

Preface

In the great majority of cases, cancer death is, in fact, “Death by Metastasis”. Primary cancers, in and of themselves, are seldom fatal, and it is only the distal colonization of vital organs by metastatic cells that results in the demise of the patient.

Metastatic disease is a late event in the evolution of a cancer, and requires the development of a subset of cells in the tumour that can survive the successful cellular odyssey required for metastatic disease to occur. Amongst the biological properties that such cells must acquire include those of self-sufficiency, the capacity to withstand anti-growth signals, resistance to factors inducing apoptosis, and the limitless capacity for reproductive potential. In addition, the metastatic cellular invaders must be able to establish sustained angiogenesis for metastatic lesions to become entrenched and grow. The events resulting in secondary tumours is a remarkably orchestrated change in both the genetic and proteomic expression of the malignant cells. This is a magnificent biological process, but unfortunately it almost invariably results in a terrible outcome for the patient.

The individual steps that allow the relatively fragile metastatic cells to detach from the mother lode of the primary cancer and then interact with what must be considered the hostile microenvironment of the host continue to be unravelled. Indeed, the tumour microenvironment plays a critical role in both primary and metastatic tumour development. This interstitium consists of both a blood and lymphatic vasculature with endothelial linings, as well as a variety of cells (fibroblasts, adipocytes, and host inflammatory cells) secreting extracellular matrix proteins, with all of which the primary and metastatic cells must interact successfully, to survive and grow.

After accomplishing the journey through either the blood or lymphatic vasculature, the metastatic cells must find an appropriate tissue in which to establish secondary tumour sites. Here, the ‘seed and soil’ hypothesis requires that the micrometastases find what has been referred to as “fertile soil” in which to come to rest, often referred to as site-specific metastasis, or ‘homing’. Just exactly what “fertile soil” implies, has not really been clearly defined. The possibility that breast cancer metastases, having developed in a calcium rich environment, seek bone with a comparable microenvironment, is an interesting concept. However, breast cancer cells will also make their way to the liver and the lung. Regardless of the secondary target organ selected, there can be little doubt that the establishment of a secondary tumour site

again requires successful interaction with the unique microenvironment of the target organ.

It is well established that the vast majority of metastatic cells never go on to develop secondary lesions. Whether this is due to apoptotic cancer cell death, through host-generated immune reactions, by inhibition of angiogenesis, or by factors yet to be determined, is under intense investigation. Metastatic dormancy certainly occurs in many tumours, the prototype of which may well be uveal melanoma. Micrometastatic uveal melanoma cells are clearly demonstrable in the circulation both before and after tumour excision or radiation, yet it is not at all uncommon for the initial clinically manifestations of liver metastases from a uveal melanoma to occur only a decade later. Have the metastatic cells taken up initial residence in the liver and simply 'waited' for the appropriate opportunity in order to multiply, or have they been resident elsewhere, and only latterly moved into the liver, with immediate growth?

With the foregoing factors in mind, the co-editors of this splendid volume, Miguel and Julia Burnier, father and daughter, have compiled a remarkable text with contributions from outstanding experts in every aspect of the metastatic process. Many of the cellular and molecular factors in metastatic disease that have been noted above, and many others, are addressed in the various comprehensive chapters of the book, each written by an expert in the field. The problems of metastatic cell survival, the route around metastatic suppressor factors, the role of growth factor systems and angiogenesis are clearly defined, and the problems yet to be solved are discussed. Our knowledge about the ever-increasing importance of the role of the microenvironment in tumour progression is expertly defined, and such parameters as metastatic cell dormancy as it occurs in such tumours as uveal melanoma, is considered.

Taken together, this is a volume that should find its way to the bookshelves of virtually all Oncologists and, indeed, all physicians and surgeons involved in the care and treatment of cancer patients.

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