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Review

Cellular determinants and microenvironmental regulation of prostate cancer metastasis

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ABSTRACT

Metastasis causes more than 90% of cancer-related deaths and most prostate cancer (PCa) patients also die from metastasis. The 'metastatic cascade' is a complex biological process that encompasses tumor cell dissociation (from the primary tumor), local invasion, intravasation, transport in circulation, extravasation, colonization, and overt growth in end organs. It has become clear that successful metastasis not only involves many tumor cell-intrinsic properties but also depends on productive interactions between cancer cells and the tumor microenvironment. In this Review, we begin with a general summary on cancer metastasis and a specific discussion on PCa metastasis. We then discuss recent advances in our knowledge of the cellular determinants of PCa metastasis and the importance of tumor microenvironment, especially an immunosuppressive tumor microenvironment, in shaping metastatic propensities. We conclude with a presentation of current and future therapeutic options for patients with PCa metastasis, emphasizing the development of novel, mechanism-based combinatorial strategies for treating metastatic and castration-resistant PCa.

1. Introduction

Despite the overwhelming prevalence of metastases-associated deaths in cancer patients, many biological programs underlying this complex process remain unknown. Research has been hindered in part by the complexities surrounding the metastatic process and the complex nature and heterogeneity of metastatic tumors. With the advent and continuous augmentation of the field of 'cancer genomics', along with other advancements, recent progress has been made in the field of metastasis in elucidating cellular programs that drive cancer metastasis. Several fundamental concepts of dissemination and metastatic outgrowth of cancer have been outlined. Metastasis is a complex process that occurs through a multi-step process, wherein the fate of a metastatic cell is influenced by and depends significantly on its interaction with components of the primary tumor, circulatory/lymphatic, and distant organ environment. The complexity increases due to the cell-intrinsic properties within that cancer cell as well as adaptive programs that impel that cancer cell to survive during metastatic colonization, both of which vary between various cancer types. These mechanisms, guiding cell-intrinsic and adaptive programs, have proven more difficult to elucidate. This Review aims to summarize the recent progress in elucidating unique cellular mechanisms and adaptive programs that drive prostate cancer (PCa) metastasis. This progress can be partially attributed to improvements in experimental models of metastasis, and we will provide experimental data confirming the value of these models. As these novel mechanisms inevitably offer potential therapeutic targets and strategies for the management of metastasis, the Review will end with a discussion on current therapeutic efficacies and future proposals.

2. Metastatic cascade: a primer

Metastasis occurs when cancer cells leave the primary tumor mass, travel, and survive in other locations in the body. This process is complex comprising many stochastic events that are dependent on both intrinsic properties of tumor cells as well as reciprocal responses from and interactions with numerous other cell types in the microenvironments of both primary tumors and end organs [1–4]. Metastatic cells can be generated via clonal evolution or clonal selection, wherein time-dependent acquisition of mutated genetic drivers within tumor cells, confer proliferative and invasive properties. Alternatively, cancer stem cells (CSCs), which pre-exist in primary tumors, may be endowed with intrinsic metastatic propensity. Both clonal selection and CSCs likely cooperate to generate cells that have metastatic capabilities. The ultimate success of metastasis also depends on cross-talk between metastatic cancer cells (the 'seeds') and specific end-organ microenvir-

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onments (the 'soil') [1]. Thus, through evolutionary time, genetic diversity, epigenetics, and the tumor microenvironment together contribute to metastatic success. Metastasis consists of many interrelated events including dissociation of prospective metastasizing cells from primary tumors, local invasion, intravasation, transport in the circulation, arrest in microvessels of various organs, extravasation, seeding and latency, formation of micrometastasis, and colonization and subsequent formation of macrometastasis [3]. With numerous variables at each step, metastasis is a highly inefficient process and tumor cells must constantly adapt in order to successfully colonize distant organs and form clinically overt lesions.

In the first stage of metastasis, the pre-colonization phase including local invasion and intravasation into the tumor vasculature or lymphatic system [3], tumor cells can be activated by the local microenvironment and inflammatory signaling to invade and migrate through the stroma via cytoskeletal rearrangements and the secretion of proteases that degrade extracellular matrix (ECM) proteins. Once shed into the circulation, tumor cells are called circulating tumor cells (CTCs), which must survive a variety of stresses especially the hemodynamic shear stress. CTCs can transport as CTC clusters containing tumor cells or mix of tumor cells and host cells such as macrophages, platelets, and leukocytes, which can provide several benefits [5–7]. For example, platelets may physically protect CTC clusters from shear forces, can induce reversible metabolic changes in tumor cells that increase their ability to withstand oxidative stress in the bloodstream, and can increase invasiveness via releasing signaling molecules [5,7].

The next phase, organ colonization, includes arrest of CTCs in capillaries at distant sites, extravasation, seeding and latency, and overt colonization [3]. The first capillary bed that a CTC encounters is largely determined by patterns of blood circulation, which influences the final destination of metastasis. Cancer cells then exit capillaries into the tissue parenchyma by penetrating the endothelial cell and pericyte layers, a process known as extravasation. The differing structures of the capillary walls in each organ, and the capacity of CTCs to pass through endothelial walls both influence the organ tropism of metastasis. Additionally, cancer cells may possess the ability to specifically target niches, such as the bone marrow hematopoietic stem cell (HSC) niche, as their final metastatic destination. Thus, a combination of priming signals from the tumor stroma, the composition of CTC clusters, blood-circulation patterns, the structure of target-organ capillary walls, cancer-cell-autonomous functions, and metastatic niches, together, determine metastatic infiltration of specific organs.

If CTCs infiltrate distant organs *and* survive, they are called disseminated tumor cells (DTCs). The foreign microenvironment, which encompasses stromal cells, ECM constituents, growth factors and cytokines, and even the microarchitecture of the tissue itself, are all factors that influence the survival and tumor-initiating activity of DTCs. After extravasation, DTCs must develop resistance to immunity (i.e., immune surveillance) and other host-tissue defenses. DTCs must also remain in supportive specialized niches, in which pro-metastatic stromal mediators would ultimately activate stem-cell support pathways and pathways that integrate cell metabolism and survival. DTCs can also enhance their own survival by expressing autocrine factors or by recruiting stromal cells as a source of soluble activators and amplifiers. DTCs then enter a latent state, during which they must achieve long-term survival [8].

In the final stages, cells break out of latency, reinitiate overt outgrowth, overtake the local tissue microenvironment and expand into large macroscopic metastases. The initiation of overt colonization differs in each organ and involves the selection of organ-specific metastatic traits, which gives rise to organ-specific populations of metastatic cells. When macroscopic metastases are detected, the patient is treated with combinations of conventional chemotherapy, targeted therapy and immunotherapy, which can reduce metastatic burden. Nevertheless, a population of residual cancer cells will withstand treatment via alteration of intracellular pathways for survival and via survival signals from non-neoplastic stromal cells until drug-resistant clones emerge. As a result, the cure rates of patients with metastasis remain disappointingly low.

These sequential steps outlining the metastatic cascade are the basis for all cancer types. However, the effect of specific environmental interactions with cancer cells harboring inherent attributes, lead to novel mechanistic differences between different cancer types. In the following section, we highlight specific examples of the adaptive programs found in PCa cells that lead to metastatic PCa.

3. Prostate cancer metastasis: recent advances and experimental assays

PCa remains the most prevalent non-cutaneous cancer in men in North America and the second most common cause of cancer death worldwide. Age is the greatest risk factor for PCa, as the majority (64%) of PCa patients are over 70 years and < 1% are under age 50. The growth of normal and malignant prostate tissue is regulated by androgens through action of the androgen receptor (AR) in both epithelial and stromal cells. Thus, the primary treatment for metastatic PCa (mPCa) is androgen-deprivation therapy (ADT), and in the majority of patients, this provides a temporary control of the disease. However, cancer cells eventually become castration resistant resulting in disease progression to metastatic castration-resistant prostate cancer (mCRPC). The survival rate for both patients with mPCa at diagnosis and patients with mCRPC upon ADT failure is poor. Interestingly, overall survival (OS) time in men with mCRPC is associated with sites of metastasis, with a shorter OS observed for lung and liver metastases as compared with bone and non-visceral involvement [9].

The development of an efficacious cancer therapy critically relies on the existing paradigm of cancer pathogenesis. The oligometastatic state, first proposed in 1995, was defined as an intermediate stage of cancer spread between locally confined disease and widely metastatic disease [10] At the time, the cell-of-origin, the specific cellular and molecular mechanisms as well as the importance of the microenvironment leading to the development of cancer were unknown or excluded, and tumor size was the principle basis for tumor staging. The clinical implication was that ablation of these limited and treatable cancer metastases, along with primary tumor resection, could potentially result in a cure. Today, the emergence of high-resolution genome technologies has revolutionized the field of cancer genomics. Within the PCa field, this technology has led to data generally supporting a monoclonal origin of multifocal PCa [11]. These studies suggest that primary tumors are composed of many different subclones, each one comprised of genetically identical cells, distinguishable from other subclones by their specific acquired mutations. Subclones with advantageous survival attributes such as intrinsic drug resistance, become dominant and survive. Interestingly, recent studies also provide evidence that PCa, in the context of ADT-associated metastasis, displays dynamic patterns of evolution [12]. Metastasis-to-metastasis spread was found to be common via two mechanisms. First, subclones within a metastasis can originate from another metastatic site rather than the primary tumor, a process called 'cross-metastatic seeding' [13]. This phenomenon was also demonstrated in response to therapy in a patient with lethal PCa [14]. Second, the same sets of subclones can seed multiple sites of metastasis, a process called 'polyclonal seeding' [13]. Multiple subclones may be shared between such polyclonal seeds for two or more metastases, suggesting that these subclones might functionally cooperate with one another to promote metastatic progression. Distant metastases could also reseed the surgical bed suggesting that PCa cells may take advantage of pre-existing supportive niches [14]. This process of 'tumor self-seeding' has previously been observed with PCa CTCs, which could lead to additional recruitment of CTCs and confer enhanced tumor growth [15]. Despite these breakthroughs in analysis of the PCa genome, clinical diagnoses for oligometastatic PCa are still based on the number of extrapelvic lesions, as a gap still remains