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Review

Mesenchymal stem cells and prostate cancer: A concise review of therapeutic potentials and biological aspects

Maryam Rahimi Tesiye [a], Zahra Abrishami Kia [b,*], Hassan Rajabi-Maham [a]

[a] Faculty of Life Science and Biotechnology, Shahid Beheshti University, Tehran, Iran
[b] Faculty of Physical Education and Sport Sciences, University of Mazandaran, Babolsar, Iran

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ABSTRACT

Prostate cancer (PCa) arises from a cancer stem or progenitor cell with homogenous characteristics, especially among the aging men population. Over the past decade, the increasing PCa incidence has led to significant changes in both disease diagnosis and treatment. Recently, the therapeutic aspects of stem cells in many cancers, including PCa, have been debatable. The new generation of PCa studies seek to present definitive treatments with reduced therapeutic side effects. Since discovering unique properties of stem cells in modulating immunity, selective migration to inflammatory regions, and secretion of various growth factors, they have been a promising therapeutic target. The existing properties of stem cell therapy bring new opportunities for cancer inhibition: transferring chemotherapeutics, activating prodrugs, affecting the expression of genes involved in cancer, genetically modifying the production of anti-cancer compounds, proteins, and/or deriving extracellular vesicles (EVs) containing therapeutic agents from stem cells. However, their dual properties in carcinogenicity as well as their ability to inhibit cancer result in particular limitations studying them after administration. A clear understanding of the interaction between MSCs and the prostate cancer microenvironment will provide crucial information in revealing the precise applications and new practical protocols for clinical use of these cells..

1. Introduction

Prostate cancer (PCa) represents the second most common malignancy in men worldwide (Bray, et al., 2018). For most people, the increasing age with the average age at the time of diagnosis being 66 years, strongly correlates with the incidence and mortality rate of PCa worldwide. Besides genetic and family history, people of black race and those with obesity (BMI $>$ 25) have a greater risk of growing PCa (Panigrahi et al., 2019; Chu, 2011; Rawla, 2019). In 2018, the European association of urology (EAU) introduced 1,276,000 cases of PCa patients worldwide (Barsouk et al., 2020; Boustany et al., 2021). Despite high prevalence of prostate cancer disease among men, there is not enough information about the etiology of PCa. The biological heterogeneous PCa with its complicated characteristic results in interpatients, intertumoural, intratumoral, and genetical challenges during treatment (Frame et al., 2017). Although PCa is treatable if diagnosed early, in advanced stages it may arise metastasis to other tissues. Since PCa is depended in androgen receptor signaling for its growth and survival, many studies have focused on examining the role of androgens in carcinogenesis and the development of PCa (Dai et al., 2017; Feng and He, 2019; Corella et al., 2020).

In the 1940 s, androgen deprivation therapy (ADP), presented by Huggins was known as the most efficient treatment for early diagnosed PCa. This strategy targeted the androgen receptors signaling which consequently caused relative disease recovery (Li et al., 2021; Huggins and Hodges, 1972). Huggins method still is utilized in early stage PCa, however, following disease progress, the second line of treatment including chemotherapy, surgery, radiation, or a combination of them are replaced (Hurwitz, 2018; Nyrop et al., 2016). Radiation resistant stem cells, the complexity of tumor microenvironment, the increased secretion of inflammatory cytokines and growth factors, besides overexpressed receptors may result in cancer recurrence or resistant tumors (Abbasian Ardakani et al., 2017). Restrictions such as: the resistance occurred against treatment, limitations in controlling cancer progression, bone metastasis following induced toxicity, and low patient survival rates (average 8 to 12 months) will cause to apply other treatment methods (Mottet, 2014; Fizazi et al., 2015).

Pro drug-converting enzymes as a novel therapeutic approach

* Corresponding author at: Department of Exercise Physiology, Faculty of Physical Education and Sport Sciences, University of Mazandaran, Babolsar, Mazandaran Province, Iran.
E-mail address: nikooabrishamikia@yahoo.com (Z. Abrishami Kia).

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through directly tracking and targeting the tumor cells, effectively increases cancer improvement and declines drug's side effects. The ability of alteration, migration into tumor site and also antitumor components secretion over a long period of time are some of specific potential properties of genetically engineered stem cells making them overcome cancer treatment limitations. to improve cancer therapeutic indicators via delivering drug-activating enzymes into malignant tissue, pro drug-converting enzymes are used instead of systemic administration of nontoxic prodrugs to eliminate tumor cells (Stuckey and Shah, 2013; Aboody et al., 2013). This method still remains controversial due to the dual biological role of MSCs in both cancer suppression and promotion despite its accurate medication delivery to the targeted tissue, and non-spreading toxicity to surrounding lesions. In this study, we aimed to generally review the published reports on stem cells especially MSCs therapy in PCa treatment.

2. Mesenchymal stem cells (MSCs)

The multipotent Mesenchymal Stem Cells (MSCs) with the ability in differentiation to various types of cells (chondrocytes, adipocytes, smooth muscle cells, fibroblasts and osteoblasts) migrate and effectively inhibit the tumor progression by exchanging the microRNAs, exosomes, or inducing neovascularization (Dominici et al., 2006; Abd Elmageed et al., 20142014). The inflammatory molecules originating from impaired tissues such as cytokines, chemokines, and growth factors are introduced as the primary mediators of MSCs homing property (Hill et al., 2017). These cells also secrete many growth factors, anti-apoptotic, angiogenic, pro-survival, anti-scarring, and signaling molecules such as TGF-β, VEGF, FGF, IL-10, and IL-6 (Holan et al., 2019; Xu, 2016; Lin and Du, 2018; da Silva Meirelles et al., 2009). Additionally, they exert immunosuppressive effects and influence carcinogenesis through expressing paracrine factors: HGF, PGE2, IDO, LIF, TSG and TGF-β, IL-6, and IL-10 (Brennen et al., 2016; Brennen et al., 2013; Fontaine et al., 2016). As a result, MSCs, through stimulate growth and cancer cell survival, summon angiogenesis and cancer associated fibroblast, and inhibit anti-tumor immune activity onset cancer (Brennen et al., 2013; Shi et al., 2017).

Tumor cells are capable to change the functional profile of MSCs from normal trophic to pro-tumor, through extracellular vesicles (EVs). As a consequence of this alteration, EVs from reprogrammed MSCs affect other tumor microenvironment cells, such as fibroblasts, immune and endothelial cells. The mechanisms underlying the effects of MSCs in carcinogenesis are not yet fully clear. It is believed that they are likely related to the complicated relation of MSCs and the immune system which is coupled with the tumor microenvironments heterogeneity and the cytokine profiles (Gilazieva et al., 2022).

Some inflammatory factors such as chemokines, cytokines, and growth factors of injured tissues mediate their homing into tumors. The expression of these cytokines mobilizes reservoirs of BM-MSCs (inflammatory and immunomodulatory cells), which are recruited to prostate cancer lesions. Additionally, a wide range of cytokine receptors which mediate cytokines trafficking to inflammation and cancer sites and immunomodulatory, growth, and signaling molecules including TGF-B, GM-CSF, RANTES, CCL2, VEGF, HGF, IL-6, and IL-10 are directly affected and expressed by MSCs. Under pathological conditions, modulatory rule of MSCs will provide initiate self-reinforcing loop leading to chronic inflammation. Not surprisingly, MSCs are present in the prostate during tissue regrowth, as well as inflammation-associated pathologies benign prostatic hyperplasia (BPH) (Brennen et al., 2013).

When the "educated" MSCs arrive within the tumor microenvironment, they form pro-metastatic behaviors: cancer immunosuppression modulating, and tumor associated-MSCs *trans*-differentiating into cancer-associated fibroblasts that induce epithelial-mesenchymal-transition program in tumor cells. In this regard, however, it was reported that, the age of the donor is the determining factor for the ability of MSCs to differentiate into neuronal cells. MSCs derived from younger donors (<45) are involved in the process of formation and modelling of pre-metastatic niches which create a supportive environment for colonization of circulating tumor cells (Brohlin et al., 2012; Hermann et al., 2010).

Immune-privileged MSCs are mainly implicated in tumorigenesis through promoting proliferation, angiogenesis, and metastasis, as well as generating the immunosuppressive microenvironment (Hayal, 2018).

In this manner, Brennen et al., reported that, on samples prior to expansion in tissue culture, in core biopsies from primary human prostatectomies, MSCs formed 0.01–1.1 % of the total cells present. In their study, MSCs on prostatectomy samples were FAP-, $CD90^-$, $CD73^+$, and $CD105^-$positive, and $CD14^-$, $CD20^-$, $CD34^-$, $CD45^-$, and HLA-DR-negative. They demonstrated that, prostate cancer-derived stromal cells (PrCSCs), and BM-MSCs were differentiate into osteoblasts, adipocytes, & chondrocytes. Contrary, primary prostate cancer-derived epithelial cells that were fluorescently-labeled PrCSCs & BMMSCs following IV injection, showed the ability to home to CWR22RH prostate cancer xenografts. According to studies, in sites of prostate cancer, MSCs may contribute to carcinogenesis, however, under therapeutic and/ or diagnostic circumstances, they may also potentially be capable to deliver cytotoxic or imaging purposes. Undoubtedly, MSCs play role in tumor progression; although the exact mechanisms of action of them on tumor cells are still being investigated (Brennen et al., 2013).

In addition, PCa-infiltrating MSCs like canonical MSCs derived from bone marrow, in response to inflammatory stimulus mobilize from their niche, and inhibit *T*-cell proliferation which based on tissue sources, species, culture methods and the activation pathway, and consequently will end in PCa progression. Moreover, the expression of bFGF, VEFG, and proteolytic enzymes like MMP cause extracellular matrix degradation, thus, tumor-infiltrating MSCs removal, restore immunological recognition and eliminate cancer cells through re-activating cytotoxic pro-inflammatory pathway (Krueger, 2019).

In contrast, PCa tumor generally expresses high levels of pro-inflammatory chemokines, such as CCL5 (RANTES), CXCL12 (SDF-1), and CCL2 (MCP-1), mobilizing the systemic immunomodulatory and inflammatory cells reservoirs such as MSCs recruited to PCa lesions. MSCs can also express various cytokine receptors to efficiently traffic into cancer and inflammation sites (Brennen et al., 2013). Chronic inflammation as a significant stimulus of developing benign prostatic hyperplasia (BPH) and PCa, transmits local or systemic chemotactic signals, uptakes innate immune factors, mediates MSCs absorption into injury sites, suppresses immune system and blocks regeneration functions. The uptake of stem cells into the tumor microenvironment by the circulatory system and their immunosuppressive actions indicates their potent therapeutic property for drug delivery or other aspects of therapy. MSCs can also be charged by micro-particles encapsulating pro-drugs or become genetically modified to express an altered form of effective protoxin or other components. They seem to be an ideal candidate to selectively deliver therapeutic ingredients to the PCa target sites. Therefore, they can be considered as tumor targeting vectors that carry genetic engineering platforms or micro-particles to malignant tissue (Williams et al., 2007; Ankrum et al., 2014; Zhao et al., 2015; Brennen et al., 2017).

3. Mechanism of action:

3.1. Regulation of gene expression

Since MSCs act in both tumorigenesis and tumor inhibition, efficiently manipulating them expresses particular genes and leave specific therapeutic effects. It was shown that charging MSCs with suicide genes such as caspase 9, herpes simplex virus, and thymidine kinase (TK) exerted potent antitumor effect. TK, the catalyzer of deoxythymidine phosphorylation, provides the phosphorylation of a wide range of nucleotide analogues, including prodrug ganciclovir (GCV). In suicide gene therapy, immortalization of human MSCs derived from fetal bone

marrow by simian virus 40 (SV40-hfBMSCs) was introduced as a stable source of MSCs for clinical aims. It is confirmed that MSCs expressing TK, in the presence of the prodrug GCV (a common antiretroviral drug) will express potent antitumor effects (Lee, 2013).MSCs derived from adipose tissue AD-MSCs incubated with prostate tumor cell upregulated apoptosis cell cycle regulator: caspase 3/7 genes and downregulated metastatic/invating gene: CCNA1. Reactivated GPX3 (tumor suppressor/proapoptosis gene) and downregulated genes in PCa such as SFRP1 GCA TIMP2 are other consequenses of. It has tratment with MSCs. It has been reported that MSCs treatment typically overexpressed some downregulated genes in PCa (GNRH1 EGR3 and CAMKK1). This study also revealed that AD-MSCs one of the molecules undergo downregulation in PCa exerted more potent antitumor effects while charged by pigment epithelium–derived factor (PEDF). This result is associated with arresting cell cycle inhibition of angiogenesis and decreased expression of genes involved in PI3KI/AKT signalling pathway androgen receptors growth and inflammatory pathways (COX3 IGF1) and metastatic genes such as PES (Zolochevska et al., 2014).

In 2014 Takahara et al. reported in vivo/in vitro effects of AD-MSCs on growth, and development of PCa cells, using androgen-nonresponsive (PC3) and androgen-responsive (LNCaP) cells. They examined the role of upregulated secretory factor, TGF- β1, as a carcinogenesis booster in PCa. TGF- β1 family proteins are involved in cell growth, division, survival and cell migration as well as pathophysiological responses. Based on clinical research, both up-regulated TGF-β1 in PCa tissues, and high urinary/serum levels of TGF-β1, are connected to angiogenesis, tumor metastasis, and consequently poor clinical outcome. Additionally, it is considered as a potent suppressor of cell cycle progression in various cell types. However, the researchers believe that TGF-β1 signaling stimulates AD-MSCs to leave antitumor effects. TGF-β1 restricts the growth of androgen-sensitive or castration-resistant cancer cells through inhibiting Smad2/3 or activating caspase3/7 signaling pathway which in turn induces apoptosis in cancer cells. Moreover, AD-MSCs through transforming lymphocyte T to cytotoxic phenotype inhibits prostate tumor progression leading to apoptosis induction (Takahara et al., 2014; Miles et al., 2012).

In a precise study on PCa gene therapy, AD-MSCs were used to deliver antiangiogenesis and proapoptotic cytokines, pigment epithelial-derived factor (PEDF) or melanoma differentiation associated gene-7 (MDA-7) to effectively reduce tumor cell viability in cancer cell culture medium. These two factors induced their anti-angiogenesis effects by inducing apoptosis and reducing endothelial tube formation. Both PEDF and MDA7 resulted in SDF1upregulation in AD-MSCs, while PEDF alone downregulated TNF, CXCR4 and upregulated TRAIL, on the other hand TNF was overexpressed by MDA7. Since these cytokines modulate SDF1/CXCR4 genes and MSCs migration toward the tumor site, it seems that SDF1/CXCR4 signaling pathway is involved in AD-MSCs migration ability and even in their survival and proliferation. Moreover, it has been reported that AD-MDA7 therapy potentially delayed the growth of PCa cells in vitro, suggesting MDA7 as an immune system mediator to exert antitumor effects. Generally, AD-PEDF seemed more effective in vivo and in vitro compared with AD-MDA7 in the manner of restricting tumor establishment. According to this, AD-PDEF could independently act as an antitumor agent (Zolochevska et al., 2012).

Co-culturing MSCs expressing lentivirus-mediated signal peptide TNF-α-Tumstatin 45–132 (SPTT-MSCs), with PCa cell exerted reliable anti-tumor effects. The tumor blood vessels were impaired by the TNF- α but Tumstatin left its effects via the death receptor-dependent apoptotic, blocked angiogenesis and expressed antitumor effects through amino acids 54–32. Zhang et al. also evaluated the alterations of ERK-1/2 (cell growth and survival operator), p-ERK-1/2, Akt and p-Akt in vivo and in vitro in SPTT-MSCs presence. The results implied a significant reduction in phosphorylation of ERK-1/2 and Akt. It seems that the activation of these signaling pathways have a vital role in antitumor treatments. Thus, lentiviral-transduced MSCs exerts antitumor effects through inducing apoptosis and inhibiting cell cycle or angiogenesis (Zhang et al., 2011). Table 1..

Yu et al. in 2016 focused on Sirtuin 1 overexpression in MSCs (MSCs-Sirt1) and their effects on PCa cell growth and development. NAD-dependent deacetylase, Sirt1, modulate various biological functions such as: metabolism, aging, DNA impairment, and tumor development. Histological analysis of PCa showed some remarkable changes in prostate tissue and low cell density. The necrosis also was observed by condensed chromatin staining and pykonosis. MSCs-Sirt1 antitumor activity is through modulating the inflammatory mediators. It has been shown that, the rats treated with MSC-Sirt1 have higher serum levels of IFN-γ-secreting natural killer (NK), mediated by JAK-STAT pathway. In addition, the CXC motif chemokine receptor 3 (CXCR3), activated in NK, regulated NK migration and also increased chemotaxis toward CXC motif chemokine ligand 10 (CXCL10) in rats treated with MSC-Sirt1. According to these results, MSCs-Sirt1 could successfully suppress PCa development by applying NK cells or macrophages in the tumor microenvironment (Yu et al., 2016).

The soluble signals that are generated by MSCs can mostly influence both PCa cell proliferation and growth, and also exert immune privilege activity. Since checkpoints are involved in cell cycle development or arrestment, fine-tuned cell cycle has a critical role in balancing cell division, differentiation and death. During the G1 phase, through stimulating the expression of proto-oncogenes, the cell cycle will transfer to S1. D-type cyclin induced by mitogens, promotes Cdk4/Cdk6 activity which in following leads to expression of E1/E2 cyclins and increases the action of Cdk2. These complicated pathways lead to G1 / S transmission and cell division enhancement. It seems that MSCs through paracrine or autocrine pathways can regulate cell cycle checkpoints, or restore them to normal. In S and G2M phases, the remarkable reduction in cell percentage prevents improper cell division. Blocked cancer progression is known as the primary outcome of this treatment (Rolfo et al., 2014).

3.2. Drug/gene delivery system

Transferring or expressing some specific genes into tumor site are known as unique methods of treatment. For this purpose, different vectors such as synthetic, cell-based, and viral vectors have been widely used. However, there are still some known limitations like low efficiency, lack of proper distribution in tumors and becoming sequestered by the reticuloendothelial system. The activated immune system following gene and virus-based therapies, may result in unwilling responses (Pahle and Walther, 2016; Raisin et al., 2017). Due to high ability to migrate in the tumor site, MSCs are pointed as suitable vehicles for gene therapy. In 2019, Muhammad, et al. represented two types of viral vectors; 1) conditionally replicating adenoviral vectors (CRAd), and 2) replication-defective adenoviral vectors (Adbic). These vectors enter the tumor site and replicate or lysis cancer cells. They can also carry therapeutic genes such as p14ARF/p53 tumor suppressors. In this manner, human MSCs are known as critical replicators of adenoviruses acting as vehicle systems to deliver adenovirus (type C) E1A/B genes. As the results indicated, MSCs-E1-mediated delivery of adenoviral vectors not only overcame systemic barriers to the delivery of adenoviruses or therapeutic genes, that also create proper propagation at tumor site. Tumor tropism of MSCs-E1 is associated to the expression of various growth factor receptors secreted from tumor cells, such as: PDGF, IL-6, leucine-37 (LL37), (PGE-2), SDF-1. The increased expression of apoptosis pathways of tumor suppressor genes P53 and p14ARF in prostate tumors results in apoptosis, suppressed angiogenesis and finally tumor progression (Muhammad et al., 2019).

As mentioned above, MSCs' ability to migrate, depends on the expression of chemokine and cytokine receptors which moves them toward the chemotactic proteins secreted by tumor cells. In the suicide gene therapy method, AD-MSCs get charged with non-toxic prodrugs. These components then become activated by MSCs enzymes to carry the suicide genes. For instance, the TK enzyme, as a deoxythymidine phosphorylation catalyzer can activate GCV, a synthetic

Table 1
List of summarized articles.

Model or cell line	Type of stem cell	Type of modification	Type and amount of injection/ Transplantation	Measured parameters	Findings	Ref
In vitro: DU145 and PC3 cells In vivo: nude mice bearing human PCa cells	Human fetal bone marrow-derived mesenchymal stromal cells (hfBMSCs)	Transduction of simian virus 40 (SV40) and herpes simplex virus thymidine kinase (TK) in hfBMSCs	The cell scaffolds containing 1×10^6 cells were implanted subcutaneously in the dorsal sides of mice (four scaffolds per mice)	Anti-tumor activity of hfBMSCs in presence of the prodrug ganciclovir	Inhibited tumor growth/ Low-volume but intermittent injection of MSCs has the same effects as high-volume single-dose injections	(Lee, 2013)
In vitro: PC3 prostate cancer cell	Human adipose-derived stromal mesenchymal stem cells (hAD-MSCs)	hAD-MSCs expressing pigment epithelium–derived factor (PEDF)	5×10^5 hAD-MSCs in conditioned culture medium exposed to PC3 cells	Prostate tumor cell growth, migration/ gene expression/ methylation changes in PCa/ Apoptosis/ Angiogenesis	hAD-MSCs -PEDF reduced tumor cell growth and angiogenesis/ ADSCs have the innate ability to migrate toward tumor cells/ They were non-tumorigenic/ Decreased androgen receptor signaling pathway and cell migration ability	(Zolochevska et al., 2014)
In vivo: LNCaP and PC3 cells induced in athymic nude mice	Human adipose-derived stromal cells (hAD-MSCs)	–	–	LNCaP cell or PC-3 cell proliferation and apoptosis/ tumor size	hAD-MSCs exerted inhibitory effects on LNCaP and PCa cells proliferation and induced apoptosis through caspase3/7 and TGF-β1 signaling	(Takahara et al., 2014)
In vivo: TC2Ras and PC3 cell were injected in mouse model	Adipose-derived stromal/ mesenchymal stem cells (hAD-MSCs)	hAD-MSCs delivering melanoma differentiation associated gene-7 (MDA-7) or pigment epithelial-derived factor (PEDF)	2×10^5 human hAD-MSCs -MDA7, or PEDF were commixed with 10^6 PC3 human PCa cell 4×10^5 mouse hAD-MSCs were commixed with 2×10^6 TRAMP-*C*2-Ras mouse PCa subcutaneously implanted into recipients	Tumor cell growth, angiogenesis / hAD-MSCs migration ability	Migration of hAD-MSCs expressing cytokines toward the tumor site / inhibition of tumor growth and angiogenesis / induction of apoptosis	(Zolochevska et al., 2012)
In vitro: PC3 and LNCaP cells In vivo: six-week-old male mice	Bone marrow mesenchymal stem cells of 8-week-old Wistar rats (BMSCs)	lentivirus-mediated signal peptide TNF-α-Tumstatin45–132-expressing in BMSCs (SPTT-MSCs)	In vitro: PC3 cells (5×10^4 per well) were cultured with 1×10^4 SPTT-MSCs In vivo: first 2×10^6 PC3 cells in 200 μl PBS, then after 2 weeks, then were injected with 2×10^6 SPTT –MSCs	Anti-tumor effects of SPTT-MSCs / tumor growth and proliferation	SPTT-MSCs inhibited cancer cell proliferation and induced apoptosis and exerted cytotoxic effects on cancer cells/ Akt and ERK signaling pathway are involved in anti-tumor effects	(Zhang et al., 2011)
In vivo: 6–8 weeks old C57BL/6 mice	Bone marrow mesenchymal stem cells 4–6 weeks old mice (BMSCs)	BMSCs overexpressing an NAD-dependent deacetylase sirtuin 1 (MSCs-Sirt1)	Subcutaneous administration of 1×10^6 RM-1 or PC2 cells in 200 μl PBS and then 2×10^5 MSCs	Tumor growth/ necrosis/ inflammatory responses	MSCs-Sirt1 suppresses tumor growth/ Macrophages and NK cells are main antitumor effectors of the MSCs-Sirt1/ IFN-γ and CXCL10 were highly expressed in MSCs-Sirt1 mice	(Yu et al., 2016)
In vitro: PC3 and LNCaP cells	Human amnion-derived mesenchymal stromal cells (hAMSCs)	–	–	PCa Cell proliferation	hAMSC conditioned media inhibited PCa cells proliferation and cell cycle progression	(Rolfo et al., 2014)
In vitro: LNCaP and C 4 – 2 cell line In vivo: subcutaneous xenograft models for human PCa in 6 to 8 week old mice	Human mesenchymal stem cells	Modified human MSCs with the adenovirus (type C) E1A/B genes	3×10^6 MSCs-E1s	Tumor growth/ anti-tumor activity/ apoptosis induction/	Transfer of therapeutic genes to the tumor site / no toxicity/ both vector exerted anti-tumor effects/activation of apoptosis pathway and its downstream pathway	(Muhammad et al., 2019)

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Table 1 (*continued*)

Model or cell line	Type of stem cell	Type of modification	Type and amount of injection/ Transplantation	Measured parameters	Findings	Ref
In vitro: human PC3 prostate cancer cells In vivo: SICD mic	Human adipose-derived mesenchymal stem cells (hAD-MSCs)	hAD-MSCs expressing Thymidine kinase (TK) in combination with ganciclovir (GCV) (TK-hADSCs/GCV)	In vivo: 5×10^5 PC3 cells Subcutaneously implanted, then intratumorally with 200 μl of TK-hAMSCs-MT or GCV 10 mg/mL	Cell migration ability/ anti-tumor activity	TK- hAD-MSCs migration towards the tumor tissue for an efficient tumor killing effect	(Blanco-Fernandez, 2021)
In vivo: nude mice	Human adipose mesenchymal stromal cells (hAD-MSCs)	ADSCs expressing thymidine kinase (TK), as cellular vehicles for ganciclovir (GCv), (TK- hAD-MSCs /GCV)	In vivo: 2.5×10^5 PC3 cells injected in the thigh muscle of mice and then 1×10^6 TK-hAD-MSCs /GCV	Drug delivery potential/ tumor therapy	hAD-MSCs survive long time within tumors/ hAD-MSCs useful vehicles to delivery therapeutic agents	(Vilalta et al., 2009)
In vitro: PC cells Du145, PC3, and LNCaP In vivo: Six- to 8-week-old athymic nude mice	Human adipose tissue–derived mesenchymal stem cells (AD-MSCs)	AD-MSCs engineered to express the suicide gene cytosine deaminase::uracil phosphoribosyltransferase (CD::UPRT)	In vivo: 3.0 × 106 PC3 cells, then 2×10^6 CDy-AD-MSC, or 10^6 AT-MSCs in 200 μl of PBS per each animal, intravenously injected into the lateral tail vein	Their potential to be a prodrug-activating enzymes/ PCa cell growth and development/ anti-tumor activity	Tumor regression in a dose dependent manner/ inhibiting the growth of tumor/ Activate prodrugs and prevent disease progression	(Cavarretta et al., 2010)
In vivo: tumor-bearing adult mice	Human neural stem cells (hNSCs) derived from human fetal telencephalon at 15 weeks of gestation	hNSCs encoding cytosine deaminaseh CD (HB1.F3.CD) \	In vivo: 1×10^6 TRAMPC2 PCa cells were injected subcutaneously then, 1×10^6 HB1.F3.CD stem cells in 100 μl saline systemically transplanted injected into the left ventricle	Chemoattractant ligands and receptors/ stem cell migration ability/ tumor growth	Stem cells migrated toward the tumor/ in combination with prodrug 5-FC decreased tumor/ cellular vehicles for cancer chemotherapy/ reduced tumor volume	(Lee et al., 2013)
In vitro: LNCaP cells	Human neural stem cells (hNSCs)	hNSCs transduced with cytosine deaminase (CD), rabbit carboxyl esterase (CE) or human interferon-beta (IFN-β)	–	Cell migration and proliferation/ Prodrug activating potential/ tumor trophic ability/ cancer cells viability	Successful transfer of therapeutic genes and prodrugs/ antitumor effects	(Yi et al., 2012)
In vivo: transgenic adenocarcinoma of the mouse prostate model (TRAMP) and C57BL/6 mice	Adipose-tissue and bone-marrow MSC derived from murine or human MSC (ADSCs/BMSCs)	hAD-MSCs /BMSCs expressing prodrug converting; cytosine deaminase::uracil phosphoribosyltransferase (CD-MSC)	In vivo: 2×10^6 TRAMPC1 and TRAMPC2 cells subcutaneously injected in mice, then 2×10^6CD-MSC cells intravenously injected which followed by intraperitoneal administration of 5-fluorocytosine	Prodrug activating potential/ stem cell survival/tumor regression	Autochthonous prostate tumor regression in immune-competent mice/ inhibiting tumor growth/ MSC as vehicles of prodrug activating enzymes	(Abrate et al., 2014)
In vitro: PC3 and DU145 cell line In vivo: subcutaneous PC3 tumor model in nude mice	Bone marrow mesenchymal stem cells (BMSCs)	BMSCs overexpression of TK-BMSCs, in the presence of prodrug ganciclovir (GCV).	2×10^7 PC3 or DU145 cells subcutaneously injected at the dorsal site of nude mice, then10^6 TK-BMSCs was injected intravenously	Antitumor agent delivery vehicles/ tumor tropism capabilities/ tumor development	Ability to migrate toward PCa cells/ inhibited tumor growth in the presence of prodrug ganciclovir	(Song et al., 2011)
In vitro: PC3, LNCaP and C4-2B cell line	Human bone marrow mesenchymal stem (BMSCs)	BMSCs expressing death ligand TRAIL (TRAIL) full-length TRAIL (FL-TRAIL) or soluble TRAIL (sTRAIL)	–	Inducing apoptosis/ metastatic cytokines expression	TRAIL-induced apoptosis/ MSCs producing sTRAIL have more potent effects than cells expressing FL-TRAIL/ TRAIL can induce cytokines	(Mohr et al., 2019)
In vitro: PC-3, DU145, LNCaP, 3 T3 cell lines In vivo:PC-3 PCa cells were implanted in the flank of mice	Mesenchymal stem cells (MSCs)	MSCs and their secreted microvesicles containing assembled gold nanostars (GNS) –	Intravenous injection (218.65 μg of GNS in 5 × 10^5 MSCs, 200 μl)	Photo-thermal response/ tumor inhibitory effects/ GNS distribution into tumor site	GNS-loaded MSCs showed a broad distribution in tumor/ treated group showed a better photo-thermal response/ tumor inhibition effect/ tumor suppressive effect/ a broad distribution of the GNS/ improved the anti-tumor PTT efficacy	(Huang et al., 2019)

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Table 1 (*continued*)

Model or cell line	Type of stem cell	Type of modification	Type and amount of injection/ Transplantation	Measured parameters	Findings	Ref
In vivo: transgenic adenocarcinoma of the mouse prostate (TRAMP) mice, 6-week-old	Human umbilical cord blood mononuclear cells (HUCBs)		200×10^6 HUCBs were injected *retro*-orbitally into the venous plexus	Survival/ PCa development	Delay the onset of prostate cancer and improve survival/ increased the life span/ retards the development of prostate cancer	(Ende et al., 2006)
Human subjects	Bone marrow-derived mesenchymal stem cells (BMSCs)	–	systemically infused allogeneic MSCs single intravenous infusion 4–6 days prior to prostatectomy 1×10^6 or 2×10^6 cells per kilogram	BMSCs accumulation within PCa tissue/ dose dependent toxicity/ homing ability	MSCs were undetectable in all subjects/ MSCs did not home primary tumors in sufficient levels	(Schweizer et al., 20192019)
In vivo: Male NU/J athymic nude mice	iPSC-MSCs derived from mesenchymal stem cells (MSCs)	Nanovesicles are made from intact iPSC-MSCs (NVs- iPSC-MSCs)	5 mg/kg body weight NVs- iPSC-MSCs twice a week for 3 weeks	Tumor growth / drug and other ligand delivery	Inhibit tumor development/ effectively drug delivery	(Zhao et al., 2021)
In vitro: PC3 and MCF7 cells In vivo: mice bearing PC3 cells	Mesenchymal stem cells (MSCs)	Nanoghosts (NGs) produced from the membranes of MSCs (NGs-MSC)	Intraperitoneal (IP) or intravenous (IV) administration of MSCs-NGs	Tumor targeting ability/ effect of drug loaded MSC-NGs/	Tumor accumulation of MSC-NGs and effectively drug delivery/ destroy cancer cell	(Toledano Furman et al., 2013)
In silico In vitro: LNCaP cells In vivo: male BALB/c nude mice- 5 week -old	Human bone marrow mesenchymal stem cells (BMSCs)	Exosomal miR-205 derived from BMSCs	5×10^5 BMSCs were injected into each nude mouse through a tail vein	PCa cell proliferation/ invasion, migration, and apoptosis were detected in vitro/ f hBMSCs-miR-205 on tumor growth were investigated in vivo	hBMSCs -derived exosomal miR-205 caused retards prostate cancer progression by inhibiting RHPN2/ Overexpression of miR-205 inhibits cell proliferation, invasion, and migration, and promotes apoptosis in prostate cancer cells	(Jiang et al., 2019)
In vitro: LNCaP and MDA-MB-231 cells In vivo: male athymic nude mouse, 6wk old	Human mesenchymal stem cells (MSCs)	MSCs were loaded with poly (lactic-*co*-glycolic acid) (PLGA) microparticles (MPs) that encapsulate the macromolecule G114	1×10^3 to 1×10^5 MSCs was inoculated subcutaneously to the left armpit of each nude mouse	Prostate specific antigen level/drug delivery platform/ cell growth/ promotion of apoptosis	PSA-secreting PCa cell line were decreased/ tumor degradation/ induction of apoptosis	(Levy et al., 2016)

deoxyguanosine analogue mainly used as an antiviral drug that its phosphorylation induces apoptosis by inhibiting DNA polymerase and chain termination. Phosphorylated GCVs are also transmitted from transduced dying cells through passive transfer or gap junctions to neighboring. In the current study, a bio-hybrid scaffold was developed to elevate the persistence of the MSCs expressing TK in the tumor. Based on the results TK-MSCs/GCV platform had a potential antitumor activity (Blanco-Fernandez, 2021). A similar result was obtained by using AD-MSCs as TK /GCV vehicles. In this method, long survived AD-MSCs were suitable means of therapeutic transmissio in the environment around the tumor (Vilalta et al., 2009).

Inactive and/ or non-toxic prodrugs can biologically get activated when delivered into the targeted environment. The stem cells that contain their own activator enzymes are also sufficient prodrug carriers. In 2010, by Cavarretta et al., AD-MSCs were engineered via retrovirus transduction to express the yeast suicide gene cytosine deaminase:: uracil phosphoribosyl transferase (CD::UPRT). This method aimed to convert a low toxic antifungal substrate 5-fluorocytosine (5-FC) into a very toxic antitumor form, 5-fluorouracil (5-FU). Based on results co-administration of engineered AD-MSCs with 5-FC can inhibit androgen-independent PCa cell growth. After intracellular processing stages, 5-FU metabolite inhibited the cell growth and proliferation by suppressing RNA and DNA synthesis. By the increasing passages, the genes will sensitize their carriers and consequently decline their survival rate. In chemotherapy, focusing on effective treatment and preventing toxicity are major approaches for cell survival rates (Cavarretta et al., 2010).

It was also reported that immortalized human neural stem cells (hNSCs) rapidly expand to the required therapeutic amount. Based on their migration ability and tumor tropism properties, NSCs are used to carry the CD gene. These modified cells can be utilized in therapeutic applications according to their high transduction efficiency. Some molecular chemoattractant/receptor pairs such as SCF/c-kit, SDF-1/CXCR4 and VEGF/VEGFR-1/2/3, EGF, PDGF are also known as the mediators of NSCs brain tumor-targeting behavior. Lee et al. confirmed the transcription of various ligands which play a role in cell migration ability such as SCF, SDF-1 and VEGF in PCa cell line (TRAMPC2) and the corresponding receptors, c-kit, CXCR4, and VEGFR1/2/3 in the NSCs. Generally, NSCs that migrate toward tumor cells are suggested as a cellular vehicle for cancer chemotherapy in PCa (Lee et al., 2013).

Another study also confirmed that hNSCs transduced with bacterial CD could prevent disease alone or in combination with the encoding rabbit carboxyl esterase (CE) or human interferon-beta (IFN-β) to generate HB1.F3.CD, HB1.F3.CE and HB1.F3.CD.IFN-β cells. It is well established that tumor and stem cells rolling in MSCs tumor trophic effects, respectively express high levels of VEGF and VEGFR 2. However, both CD and CE can convert non-toxic 5-FC and CPT-11 into toxic compounds, 5-FU or sN-38. In the presence of 5-FC, PCa cells are remarkably suppressed by B1.F3.CD and HB1.F3.CD.IFN-β cells. HB1.F3.CD.IFN-β cells demonstrating the “double punch system” involved in the simultaneous expression of CD and IFN-β. As the result, this healing treatment method induced cancer cells apoptosis (Yi et al., 2012).

Abrate and colleagues utilized the tumor lesions tracking property of MSCs through suicide gene, in which by converting 5FC into activated drug 5FU, vehicle the yeast fusion gen CD. They reported that

intravenous injections of MSCs expressed CD and administration of the prodrug 5FC lead to autochthonous PCa tumor regression in immune-competent mice. There was no significant increase in IL-2 of mice treated with murine or human MSCs. Also, any significant difference in body weight and no apparent sign of therapy-related toxicity was observed in experiments. They reported tumor growth inhibition while controlling tumor regression seemed unsuccessful, as a possible result of inefficient dosage of prodrug, untimely therapeutic intervention and immune system deficiency. In this report, to indicate the therapeutic cell survival duration, the amount of injected pro drug, and delayed tumor progression tumor volume was carefully monitored (Abrate et al., 2014).

Moreover, song et al. used self-inactivating vectors as lentiviral systems. They examined MSCs toward four different tumor cell lines in vitro; the cells were infected with the herpes simplex virus TK gene using lentiviral transduction. The results showed a rise in homing ability of MSCs-TK of tumor sites in vivo which lasted enough to exert anti-tumor effects. The cancer cells or their microenvironments secrete various cytokines or chemokines moving towards each other that express cytokine and chemokine receptors on the MSCs. However, MSCs-TK-GCV in addition to being a suitable delivery vehicle also prevented toxicity (Song et al., 2011).

The dead ligand TRAI (therapeutic gene) with the property to be carried by MSCs, comes in two main forms: 1) the full-length/membrane-bound protein (FL-TRAIL), and 2) The engineered soluble TRAIL version (sTRAIL). TRAIL can trigger cancer cell death by its apoptosis-inducing receptors named TRAIL-R1/2. Since PCa cells and some other tumors are TRAIL resistant, it is necessary to apply other sensitized treatments. In resistant PCa, mutations in PTEN elimination can activate PI3K.AKT signaling, which consequently may result in cancer progression. Besides this, activation of the AKT signaling pathway causes resistance to TRAIL. sTRAIL and rTRAIL induce IL-6 and CXCL5/ENA-78 expression in TRAIL-resistant PCa cells. CXCL5/ENA-78 the member of CXC chemokine family can be activated by inflammatory cytokines such as TNF-α or IL-1 and role disease progression enhancement however, IL-6 with its dual role can act as a pro or anti-inflammatory factor. Based on evidence, by the expressed combination of MSCs-sTRAIL or MSC-FL-TRAIL, and PC3, IL-6, the levels of CXCL5/ENA-78 remained unchanged. Although the exact mechanisms were not understood, it seems that MSC-delivering TRAIL in combination with AKT inhibitor revealed a therapeutic approach in treatment of advanced PCa. Moreover, following more robust apoptosis induced by MSCs-FL-TRAIL, MSCs-sTRAIL acted more effectively (Mohr et al., 2019).

In recommend photo-thermal therapy (PTT), photosensitive agents are needed to achieve selective thermal ablation in response of laser irradiation. Gold nano-particles (GNS) are known as a promising photo-thermal agents for PTT, in which a wide distribution of nanoparticles and accurate tumor targeting is essential for cancer cells removal. Different carriers with the ability to cross the biological barriers, such as platelets, macrophages, iPSCs, NSCs, and MSCs, are applied to increase the distribution and accumulation of nanoparticles. MSCs, for example, are widely used as powerful platforms to carry on nanoparticles. Huang et al. in 2019, reported that GNS loaded MSCs could migrate to the prostate tumor site and have extensive intratumoral distribution, once penetrated, released GNS-containing micro-vesicles into cancer cells. As a result, this treatment facilitated intratumoral GNS distribution, which in turn led to the better PTT effect in vivo. Moreover, the combination of MSCs with GNS inhibits teratoma formation, which is a significant concern of stem cell transplantation (Huang et al., 2019).

The transplantation of the human umbilical cord blood mononuclear cells into transgenic adenocarcinoma in a mouse model of PCa (TRAMP) showed: 1) remarkably delayed malignancy appearance in mice as the result of MSCs injection into the systemic circulation. 2) significantly increased survival rate in mice by receiving this treatment before and after malignancy appearance and 3) increased survival rate in the mice models with these cells present in their blood samples, compared to control group (Ende et al., 2006).

In another study, despite the well-tolerated systemic injection of MSCs, the lack of enough stem cell homing into tumor area resulted in limited effectiveness. It has been shown that $\geq$1 % of total tumor cells of microparticles surrounded MSCs charged by PSA-activated prodrugs were adequate. However, genetic engineering, preconditioning regimens, and cell surface modifications can effectively increase stem cell yields (Schweizer et al., 2019).

4. Mesenchymal stem cell derivatives

In 2016, natural extracellular vesicles (EVs) and EV-mimetic nanovesicles (NVs), were reported by Kim et al. as more likely absorbed by cancer cells through endocytic mechanisms than synthesized nanoparticles. They also observed that in drug resistance cancer cells, such drug vehicle acted properly. In comparison with free drugs that are mainly absorbed by cell membranes through passive diffusion, drugs carried by NVs and EVs, are released distally to the cell membranes (Kim et al., 2016). This property may prevent them from being extruded by cell membrane transporters (Raisin et al., 2017). Additionally, advanced PCa cells can express high levels of Integrin α3, α6, and β1 (ITGA3/A6/B1), EphA2 at their surface, and also can increase the levels of extracellular matrix (ECM) components including fibronectin (FN), osteopontin (OPN), and hyaluronan in tumor stroma. Excessive expression of these molecules leads to cancer stem cells survival and metastasis, which prolongs treatment. MSCs and their EVs can carry various ligands of each named molecule, including Integrin α4, α11 and β1 (ITGA4/A11/B1), CD44, CD63, TSPAN4, ICAM1, VCAM1, CD9, CD81, and Cx43. PCa cells are more likely to absorb EV-mimicking nanovesicles from MSCs derived from human induced pluripotent stem cells (iPSCs) than others drug carriers such as EVs, nanoghosts, and liposomes. The nanovesicles effectively transfer the cytoplasmic compounds toward the tumor site. It was reported that, nanovesicles loaded with docetaxel (a chemotherapeutic drug), successfully crossed the cell membrane barrier effectively suppressed PCa tumor growth (Zhao et al., 2021).

Various surface molecules are the bridge to link MSCs and PCa cells. Interestingly, the isolated membrane fractions of tumor cells are potent MSCs attractants containers. Nanoghosts (NGs), with the ability of entrap medications, are derived from membrane of MSCs in a reproducible process. The hypo-immunogenicity and the capability of targeting various cancers in different stages make NGs a better option compared with MSCs in treatment. This procedure is suitable for active cancer-targeted drug delivery. Based on findings, after IP or IV administration of NGs-MSCs, encapsulating the sTRAIL, they home into tumor environment and significantly exerted an anti-cancer effect. After both administrations, a significant amount of NGs was accumulated at the tumor site, but one week later, substantial NG accumulation of NGs were observed in IP-administered mice. It seems that binding and NGs fusion within the tumor cells can destroy the cell membrane and disrupts the organization of the cytoskeleton. Although factors such as toxicity or short half-life are limited aspects of this cancer treatment, the results suggested that such treatments in the future can be considered as effective solution (Toledano Furman et al., 2013).

Even small volume of stem cell-derived exosomes (40 ~ 100 nm) is known as potential therapeutic target for cancer treatment and paracrine actions of MSCs carrying on proteins, mRNAs and miRNAs, among cells (Zhu et al., 2012). Studies revealed the reduced amount of miR-205 expression in PCa; additionally, exosomes derived from human BMSCs overexpressed miR-205 inhibited cell proliferation, migration and invasion. Downregulated rhophilin Rho GTPase binding protein 2 (RHPN2), which encodes members of the rhophilin family of Ras-homologous (Rho)-GTPase binding proteins, resulted in apoptotic pathways activation and tumor inhibition (Jiang et al., 2019). It has been reported that poly lactic-*co*-glycolic acid (PLGA) micro particles-charged MSCs, can encapsulate a thapsigargin-based PSA-activated prodrug, called macromolecule G114. Moreover, stem cells are also

proper carriers to deliver prodrugs to the tumor sites in the case of preventing tumor growth and inducing the death of PSA-secreting cells (Levy et al., 2016).

5. Limitation

Limitations in providing a large biological bank of MSCs in various animals make them remain with restricted proliferation capacity. On the other hand, such cells from diverse donors are prepared with different types of protocols in numerous laboratories thus it is difficult to classify cells and to compare reported data by different laboratories. Therefore, to perform such studies a large bank of these cells should be collected (Zhao et al., 2015).

Based on the evidence, MSCs through activating the Jagged1/Notch1 pathway mediates tumorigenesis process in the prostate cancer tumor environment. These cells cause PCa cells to acquire the characteristics of MSCs, thus to contribute the progression of the disease. Inhibiting this pathway in vivo/ in vitro is known as a therapeutic target to control the disease (Cheng et al., 2021). However, clinical studies have shown that, MSCs containing prodrug activators encapsulated in internalized microparticles must have access to more than one percent of all tumor cells in order to exert their therapeutic effects. Physical barriers may also prevent them from reaching the tumor site sufficiently. Moreover, in contrast with the non-inflammatory immune microenvironment of the PCa cells with low levels of cytotoxic *T*-cells, the homing ability of injected MSCs can be catalyzed (immunosuppressed) by myeloid-derived suppressor cells, regulatory *T*-cells, and already presented endogenously recruited MSCs within the tumor [70]. Therefore, despite the proven therapeutic usage of these cells in various studies, further studies are needed to investigate their exact role.

6. Conclusion

Diverse donors extracted MSCs with complex roles in the biology of malignant tissues are strongly recommended in a wide range of experimental and clinical protocols. The property of MSCs cells is particularly known in both pro and anti-tumorgenic effects. As it is realized MSCs can either promote tumorgenesis through modulating immunity or inhibit tumor progression. However, the whole story is far more complex and for future research on prostate cancer microenvironment studies.

Despite our incomplete understanding of stem cells in cancer physiology and treatment, available data demonstrates such cells have basically inherent troposim for prostate cancer tumor. These cells with the natural capacity of tumor trafficking, transferring or exposing drugs into tumor sites and immonustimulatory effects are represented as cell-based delivery vector potential for therapeutic and diagnostic purposes. Although there are some limitations in utilizing MSCs, but their ability to transmit genes or activate drug systems has been mentioned them. As recently reported, stem cells role in both the initial and advanced levels of PCa yet have to be fully elucidated but over the past few years we are sure to represent it as a reliable growing trend in anti-prostate cancer strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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