HHS Public Access

Author manuscript

Bone. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Bone. 2019 February ; 119: 82–86. doi:10.1016/j.bone.2018.02.025.

Parallels Between Hematopoietic Stem Cell and Prostate Cancer Disseminated Tumor Cell Regulation

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Abstract

The bone marrow is primary site of hematopoiesis and home for hematopoietic stem cells (HSCs) in adult mammals. Prostate cancer commonly metastasizes to bone and forms bone metastases in almost all patients who die of the disease. Prostate cancer bone metastases are thought to develop after rare bone marrow disseminated tumor cells (DTCs) escape a dormant state and reactivate. Prostate cancer DTCs and normal HSCs have been shown to compete for residence in the bone marrow and share many of same regulatory mechanisms for survival, proliferation and homing. In this review, we highlight these parallels in order to help our readers use the literature in HSC and DTC biology to inform their research and generate hypotheses in both fields.

Keywords

prostate cancer; disseminated tumor cell; hematopoietic stem cell; dormancy; recurrence; GAS6; CXCL12; stem cell; niche

Introduction

Prostate cancer (PCa) is a large public health problem with over 180,000 new cases and over 26,000 deaths per year in the United States alone[1]. Of PCa patients with distant metastases, 90% have metastases to bone[2]. Prostate cancer cells are thought to spread to the bone marrow early in the disease process, even at or before the time of curative intent surgery or radiation therapy to the prostate. At this time, they are termed disseminated tumor cells (DTCs) or micro-metastases. These cells are found in bone marrow or other tissues rather than circulating in peripheral blood, which most investigators term circulating tumor cells, or CTCs. The presence of bone marrow DTCs in PCa patients at the time of radical prostatectomy has been demonstrated by research groups at three institutions using various

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techniques including, RT-PCR for prostate specific antigen (PSA), immunohistochemistry for PSA and single cell selection of epithelial cell adhesion molecule (EPCAM) positive cells by single cell isolation after prior negative and positive selection[3–7]. Furthermore, their presence was shown by all three groups to correlate with PCa recurrence[5,8,9]. However, recently investigators reported being able to detect these cells in only a small minority of patients with localized PCa[10]. This report highlights the challenges in conducting this type of research and suggests further investigation.

PCa DTCs can remain viable but dormant for long time periods; as illustrated by the fact that about 20% of PCa recurrences after surgery occur greater than 5 years after patients were thought to be cured[11]. Reactivation or dormancy escape of bone marrow DTCs is thought to be a major cause of relapse in PCa and other malignancies[12]. Furthermore, an understanding of the biology of how DTCs or micrometastases are different from macroscopic tumors and how they interact with bone microenvironment has the potential to lend insight into later stages of the disease when metastases are visible on imaging. Therefore, understanding the biology of DTCs in the bone environment is crucial for prevention of relapse or treatment of relapsed disease.

There are two major models which have been invoked to describe tumor heterogeneity, either of which could describe the behavior of DTCs. The cancer stem cell (CSC) model suggests that subpopulations of cancer cells form a hierarchical cluster of tumor initiating cells[13]. These CSCs often feature parameters present in normal tissue stem cells, and like normal stem cells maintain themselves through self-renewal, but also differentiate into progenitor cell populations and ultimately into mature or non-stem cancer cells (NSCCs). The second major model for tumor development is the stochastic model. In the stochastic model, tumors develop by clonal evolution to progress into heterogeneous populations which are influenced by both intrinsic and extrinsic environmental factors[14].

Many tissues which harbor DTCs, including lung, liver and bone marrow, are also sites in which clinical relapse can eventually occur. Each of these organs support stem cell populations and tightly regulates proliferation as a component of normal function. This suggests that the normal activity of the host tissues to regulate stem cell function, be it the induction or maintenance of quiescence, ultimately becomes insufficient to enforce dormancy of DTCs. Yet, whether DTCs are primed for proliferation but constantly kept in check by suppressive signals or rather reprogrammed into a semi-permanent dormant state by the microenvironment remains unclear. In several experimental systems DTCs isolated directly from humans or from preclinical models are difficult to grow *in vitro*, and only proliferate after extended culture periods[12,15]. The implication from these studies is that DTCs, at least in these organs, are reprogrammed into a dormant state rather than held in check by the continual presence of negative regulators. Alternatively, there is ample evidence that immune regulation of DTCs plays a major role in controlling DTC proliferation[16–19]. How the host is able to distinguish normal stem cells from tumor cells, be they CSCs or NSCCs remains unclear.

We and others have hypothesized that DTCs reside in similar environments or “niches” as hematopoietic stem cells (HSCs) and compete for occupancy of the bone marrow

microenvironment[20]. Likely because of shared interactions with stromal cell types, research over the past one or two decades has discovered shared regulatory mechanisms between DTCs and HSCs. In this review, we use HSC biology to frame a discussion of PCa bone marrow DTC regulation in hopes that we will help our readers gain intuition into DTC biology and help them generate new hypotheses by drawing on the more extensive HSC literature. We concentrate here on PCa, but note that many of the same concepts will apply to breast cancer and other malignancies which metastasize to bone. The mechanisms discussed below are summarized in Figure 1.

Homing

Perhaps the most established and robust parallel between DTCs and HSCs is in homing to the bone marrow, much of which involves the cytokine CXCL12 (SDF-1). Over a decade ago, CXCL12 was suggested to be important for PCa bone metastasis[21]. Subsequently, blocking CXCL12 was shown to inhibit transit of PCa cells to the bone marrow. CXCL12 and was also shown to strongly co-localize with metastatic PCa cells – principally in the metaphysis of long bones in the mouse models used for these studies[22]. There is an extensive literature on the role of CXCL12 in the HSC niche and homing. The niche constituent Cxcl12 abundant reticular cell (CAR) cell is defined by the high expression of CXCL12 as measured by a fluorescent reporter gene[23]. Furthermore, the effect of other cells on homing and the HSC niche are in part through effects on CXCL12 – namely that the effects of the sympathetic nervous system on the HSC niche are proposed to be through modulation of CXCL12 expression in peri-vascular cells and osteoblasts[24,25]. Most recently, the pre-metastatic niche for both PCa and breast cancer was proposed to consist of vasculature associated mesenchymal stromal cells. Similarly, our group found a role for the adhesion molecule, Annexin 2, in homing of both HSCs and PCa DTCs to bone marrow[26,27]. In keeping with the central role of CXCL12 for homing of both cell types, Annexin 2 appeared to act by stabilization of CXCL12[28].

Location

We and others have shown that HSCs and DTCs functionally compete for residency in bone marrow[20]. In an analogous fashion to its function of maintaining HSCs in a pluripotent state, the bone marrow environment appears to cause PCa cells to assume a more primitive or cancer stem cell phenotype. Although this was long hypothesized, Shiozawa and colleagues recently showed a rapid assumption of a stem-like phenotype as defined by increased percentage of $CD133^+/CD44^+$ positive PCa cells[29].

However, the precision location and cellular makeup of the HSC and especially DTC niches remains much less well defined. There has been much more work published on the location of the HSC niche than the precise location of DTCs in bone marrow. However, even for HSCs, the publication of multiple high impact papers has not brought clarity to this discussion. After decades of study, multiple cell types have been implicated as constituents of the bone marrow HSC niche, most of which are derived from mesenchyme. Earlier studies predominantly suggested an endosteal and osteoblast associated location of the HSC niche[30–32]. However, more recent studies using mouse genetic manipulations have found

perivascular locations to be more important[33–35]. Among the peri-vascular cell types that are proposed to support HSCs are Cxcl12 abundant reticular (CAR) cells lining sinusoids and nestin positive cells adjacent to arterioles[23,36]. Nerve fibers are often associated with vasculature in bone marrow as in other parts of the body. More recently than some other cell types, the sympathetic nervous system has also been reported to regulate bone marrow HSCs and more recently DTCs as well[24,37].

The relatively small number of studies examining the location of PCa DTCs in mouse models with microscopy have placed them predominantly at the metaphyses or otherwise adjacent to the growth plates[38,39]. These are also the locations where macroscopic bone metastases most commonly ultimately form. DTCs at the metasphasyses are predominantly within a few cell diameters or less than about 100 μm from the endosteal surface, which suggests an endosteal or osteoblastic location for PCa DTCs. Some have suggested that cancer associated fibroblasts are also important for tumor development in these endosteal locations[39]. However, it is also important to note that the metasphasyses of mice are very heterogenous with a high vessel density, and many other cell types including hematopoietic precursors and immune cells. Furthermore, because the growth plate closes in humans but not rodents, the location of DTCs in humans might also differ. In breast cancer, investigator have shown the importance of a perivascular niche for breast cancer bone marrow DTCs and that vessel outgrowth promotes dormancy escape[40]. Alagous micro-anatomy and mechanisms are plausible in PCa but to our knowledge have not be directly studied.

Stress Response and Survival

A commonly proposed reason for “why” DTCs become dormant is as a survival mechanism[41]. After hematogenous spread to a new location such as the bone marrow, DTCs might not have the same proliferative signals present in the primary tumor and therefore stop cycling, which has been shown to correlate with resistance to chemotherapy and other causes of apoptosis. Prominent molecular mediators of this survival signaling include TGF-β2, p38 MAPK and the endoplasmic reticulum stress response[6,41–43]. Even more recently, the importance of transcription factors best known for induction of pluripotency in embryonic stem cells has become apparent. These include SOX2, SOX9, NANOG, and retinoic acid receptor β[44,45].

Dormancy vs. Proliferation

Many of the best characterized regulators of PCa dormancy have analogous roles in regulation of HSC quiescence vs. proliferation. TGF-β2 is perhaps the best characterized factor maintaining dormancy in DTCs from PCa and other cancers[42]. Similarly, the TGFβ family member BMP-7 also maintains PCa DTC dormancy[46,47]. TGF-β family members have analogous effects for HSCs. TGF-β2 maintains HSCs in a quiescent state but increases their ability to engraft. Conversely, TGF-β1 inhibits HSC reconstituting ability[48].

It is interesting to consider further that the bone marrow microenvironment is a rich source of growth factors and cytokines with capacity to regulate DTC growth. Numerous molecules present in the marrow including basic fibroblast growth factors (bFGF), insulin-like growth

factors I and II (IGF-I and –II), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and transforming growth factor alpha (TGF-α) may serve as mitogens for DTCs[49]. In fact, even some forms of TGF-β may stimulate the growth of DTCs[50–53]. Stromal-derived factor-1 or CXCL12 is well established as a critical regulator of DTC homing and mobilization[54–56]. However, inhibition of CXCL12 signaling demonstrates anti-mitogen activities, which in part is due to autocrine signaling but could also be due to stromal control of DTC activiites[28,57].

In a similar way, bone morphogenetic protein 7 (BMP7) produced by bone marrow stromal cells triggers dormancy of PCa cells. When PCa cells were co-cultured with bone marrow stromal cells, prostate cancer cells entered dormancy through the activation of the cell cycle inhibitor p21, the metastasis suppressor gene N-myc downstream-regulated gene 1 (NDRG1), and p38 MAPK phosphorylation[46]. Additionally, BMP7 dramatically suppresses the ERK MAPK pathway[46]. These observations are consistent with previous studies by Aguirre-Ghiso's group, proposing that the ratio of ERK and p38 MAPK pathways plays a pivotal role in the determination of tumor dormancy[42]. Dormancy is prevented when BMP7 secreted by bone marrow stromal cells is blocked by shRNA or pan-BMP inhibitor Noggin. Moreover, the effects of BMP7 on dormancy of PCa cells both *in vitro* and *in vivo* are attenuated when BMP receptor 2 (BMPR2) on PCa is down-regulated[46].

We have reported that growth arrest specific-6 (GAS6) expression from osteoblasts in the bone marrow environment plays a critical role in establishing prostate tumor cell dormancy[58]. GAS6 signaling inhibits PCa proliferation, as it does with hematopoietic progenitor cells[59] suggesting once DTCs enter the niche, interactions between GAS6 and its receptors may regulate PCa dormancy[58]. Interestingly, GAS6 expression is not uniform amongst different bone locations as significantly higher expression of the protein can be detected in murine femurs vs humeri[60]. These observations correlate well with the prevalence of human PCa metastasis in immune deficient mice were the predicted probability across all animal models was 7% (range 5-10%) for the forearms and 33% (range 28-38%) for the leg bones[60]. GAS6 signals predominately through the TAM family of receptor tyrosine kinases Tyro3, Axl and Mer tyrosine kinase (MERTK). Subsequently, we have shown that DTCs recovered from marrow of immune deficient mice differ in their expression of two of the major GAS6 receptors such that a balance between the expression of Axl and Tyro3 may serve as a molecular switch between a dormant (predominatly Axl expression) and a proliferative phenotype (Tyro3 expression) in PCa bone metastases[61]. Similarly, further investigations found that MERTK signaling stimulates dormancy escape and stimulates formation of a CSC phenotype[29,45]. Although, there is scant literature for a role of GAS6 in normal HSC function, it is intriguing to note that AXL signaling was recently found to regulate the self-renewal of malignant HSCs in chronic myelogenous leukemia[62]. This was found to be due to β-catenin signaling, which has a well-established role in the function of CSCs for PCa and other solid tumors[63].

It is not surprising that HSC quiescence is tightly regulated given the importance of these cells in maintaining normal homeostasis, or in response to injury. In fact multiple pathways are thought to intersect for the purpose of providing redundancy and for maintaining stem cell activities[64–68]. Thus it should come as no surprise that DTCs, as molecular parasites of

the HSC niche, are likely to be maintained in a dormant state by many intersecting signals. As an example, when DTCs come into close proximity to niche osteoblasts they upregulate their expression of Axl[43]. Recently we found that expression of both TGF-ß and its receptors were regulated by Axl expression in PCa cells, while blockade of TGF-ß signaling limits the ability of the osteoblasts to induce dormancy of PCa cells[43]. Importantly, both Gas6 and Axl are required for TGF-ß2-mediated cell growth suppression[43]. Together, these data suggest that a feedback loop between GAS6 and TGF-ß signaling is likely to provide intersecting and redundant systems critical to maintaining PCa cell dormancy (Illustrated in Figure 2).

From the preceding discussions it is implied that DTCs are tumor-initiating and are kept in check by proliferative inhibitory signals emanating from the host tissue[12]. At the same time, clinical observations suggest that a loss of immune function is associated with resurgence of tumor progression[16–19]. Recently Malladi *et al* demonstrated that a distinct class of stem-like DTCs are primed to enter quiescence and evade innate immunity[69]. As part of the phenotype of a tumor-initiating stem/progenitor population, the cells through production of DKK1, enter a dormant like state which is predicated to counteract WNT signaling[69]. Excitingly, in this state the DTCs are able to evade NK cell surveillance and thus acquire a long-term survival advantage which poises the population for proliferation as immune function changes over time[69]. Furthermore, in keeping with the studies discussed above on the role of GAS6 in maintaining PCa DTC cellular dormancy, AXL signaling was recently shown to induce development of natural killer cells[70].

The sympathetic nervous system has been proposed to stimulate HSC proliferative activity and bone marrow regeneration. For example, Lucas *et al* showed that hematopoietic regeneration was inhibited by damage to bone marrow sympathetic nerve fibers from chemotherapy drugs, especially cisplatin[71]. Similarly, Heidt et al showed that chronic variable stress increased proliferative activity of HSCs[72]. The resultant increased production of inflammatory cells elevated the risk of myocardial infarction and stroke in an animal model. Likewise, in PCa the sympathetic nervous system stimulates the development of the primary tumor[73]. Our group recently showed that sympathetic neurotransmitter norepinephrine stimulates escape from dormancy in a PCa model. This effect of norepinephrine was through direct action on PCa cells and also through decreased expression of the well know dormancy associated molecule GAS6 by osteoblast lineage cells[37].

Conclusions and Perspective

Over the prior 20 years, we have seen remarkable parallels develop in our understanding of the biology of PCa DTCs and normal HSCs. This includes the study of localization, homing, survival, and proliferation. Frequently, the advances in normal hematology have preceded concurrent findings in solid tumor biology. This has provided enormous opportunities for hypothesis generation for investigators studying the biology of PCa DTCs. We are confident that these research parallels will continue in the future. This will provide fertile ground for both hematology and PCa researchers to the benefit of their respective patients.

Acknowledgments

Financial Support: Direct funding was provided by the NIH/NCI P01-CA093900, the NIH/NCI Tumor Microenvironment Network U54-CA163124 and supplement, Department of Defense W81XWH-14-1-0403. And Prostate Cancer Foundation Challenge award 16CHAL05. R.T. receives support as the Major McKinley Ash Colligate Professor. F.C. receives support from a Career Enhancement Award from the NIH/NCI Prostate Cancer Specialized Program in Research Excellence (SPORE) #F048931, sub-award of #F036250 at the University of Michigan.

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Highlights

- Prostate cancer disseminated tumor cells (DTCs) and hematopoietic stem cells (HSCs) have analogous functions.
- Both home to the bone marrow, for which CXCL12 is critically important.
- HSCs and DTCs share a home or “niche” as shown in part by competition experiments.
- The niche regulates survival and dormancy vs. proliferation of both cell types.

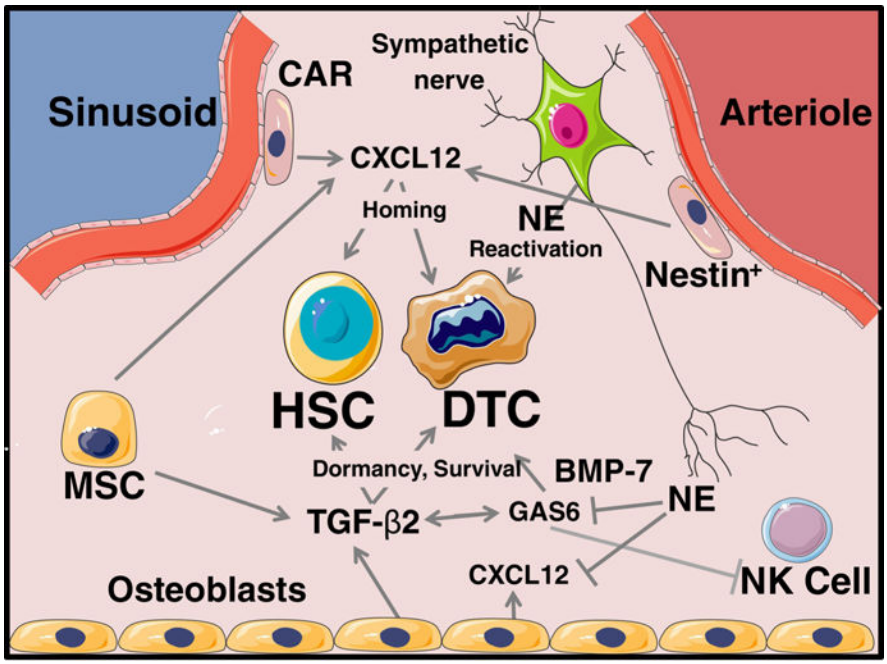

Figure 1.

Key cells and secreted factors regulating HSCs and prostate cancer DTCs. HSC; hematopoietic stem cell, DTC; disseminated tumor cell, NE; norepinephrine, CAR; Cxcl12 abundant reticular cell, MSC; mesenchymal stem cell, NK Cell; natural killer cell.

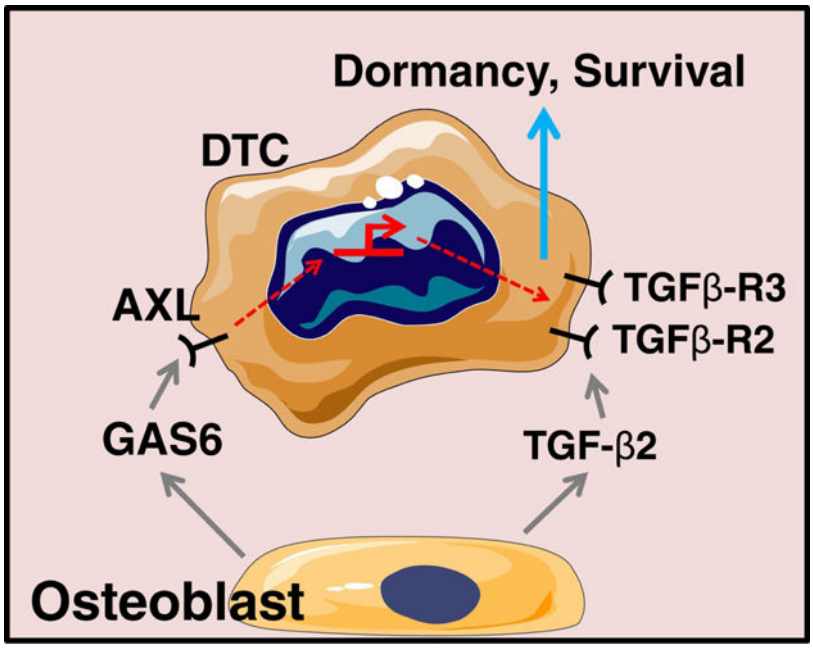

Figure 2.
Crosstalk between TAM and TGF-β pathways in dormancy induction and maintenance.