The Biology of Pulmonary Metastasis

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KEYWORDS

• Metastasis • Pulmonary metastasis • Seed and soil hypothesis

KEY POINTS

- The process of metastasis relies on a series of stochastic and sequential steps, with selective pressure exerted on a large number of genetically volatile cancer cells to produce a very small fraction of tumor cells with the ability to navigate the transition from primary tumor cell to end-organ metastasis.
- Metastasis is intricately determined by cell-microenvironment interactions, of which we are steadily gaining a mechanistic understanding.
- The continued elucidation of pathways that govern these interactions offers potential therapeutic options to patients with advanced disease.

INTRODUCTION

The study of cancer metastasis has been a process spanning nearly 2 centuries, and only over the few decades have we begun to mechanistically break down the complex interactions that influence a transformed cell to progress to metastasis. Investigations from recent literature have demonstrated that from the potentially millions of cancer cells shed into the circulation, only a minute fraction of these cells have the capability of forming metastasis in distant organs. This process is not governed simply by the volume of exposure to an organ, but is marked by stochastic intrinsic cellular events and is influenced by selective evolutionary pressure exerted on the cell by its local environment. This process was elegantly described more than 100 years ago by Stephen Paget, who published his enduring article on the "seed and soil" hypothesis to explain the nonrandom pattern of metastasis.[1] He observed a discrepancy between the blood supply and frequency of metastasis to distant organs based on autopsy records from 735 women with breast cancer. He posited that "remote organs cannot be altogether passive or indifferent regarding [tumor] embolism."

The biological cascade of events required for cancer metastasis includes increased motility, loss of cellular adhesions, intravasation to the circulation, survival while in transit, extravasation to distant organs, and colonization. Each step in the process is necessary, and failure of any these can prove to be rate limiting. Clinicians have become increasingly aware of the various genes and pathways that regulate these interactions between tumor cell and host. As research continues to elucidate the biology of cancer metastasis and identify molecular pathways and mediators we can begin to more accurately determine molecular signatures that serve as surrogate markers for a metastatic phenotype. Furthermore, as the understanding of the mechanistic processes of cell and microenvironment interactions increases, therapeutic interventions can be developed to target specific stages in the progression of a cancer cell to a metastasis.

AN OVERVIEW OF THE PATHOGENESIS OF METASTASIS

The cascade of cancer metastasis consists of a sequential and interrelated series of steps, each

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of which can be rate limiting.[2] The progression to metastasis involves establishing neovasculature,[3] altered cellular adhesion,[4] increased cell motility,[5] disruption of the basement membrane,[6,7] intravasation to the circulation,[2,8] escaping host immune surveillance,[9] tumor embolization, and arrest in capillary beds and eventual colonization of a distant site.[10,11] As outlined in the seed and soil hypothesis,[1] the interaction between host and cell factors determines which organs can support the survival of metastasis.

The Heterogeneity of Metastasis

It has been well demonstrated that not all cells located in the primary tumor have a similar potential to metastasis. Prior experiments have demonstrated that cells with differing metastatic potential have been isolated from the same parent tumor[12] and that highly metastatic clones from tumor cell populations demonstrate a higher rate of genetic mutability than nonmetastatic clones from the same tumor.[13] Heterogeneity within a population is a requirement of any evolutionary process, and allows a source of advantageous traits from which to select from. When applied to the biology of metastasis, several factors contribute to the instability of the cancer genome: DNA mutations, chromosomal arrangements, and epigenetic alterations.[14] Several mutations have been proposed that cause genomic instability and lead to tumor proliferation. Inactivation of cell-cycle suppressors,[15] disabling DNA-damage sensors,[16] and telomeric crisis[17] are a few of the putative pathways. Epigenetic plasticity also plays a significant role in metastatic heterogeneity.[18,19]

The Clonality of Metastasis

Previous animal experiments have demonstrated that tumor progression is associated with increasing genetic instability and spontaneous mutation rates,[13] supporting the hypothesis that acquired genetic variability within developing clones of tumors, coupled with selection pressures, results in the emergence of tumor cell variants with increasing malignant potential.[20] To determine the clonality of cancer metastasis, Talmadge and colleagues[21] conducted a series of experiments in which random chromosome breaks were used as unique indelible markers. The metastatic phenotypes of spontaneous lung metastases derived from subcutaneously implanted tumors were analyzed whereby unique karyotypic patterns of abnormal marker chromosomes were identified, indicating that the metastases had originated from a single progenitor cell. Several other reports have demonstrated the clonality of other tumors in melanoma, breast, and fibrosarcoma.[22]

SEED AND SOIL, REVISITED

In 1889, Stephen Paget was the first to address the question, "What is it that decides what organs shall suffer in a case of disseminated cancer?"[1] In doing so he established the framework for tumor-cell interactions, referred to commonly as the "seed and soil" hypothesis. He further went on to elaborate on this theory, stating "when a plant goes to seed, its seeds are carried in all directions, but they can only live and grow if they fall on congenial soil."

Even after more than 120 years, Paget's seed and soil hypothesis is the foundation of ongoing investigation. With continued refinement we may recognize the "seed" now as a progenitor cell, initiating cell, cancer stem cell, or metastatic cell, and the "soil" as a host factor, stroma, niche, or organ microenvironment.[23] In a more recent article on the biology of cancer metastasis, Talmadge and Fidler revised the concept of this hypothesis to include 3 main principles,[10] the first being that primary neoplasms (and metastases) consist of tumor and host cells. Host cells include epithelial cells, fibroblasts, endothelial cells, and infiltrating leukocytes. Furthermore, neoplasms contain biologically heterogeneous populations of tumor cells, each of which has the ability to complete some of the steps in metastatic process, but not all. The second principle is that the successful metastatic cells ("seed") are selected for their ability to succeed in invasion, embolization, survival in the circulation, arrest in a distant capillary bed, and extravasation into and multiplication within organ parenchyma. Metastasis favors the survival and growth of a few subpopulations of cells within the parent neoplasm, and current studies support a clonal origin for metastases. The third principle is that metastases develop in specific organs, or microenvironments ("soil"), which are biologically unique. There is a differential expression of cell-surface receptors and growth factors that can be either supportive of or inhospitable to metastases.[24,25]

THE BIOLOGY OF SUCCESSFUL METASTATIC CELLS ("SEED")

Successful metastatic cells are selected for their ability to undergo the processes of invasion, intravasation, arrest, extravasation, and colonization of distant organs.[10,26] Invasion initiates the metastatic process of a tumor cell, and involves