prostate and bladder cancer research

The latest research on the impact of MSCs on the tumour microenvironment focuses on finding molecules that determine the direction of their influence on cancer progression. Asporin (ASPN) seems to be one of the promising markers in prostate cancer. Preclinical and clinical studies indicate a significant relationship between ASPN expression and disease relapse after radical prostatectomy [11, 12]. Moreover, a study in which MSCs showing the overexpression of ASPN were transplanted into the mouse prostate manifested an increased number of metastases, indicating both the prognostic and biological role of this protein. Research also suggests a different influence of different ASPN variants on the regulation of ECM proteins, the dynamic development of which plays an extremely important role in cancer progression [13]. It is also indicated that the association of ASPN with progression and metastasis may also result from the promotion of the invasion of CAFs through the positive regulation of fibroblast growth factor-2 (FGF2) [14]. However, it seems necessary to further deepen the knowledge of indirect interactions related to signalling pathways, of which individual variations of the ASPN protein are part. Recent reports also indicate that their influence on the malignancy of cancer is associated with the presence of tumour-activated platelets. Bhunija et al. indicated that tumour-activated platelets bind to MSCs in the tumour's microenvironment, inducing the so-called vascular mimicry (VM). It is a term for the formation

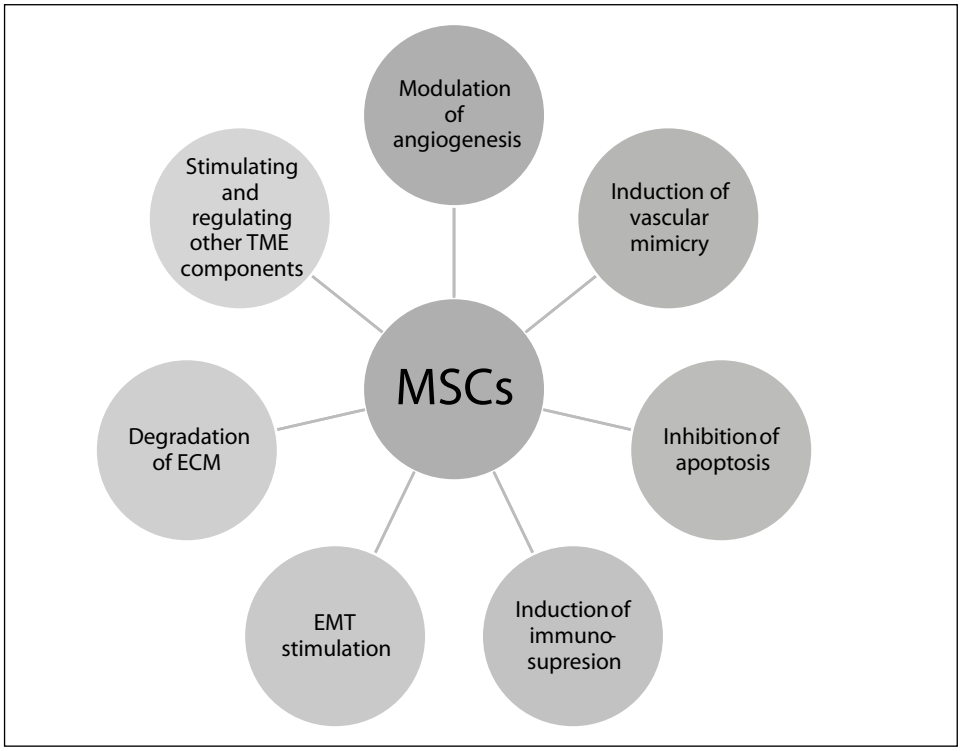

Figure 1. Main mechanisms of tumour growth promotion by MSCs

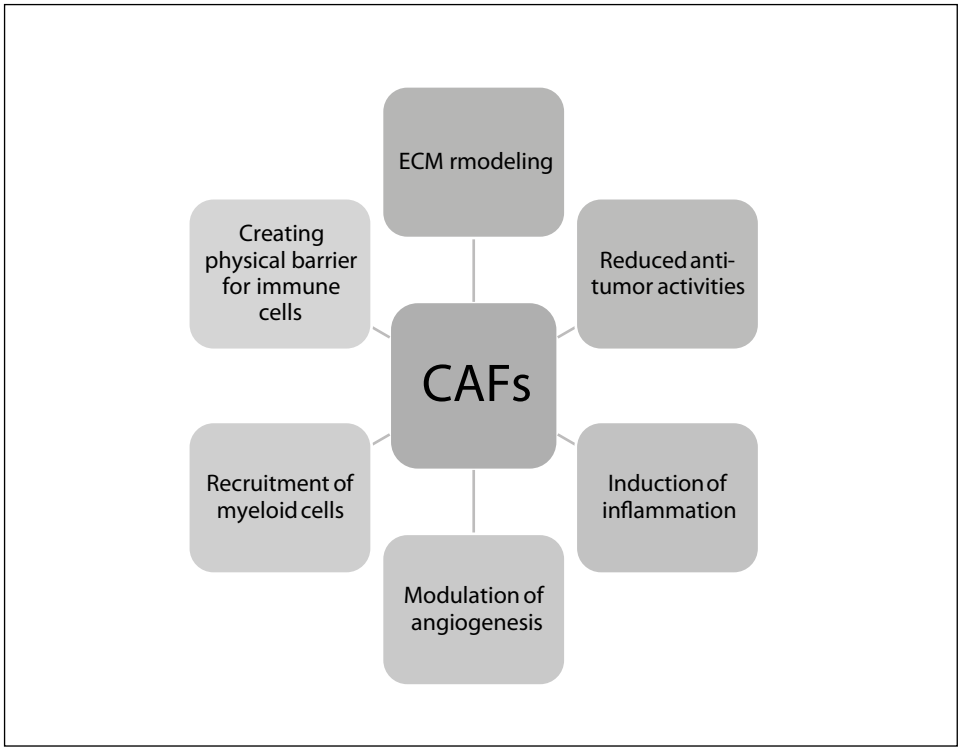

Figure 2. Main mechanisms of tumour growth promotion by CAFs

of pseudo-vascular structures by cancer cells [15]. Another lately popular investigated mechanism is the SDF-1/CXCR4 and its role in tumour progression. *In vitro* and *in vivo* studies of Luo et al. showed that MSCs can use this pathway to promote the proliferation and migration of prostate cancer cells [16].

In bladder cancer, studies on the effects of MSCs on cancer cells are extremely important not only in terms of looking for a prognostic marker or a new therapeutic target but also in terms of using MSCs in regenerative medicine. A significant problem of using the paracrine abilities of MSCs during the regeneration of the bladder in oncological patients is the possibility of activating cells with cancerous features remaining after chemotherapy [17]. Mediators synthesized by MSCs may affect other cells either directly through signalling pathways or indirectly by inducing the secretion of active molecules from neighbouring tissues. Halim et al. identified 54 proteins synthesized by MSCs, 44 secreted extracellularly, 43 of which supported the regeneration of the urinary tract epithelium by stimulating migration and proliferation capacity, or by initiating EMT [18]. It follows that the same interactions supporting regeneration also can support cancer progression. Due to the variety of reports and interactions of MSCs, studies on their safety in oncological patients are still ongoing.

MSC-based drug delivery strategies

Another important aspect of research into the effects of MSCs on cancer cells is their use to deliver drugs directly to TME. As previously mentioned, MSCs can migrate to the inflammatory environment and thus to TME. The tumour tropism of MSCs can be used to send anticancer drugs directly to the tumour area. Thus, eliminating several side effects present in systemic therapy. Pessino et al. in 2011 showed the results of their research on the strategy of drug delivery by non-genetically modified MSCs. They used Paclitaxel (PTX) as a delivered drug, a drug with cytotoxic activity by inhibition of microtubules. In the initial phase, the hMSC was treated with PTX in culture. The effect of the drug on the stromal cells and the ability of these cells to release the drug were then examined. In the next phase, a series of *in vitro* and in vivo tests were carried out to check how the drug released from MSCs affects cancer cells. The study showed that MSCs released the previously loaded drug in an amount sufficient to affect the proliferation of cancer cells and reduce tumour growth [19]. Another MSCs drug delivery strategy is to combine them with nanoparticles (NP). Nanoparticles are used to introduce genetic modification in MSCs by replacing viral vectors, stimulating their proliferation and migration, and what is more, protecting them against the cytotoxic effects of the drugs carried, or controlled drug release [20]. Mathilde et al. studied MSCs as carriers of NPs in brain tumours. The study suggests that MSCs may be effective drug carriers for TME brain tumours without affecting their viability [21]. Levy et al. conducted an experiment in which they checked the effectiveness of the designed drug platform for disseminated prostate cancer. The platform consisted of MSCs as the activated prodrug carrier. Prodrug-releasing MSCs were shown to selectively induce apoptosis in prostate cancer line cells. Moreover, the platform design used in the xenograft studies inhibited tumour growth, suggesting that MSCs as a carrier did not lessen the action of the particles. Researchers demonstrated the effective operation of the designed platform in an *in vivo* prostate cancer model [22].

Another system increasingly being raised is the use of exosomes as paracrine factors secreted by MSCs to deliver other factors than drugs, such as RNAs. Kurniawati with the study group designed a Lethal 7c (let-7c) delivery experiment for prostate cancer using MSC exosomes. The team used previous results suggesting that low expression of let-7c is associated with the aggressive course of prostate cancer — overexpression of let-7c is indicated to reduce proliferation and survival of prostate cancer cells by suppressing IL-6. Presented results indicate that miR-let-7c can be delivered using exosomes secreted by MSCs and the proliferation and migration in the cell model used can be reduced thereby [9]. In another study using exosomes as a vector for RNA delivery, Greco et al. designed PLK-1 siRNA transport to bladder cancer cells. The experiment aimed to demonstrate the effectiveness of silencing PLK-1 kinase, the overexpression of which is detected, among others, in recurrent and metastatic bladder cancer. The research team confirmed the possibility of using natural exosomes secreted by MSCs as a carrier of PLK-1 small interfering RNA (siRNA), which effectively silences the kinase, causing a decrease in proliferation and induction of apoptosis of bladder cancer cells [23]. These studies indicate that the MSC-based drug delivery system can also effectively be used to target TME components that regulate cancer progression.

However, it should be noted that these studies did not analyse the effect of other mediators interacting with each other synthesized by stromal cells and having a large impact on cancer cells.

Cancer-associated Fibroblasts in TME

Fibroblasts are the most numerous cells of the connective tissue proper, derived from the mesoderm. They are the main source of ECM proteins and are responsible for tissue integrity. Recently, their similarity to MSCs

has been investigated. In conformity with Soundararajan et al. MSCs and fibroblasts have similar proliferative and differentiation abilities and many overlapping surface markers, however, they differ in gene expression, DNA methylation pattern, and immunomodulatory abilities [7]. *In vitro* studies indicate not only the similarity in the expression of surface markers but also the possibility of differentiation in osteoblastic, chondrogenic, and adipogenic cell type, morphology, or high proliferative capacity [24, 25]. It has been reported that fibroblasts isolated from the tissue can survive unchanged in a similar number of passages as stem cells [26]. In the context of TME research, all these similarities constitute an obstacle to the proper identification of cells and their corresponding functions in tumour progression.

Fibroblasts form most non-cancerous cells in TME. Under the influence of mediators secreted by cancer cells, fibroblasts surrounding the tumour differentiate into cells called cancer-associated fibroblasts (CAFs) or myofibroblasts. After activation, CAFs become metabolically active, proliferate, and secrete many soluble factors, thus affecting communication in TME. Consequently, they play a key role in the development of cancer [27].

One of the factors leading to the activation of CAFs is the transforming growth factor-beta (TGF-β), which influences the processes of cell growth and differentiation. In an *in vitro* study, Goulet et al. examined how exosomes from bladder cancer affect the activation of fibroblasts. For this purpose, vesicles from cancer tissue were isolated and then co-cultured with fibroblasts. It has been hypothesized that TGF-β is released from the vesicles and binds to the surface of fibroblasts, activating the TGF-β/SMAD pathway. The study showed a significant effect of TGF-β on the transformation of fibroblasts into CAFs [28]. Another study suggests that the same signalling pathway causes the differentiation MSCs into CAFs. Shangguan et al. by blocking TGF-β/SMAD signalling, prevent the differentiation of MSCs towards CAFs while maintaining the properties of stem cells [29]. MicroRNA (miRNA) appears to be another factor that can activate CAFs. Tanaka et al. showed that the transfected fibroblasts by miRNA displayed a phenotype and secretome similar to CAFs. Among other things, the expression of Alpha-smooth muscle actin (α-SMA) and increased production of TGF-β has been demonstrated [30]. IGF1/IGF1R is one more signalling pathway responsible for the transformation of fibroblasts in TME. Vincenzo et al. observed the activation and mobilization of fibroblasts co-cultured with breast cancer cells associated with increased expression of insulin-like growth factor I (IGF-1). After silencing the expression of IGF-1 or the receptor for IGF-1 (IGF-1R), decreased α-SMA expression and migration activity were observed. The study also shows that the IGF1/IGF1R pathway promotes the remodelling in TME through paracrine and chemotactic effects on CAFs, thereby increasing the invasiveness of cancer cells [31].

One of the most dangerous features of CAFs is the induction of an immunosuppressive environment. Li et al. conducting research in an in vivo model, found a positive correlation between CAFs and programmed cell death ligand 1 (PD-L1) expression. CAFs showed increased expression of CXCL5, while CXCL5 promoted PD-L1 expression through the PI3K/AKT signalling pathway. According to the authors, it is a potential therapeutic biomarker [32]. CAFs constitute a heterogeneous population of cells. Several subpopulations of these can mediate tumour-promoting inflammation by interacting with immune cells. It is possible through the recruitment of myeloid cells, i.e. monocytes, mast cells, or granulocytic Myeloid-derived suppressor cells (MDSC) [33]. Ellem et al. studying the interplay between androgens and oestrogens in prostate cancer showed that CAFs can recruit mast cells by secreting CXCL12 in a CXCR4-dependent manner [34]. Furthermore, CAFs in a paracrine manner can regulate the function of T-cells. One of the factors produced by CAFs is prostaglandins (PGE), secreted PGE2 contributes to the reduction of T-cells activity, increases their differentiation towards Th17, and increases the production of IL-6 [35]. Overexpression of IL-6, in turn, is associated with aggressive tumour growth and shorter patient survival [36]. It regulates not only tumour growth but also the invasion of cancer cells [37]. Moreover, as in the case of PGE2, it is involved in the process of differentiation of T-cells to Th17. Another obstacle for immune cells to fight cancer may be the physical barrier created by the CAFs-rich stroma. This phenomenon is called immune exclusion and may be associated with the patient's lack of response to treatment with PD-L1 or Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) blockade [33].

ECM consists of proteins and glycosaminoglycans and creates an environment that facilitates communication and cell adhesion. The primary function of fibroblasts is to degrade and synthesize ECM components in response to changing conditions. Therefore, CAFs can constantly rebuild the ECM with the help of metalloproteinases (MMPs), which creates a physical space for the proliferation and migration of cancer cells. Moreover, during the remodelling, ECM is modified, and the growth factors and chemokines that support the functioning of the tumour are released. In addition, molecules secreted in the tumour microenvironment can lead to modification of the ECM of distant organs, which in turn is associated with metastasis [38, 39].

As with MSCs, CAFs can induce EMT in cancer cells. In an *in vitro* study of TME's effect on cancer cells, Wang et al. showed that CAFs are the main source

of IL-6 in the ovarian cancer environment. The study showed that IL-6, in addition to promoting the proliferation, invasion, and survival of ovarian cancer cells, also promotes EMT. Furthermore, investigators inhibited EMT by inhibiting TGF, which resulted in reduced resistance to paclitaxel by affecting the apoptosis of ovarian cancer cells [40]. Another study found that IL-6 synthesized by CAFs expressing α-SMA induces EMT in non-small cell lung cancer (NSCLC) cells, resulting in cisplatin resistance [41]. As in the case of MSCs, the influence of CAFs on the SDF-1/CXCR4 signalling pathway has recently been extensively studied. Recent studies show a significant influence of CAFs on this pathway, which interplay to among others, invasiveness and metastasis of NSCLC or progression of endometrial cancer [42, 43]. Wang et al. already in 2008, indicated that this pathway may be a promising therapeutic target, in their research they showed that the overall survival time of patients with positive CXCR4 in pancreatic cancer was lower than that of patients without this marker [44]. Thus, except for the potential therapeutic target, this CXC4 chemokine receptor may also be a prognostic marker. More and more basic studies concluded that CAFs, which are a large part of TME, are crucial in cancer progression. In addition to affecting the chemoresistance of cancer cells, it is also indicated that CAFs can induce radioresistance. Huang et al. conducted *in vitro* and *in vivo* studies of TME's influence on radiotherapy in Nasopharyngeal carcinoma (NPC), concluding that CAFs induce radioresistance via the NF-κB signalling pathway [45]. In turn, the team of Steer et al. also at *in vitro* and *in vivo* studies, proved that CAFs affect the sensitivity of prostate cancer cells and breast cancer to radiotherapy. This Research Team points to the need for more experiments to distinguish between fibroblasts and activated fibroblasts in TME. They also emphasize the variety of results depending on the used cell line [46].

CAFs in prostate and bladder cancer research

One of the widely studied proteins synthesized by CAFs is growth factor 15 (GDF15), also called MIC-1 (macrophage inhibitory cytokine), which belongs to the TGF-β family. Bruzzese et al. conducted *in vitro* and *in vivo* studies of the influence of MIC-1 on prostate cancer. It has been shown, inter alia, that CAFs are the main source of this protein in TME. Moreover, increased expression of MIC-1 in the tumour stroma than around non-neoplastic tissue was demonstrated, which indicates a potential tumour marker in prostate cancer. Also, tumour growth stimulation was demonstrated in a mouse xenograft model, suggesting an important role in the spread of cancer cells [47]. Research shows that MIC-1 may not only be a tumour marker and a therapeutic target but also can be used to monitor the advancement of the disease [47, 48]. Interleukin (IL-33) is another noteworthy molecule that comes from the IL-1 family. Saranchova et al. discovered that IL-33 could be a potential marker to assess the metastatic potential of prostate cancer. IL-33 expression has been shown to decline as the tumour progresses to metastatic disease. This process is related to the escape of the tumour from immune surveillance [49]. The authors revealed that the expression of IL-33 correlates with the expression of major histocompatibility complex class 1 (MHC-1). Therefore, a reduction in IL-33 expression in TME leads to decreased immune surveillance and increased metastatic potential. The study disclosed the important role of IL-33 in personalized cancer therapy [49].

Miyake et al. investigated the CXCL1 chemokine in the TME of bladder cancer. The study suggests that CXCL1 and IL-6 mediate the recruitment of CAFs to TME. CAFs, on the other hand, provide growth factors and CXCL1 for cancer cells, creating a paracrine loop. As a result, CXCL1 may participate in inducing bladder cancer recurrence or be the cause of disease progression. The authors suggest an attempt to inhibit the CXCL1 signalling pathway to inhibit progression in patients with resistance to bladder cancer. It can be the next potential marker of targeted therapy for tumours of the genitourinary system [50].

Conclusions

Both the tumour-promoting CAFs and MSCs are at least partially responsible for the acquisition of an immunosuppressive, pro-inflammatory environment, they also have a pro-proliferative, pro-angiogenic, and pro-invasive effect on cancer cells. Through direct and indirect interactions, they lead to aggressive cancer formation. It seems extremely important to study these interactions and search for intermediary molecules that can be used as a target in personalized medicine. These cells are key factors in the malignant development of cancer and represent an important research line. There is no doubt that soluble mediators and extracellular vesicles are critical to these interactions.

In addition, due to the use of paracrine properties of stem/stromal cells in regenerative medicine, one of the significant problems in the process of bladder regeneration by tissue engineering methods in patients after radical cystectomy is the possibility of initiating cancer relapse. For their safe and wide use, their heterogeneity and interactions in TME should be further investigated.

Furthermore, to establish the safety of using MSCs as medication transmitters in oncological patients, it is necessary to test their properties from every angle. Therefore, basic research into cell interactions is crucial.

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