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Mini-Review Article

Hylonome

Cancer cell metastases

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Metastasis, the spread of cancer cells to distant sites in the body, and the invasion of normal tissue by cancer cells is the hallmark of malignancy. Our understanding of rules governing the formation of human tumor cells and metastasis is progressing rapidly. Over the past decade we have learned far more about the many steps involved in the conversion of normal cells to cancer cells, and the subsequent processes involved in establishment of metastasis. The formation of human tumors is a complex, multi-step process that probably requires many years to complete. Various lines of evidence suggest that at least five distinct regulatory pathways need to be perturbed for tumorogenic conversion of normal human cells. The candidate molecules include talomerase gene (hTERT), Ras, p53, pRb and PP2A proteins. Additionally, in order to metastasize, the cancer cell(s) have to detach from the primary site (which is often an epithelial tissue) and breach the basement membrane separating them from other tissue layers. Some of these invasive cells can enter the circulation by penetrating the basement membrane surrounding a blood or lymph vessel, as well as the layer of endothelial cells lining it. Once in the blood or lymph system, the cancer cells are free to circulate, but must survive the hostile environment in the bloodstream, in particular attack by host immune cells. Eventually a cancer cell(s) may lodge in a capillary, adhere to and penetrate the capillary wall and migrate into the tissue where growth and formation of the secondary (metastatic) tumor occurs. In most cases by the time the "primary" tumor is detected, cancer cells have already moved from their organ of origin and settled in other organs to continue their secondary growth gaining a "head-start" in the race against malignancy, that patients rarely win.

It is well known amongst physicians that some tumors are more "metastatic" than others. It has been postulated that the individual cells in any given tumor differ in their ability to metastasize. The earliest work indicating that cells in a single tumor might differ in their ability to metastasize came from studies conducted by Fidler and Kripke utilizing melanoma cells in a nude mouse model[1]. They found that certain clones produced far more metastases compared to others, and some clones did not metastasize at all. The variability in phenotypes of tumor cells derived from the same population of cells has become one of the hallmarks of developing neoplasm. The phenotypic variability of tumor populations is well documented for a number of cell properties including immunogenecity, invasion and metastasis, drug sensitivities and antigenecity, to name only a few[2-4]. Each step of the metastasizing process is probably controlled by a different molecular system, a failure of which would most likely render a tumor cell incapable of metastasizing. It has been hypothesized that variants within a tumor cell population arise as a result of genetic instability and are subject to environmental and immune selective pressures by the host. In this way, only those sub-clones that can successfully compete for nutrients and avoid elimination survive, resulting in an enhanced malignant phenotype. The primary tumor then acts as the raw material for metastases and the selection and evolution of the tumor ensure its refinement to the point where some cells can survive, migrate, and grow in their new environment. This process of continuing evolution of a tumor is referred to as progression[5-9].

Circulatory system physiology explains much about why various metastatic cancers spread preferentially to certain tissues. Circulating tumor cells usually get trapped in the first vascular (capillary) bed encountered "downstream" from their point of origin. The first vascular bed encountered by blood leaving most organs is in the lungs, an exception is the intestines from which blood goes to the liver first. Accordingly, the lungs are the most common site of metastasis, followed by the liver and bones. Indeed, some types of cancer show a striking preference for organs other than lungs and liver, for example prostate and breast tumors demonstrate a proclivity to invade bones[9-11]. This tendency may result from an affinity between receptors on the prostate and breast tumor cells and molecules in the bone tissue, but also from interaction between the tumor cells and bone marrow stroma. The interaction between tumor cells "seed", and

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bone microenvironment "soil", was recognized by Paget more than a century ago. Stromal cells in the primary and metastatic target organs are important mediators of cancer cell extravasation, chemoattraction, target organ endothelium adhesion, and tumor cell growth at the site of the metastasis. Paget's original theory was experimentally confirmed many times providing a rational basis for the development of current therapeutic strategies targeting bone metastases, such as new nitrogen-containing bisphosphonates.

All metastases have severe impact on the quality of life of cancer patients. Consequences of bone metastases include intractable pain, fractures, nerve compressions and/or pulses, marrow suppression, and hypercalcemia of malignancy. Once established, bone metastases are more resistant to therapy than cancers in other sites. Anticancer treatment, particularly estrogen and androgen ablation in breast and prostate cancer patients also has severe impact on already compromised skeletal tissue and can cause osteoporosis[12-14]. Radiation therapy, cytotoxic therapy and glucocorticoid therapy along with muscular weakness and inactivity further add to bone loss and propensity for fracture. Therefore, improved treatment of the skeletal consequences of malignancy will impact the disease progression, but perhaps more importantly will improve the quality of life of patients affected with metastatic disease.

Interest in the skeletal complications of malignancy continues to increase. There are several reasons for this growing trend including an aging population, higher incidence of cancer, improved diagnostic tools, and more effective anticancer therapy. In addition, life expectancy has been prolonged, in particular in the patient population suffering from breast and prostate cancer. The development of new therapies for metastatic carcinoma requires a better understanding of the mechanism of homing of the tumor cells to bone, liver and lungs and the factors required for their growth in these organs. Future drug development will focus on integrating systemic therapy with therapies targeting specific microenvironments to overcome classical drug resistance often seen at the sites of tumor metastasis. The session "Cancer Cell Metastasis" will cover some of the most relevant issues regarding metastatic disease with emphasis on principles of the cancer metastasis process and cell-cell communication, breast and prostate cancers and bone metastases, and finally on available high-throughput screening methods that should facilitate our understanding of metastatic process and help drug discovery efforts.

Further reading

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