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REVIEW

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Stephen Paget and the 'seed and soil' theory of metastatic dissemination

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Abstract The outcome of cancer metastasis depends on multiple interactions between selected metastatic cells and homeostatic mechanisms unique to some organ microenvironments. The English surgeon Stephen Paget (1855–1926) is credited with being the first to postulate the important role played by microenvironment in metastasis formation. The concept of his 'seed and soil' theory has been supported and confirmed by numerous publications. This review article summarises the most important literature data about this matter.

Key words History of medicine • Metastasis • Tumour growth

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Introduction

Cancer metastasis represents the major cause of morbidity and death for cancer patients. In fact, whereas the primary tumour is in most cases susceptible to eradication by combined surgical and radiochemical treatments, its metastases, when distributed throughout the body, are most difficult to treat by any therapeutic means, and finally cause the patient's death.

It has long been accepted that most malignant tumours show an organ-specific pattern of metastasis. For example, colon carcinomas metastasise usually to liver and lung but rarely to bone, skin or brain and almost never to kidneys, intestine or muscle. In contrast, other tumour entities, such as breast carcinomas, frequently form metastases in most of these organs. This specific formation of secondary tumours at distant sites appears to require the successful completion of a number of steps by metastasising tumour cells [1].

Various explanations have been proposed for the site selectivity of blood-bone metastases, including tumour cell surface characteristics [2–4], response to organ-derived chemotactic factors [5], adhesion between tumour cells and the target organ components [6, 7] and response to specific host tissue growth factors [8]. The relative importance of pre-existing tumour subpopulations with specific metastatic properties and the organ environment characteristics in determining metastatic homing have been debated [6, 9–11].

An alternative explanation for the different sites of tumour growth involves interactions between the metastatic cells and the organ environment, possibly in terms of specific binding to endothelial cells and responses to local growth factors. Endothelial cells in the vasculature of different organs express different cell-surface receptors and growth factors that influence the phenotype of the corresponding metastases. Greene and Harvey [12] first suggested that the organ distribution patterns of metastatic foci

were dependent on the formation of sufficient adhesive bonds between arrested tumour cells and endothelial cells, and they hypothesised that these interactions were similar to lymphocyte/endothelial cells at sites of inflammation.

The development of organ-derived microvascular endothelial cell cultures has allowed more specific studies on the preferential homing of tumour cells. Auerbach and co-workers [13] found that different tumours showed differences in their adhesive propensity and preference for different endothelial cells, and in a few cases preferential adhesion was observed to the endothelial cells derived from the organ of origin and the target organ.

Paget's theory

Stephen Paget (1855–1926) was an English surgeon, son of the famed surgeon Sir James Paget. He trained at St. Bartholomew's Medical School, and then practised surgery in London, where he developed a strong interest in supporting cancer research. In 1908 he founded the Royal Defense Society to provide scientific input into animal-welfare debate and to support experimental research for the benefit of cancer patients.

In 1889, Paget proposed that the processes of metastasis did not occur by chance but, rather, that certain favoured tumour cells with metastasis activity (the 'seed') had a special affinity for the growth-enhancing milieu within specific organs (the 'soil', i.e., organs providing a growth advantage to the seeds). He concluded that metastases developed only when the seed and soil were compatible. In other words, Paget suggested that the site of metastasis depended on the affinity of the tumour for the microenvironment [14].

Paget analysed autopsy records of 735 women with breast cancer. His analysis documented a non-random pattern of metastasis to visceral organs and bones, suggesting that the process was not due to chance but rather that certain tumour cells had a specific affinity for the milieu of certain organs.

Auerbach [15], in his comments about organ selectivity of metastasis, writes: "Paget is almost apologetic as he contrasts the work of those that study the 'seed' to his own work on the 'soil': the best work in the pathology of cancer is done by those studying the nature of the 'seed'. They are like scientific botanists; and he who turns over the records of cases of cancer is only a ploughman, but his observations of the properties of the 'soil' may also be useful". Auerbach then adds: "Those individuals who study the properties of the host environment should not be ignored. Not only are the observations of the 'soil' useful, they provide essential information without which we will not be able to understand the nature of the metastatic process".

Ewing's viewpoint

In 1928, James Ewing challenged Paget's 'seed and soil' theory and hypothesised that metastatic dissemination occurs by purely mechanical factors that are a result of the anatomic structure of the vascular system [16]. Thus, it would be completely accounted for by the vascular connections of the primary tumour: intravasating tumour cell emboli are much more like to be mechanically trapped in the circulatory network of the first connected organ, which will then sustain the highest burden of metastatic colonisation. Other organs receive less tumour cells, and develop fewer metastatic colonies.

Ewing's viewpoint prevailed for several decades. His proposal, however, does not explain the observation that some organs, such as brain, bone and adrenals, are served by a very small fraction of the circulatory system, yet they are often involved in metastatic deposits of certain cancers. Moreover, other organs, such as heart, muscle, skin, kidney and spleen, each receiving a considerable supply of blood, are only sporadically colonised by cancers.

Sugarbaker [17] pointed out that common regional metastatic involvements could be attributed to anatomical or mechanical considerations, such as afferent venous circulation or lymphatic drainage to regional lymph nodes, but that metastasis to distant organs by metastatic cells from numerous types of cancers had a different pattern of site specificity.

This specificity was demonstrated by Tarin and co-workers [18] in 1984. Patients with incurable abdominal ascitic cancer were treated with peritoneal-venous shunting in order to alleviate abdominal pain and distension. In this procedure, the abdominal effusion is returned to the circulation via an anastomosis, containing a one-way valve, between the peritoneal cavity and the lungs. Therefore, a large number of tumour cells are directly infused into the circulation. Despite this huge tumour load, many patients did not develop evident metastases and among those who did, the distribution of secondary deposits was unexpected, in that metastases did not form in the organ containing the first capillary bed encountered, i.e., the lungs.

The contribution of experimental pathology to the study of the process of metastasis

In 1950, Zeidman and co-workers [19] reported that the number of metastases was directly proportional to the number of tumour cells injected intravenously, but that most injected tumour cells still failed to form tumours.

In 1951, Coman and co-workers [20] reported that the direct intravascular injection of tumour cells into animals

produced metastases in some, but not all, visceral organs. The authors found that in those organs, circulating tumour cells were lodged in the capillaries, whereas in organs that were rare sites of metastasis, circulating cells lodged in arterioles. This observation indicated that the distribution of metastases was largely dependent on mechanical factors, that is, on the arrest of emboli in capillaries of secondary organs.

In 1952, Lucke and co-workers [21] compared carcinoma metastases in the livers and lungs of rabbits, and found that liver metastases were larger and more numerous. Human cancer patients also develop a larger number of liver, rather than lung, metastases, so both mechanical and local 'soil' factors are likely to determine whether or not a metastasis will develop after the arrest of tumour emboli.

In 1952 Zeidman and Buss [22] used cinephotomicrography to observe the incidence of emboli arrest in mesenteric capillaries of rabbits. They found that some tumour cells become distorted and passed through the marrow capillary tube, whereas others appeared more rigid and were trapped. The incidence of arrest varied with the type of tumour studied. This work established the morphological foundation for previous indirect demonstrations that some tumour cell emboli could pass immediately through the vascular bed of organs.

Metastasis can result from survival of only a few tumour cells

As a whole, metastasis favours the survival and growth of a few subpopulations of cells that pre-exist within the parent neoplasm. So, metastases can have a clonal origin, and different metastases can originate from the proliferation of different single cells [23].

In 1970, Fidler [24] showed that within 24 h after entry into the circulation, less than 0.1% of tumour cells are still viable, and that less than 0.01% of these cells, when introduced into the circulation, survive to produce metastases. Therefore, only a few cells in a primary tumour can give rise to a metastasis. Although it has been determined that less than 0.01% of tumour cells that enter the circulation have the potential to form secondary tumours [24–26], still hundreds of viable tumour cells each day have the possibility to lodge into distant organs.

Cells with different metastatic properties have been isolated from the same parent tumour, indicating that not all the cells in a primary tumour have the same potential to disseminate. Tumour cells were implanted subcutaneously, intramuscularly, directly into tissues or injected intravenously into mice. Tumours were then harvested, and the recovered cells expanded in culture. The behaviour of the expanded cells was compared to that of the cells of the parent tumour to determine whether the selection process enhanced metastatic capacity. This procedure was originally used to isolate the B16-F10 line from B16 melanoma [27].

In a second approach, cells were selected for the development of a phenotype that was associated with the metastatic sequence, and then they were tested in animal models to determine whether concomitant metastatic potential was increased or decreased. This method has been used by Nicolson [7] and Poste [28] to determine whether properties such as adhesive characteristics, invasive capacity, lectin resistance and resistance to natural killer cells were required for metastasis.

Experimental evidence of metastatic heterogeneity of tumours

Experimental data to support Paget's 'seed and soil' hypothesis were derived from studies provided by Fidler and Kripke [29] in 1977 using mouse B16 melanoma cells. They showed that different tumour cell clones, each derived from individual cells isolated from a parent tumour, vary markedly in their ability to form pulmonary nodules following intravenous inoculation of B16 melanoma cells into syngeneic C57BL/6 mice. Tumour growth developed in the lungs and in fragments of pulmonary or ovarian tissue that were implanted intramuscularly. By contrast, metastatic lesions did not develop in implanted renal tissue, or at the site of surgical trauma.

A detailed analysis of experimental metastasis in syngeneic mice indicated that mechanical arrest of tumour cells in the capillary bed of distant organs could indeed occur, but that subsequent proliferation and growth into secondary lesions was influenced by specific organ cells [30].

Controlled subcloning procedures showed that the observed diversity was not a consequence of the cloning procedures. This indicates that the sites of metastasis are determined not only by the characteristics of the neoplastic cells, but also by the microenvironment of the host tissue [30].

To exclude the possibility that the metastatic heterogeneity of B16 melanoma cells might have been introduced as a result of the lengthy cultivation, studies on the biological and metastatic heterogeneity of spontaneous tumours were carried out. Melanomas were induced in mice by chronic exposure to ultraviolet B irradiation and the tumour-promoting agent Croton oil, and tumour metastases were found to differ greatly from each other and from the parent tumour. In addition to differences in the number of metastases that developed from each tumour, there was also significant variability in the size and pigmentation of the metastases. Metastases to the lymph nodes, brain, heart, liver and skin were found in addition to lung metastases. Those growing in the brain were uniformly pigmented, whereas those growing in other organs generally were not [31].

Other observations relating the 'seed and soil' hypothesis were made by Pilgrim [32], using a transplantable reticulum cell sarcoma, which selectively metastasised to the mouse spleen. When equal numbers of cells were injected into the kidney and the spleen, growth in the spleen was always considerably greater than in the kidney. However, in no case was the mitotic index higher in the spleen than in the kidney. Pilgrim therefore considered that cell loss in the kidney was greater than in the spleen; however, his emphasis was on cell migration rather than cell death within the target organ. Regardless of mechanism, compared with the spleen, the kidney was therefore unfavourable 'soil' for this tumour.

Studies of experimental brain metastasis

Schackert and Fidler [33] described the development of a mouse model to study cerebral metastasis after injection of syngeneic tumour cells into the internal carotid artery of mice, which stimulates the haematogenous spread of tumour emboli in the brain. This technique can be used to examine the last steps of the metastatic process, such as release of tumour cells into the circulation, arrest of tumour cells in capillaries, penetration and extravasation of the tumour cells into the brain through the blood-brain barrier and continuous growth of the cells in the tissue. This procedure was used to study metastases of two different murine melanomas. The two melanomas differed in their brain metastatic patterns: the K1735 melanoma produced lesions only in the brain parenchyma, whereas the B16 melanoma grew only in the meninges and ventricles [33]. Similarly, different human melanomas or carcinomas injected into the internal carotid artery of nude mice produce unique patterns of brain metastasis. These results demonstrate specificity for metastatic growth in different regions within a single organ [34].

Concluding remarks

Paget postulated that microenvironment provides a fertile 'soil' for cancer cells endowed with a capacity to grow under specific conditions provided by the 'soil'. A current definition of the 'seed and soil' hypothesis consists of three principles. First, neoplasms are biologically heterogeneous and contain subpopulations of cells with different angiogenic, invasive and metastatic properties. Second, the process of metastasis is selective for cells that succeed in invasion, embolisation, survival in the circulation, arrest in a distant capillary bed, and extravasation into and multiplication within the organ parenchyma. Third, the outcome of metastasis depends on multiple interactions of metastatic cells with homeostatic mechanisms, which the tumour cells can escape.

In 1989, in his introductory remarks to the symposium commemorating the centenary of Paget's 'seed and soil' hypothesis, George Poste pointed out that: "There are few scientists, historically or contemporary, whose work will stand 100 years of scrutiny and not succumb to the depressing trend of modern publications – to ignore papers published more than five years ago".

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