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Cancer Camouflage and Osteomimicry Behind Prostate Cancer Cells Masquerade and Bone Metastasis

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Abstract

As man-made cytotoxic drugs are being discovered in cancer therapeutic research the application of such new drugs in the clinical settings motivate the malignant cancer cells to modulate new mechanisms for the survival under secondary population establishment. A recent discovery in prostate cancer has revealed osteomimicry as one such mechanism. Prostate cancer cells undergo EMT (epithelial-to-mesenchymal transition) to enable intravasation and subsequent MET (mesenchymal-to-epithelial transition) in the bone in order colonise the bones. These cells also synthesize the prerequisite components for osteoclastogenesis, which permits the seeding and proliferation of cancer cells in bone. This process effectively mimics and manipulates the bone microenvironment to support metastatic growth.

Keywords: Osteomimicry; EMT; MET; Osteoclastogenesis; Metastasis

Abbreviations: SSEAs: Stage Specific Embryonic Antigens; ESCs: Embryonic Stem Cells; BSP: Bone Sialoprotein; EMT: Epithelial-To-Mesenchymal Transition; EGF: Endothelial Growth Factor; ECM: Extracellular Matrix; MET: Mesenchymal-to-Epithelial Transition; CD: Cluster Differentitaiton; MSCs: Mesenchymal Stem Cells

Introduction

Metastatic Mimicry by Cancer Cells

Stress can function as a carcinogenic factor. Under stressful conditions such as hypoxia, cellular overcrowding, and insufficient nutrients or antioxidants, cancer cells proliferate and acquire adaptive changes to ensure survival. These adaptations include:

1. A pleomorphic appearance.
2. Expression of tumor-specific surface antigens.
3. Synthesis of various pro-tumor growth factors, chemokines, or cytokines, which are often pro-inflammatory.
4. Activation of anti-apoptotic mechanisms.
5. Inhibition of tumor suppressor genes.
6. Exacerbation of oncogenes.
7. Epigenetic modifications affecting gene and protein expression.
8. Plasticity in signal transduction pathways directing nuclear programming and transcription.
9. Expression of transport receptors for specific nutrients and metabolites (e.g., glucose, fructose, cholesterol, omega-6 fatty acids, amino acids).

Basic Characteristic Features and Adaptive Mechanisms of Mesenchymal Stem Cells (MSC)

Metastasis is a multistep process demanding that disseminated cancer cells acquire adaptive mechanisms to survive extravasation, persist in a foreign microenvironment, initiate proliferation, and induce angiogenesis, all while evading apoptosis and host immune surveillance [1]. Intriguingly, these

migratory and adaptive behaviors recapitulate features of native mesenchymal cells. Mesenchymal stem cells (MSCs) are multipotent stromal cells characterized by a spindle-shaped morphology, large nuclei, prominent nucleoli, and fine chromatin. They function as progenitors for diverse connective tissue lineages, including fibroblasts, osteoblasts, chondroblasts, and adipocytes [2].

In humans, MSCs also demonstrate a capacity to differentiate into myogenic, neurogenic, and other stromal cell types. The hallmark function of mesenchymal cells is the production of an extracellular matrix (ECM), primarily a hyaluronic acid-rich ground substance, which is foundational for forming various connective tissues during embryogenesis [3]. This differentiation is governed by a complex interplay of genetic factors (e.g., specific transcription factors) and epigenetic regulation, including DNA methylation and histone modifications.

Pools of MSCs persist in adulthood in niches such as bone marrow, adipose tissue, and the umbilical cord, where they contribute to tissue homeostasis and repair. Adult MSCs can give rise to fibroblasts and support neovascularization [2]. Furthermore, they exhibit low immunogenicity and strong immunomodulatory potential. A key mechanism of their therapeutic action is paracrine signaling; MSCs secrete a repertoire of bioactive molecular growth factors, cytokines, and extracellular vesicles-that promote angiogenesis, modulate inflammation, and facilitate regeneration, often without requiring direct differentiation [4]. The plasticity and secretory profile of MSCs thus provide a vital blueprint for tissue repair, a program that metastatic cancer cells appear to co-opt for survival and proliferation in distant organs.

Sources of Retrogressive Mesenchyme Properties in Metastatic Prostate Cancer Cells

Embryonic stem cells (ESCs) express various surface cell markers such as Stage Specific Embryonic Antigens (SSEAs) during embryonic development stages and induce self-renewal and pluripotency through transcriptional factors [5]. The flow cytometry reveals the expression of SSEA1 in glioblastoma, melanoma, and mammary cancer cells; however, the expression of SSEA-3 in colorectal and SSEA-4 prostate cancer was reported [6,7]. Maria et al. [8] correlated the human embryonic germ cell pluripotential transcription factors such as OCT3/4, SOX2, and NANOG with stemness, core pluripotency, co-expression patterns, and regulatory mechanisms of prostate-specific embryonic cell membrane antigens.

Among the cluster differentiation (CD) marker diversity, the following CD9, CD24, CD30, CD133, and CD326-exist to maintain the pluripotency at embrynoice stem cell stages, and aggressive prostate cancer expresses the CD44, CD90, CD133 and CD166. The CD133 is commonly combined with CD44 (CD44+/CD133+) which provides the proliferative metastatic ability to the epithelial-to-mesenchymal transition (EMT) of Prostate cancer cells [9,10]. The Snail family transcariptional factors were also reported in both embryonic and metastatic cancer cells. They involved in germ layer formation, cell movement, delamination and migaration and tissue remodelling. The mesenchymal properties are highly promoted by the snail through CD44+ and CD133+stemness markers, chemoresistance and protection of apoptosis during doxorubicin, cisplatin therapy, regulating molecular mechanisms like Warburg effect of fructose-1,6-biphosphatase, and Non-EMT Functions such as bypassing senescence and driving the cell cycle without check points [5,11] (Table 1).

Embryonic Recapitulation

The above event of angiogenic vessel / tube formation by the tumour indicates its embryonic recapitulation feature [12]. It may be Construed that the transformed tumour mass, like the mammalian blastocyst, may be totipotent in the initial period of proliferation [13]. Once the tumour mass reaches the threshold size, it orders to disperse from the primary site/niche. it may become pluripotent to differentiate to new blood vessels for the cell's dispersion (Valastyan & Weinberg [14]. The EMT mechanism may also be an adaptability in the cancer cells plasticity, since the circulating mesenchymal tumour cells may not be resemble detected by the Immune surveillance mechanisms, as they may constitutively with the mesodermal cell population of the blood Connective tissue [15].

Like angio-genic vessal formation the metastatic cells evacuation from their primary niche may also be construed as an embryonic differentiation event [14]. An analogous event in normal mammalian embryogenesis is the evacuation of the nerves from the retinal area by the influence of collagen factors [15]. Thus, it becomes obvious that right from transformation up to settlement in secondary niches cancer cells follow normal developmental cues bone cells instead of bone cells secreting specific proteins [13] prostate cells do that secretion.

Since the genes are restricted, the prostate cancer cells themselves secrete such proteins as osteocalcin (oc), osteopontin, bone sialoprotein (BSP) and osteonectin [16]. These Proteins expression in cancer cells enable the participation of osteoclasts and osteoblasts for enhanced osteoclastogenesis, and bone turn-over or bone pitting to create new site or secondary site for the bone Colonisation of prostate cancer cells [17,18]. During the epithelial-to-mesenchymal transition (EMT), the fully differentiated mesenchymal cell loses epithelial markers such as E-cadherin, resulting in the absence of stable adherens junctions. Interactions between these migratory cells are limited to transient gap junctions formed upon incidental contact [19]. The mesenchymal phenotype is characterized by a distinct polarity optimized for motility.

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Table 1: Meta analysis and presence of SSEA, CD Markers, and Snail promotors in Embryonic vs. Cancer Cells.

Marker/ factor	Embryonic Stem Cells (ESCs)	Cancer Cells (General)	Functional Role & Context
SSEA-1	Present on mouse ESCs and some human epiblast cells(CD15).	Often absent or variable. Can be present in some leukemias and certain solid tumors (e.g., brain (glioblastoma), thyroid, and lung cancer stem cells.breast).	Marker of pluripotency in mice. In cancer, its re-expression is linked to a poorly differentiated, aggressive state. Involved in cell-to-cell recognition and adhesion
SSEA-3	Present on human ESCs (primed/ naïve states).	Rare. Reported in some germ cell tumors and a subset of breast cancers.	Associated with the pluripotent ground state. In cancer, indicates a primitive, stem-like cell phenotype, loss of epithelial phenotype and increased invasion..
SSEA-4	Present on human ESCs.	Commonly expressed in many carcinomas (e.g., breast, lung, prostate, ovarian). Also on cancer stem cells (CSCs).	Pluripotency marker. In cancer, promotes tumorigenicity, metastasis, and drug resistance. A key CSC marker.
CD Markers	Specific Profile: • CD9, CD24, CD29: High. • CD34, CD45, CD133: Typically absent (mark lineage commitment). • CD324 (E-cadherin): High (maintains colony structure).	Highly Variable & Aberrant: • CD44<-sup>+</sup>/CD24^{-/low}: Classic breast CSC profile. • CD133: Marker for brain, colon, prostate CSCs. • CD326 (EpCAM): Often high in carcinomas. • CD324 (E-cadherin): Often lost during metastasis.	Used to identify and isolate specific stem cell or cancer stem cell populations. Aberrant CD expression defines tumor type, prognosis, and therapeutic targets.
CD44	Expressed in mesenchymal stem cells and early embryos.	Major marker for breast, colon, and head/ neck CSCs.	Acts as a hyaluronan receptor; mediates migration and survival.
CD133 (Prominin-1)	Found in human ESCs and various fetal progenitor cells.	Universal marker for brain, colon, and liver cancer stem cells.	Organizes cell membrane topology; linked to chemoresistance.
CD24	Expressed during neural and B-cell development.	Expressed in many solid tumors; often used with CD44 (e.g., $CD44^+/CD24^-$).	Modulates B-cell activation and cell adhesion signaling.
Snail (SNAI1)	Transiently expressed during gastrulation and specific embryonic EMT events (e.g., neural crest formation).	Frequently upregulated in carcinomas (e.g., breast, colon, ovarian). Associated with high-grade, invasive tumors.	Master regulator of EMT. In embryos, it allows cell migration for tissue formation. In cancer, it drives invasion, metastasis, stemness, and therapy resistance by repressing E-cadherin (CD324).
Snail1 (Snail)	Essential for gastrulation;	Associated with primary tumor invasion and poor prognosis.	helps form the mesoderm and heart.
Snail2 (Slug)	Essential for Neural Crest cell	Found in circulating tumor cells and promotes lung metastasis.	migration (forming the face, nerves, etc.).
Snail3 (Smuc)	Involved in muscle and skeletal development.	Less common; sometimes acts as a tumor suppressor (opposite of Snail1/2).	Trancription Regulation

This polarity features a highly active leading edge, rich in filopodia for probing the three-dimensional extracellular matrix (ECM), and a trailing cell body. Notably, the Golgi apparatus is repositioned anteriorly, where it facilitates the production of new membrane required for forward protrusions [20]. The initial exit from the epithelium is mediated by the extension of these filopodia and pseudopodia, which physically penetrate the basement membrane, enabling the cell to translocate into and adhere to the underlying stromal ECM. Following the acquisition of metastatic potential, cancer cells can secrete neo-angiogenic factors, such as Endothelial Growth Factor (EGF), to stimulate new blood vessel formation for intravasation.

Adaptive Plasticity and Vasculogenic Mimicry

A key aspect of adaptive plasticity is vasculogenic mimicry, where cancer cells form fluid-conducting channels independently of endothelial cells. For instance, in addition to promoting angiogenesis from existing vessels, aggressive tumor cells can create their own vascular networks, as observed in ischemia-induced models of melanoma, breast, and prostate cancers. [21] demonstrated that aggressive melanoma cells could form tubular structures with patterned deposition of laminin, heparan sulfate proteoglycans, and collagens IV and V. These cells express genes typical of vascular endothelial cells and can interconnect with

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each other, forming a functional perfusion network.

Stromal Interaction and the Vicious Cycle

Malignant cells possess the propensity to synthesize self-growth factors and utilize stromal-derived factors like transforming growth factor-beta (TGF-β1) and interleukin-6 (IL-6). The molecular crosstalk between the tumor and its stroma creates a "vicious circle/ vicious cycle" driving tumor progression events such as angiogenesis, intravasation, invasion, and metastasis to distant niches like bone. Through coordinated epigenetic mechanisms, the tumor and stromal matrix synthesize factors that prepare the bone microenvironment to receive and support metastatic cells, establishing secondary populations.

Osteomimicry: A Prime Example

Osteomimicry is a prime example of metastatic mimicry. Many solid cancers, including those of the breast, prostate, and skin, metastasize to bone. In this process, cancer cells express bone-specific genes and proteins, enabling them to interact with the bone microenvironment without misrecognition. Metastatic cells can dysregulate normal bone turnover, simultaneously increasing bone formation and resorption (osteoclastogenesis). This altered bone remodeling becomes the foundation for successful colonization and growth within the skeletal niche.

Illustration of the Metastatic Cascade

Epithelial cancer cells (primary tumor) → Epithelial-to-mesenchymal transition (EMT) → Neoangiogenesis and intravasation → Circulation → Extravasation → Bone colonization (secondary tumor/metastasis) and potential mesenchymal-to-epithelial transition (MET) (Figure 1).

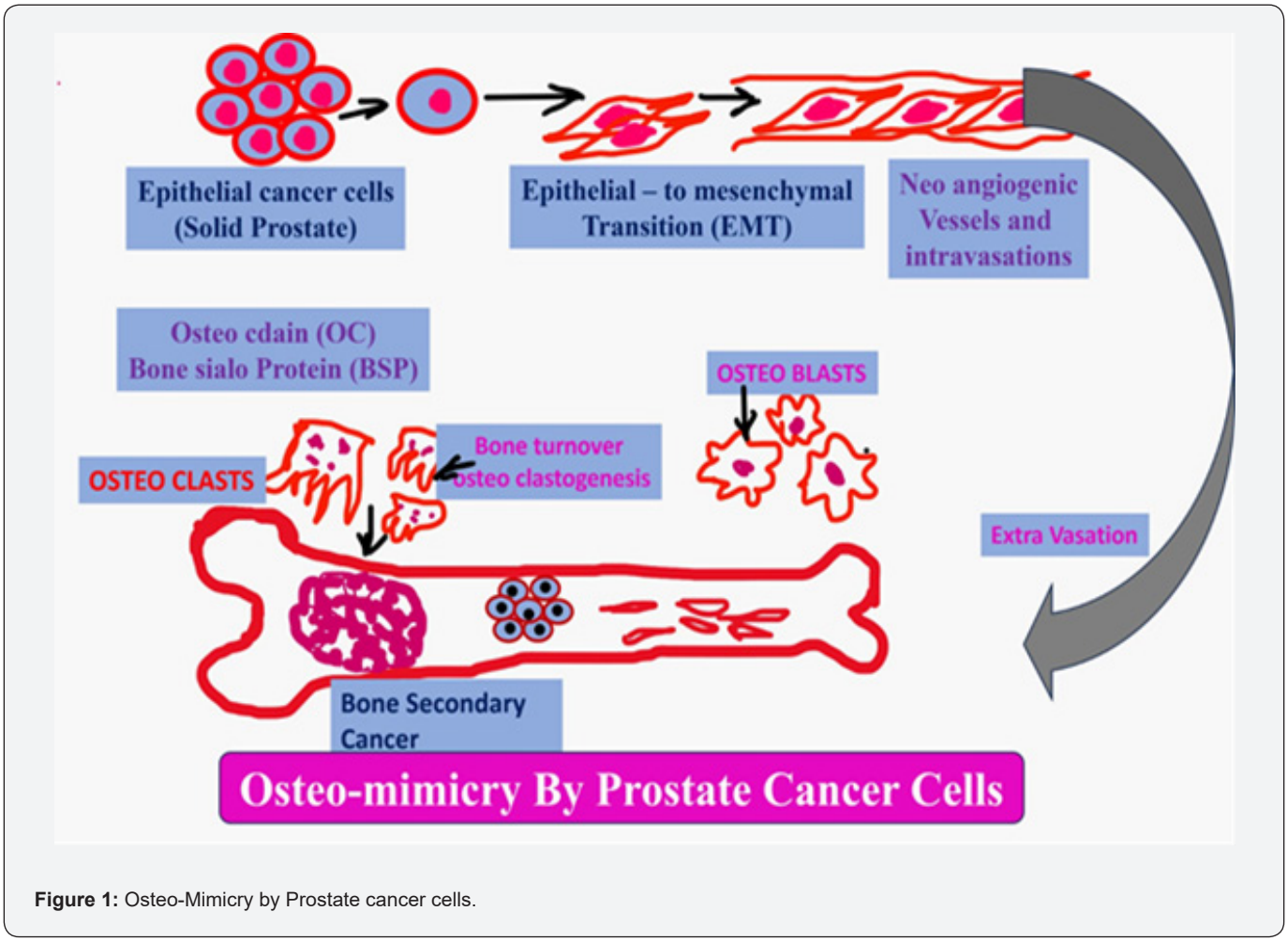

Figure 1: Osteo-Mimicry by Prostate cancer cells.

Therapeutic Implications

The malignancy in cancer, with variations in the characteristics and behaviour of cancer cells, reveals that it is not a single-cell disease. [Though genetic mutations constitute the bottom line for the disease Origin: consequent to its origin, the genetic functions of cancer cell gene expression and suppression are highly dynamic, as many switches are modulating the disease's cardinal features make the therapeutic oncologists remain in a

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fix and struggle to control the entire spectrum of the progressive and aggressive cancers. The synthesis of bone tissue constituents by the prostate cancer cells to prepare the secondary bone tissue niche, for the metastatic cells. Settle colonizes and grows is not imique to prostate alone but also for other aggressive cancers like breast and melanoma.

In this context, the molecular and cellular factors responsible for such homing mechanism of cancer cells and generating a permissive secondary niche for the incoming migratory cancer cells involve a plethora of host factors viz., chemokines, cell adhesion molecules integrins, cell surface receptors, extra cellular matrix, bone marrow, progenitor stem cells, and stromal cells etc. Thus, the strategies to arrest secondary organs metastases involve not only the primary cancer niche but also co-targeting the paraphernalia of other supporting molecules and cells. Towards these antiangiogenic drugs, radio nucleotides receptor antibodies, antibodies to the hijacked stem cells signaling, pathway, turning down the bones osteoclastogenesis by drugs like bisphosphonates natural peptides, proteins and Phyto adjuvants like EGCG, genistein, quercetin etc are of value in the clinical settings and cancer management.

Given these complexities, effective prevention of advanced metastasis requires combination strategies that target both the tumor cell chore and its supportive stroma. This involves chemotherapeutic cytotoxic drugs alongside complementary agents. Numerous phytochemical compounds-such as flavonoids, isoflavones, sulforaphane, β-carotenes, triterpenoids, saponins, catechins, and curcumin-can function as adjuvants. These agents may enhance the efficacy of cytotoxic therapies, potentially leading to a more complete eradication of the malignant population [22-27].

Summary and Conclusion

The process of osteomimicry by prostate cancer cells and their camouflaging properties imply that the entire gamut of the cancer odyssey in vivo obeys the principles of Darwinism. The embryonic properties of intensive proliferation and the evacuation of metastatic cells from their primary foci-analogous to the exit of retinal nerves during mammalian eye development-are reminiscent of evolutionary relics and reminders of recapitulation.

The transition from epithelial-to-mesenchymal transition (EMT states during intravasation, and the subsequent mesenchymal-to-epithelial transition (MET) transition for extravasation to colonize secondary organs, shed light on the Darwinian dogmatic principle of survival of the fittest. The fact that a mere 0.1 percent of metastatic cells succeed in seeding secondary organ niches serves as evidence for the above. Understanding the operation of natural selection in vivo among metastatic cells could help augment the therapeutic armamentarium against cancer.

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