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Role of Hyperbaric Oxygen Therapy in Prostate Tumor Microenvironment and Cancer Stem Cell Niche

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Abstract

Hyperbaric oxygen therapy (HBOT), has gained attention in recent years as a potential adjunct to conventional cancer treatments, particularly in addressing tumor hypoxia which is extensively employed as a post-injury treatment, is the administration of >92% oxygen at 1.5- 3.0 ATA for 60-120 minutes. HBOT is attributed to at least five mechanisms including epigenetic regulation of gene expression, mechanical effects, bacteriostatic effects, hyperoxygenation for carbon monoxide and cyanide poisoning treatment, and restoration from hypoxia. HBOT is emerging as a promising adjunct to conventional cancer treatments, particularly in overcoming tumor hypoxia—a key feature of the tumor microenvironment (TME) that drives tumor growth, therapy resistance, and metastasis. By delivering high concentrations of oxygen under pressure, HBOT improves tissue oxygenation, potentially suppressing tumor growth, reducing hypoxia-induced resistance, and enhancing the efficacy of chemotherapy and radiotherapy. Studies have shown its anti-angiogenic effects in some tumor models and its ability to alkalize the TME. In prostate cancer, HBOT has demonstrated potential in slowing tumor growth and increasing treatment sensitivity in cell lines like DU-145 and LNCaP. Additionally, it may enhance the effectiveness of radical prostatectomy and chemotherapy by synchronizing cell cycles. Therefore, the current review highlights the key aspects of HBOT in prostate cancer therapy particularly their role addressing late radiation tissue injury (LRTI) and tumor hypoxia. We have succinctly captured the multifaceted role of HBOT in modifying the TME and comprehensive overview focuses on the advanced approaches to eliminate prostate cancer stem cells (PCSCs) and exploration of their role in anti-androgen resistance, as well as stemness-related signaling pathways and growing body of evidence supporting the potential benefits of HBOT in prostate cancer treatment. Further clinical research on HBOT could lead to significant advancements in prostate cancer treatment.

Key words hyperbaric oxygen, hypoxia, tumor microenvironment, cancer stem cells, therapy

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Introduction

For the last four decades, Hyperbaric Oxygen Therapy (HBOT) has been suggested for a wide range of medical conditions [1]. After World War II, the U.S. Navy and Air Force recognized its need, leading to a hyperbaric medicine program in the 1960s [2]. Initially, HBOT was used primarily for decompression sickness in divers [3]. The concept of manipulating atmospheric pressure for medical purposes dates back to 1662, when British clergyman Henshaw designed the 'Domicilium, ' a sealed chamber where pressure was controlled with valved organ bellows [4]. Today, HBOT offers a promising non-invasive treatment, delivering elevated PO2 at pressures above 1 ATA, even allowing mechanical ventilation [5-7]. HBOT involves breathing 100% oxygen at pressures above normal atmospheric levels, typically 2-3 ATA, enhancing oxygen dissolved in the blood by five to twenty times. This increased oxygen availability supports mitochondrial function, promotes hypoxic tissue recovery, prevents reperfusion injury, strengthens immune response, and encourages collagen and endothelial cell formation. Sessions usually last 60 to 90 minutes, with critical care monitoring available if needed [7-10]. HBOT improves tumor oxygenation, counteracting hypoxia and potentially reversing its effects [11].

For HBOT to be efficacious, it can be administered through inhalation in the ambient environment, via an endotracheal tube within a monoplace chamber, or through masks, well fitting hoods, or endotracheal tubes within a larger multi-occupant chamber. The duration and barometric pressure of individual treatments may also varry, spanning from 45 minutes for carbon monoxide poisoning to nearly 5 hours for certain severe decompression disorders [12]. The decision regarding the use and qualification for HBOT was made by a collaborative team consisting of plastic surgeons, anesthesiologists, and intensive care specialists, in alignment with the guidelines set forth by the Undersea and Hyperbaric Medical Society and the criteria established by the European consensus conference on hyperbaric medicine [13]. Recent studies suggest that pre-surgical HBOT may reduce complications and it can also be combined with surgery, radiotherapy, chemotherapy, and photodynamic therapy [14, 15].

HBOT is extensively employed as a post-injury treatment [16]. HBOT chambers, which are hermetically sealed, elevate barometric pressure and provide >92% O for breathing. Treatments generally involve pressurizing the environment to 1.5-3.0 $_2$ ATA for 60-120 minutes, usually once or multiple times daily [17, 18]. HBOT can be administered through inhalation in the ambient environment, endotracheal tubes in monoplace chambers, or masks and hoods in multi-occupant chambers [19]. HBOT accelerates tissue healing and enhances physiological aspects by increasing oxygen delivery to injured areas, enhancing the oxygen diffusion gradient, and improving oxygen saturation in blood plasma, which helps overcome compromised blood flow and supports cell growth and wound healing (**Figure 1**) [20-22]. Fortunately, the side effects of HBOT are typically mild [23]. The therapeutic impact of HBOT is attributed to at least five mechanisms: epigenetic regulation of gene expression, mechanical effects, bacteriostatic effects, hyperoxygenation for carbon monoxide and cyanide poisoning treatment, and restoration from hypoxia [24, 25].

HBOT modifies signalling pathways related to hypoxia and wound healing, notably affecting hypoxia inducible factor (HIF) and heme-oxygenase (HO) pathways [26]. It also influences apoptotic pathways, including the mitochondrial pathway, tumor suppressive endoplasmic reticulum stress (ERS), and autophagy due to decreased ratio of Bcl-2/Bax, increased level of p53, cleaved Caspase3, GRP78, CHOP, and LC3 in response to HBOT combined with melatonin on gastric cancer [27]. In severe brain disorders, HBOT reduces flammation, suppresses proinflammatory cytokines (IL-1β, IL-12, TNFα, IFNγ), and boosts the anti-inflammatory cytokine IL-10, indicating potential cytoprotective effects (**Figure 1**) [28]. HBOT can stimulate angiogenesis in various organs (**Figure 1**) [29]. HBOT has been extensively documented for its ability to improve Late Radiation Tissue Injury (LRTI) in various tissue types (**Figure 1**) [30]. HBOT is known to impede the advancement of genetically restricted autoimmune manifestations (**Figure 1**) [31]. While HBOT presents significant therapeutic potential, it is not without limitations, as discussed later in this paper.

Role of HBOT in cancer therapy

Cancer poses a considerable worldwide health challenge. Some people may experience late radiation tissue injury (LRTI), which can develop months or even years after radiotherapy. Therefore, HBOT can be used as a treatment for LRTI due to its ability to stimulate neovascularization in the damaged tissues of patients who have undergone radiation therapy [32, 33]. HBOT was found to address tumor cell hypoxia and has been employed in conjunction with radiotherapy [34, 35]. Therefore, HBOT was associated with a controlled and reduced occurrence of local tumor recurrence [36]. There is a hypothesis positioning that improving oxygenation via HBOT in hypoxic tumors could potentially lead to the inhibition of STAT3 activation, thus contributing to the suppression of tumor growth [37]. From the FDA “As of July 2021, the FDA (FDA.gov) has cleared hyperbaric chambers for the following disorders (**Table 1**).

HBOT and tumor microenvironment

The effectiveness of cancer therapy is significantly impacted by the TME, mainly due to hypoxia and associated low pH within solid tumors [38]. Hypoxia represents a basic characteristic of solid tumors and significantly results in chemotherapy resistance and can result in irregular vascular growth, leading to the formation of heterogeneous regions characterized by hypoxic stress [39, 40]. Along with hypoxia, tumors exhibit three distinct degrees of oxygenation exhibited by the tumor includes: normoxic (found at the edge of the tumor and among groups of cells within the tumor mass), hypoxic (adjacent to necrotic areas, distant from blood vessels), and anoxic (at the tumor's core). This complex oxygenation pattern renders the TME hospitable to the growth of tumors [41]. This oxygenation of a tumor ultimately hinges on the equilibrium between oxygen supplied by blood vessels and oxygen taken up by the tumor cells [42]. HBOT also brings about positive biochemical and cellular outcomes, such as reducing edema, narrowing blood vessels, enhancing phagocytosis, promoting neovascularization, and stimulating collagen production by fibroblasts [43]. Since HBOT has generally been shown to promote cellular and vascular proliferation in normal tissues and wounds (though the exact mechanisms remain unclear), it was initially assumed that it might also induce angiogenesis in cancers. However, contrary to expectations and previous reports in the literature, HBOT has demonstrated an anti angiogenic effect in two mammary tumor models and one glioma model. Additionally, several studies have reported no significant changes in angiogenesis following HBOT treatment [44]. Apart from this it also suppresses the activity of HIF-1α [45]. Therefore, HBOT has been among the various approaches applied in clinical and experimental settings to enhance tumor oxygenation and alkalize the TME [46]. HBOT has been employed in conjunction with radiotherapy to address malignant tumors [47]. Basic and clinical studies have demonstrated that HBOT can enhance tumor radiosensitivity [48]. Also, administering radiotherapy after HBOT can be utilized to boost the effectiveness of clinical treatments

Table 1. The disorders that have been cleared by FDA for HBOT.

The following disorders that have been cleared by FDA for HBOT	References
Air and gas bubbles in blood vessels	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Anemia (severe anemia when blood transfusions cannot be used)	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Burns (severe and large burns treated at a specialized burn center)	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Carbon monoxide poisoning	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Crush injury	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Decompression sickness (diving risk)	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Gas gangrene	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Hearing loss (complete hearing loss that occurs suddenly and without any known cause)	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Infection of the skin and bone (severe)	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Radiation injury	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Skin graft flap at risk of tissue death	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Vision loss (when sudden and painless in one eye due to blockage of blood flow)	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts
Wounds (non-healing, diabetic foot ulcers)	https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts

[49]. HBOT has even demonstrated the ability to reduce tumor interstitial fluid pressure (IFP), which can enhance the penetration of molecules and nanoparticles and can therefore be used in nanomedicine [50, 51].

Tumor micro environment (TME)

The role of the TME in tumorigenesis is well-established, encompassing tumor cells that engage with neighboring cell via circulatory and lymphatic systems, thereby enhancing the initiation and advancement of the cancer [52]. The makeup of TME is heterogeneous, consisting of various resident and host cells, secreted factors, and extracellular matrix components (**Figure 2**) [53]. The TME typically comprises over 30 different types of non malignant cells that infiltrate the tumor [54]. Different types of immune and non-immune cells which secrete several types of factors are found within the TME framework. These in turn result in a chronic inflammatory, immunosuppressive, and pro-angiogenic intratumoral environment [55]. Several studies propose that the innate immune cells, such as macrophages, neutrophils, dendritic cells, innate lymphoid cells, myeloid-derived suppressor cells, and natural killer cells and the adaptive immune cells, including T cells and B cells, help in the development of the tumor if these cells are found in the TME, where they can be reprogrammed [56]. Hence, we can find a wide variety of tumor infiltrating immune cells in the TME, including B and T lymphocytes, natural killer (NK) cells, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), among others (**Figure 2**) [57]. The modification of the immune context within the TME leading to the tumor growth, metastasis, and resistance to immunotherapy is usually facilitated by MDSCs and TAMs (**Figure 2**) [58]. Therefore, In the TME, various mechanisms, including immunosuppression, angiogenesis in support of tumor growth and metastasis and cancer cell proliferation, are found to be enhanced by TAMs (**Figure 2**) [59]. Apart from this, A diverse group of cancer cells are also seen in the tumor tissue including cancer stem cells (CSC) which later undergo differentiation into cancer cells (**Figure 2**) [60] of which the tumor progression is mainly carried out by mesenchymal stem cells (MSCs) [61].

TME in prostate cancer

Prostate cancer (PCa) exhibits significant diversity, and gaining

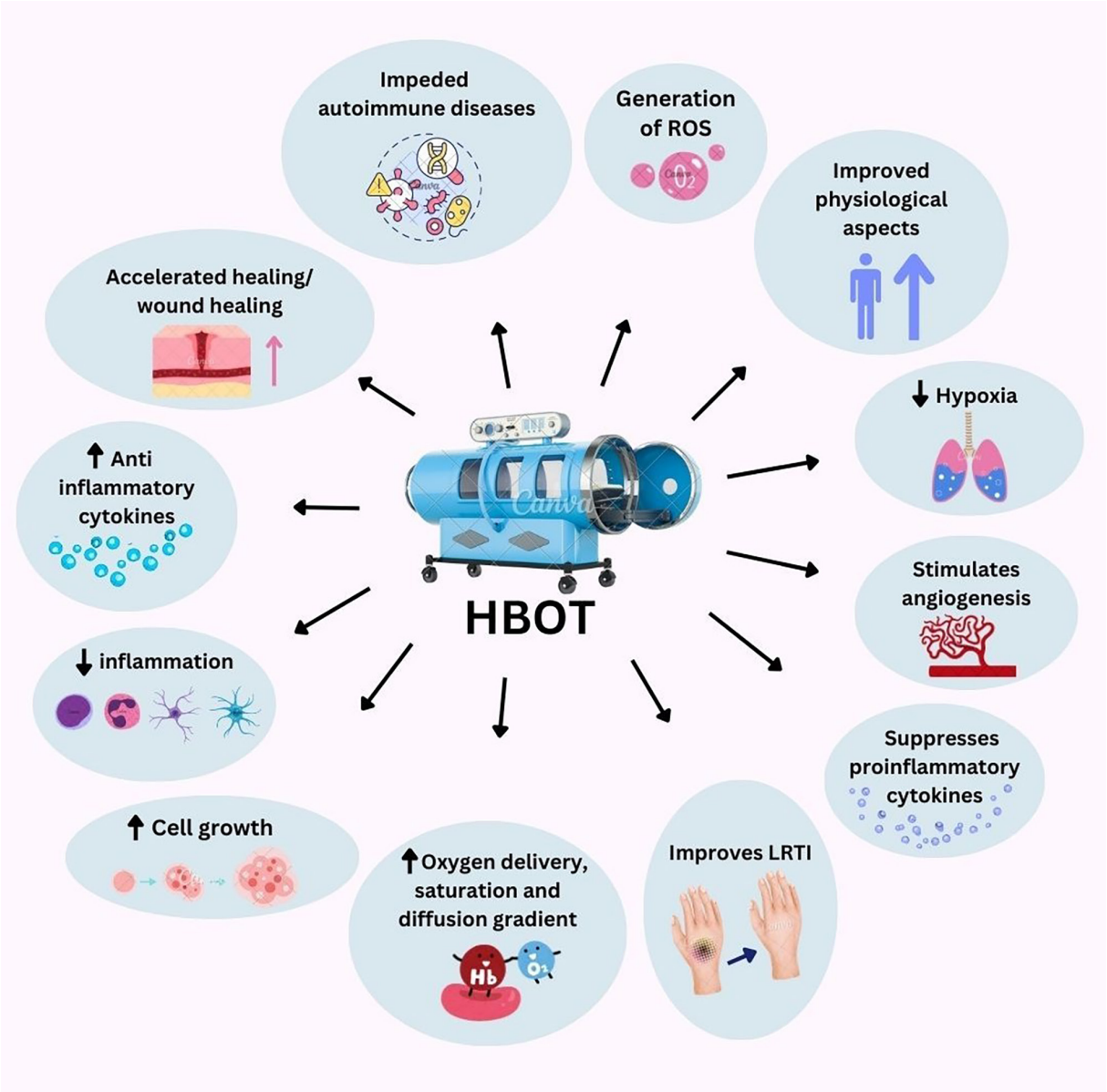

Figure 1. Effects of HBOT. This figure was created with Canva.com.

insights into the interplay between intricate genomic and epigenomic changes will facilitate the development of precision treatments [62]. PCa develops from specialized epithelial cells and/or progenitor cells due to the intricate crosstalk betwixt genetic factors, the cellular microenvironment, and the environment of the host [63]. Although there has been a decrease in the mortality rate over the past three decades due to the introduction of new treatment approaches, PCa continues to be the most prevalent form of cancer in males globally. While the five-year survival rate for localized PCa is found to be nearly 100%, the survival rate declines significantly to just 31% for metastatic prostate cancer (mPCa) [64] PCa displays a distinctive TME contour, characterized by unique features in these populations. The occurrence of cytotoxic and helper T lymphocytes at the edges of tumors has been linked to positive prognostic outcomes and clinical significance in various types of cancers [65]. TAMs are monocytes that are recruited and redirected by tumor cells through chemokine signals. This recruitment is accompanied by their migration to the TME, where they cause DNA damage in nearby endothelial cells and secrete growth factors that promote tumor growth in PCa [66]. The activation of macrophages by exosomes is now recognized as a pivotal factor in cancer advancement since macrophages activate additional signaling pathways that facilitate tumor growth, invasion, tumor-related angiogenesis, tissue inflammation, and immunological restructuring. Research has indicated that PCa cells under hypoxic conditions release exosomes containing high levels of lactate, a glycolysis byproduct which can encourage nearby macrophages, such as TAMs, to adopt M2-like characteristics, ultimately fostering an immunosuppressive environment conducive to tumor proliferation and progression (**Figure 3**) [67]. The TME plays a crucial role in influencing the survival and progression of PCa by promoting immune evolution in the cells of tumors by often involving the activation of the PD-1/PD-L1 axis (**Figure 3**) [68]. Androgens, along with estrogens and progesterone, seem to exert a notable influence not just on the initiation of prostate cancer but also on

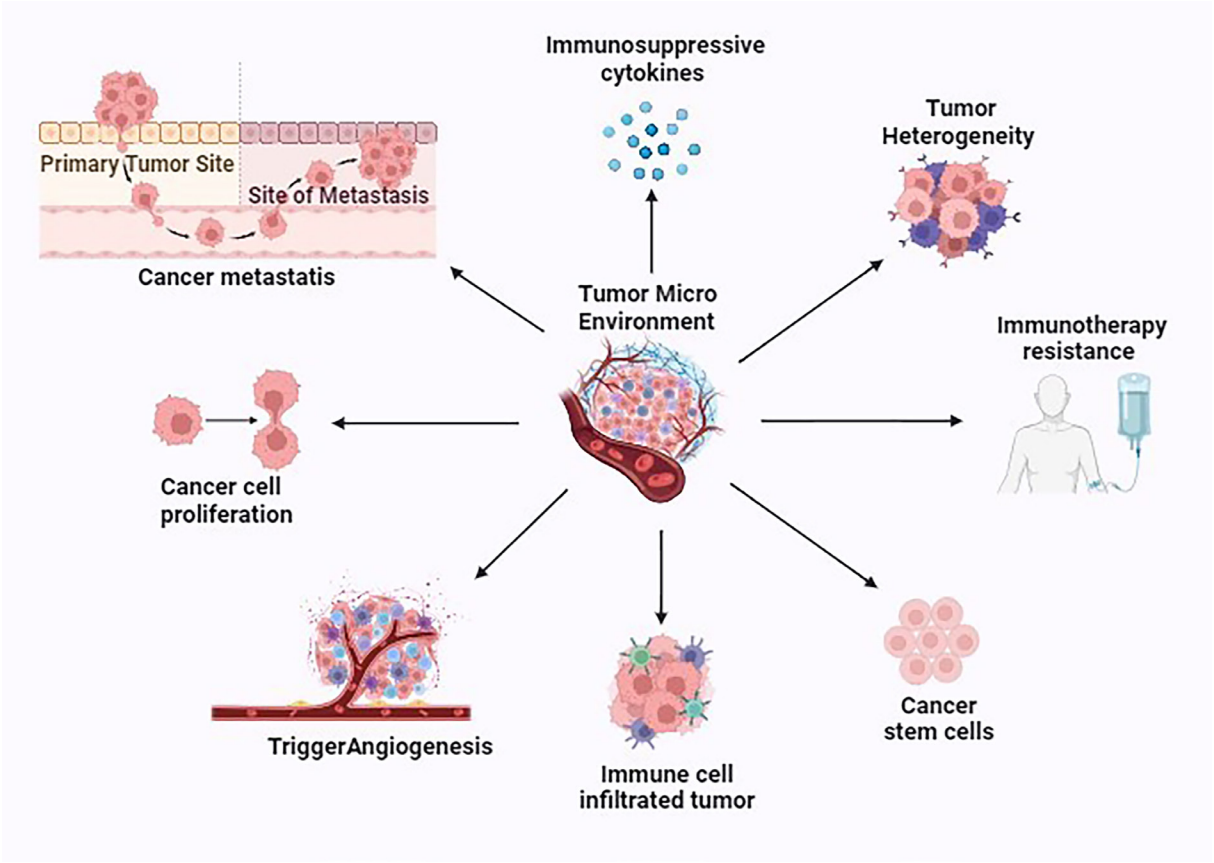

Figure 2. Various properties exhibited by the tumor microenvironment (TME). This figure was created with biorender.com.

its progression (**Figure 3**) [69]. The expression of the androgen receptor (AR) within the TME was found to be reduced in more advanced mPCa, implying that stromal AR exerts a shielding role in impeding the development of PCa [70]. The presence of arginine and the activation of pathways associated with arginine in cancerous regions have been observed to significantly influence the PCa TME which is evident not only on cancerous cells but also on the behavior of surrounding immune cells, altering growth, survival, and immune surveillance mechanisms. These effects can occur through arginase-mediated influences on polyamine and proline synthesis, or via the arginine/nitric oxide pathway in tumor cells, anti tumor T-cells, MDSC, and macrophages (**Figure 3**) [64].

Prostate cancer stem cells

Cancer stem cells (CSCs) can exhibit only a few or several of the typical stem cell characteristics, including relative inactivity coupled with a substantial capacity for proliferation, differentiation, self-renewal capability, and the crucial ability to generate and sustain tumors over an extended period while simultaneously replicating the cellular diversity found in the original tumors (**Figure 4**) [71]. CSCs can originate from various cell sources, encompassing normal stem cells, restricted progenitor cells, or fully differentiated cells [72]. On a molecular extent, CSCs exhibit the expression of specific genes, including ALDH1, POU5F1 (OCT4), CD44, NANOG, SOX2, and others, which are vital for preserving the pluripotency of stem cells, and requisite for the reprogramming of differentiated cells (**Figure 4**) [73]. The development of resistance mechanisms to drugs by the CSCs is also due to the elevated expression of membrane-bound efflux pumps, notably ATP-binding cassette (ABC) transporters like ABCB1 known as MDR1 or P-glycoprotein, as well as enzymes involved in detoxification, such as cytosolic aldehyde dehydrogenase ALDH1A1. These mechanisms are the ones offering protection to the CRCs against the detrimental effects of chemotherapy (**Figure 4**) [74].

Usually, the TME is the one that serves as a pivotal role in preserving the stem-like characteristics of Cancer. In the case of prostate tumor, a distinct subpopulation of cells possessing stem cell-like traits, including the expression of stem cell markers CD44 and CD133, is recognized as cancer stem cells or cancer repopulating cells (CRCs). These cells possess the proliferative capacity to sustain the tumor mass and they also exhibit resistance to chemotherapy, enabling them to repopulate the tumor and instigate metastasis following cancer treatment (**Figure 4**) [75]. It is believed that the presence of rare intermediate cells, which display a combination of CK5, CK8/18, and prostate stem cell antigen (PSCA), signifies the progenitor or transit amplifying cell population [76]. Recent findings indicate that calcitonin (CT), a hormone that lowers the amount of calcium in the bloodstream when secreted by the thyroid gland induces the expression of stem cell markers and other traits associated with CRC in PCa cells and enhances the metastatic potential of PCa cells by triggering epithelial to-mesenchymal transition (EMT) (**Figure 4**) [77]. miRNAs are also found to play an important role in regulating the stemness of PCSCs, both through direct control of transcription factors and biomarkers associated with stemness, indirectly impacting the process of EMT [78]. Mutations affecting the BAZ2A-bromodomain or the use of chemical agents that disrupt the binding between BAZ2A-bromodomain and H3K14ac have

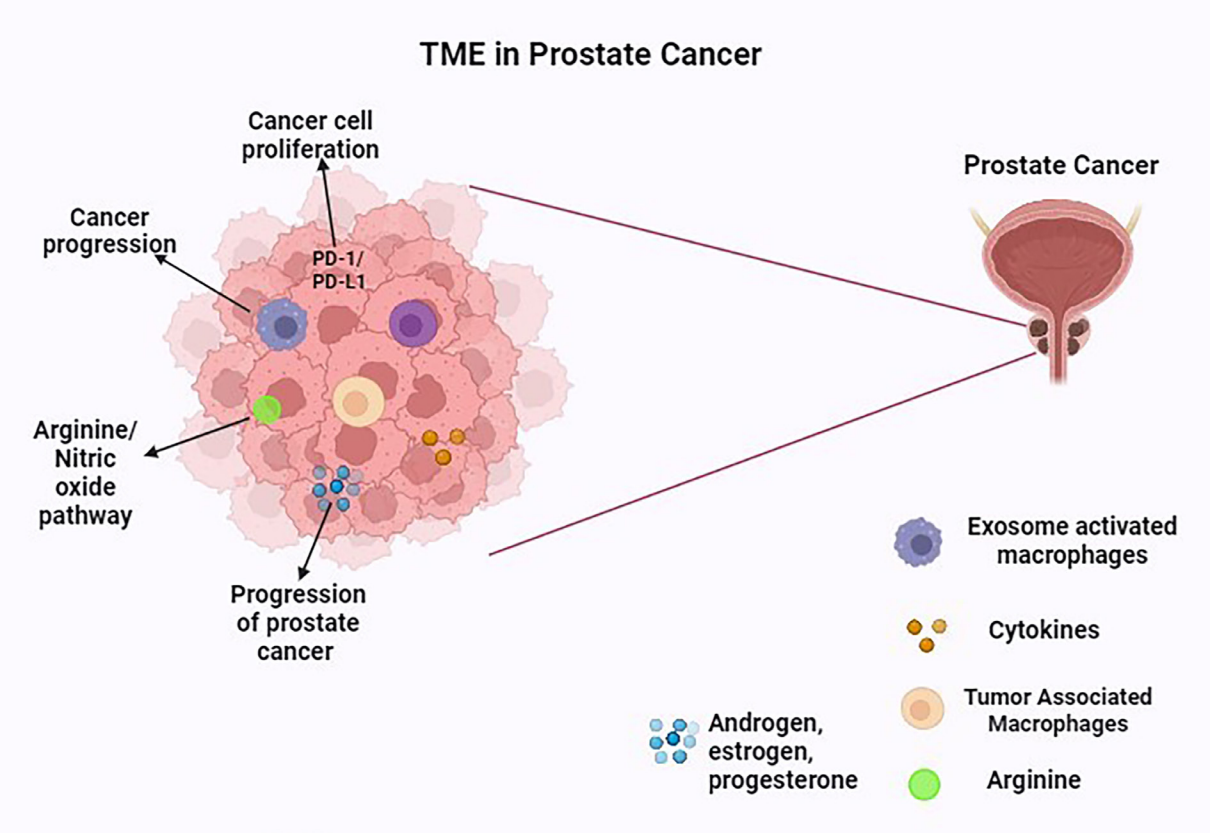

Figure 3. The TME in prostate cancer. This figure was created with biorender.com.

a detrimental impact on prostate cancer stem cells. Additionally, the pharmacological inhibition of BAZ2A-BRD hinders the oncogenic transformation resulting from Pten loss in the case of prostate organoids [77]. For the forthcoming patient-specific PCa therapies, NF-kB pathways can be used which plays a potential role by eradicating PCSCs. Treatment with TNFα was also shown to successively eliminate PCSCs (**Figure 4**) [79].

HBOT and prostate cancer

A few lab studies suggest that HBOT might help slow the growth of prostate cancer cells in vitro and make them more responsive to cancer treatments, particularly in DU-145 prostate cell line [80]. Studies on the effect of HBOT on LNCaP cells suggest that it is an effective method for inhibiting the growth of prostate cancer. Animal experiments play a crucial role in basic medical and preclinical research, forming the backbone for understanding the mechanisms of HBOT in prostate cancer [81]. In an experiment by Hae Tang and colleagues, hyperbaric oxygen therapy did not stimulate the growth of slow-growing prostate cancer in a mouse model, nor did it significantly affect the formation of new blood vessels [82]. In case of animal studies, it seems unlikely that HBO leads to cancer growth in tissues exposed to radiation. Research shows that HBO didn't speed up the growth of slow-growing prostate tumors in these cases [83]. Apart from this, there are several other animal studies that have concluded that HBOT could serve as a stand-alone treatment for prostate cancer. Chong et al. found that HBOT does not accelerate the growth of indolent prostate cancer. Their study showed no significant differences between the HBOT and non-HBOT groups in terms of tumor microvessel density, proliferative index, differentiation, or apoptosis markers. According to one study, while hyperbaric oxygen reaches a high concentration when acting on a single tumor cell, it cannot achieve the inhibitory concentration needed for tumor growth when applied locally or to the whole body, which may limit its therapeutic effect. This raises the possibility of combining HBOT with ultrasound-guided transrectal prostate puncture. By placing a probe around the tumor mass and delivering hyperbaric oxygen directly through it, a concentrated hyperbaric oxygen environment could be created around the tumor, potentially enhancing the therapeutic effect [81]. HBOT may enhance the effectiveness of radical prostatectomy or chemotherapy by inducing partial synchronization or accumulation of cells in the cell cycle. Thus, HBOT could serve as a beneficial adjunct for prostate cancer treatment, as it promotes cell cycle progression. This therapy is especially promising for tackling malignant carcinomas, particularly those with poorly vascularized tumors that have a significant number of hypoxic cells. We believe further exploration of HBOT as a treatment option for prostate cancer in clinical settings is essential, and it could lead to positive outcomes for patients [81, 84]. The findings from these studies consistently indicate that HBOT does not promote the growth of cancer cells [81].

Limitations of HBOT

HBOT, like other potent therapeutic interventions, comes with certain potential complications and should be considered when regular treatment alone proves to be less than fully effective [85]. HBOT carries a risk of adverse effects, such as ear, sinus, and lung issues due to pressure changes, temporary exacerbation of near-sightedness, acceleration of existing cataracts, claustrophobia, and

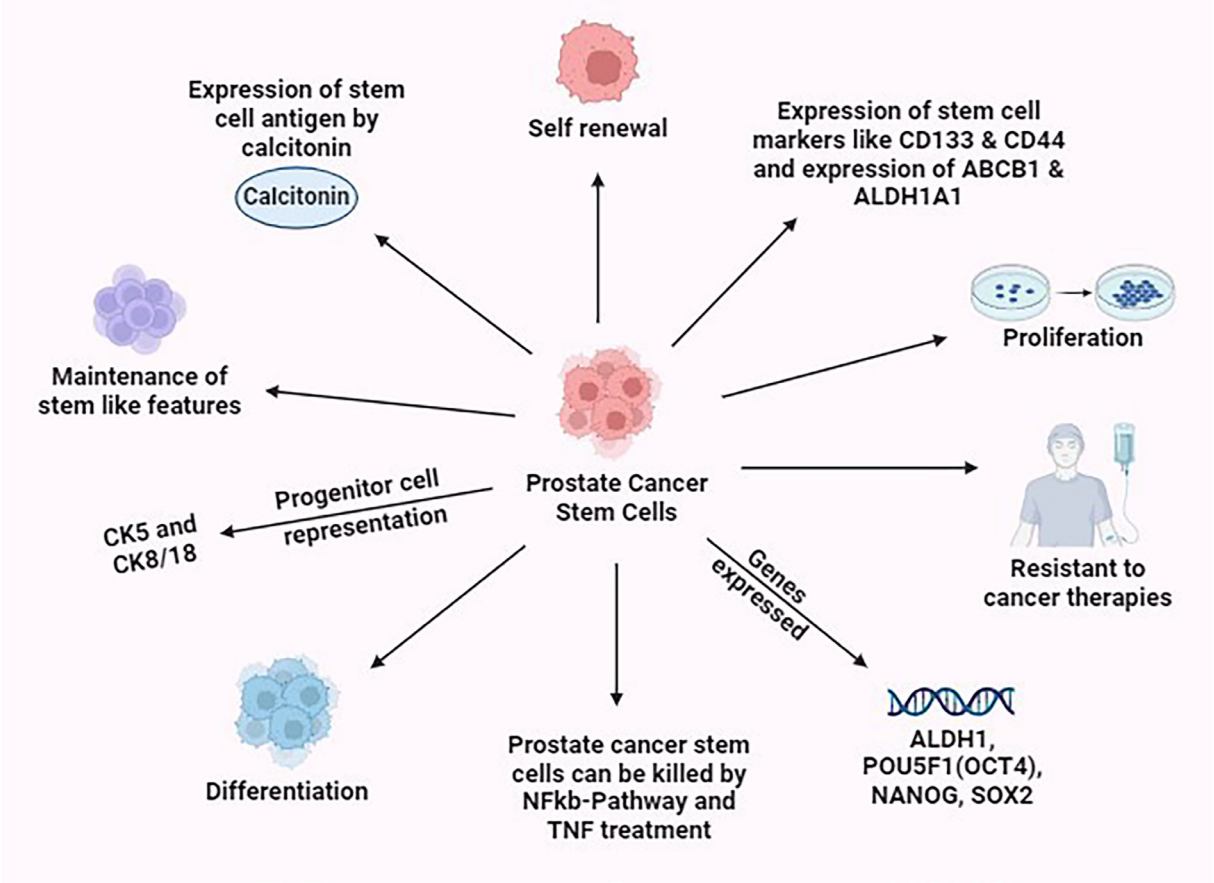

Figure 4. Various properties exhibited by the prostate cancer stem cells. This figure was created with biorender.com.

oxygen toxicity. There are also a number of stark contraindications, including untreated pneumothorax. While severe adverse effects are uncommon, HBOT cannot be considered a completely risk-free procedure, but in the hands of a skilled technician, adversed effects are minimized [86]. Sometimes the oxygen toxicity might get enhanced and might result in seizures and pulmonary toxicity while using disulfiram as it blocks superoxide dismutase and bleomycin results in interstitial pneumonitis and fibrosis and is a contraindication for HBOT [87]. But thankfully, the side effects of HBOT are typically mild. The most serious complication, being the oxygen-induced convulsions, occurs in approximately 1 out of 10,000 patients in extensive case studies [23]. Various cohort studies and randomized controlled trials conducted in diverse surgical procedures, such as abdominoplasty and pancreaticoduodenectomy, have shown reduced rates of postoperative complications and shorter stays in the intensive care unit when preoperative HBOT is employed [14]. Nevertheless, it is recommended to conduct a long term follow-up assessment to ascertain the extended effects of HBOT [88]. Anectodical evidence has suggested that patients with decreased left ventricular ejection fraction (LVEF) may be at an increased risk of acute heart failure (HF) during HBOT [89].

In addition to the previously mentioned limitations, logistical barriers can also pose challenges in the administration of HBOT. For instance, a qualitative study involving podiatrists from high-risk foot clinics near Sydney revealed that participants considered the evidence supporting HBOT for diabetic foot ulcers (DFU) to be extremely limited. Many studies were criticized for lacking scientific rigor, leading the podiatrists to recommend HBOT referrals only when requested by the patient [90].

Conclusion and perspective

In conclusion, HBOT offers significant promise as an adjunctive treatment for prostate cancer by addressing the hypoxic microenvironment often present in tumors. Hypoxia is a key driver of tumor progression, therapy resistance, and poor treatment outcomes. By delivering high concentrations of oxygen under pressure, HBOT counteracts this hypoxia, improving the effectiveness of conventional treatments such as chemotherapy and radiotherapy. Additionally, HBOT has also shown anti-angiogenic effects, alkalized the tumor microenvironment (TME), and increased treatment sensitivity in prostate cancer cell lines like DU-145 and LNCaP. HBOT may also enhance radical prostatectomy and chemotherapy by synchronizing cell cycles. Further research could unlock its potential in advancing prostate cancer treatment.

Over the decades, PCSCs have been a focal point in cancer research due to their significant role in tumor initiation, progression, and resistance to conventional therapies [91]. These cells possess the unique ability to self-renew and differentiate, which makes them a critical target in the fight against prostate cancer. The resistance of PCSCs to conventional therapies is a major challenge, as these cells can survive treatment and lead to tumor relapse and metastasis. Therefore, developing therapies that specifically target PCSCs is crucial for improving treatment outcomes. By focusing on strategies that eliminate these resilient cells, we can potentially reduce the risk of recurrence and improve

the overall efficacy of prostate cancer treatments in combination with HBOT. This approach holds promise for more effective and lasting cancer therapy, bringing us closer to better patient outcomes. In addition, nanotechnology platforms allow for precise control over the size and shape of nanomaterials, which can be optimized to target cancer cells more effectively. The combination of these nanomaterials with antibodies or nanobodies can further enhance their specificity and therapeutic impact for Prostate cancer [92] and offers exciting potential in targeting prostate cancer stem cells (PCSCs) in combination of HBOT whereby significant enhancement on therapeutic outcomes by specifically targeting PCSCs, thereby improving efficacy and reducing stemness features can be achieved and vital role of biomarkers [93] can be addressed for precised treatment.

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Ethical policy

Non applicable.

Availability of data and materials

No data was used for the research described in the article.

Author contributions

The study was directed by MH and VKL. PK searched academic literature, wrote the manuscript draft. MH and VKL supervised the review draft and approved the final manuscript submission.

Competing interests

MH is the current president of the International Hyperbaric Medical Foundation, a 501(c)3 nonprofit and holds multiple patents on hyperbaric technologies. 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 review.

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