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The inherent metastasis of leukaemia and its exploitation by sonodynamic therapy

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Contents

Abstract

Nearly all cancers are linked by the inexorable phenotype of metastasis as malignant growths have the capability to spread from their place of origin to distant sites throughout the body. While different cancers may have various propensities to migrate towards specific locations, they are all linked by this unifying principal. Unlike most neoplasms, leukaemia has inherent cell motility as leukocytes are required to move throughout the vascular system, suggesting that no mutations are required for anchorage independent growth. As such, it seems likely that leukaemias are inherently metastatic, endowed with the deadliest phenotype of cancer simply due to cell of origin. This article presents the biology of metastasis development and how leukaemia cells are inherently provided these phenotypic characteristics. It is then proposed how clinicians

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may be able to exploit the motility of leukaemia and metastatic emboli of other cancer types through an approach known as sonodynamic therapy (SDT), a treatment modality that combines chemotherapeutic agents with ultrasound to preferentially damage malignant cells. As experimental evidence has indicated, SDT is a promising therapeutic approach in need of clinical testing for further validation.

1. Introduction

The heterogeneity and extent of diversity among known cancer types is truly immense. Even within a given cancer type, there are various histologies, aberrant biochemical pathways and mutations that permeate a truly unique disease for an individual patient. However, all cancers are linked by the inexorable phenotype of metastasis. In other words, each cancer has the capability to spread from its place of origin to distant sites throughout the body (with exception to some brain cancers). While such cancers may have various propensities to migrate towards specific locations, they are all linked by this unifying principal. In fact, more than 90% of patient mortality due to cancer is a direct consequence of metastatic progression [1]. Other than aberrant cell proliferation, there is not a single more unifying phenotype in cancer biology.

Cancer occurs after cells in a tissue progressively acquire aberrant mutations to produce progeny with uncontrolled capacities of proliferation [2,3]. This uncontrolled mitosis produces a primary tumour which eventually undergoes metaplasia, followed by dysplasia and then anaplasia, resulting in a malignant phenotype. It is this malignant phenotype that provides a mechanism for intravasation into the circulation, followed by extravasation to a secondary site for tumourigenesis. Such a phenomenon is referred to as metastasis, defined as the spread of a cancer variant from one organ to another non-adjacent organ [4]. As opposed to invasion which involves the migration of cancer cells to adjacent tissue, metastasis necessitates the development of cells capable of surviving highly variable environments as they fragment from the primary tumour and migrate into the vasculature.

Most cancers (~85%) are of epithelial origin, referred to as carcinomas. Epithelial cells are normally held in place by junctions to adjacent cells as well as the basal lamina matrix [3]. Most epithelial cells require such attachments in order to survive, thereby requiring carcinomas to undergo a series of mutations that not only remove this need of cell signalling, but allow the cell to detach from the lamina foundation. However, not all cancers face such an uphill battle. Leukaemia is a highly heterogenic cancer of dedifferentiated leukocytes that causes more disease-related deaths of children (younger than 18 years of age) than any other disease in the United Kingdom or United States [5, Cancer Research UK]. The statistic includes all diseases, and is a sobering reminder of the prevalence of childhood cancer, despite the commendable advancements in cancer therapy. Unlike carcinomas, leukaemia has inherent cell motility as leukocytes are required to move throughout the vascular system, suggesting that no mutations are required for anchorage independent growth. As such, it seems plausible that leukaemias are inherently metastatic, endowed with the deadliest phenotype of cancer simply due to cell of origin. However, its most devastating characteristic may also be exposed as a fatal flaw if chemotherapeutic approaches are able to exploit the ease at which dedifferentiated leukocytes traverse the cardiovascular and lymphatic systems. This article will present the biology of metastatic progression and how leukaemia cells are inherently endowed with this devastating phenotype. Finally, it is indicated how clinicians may be able to exploit the motility of leukaemia and metastatic emboli of other cancer types through an approach known as sonodynamic therapy (SDT), a treatment modality that combines chemotherapeutic agents with ultrasound to preferentially damage malignant cells.

2. The biology of non-haematopoietic metastases

Although it may seem archaic by contemporary standards, the existence of metastasis was accurately predicted by Stephen Paget in his article, "The Distribution of Secondary Growths In Cancer of The Breast," published in a 1889 volume of *The Lancet*. In the article, Paget examined post-mortem data that had been assembled from 735 women with breast cancer and noted that the organ distribution of cancer cells in these patients followed particular migratory patterns. Due to these observations, Paget suggested that the movement of malignancy is not due to chance events; rather some tumour cells (the "seed") grew preferentially in the microenvironment of select organs (the "soil") and that migration to secondary sites resulted only when the appropriate seed was implanted in its suitable soil [6]. Paget's assertion that the microenvironment plays a critical role in regulating the growth of metastases has since been supported by numerous experimental studies; a remarkable insight for the time that has since dramatically improved the understanding of cancer biology.

In order for normal cells to transition into malignant potency, there are several crucial aberrations that need to occur. Such characteristics include mitosis in the absence of external growth stimulatory signals, substantial growth in spite of exogenous inhibitory signals, angiogenesis (excluding various haematological malignancies), the potentiation of cell immortalization, and finally, the capacity of invasion and metastasis [2]. This is typically the last step in malignancy (Fig. 1A), and is the phenotypic characteristic that kills most patients [7]. It should be noted that there is a considerable difference between invasion and metastasis. Invasion refers to the ability to thrust aside and displace

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