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The sleeping ugly: Tumour microenvironment's act to make or break the spell of dormancy

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A B S T R A C T

Metastasis is the main cause of death for most cancer patients. It appears clear from clinical observations that the majority of cancers, particularly carcinoma do not follow a linear model of metastatic progression, where cancer cells shed from the primary tumour, disseminate to a distant organ and immediately outgrow to form clinical metastasis. Certainly, while cancer spreading is an early event, metastasis occurs much later during tumour progression and frequently arises several years after primary tumour resection. The time spent by disseminated cancer cells (DTCs) in a distant organ before their outgrowth is termed metastatic latency. We will examine here the current knowledge of the mechanisms allowing metastatic latency and discuss the crucial role of the DTCs' tissue microenvironment in this process.

1. Introduction

Metastasis is the main cause of mortality for many cancer types. Metastatic progression begins when cancer cells infiltrate the local tissue surrounding the primary tumour, reach the circulation and spread to reach distant organs where they face the challenge of growing secondary tumours in a foreign environment [1]. Metastatic progression is not necessarily a linear process. Tumours start shedding cells in the circulation, termed circulating tumour cells (CTCs), very early [2], however the number of metastatic lesions that develop are a tiny fraction of the total CTCs found in the blood of patients [3] highlighting the inefficiency of the metastatic colonization of distant tissue. When CTCs exit from the circulation and infiltrate distant organs they become disseminating tumour cells (DTCs). Which DTCs will grow and which will not is a fundamental question in cancer biology. Certainly, the heterogeneity of cancer cells in a tumour results in a great disparity in their intrinsic tumourigenic potential [4]. Therefore, successful DTCs are required to possess at least an intrinsic tumour initiation potential needed to reconstitute tumour growth in a favourable environment. Yet, DTCs originating within a complex tumour-supporting milieu are unlikely to readily find a favourable environment in distant naïve tissue. Indeed, metastatic cancer cells, in addition to their intrinsic tumour initiation potential, are required to retain further characteristics allowing them to kick start a supporting microenvironment or niche [5]. The tumour niche, comprised of extracellular matrix proteins and a collection of non-malignant cells, is an integral part not only of primary tumour structure but also of metastases. An efficient niche initiation via crosstalk with local tissue cells is required for DTCs' adjustment to the new location and outgrowth [6]. The niche cellular components and functions are tailored to support cancer cells through temporal and spatial changes, and therefore a constant interaction between cancer and niche cells guarantee their coordinated evolution [7,8].

DTCs within a distant organ have more than a binary fate of successful growth or unsuccessful death. A third option was already proposed in 1934 by the Australian pathologist Rupert Willis that originally coined the term 'dormant tumour cells' [9]. When observing that metastases can grow at distant organs many years after the resection of the primary tumour he postulated that tumour cells might have spread and remained repressed in their proliferation for a long time before initiating growth (Fig. 1). For certain tumours, such as breast cancer, the metastatic latency period can be as long as 25 years after primary tumour resection [10]. Conversely, late recurrences of more than 10 years after initial treatment were documented in the clinic for more aggressive tumour types such as cutaneous melanoma [11,12]. Other powerful clinical evidence that malignant cancer cells reside dormant is from allograft recipients when organs that transmit malignancy are donated from cancer patients long after primary tumour resection [13,14].

In this review we will discuss how best to define the phenomenon of cancer dormancy and discuss the most recent advancements in the field. We will analyse the relationship between cancer cell quiescence and stemness, which represents the key for the maintenance of the dormant tumour initiation potential: the core of the clinical relevance of the phenomenon.

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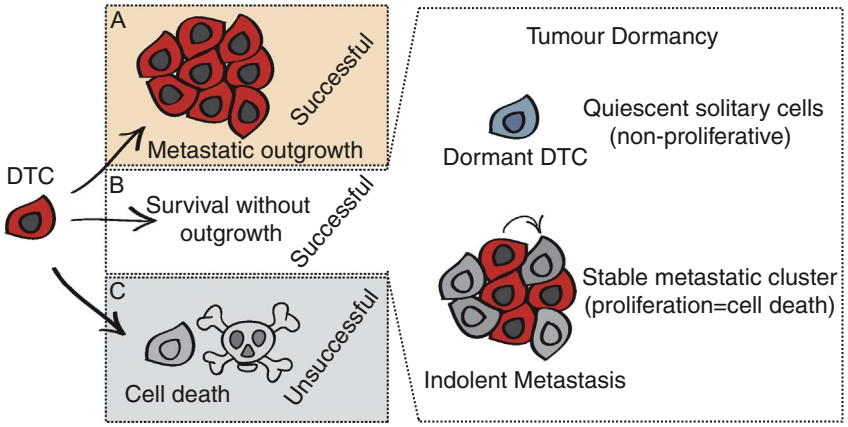

Fig. 1. Overview of the different fates faced by a disseminated tumour cell (DTC) in a distant foreign tissue. (A) Successful survival and growth in the new tissue causes clinical metastasis. (B) Successful survival of DTC in the tissue with maintenance of latent metastatic potential. A DTC can either remain in the tissue dormant and nonproliferative (Dormant DTC) or display a limited proliferative potential giving rise to a small cancer cell cluster with a high level of cell death that prevents its outgrowth (Indolent Metastasis). (C) DTC fails to survive in the tissue.

2. Defining tumour latency

The clinical phenomena of tumour dormancy or latency can be described as the period between the primary tumour resection and the presence of clinically relevant metastatic outgrowth. A clinical metastasis is characterized by substantial exponential growth causing clinical signs and the potential for a progressive malignant evolution to spread and source other metastatic foci. CTC dissemination can be observed in mouse models as well as in breast cancer patients as an early event during primary tumour formation [2]. Therefore every patient without sign of metastatic progression at the time of primary tumour resection has the risk of having DTCs, which ultimately may never develop metastasis. How likely is it that cancer cells survive dormant in a normal tissue? And how likely is it that a dormant cancer cell reactivates? Clinically it is not possible to answer these questions, as these cells are completely undetectable unless they reactivate and generate clinical metastasis. Therefore, experimental approaches should be targeted to answer those key questions, in order to estimate the actual risk for late recurrences. Increased understanding of this phenomenon is paramount to improve cancer patient's care and monitoring, potentially leading to longer patient survival.

To understand tumour dormancy as a biological process it is important to distinguish how DTCs in a given tissue exist during the latency period. There are two potential scenarios for tumourigenic DTCs explaining their failure in generating clinical metastasis (Fig. 1). Firstly, DTCs can remain in the distant tissue as non-proliferating single cells or few-cell clusters (Dormant DTCs). Alternatively, DTCs could start growing but with a high proportion of cell death causing the generation of small non-clinically relevant indolent metastatic masses (Indolent metastasis). Here the equilibrium between proliferation and cell death prevents the outgrowth potential of cancer cells. Both these biological phenomena of dormant DTCs and indolent metastasis can explain the clinical phenomenon of tumour latency, however they are distinct events generated by different properties of DTCs. Importantly, dormant DTCs and indolent metastasis are likely to have differential mechanisms of their reactivation and response to therapy.

3. Metastatic dormancy

DTCs capable of surviving in a given distant tissue will maintain their "cancer" identity provided by the oncogenic mutations they carry. Dissemination can be an early event in cancer progression, and it can be observed in genetic models of pancreatic and breast cancer even before the establishment of primary tumours [2,15]. Two recent studies, using a Her2-driven mouse breast cancer model, also reported that early lesion cells display high migration activity and disseminated very early to distant organs. Importantly these early-disseminated cells were shown to display metastatic potential [16,17]. This early migratory activity was reported to be progesterone induced and seems to be governed by mechanism of mammary branching activity. Strikingly, the majority of metastases in this mouse model originated from early-disseminated cells. Moreover, analysis of human DTCs also confirmed the phenotype of early disseminating cells, strongly suggesting the presence of early dissemination in human malignancies [16]. These studies represent the first mechanistic evidence of early cancer dissemination with the maintenance latent metastatic potential and challenge a linear model of metastatic progression where subsequent accumulation of genetic abnormality within the primary tumour would be prerequisite to gain metastatic ability. Now an alternative model of parallel progression can be proposed, where cells can leave early during primary tumour onset and still be capable of originating metastatic disease after a latency period [18]. Considering this early dissemination, distant tissues are likely to receive high numbers of DTCs from the primary tumour. However, the majority of DTCs in human patients are unlikely able to survive within the distant organ, and, importantly, even when they do they rarely switch to a growth modality immediately. Moreover, the likelihood of their outgrowth decreases the longer they persist in the tissue. Indeed the higher metastatic risk window is within the first five years after tumour resection even for tumours with long metastatic latency [10]. Clinically, it will be crucial to be able to estimate the risk that DTCs actually will reactivate and start metastatic outgrowth. To do this we need to understand the mechanisms allowing DTCs to persist in the tissue as well as clarify the main cause for their reactivation.

3.1. Core programs: dormancy vs proliferation

A dormant program will require inducing cell cycle arrest and activating pathways to support cell survival. Akt activity was found to be an important driving force in maintaining the survival of cancer cells as either non-proliferating or entering a proliferative state after a latency period. This pathway seems to be important for survival and late metastasis of breast cancer cells in the bone environment, but also for survival of quiescent melanoma cells, suggesting that this pathway can regulate both quiescence and proliferative behaviour [20,21]. A recurrent molecular signature of dormant cancer cells that is conserved throughout different tumour types is the activation of p38 mitogen-activated protein kinase (MAPK), and the expression of protein actively blocking proliferation, typically cyclin-dependent kinase inhibitor p21 or p27 mediating cell cycle arrest [22–27] (Fig. 2). The entire