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Forum

Tumour Dormancy and Reawakening: Opportunities and Challenges

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Tumour dormancy presents challenges for clinical control and opportunities for scientific discovery. Current pictures of the mechanisms of tumour dormancy and reawakening remain incomplete. The Cancer Research UK's third Marshall Symposium explored tumour dormancy and reawakening in all their forms. In this forum article, we highlight the key challenges and opportunities discussed at this symposium.

Dormancy and the Metastatic Cascade

Despite major advances in controlling cancer in recent decades, most of our progress has been achieved through diagnosis and treatment of premetastatic disease, while metastatic disease remains largely incurable for most cancers. As an evolutionary phenomenon, metastasis can be thought of in terms of the metastatic cascade. Cells must acquire a series of adaptations, including local invasion, intravasation and extravasation, and colonisation, in addition to coping with foreign environments very different from those experienced in their tissue of origin.

The paradigm of the metastatic cascade describes the often high and variable delay between detectable local disease becoming detectable metastatic disease. Adaptations are contingent on stochastic events, and there is a high attrition rate of cells in hostile environments, providing one explanation for the long periods of apparent stability or dormancy.

In this context, dormancy and reawakening encompass a variety of phenomena and scales, from individual cells to the tumour and metastatic tumour mass. The word dormancy implies cells have become inactive, and may suggest dysfunction, but cancer dormancy may also include periods during which cells maintain competency. While research has understandably focused on individual cancer cells and molecular mechanisms, equally important are the interactions between the cancer cell and stroma, including other cell types, extracellular matrix proteins, and the immune system. Indeed, the appearance of dormancy can represent a dynamic equilibrium between intrinsic tumour promoting and extrinsic tumour suppressing activity.

Tumour dormancy and reawakening have profound implications for prognosis, therapeutic success, and for research priorities and methods. Tumours that recur earlier are typically more aggressive. In breast cancers, for example, Rueda *et al.* recently showed that shorter duration between primary diagnosis and detectable metastatic disease is associated with shortened overall survival, suggesting associations between dormancy and the aggressiveness of recurrent or metastatic disease. This raises the question of whether a better understanding of dormancy could enable us to predict the duration of dormancy, recurrence, and even subsequent tumour behaviour [1].

The formidable challenge that dormancy presents for therapy is most dramatically demonstrated by post-treatment recurrence, driven by disseminated cells that remain dormant throughout therapy and sometimes for years afterwards before reawakening. This raises the question of whether dormancy might itself be targetable as part of adjuvant treatment strategies. Disseminated cells that have made the first step into the perivascular niche, for example, may exhibit dormancy in the form of quiescence, limiting the uptake of cytotoxic antimetabolites, and have also been observed to have reduced MHC expression. Both observations present potential pathways for targeting these cells in tandem with existing therapies.

Finally, dormancy presents an opportunity to rethink therapeutic strategies in which attempts to eradicate disseminated cancer cells have failed, and instead consider the possibility of controlling reawakening. In most cases, the events that precipitate reawakening remain opaque. Reawakening may variously be driven by events within the cells in a micrometastasis, by changes to the microenvironment in which these cells reside, by changes in remote signals, or by changes in endocrine or immune activity. Each of these putative mechanisms allows us to speculate about potential strategies for preventing reawakening, while highlighting where we need to first focus efforts in mechanistic discovery research.

Dormancy and the Microenvironment

One of the striking features of metastasis, observed for well over a century, is that cancers of different primary origin show preference for colonising select tissues, and so we see distinct patterns in where metastases establish. A typical way of explaining this apparent tropism is the seed and soil analogy in which seeds only germinate in soils that provide the conditions they need. However, this picture of metastasis may lead us to think of the 'soil' as a passive container and source of nutrients, neglecting the importance of the host tissue as a dynamic environment with an active role in determining the fate of disseminated cancer cells.

The evolutionary understanding of the metastatic cascade introduces many elements of chance to cancer's progression, and chance provides one obvious solution to how, once they have made their way into circulation, tumour cells establish at specific metastatic sites. That is, once scattered, the seed will land in any and all soils, and with each environment providing unique challenges, natural selection leads to the specific pattern of surviving sites; but this solution may not be a complete explanation for metastatic tropism. Initial expansion of cells is needed to select for adaptation in each site, and finding an environment with the right growth factors, chemokines, and extracellular matrix properties to support some proliferation may be a barrier to the formation of distant metastases.

Box 1. Case Study: Brain Metastases

Circulating cancer cells easily reach the abundantly perfused capillary beds of the nervous tissues. However, only a minority of these cells possess the essential transcriptional programs that enable entry across the blood brain barrier. Once within the brain, a small minority of these cells successfully evade astrocytic anticancer responses by engaging astrocytes through the generation of gap junctions between cancer cells and astrocytes. A subpopulation of these cells generates sufficient blood supply and reprograms their metabolism to support biomass production. Each step of this process is extraordinarily inefficient, not only requiring a highly heterogeneous population but also potentially a plastic subpopulation to continually generate new variability. Each of these steps suggest potential strategies that will prevent both the growth of an established brain metastasis and the generation of additional brain metastases. Targeting of cancer cell–astrocyte gap junctions, for example, enables the dominance of the initial anticancer astrocytic response, rendering the cells sensitive not only to endogenous Fas ligand but also exogenous chemotherapy [5].

The seed and soil analogy may also serve to deemphasise the fact that no 'soil' is a hospitable environment for disseminated tumour cells, and their success is rare, as indicated by the long delay typically seen between a tumour beginning to disseminate cells and the establishment of any detectable metastasis. While there is evidence that many different mechanisms can have a role in this delay, each cancer type and secondary site raises its own questions about the nature and relative importance of those mechanisms, brain metastases provide an illustrative example (Box 1). Are there barriers that filter disseminated cells before they reach or enter the secondary site? Are they entering the secondary site and then remaining dormant until changes in either the cells themselves or in the stroma enable reawakening?

The effect of ageing may be another important consideration in understanding the tempo of tumour progression and the mechanisms of reawakening. In ageing skin, for example, Kaur and colleagues recently showed how secretory changes and remodelling of the collagen matrix driven by dermal fibroblasts – both normal effects of ageing – can affect promotion of metastasis while alleviating suppression of immune infiltration in melanoma. This work explains why melanoma is typically more aggressive in older patients, as well as recent observations that older melanoma patients are typically more likely to respond to checkpoint inhibitor therapies [2].

Dormancy and the Immune System

The immune system can have a central role in maintaining cellular dormancy or disrupting a dynamic equilibrium between tumour and stroma. Within this process, immunological visibility to T cells and natural killer (NK) cells is key to eradicating dormant cancer cells, making immunotherapy an obvious focus for efforts to understand tumour dormancy and reawakening. Immunotherapies of all modalities currently face the challenge of a high proportion of nonresponding patients, even those with highly visible tumours. When is this simply a function of using the wrong immunotherapy modality or targeting the wrong antigen? What part does T cell exhaustion play? Does organ-specific immunity have a role?

However, in the excitement surrounding immunotherapy, there is a risk that we take the innate immune system for granted, as garbage collection that comes after the important business. Yet we already know that the relationship between innate immunity and metastasis is more complex. Macrophages can be turned into promoters of metastasis, with roles supporting metastatic niche formation and angiogenesis, and a picture is emerging of how neutrophils can reawaken dormant disseminated tumour cells during sterile and nonsterile inflammation [3]. But our understanding of the role of innate immune cells in cancer more generally is very immature, held back by a lack of suitable experimental tools and models for studying and manipulating these myeloid cells *in situ*. Development of immunotherapies has outpaced our understanding of the many roles and mechanisms of both innate and adaptive immune cells in cancer, and we must address this gap if we are to reduce the high rate of nonresponse.

In addition to the roles that the immune system has in tumour and cell dormancy, it may be instructive to consider whether lessons can be learned by drawing an analogy with the normal biology of the immune system, which involves cells of several types colonising different tissues and remaining in dormant states. For example, foreign cells from a foetus are able to migrate into organs of maternal hosts and reside there forever. Similarly, macrophages provide a potential model for widely disseminated cells that live within tissues for very long periods in a kind of dormancy, while remaining alert to signals in the environment. Meanwhile, our understanding of T cell exhaustion is moving beyond this being a simple dysfunction to being purposeful reprogramming into states of dormancy, either to prevent pathological immune responses or as a 'sleep' state that enables rejuvenation [4]. The extreme complexity, robustness, and plasticity of the immune system might raise many challenges, but it also leaves us with reasons for optimism as we anticipate the impact of breakthroughs in our fundamental understanding of immunology.

Dormancy as a Winning Strategy

In oncology, we associate dormancy with failure: it is how cells evade immune detection and therapeutic mechanisms. But infectious diseases provide examples in which dormancy has proved a successful clinical strategy for controlling otherwise grave illnesses. Most dramatically, immune modulation strategies have become so successful at maintaining the dormancy of HIV that this once catastrophic infection can be transformed into a manageable and asymptomatic chronic condition.

Like cancer, HIV represents a fast-moving target, which rapidly forms a heterogenous population as it expands. Attempts to control either condition through any means other than their most mission-critical and evolutionary conserved systems are likely to fail, leaving at best resistant disease, and at worst creating opportunities for more virulent strains to expand. Rather than continue an unwinnable evolutionary arms race, we must find alternative strategies to de-escalate the conflict.

The transformation achieved with HIV infection has been accompanied by a commensurate shift in perception of a condition that was once, as a cancer diagnosis typically still is now, a cause of great fear and anxiety. Recent developments, such as the evolution of our approach to localised prostate cancer towards watchful waiting, hold the promise of changing attitudes to living with cancer, if the disease can be transformed from a death sentence into a manageable condition free from major symptoms.

In cancer, dormancy takes many forms, unique to each type of the disease, and the complexities of the mechanisms and systems involved pose a formidable challenge to defeating cancer. But radically changing our approach and embracing dormancy presents many promising roads forward for research.

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