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Cancer metastasis, challenges, progress and the opportunities

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1. ABSTRACT

The spread of cancer cells in the body - 'metastasis,' is a challenging issue for cancer patients and for cancer research. From a clinical point of view, the majority of the cancer-related deaths in patients who suffer from solid cancers are metastasis-related. Although this life threatening consequence in cancer is recognised almost immediately at the time of diagnosis, the current-state-of-knowledge on the mechanisms and effective ways to combat cancer metastasis in clinical settings is far from being realized. Thus, making the necessity of continuing research into cancer metastasis evermore demanding and critical. This issue of the journal is directed toward consideration of some of the salient aspects of cancer metastasis, with a focus on recent progress of the molecular and cellular mechanisms of cancer invasion and metastasis.

2. INTRODUCTION

'Metastasis,' the spreading of cancer cells in the body and establishment of new tumour foci in organs/locations other than where a solid tumour originated, is the most life threatening disease. Patients with solid malignant tumours will eventually develop metastasis, if the patients do not suffer mortality due to other conditions, i.e., co-morbidities. The time from the diagnosis to prevalence of metastasis varies dramatically, from cases in which cancer is diagnosed as the result of discovering a metastatic lesion to decades after the initial diagnosis. Patients can be 'free' from metastasis for the entire clinical course, although 'free from metastasis' mostly refers to 'free from macrometastasis'. In almost all the patients with cancer, micrometastasis is detectable at some stage of the clinical course of disease.

After more than a century from the initial proposal by Stephen Paget in 1889, of the 'seed and soil' theory to describe the occurrence and mechanisms of cancer metastasis (1), there has been a great deal of progress in our knowledge of metastasis at the genetic, molecular, cellular and clinical levels. For example, the development of metastasis has been frequently referred to as 'the metastatic cascade'. This suggests that once a malignant tumour is developed at the primary site, tumour cells will utilise mechanisms, predisposed or acquired, as the result of microenvironment in the body, to breakdown various barriers, manage to enter the systemic circulation and, after travelling close or afar, settle in a suitable location to continue its uncontrolled division to form new metastatic tumours (2-4). Broadly speaking, most topics that we are discussing and researching fall well within the framework of the 'seed and soil' theory.

In the metastatic spread of cancer cells, a number of molecular and cellular events have been well defined. For example, a certain number of genes, referred to broadly as 'metastasis-related genes' have been identified that are essential for the aggressive and metastatic characteristics of tumours. Mechanisms for cancer cells to break away from the main mass, such as loss of cell-cell adhesion at the primary site and acquisition of cell motility, have been extensively investigated. The mechanics for cancer cells to break down the basement membrane (BM) and extracellular barrier, via namely proteolytic enzymes and their migratory capability are well established. The survival methods for cancer cells in the circulation and the way by which tumour cells identify a destination for their subsequent location have also been reported. The need for angiogenesis, lymphangiogenesis and cellular signals to awaken the quiescent (dormant) cancer cells in a distant organ have also been described. There has been a wealth of literature in the area of cancer metastasis, which continues to expand at a rapid pace. The following are some of the salient aspects that are key to cancer metastasis as extensively discussed in the present issue.

2. CELLULAR MIGRATION AND EPITHELIAL-MESENCHYMAL-TRANSITION (EMT)

The ability of cancer cells to vigorously migrate within the tissues and in the body is essential for establishing a distant metastasis (5,6). In fact, a new term, namely "motogen," was coined to describe protein factors that are linked to cell migration (7). There are a number of motility factors, some being specific for cell migration, e.g., autotaxin and AMF, and some having a diverse effect on migration and cell growth. Within the cells, they are coordinated by the action of intracellular intermediates and the cytoskeleton in order to facilitate cell migration. Wells and colleagues (8), in an elegant and comprehensive overview, have discussed cell motility and its role in EMT. EMT has been recognised as an important cellular switch associated with cancer metastasis and has important implications in cancer treatment (9). Here, the impact and intimate regulation of cell migration during the EMT process has been explored. Yu *et al* (10) have discussed the importance of a group of cytoskeletal regulators, namely the FERM family of proteins in the spread of cancer cells. These are an interesting group of proteins known to regulate the cytoskeleton-membrane interaction, serve as an anchor for cells surface proteins including CD44 and ICAMs, and which have occasionally been referred to as the "Homing molecule" for metastatic cancer cells.

3. CELL ADHESION AND BARRIER FUNCTIONS

The importance of cell-cell and cell-matrix adhesions in cancer metastasis have been fully explored and recognised in the past two decades. Cell-cell adhesion as a mechanism for the initial departure of cancer cells from the primary tumour, their homing and the role of cell-matrix adhesion in the migration and matrix degradation process have been well established. One of the lesser recognised areas in cell adhesion are the tight junctions which govern cell-cell adhesion, paracellular permeability and the barrier functions. The structure of tight junctions of epithelial and endothelial cells are critical in the control of paracellular permeability of macromolecules. They are also critical in the control of the passage of cancer cells through the endothelium during their dissemination. The tight junction is the critical cellular structure for the blood brain barrier (BBB), central to the health of the central nervous system. Martin *et al* (11) and Escudero-Asparza *et al* (12) have provided indepth reviews for the role of tight junctions in cancer metastasis, particularly a group of proteins, known as "claudins." The foregoing reviews are reflective of the increased interest in the role and the nature of BBB to the metastasis of cancer cells in the brain.

4. GROWTH FACTORS, ONCOGENES AND CANCER METASTASIS RELATED GENES

Growth factors, as they are involved in carcinogenesis and the development of cancer, are fully engaged in the metastatic process. Apart from acting as carcinogenic and cell growth regulators, a great number of growth factors are fully involved in the metastatic process, inclusive of such events as cell migration, angiogenesis, lymphangiogenesis, EMT, and regulation of cell adhesion, etc. Yang *et al* have provided a comprehensive list of these factors (13). In their contribution, Xie *et al* have provided an important overview of the metastasis related gene, MTSS-1 (14). MTSS-1 is a protein found to be lost or reduced in metastasis. There is increasing evidence indicating that MTSS-1 is an interesting molecule in the control of the invasive and migratory behaviour of metastatic cancer cells. A newly recognised role for PAK in cancer metastasis has been documented by Whale *et al* (15). Traditionally regarded as a regulator of cell growth and proliferation. there is growing evidence that PAK is a key intermediate in cell migration and invasion. An important aspect of endocrine-related cancer is the role of hormone and hormone resistance in the development cancer metastasis and in hormonal/endocrine therapies. The relevance of in breast cancer has been discussed in the article by Hiscox and colleagues (16). NF1, another example of a tumour and metastasis suppressor gene and its role in malignant peripheral nerve sheath tumours has been considered by Upadhyaya (17).

An article by Ye *et al* (18) has documented the growing interest in the expanding protein family-bone morphogenic proteins (BMPs) in metastasis, including bone metastasis. BMPs belong to the TGF-beta superfamily with more than 20 members so far identified. The proteins have diverse roles in cancer metastasis, while some are highly pro-metastatic, e.g., BMP-6 and BMP-7, others are anti-metastatic, namely BMP-9 and BMP-10. It is envisaged that there will be more interest in this protein family, as well as the BMP receptors, both in metastasis research and in the development of therapies using BMP as targets/therapeutic tools.

5. EXTRACELLULAR MATRIX AND PROTEOLYTIC ENZYMES IN CANCER METASTASIS

The manner and mechanisms by which cancer cells break down matrix barriers have been extensively studied and well established. Proteolytic enzymes including MMPs and uPAs are known to be involved in the progression and metastasis of a variety of cancer cells and solid tumour. Notable with reference to MMPs, tumour-derived MMPs also react with a patient's immune cells in the primary tumour facilitating escape of tumour cells from immunosurveillance by inducing proteolytic cleavage of IL-2Rα, thereby suppressing the proliferative capacity of sensitized T cells (19). Also, immune cells, e.g., macrophages, known to contain MMPs, may under select environmental conditions, contribute to the passage of tumour cells by proteolysis of the BM (19). The targeting of some of the enzymes has been demonstrated to have therapeutic values in cancer treatment.

In addition to the foregoing, as considered by Wagstaff *et al* (20), a new class of enzymes in cancer metastasis has been recognised. Here, two of such groups, namely ADAMTS and matriptases have been explored.

The human ADAMTS (a disintegrin and metalloproteinase with thrombospondin-like motifs) family of 19 secreted proteolytic multidomain enzymes are involved in a wide range of biological processes including ECM degradation and assembly, hemostasis, organogenesis and the regulation of angiogenesis (20). Abnormalities in certain family members give rise to inherited human genetic diseases, while aberrant expression of other ADAMTSs has been linked to the pathogenesis of arthritis, cancer and metastasis (20). Webb *et al* (21) have documented the important, yet contrasting role of matriptases in cancer metastasis. Interestingly, the two closed related members -matriptase-1 and matriptase-2, have a clear contrasting role in cancer metastasis, i.e., a pro-metastasis role for matriptase-1 and an anti-metastasis for matriptase-2.

6. ANGIOGENESIS AND LYMPHANGIOGENESIS

Angiogenesis, the development of new vasculatures in tumours, has been recognised as essential for the continued and uncontrolled growth of primary tumours, but also critical for the spreading of cancer cells. The role of angiogenic vasculature in tumours in providing oxygen and nutrients has long been recognised. The newly developed vasculature, albeit deficient in functions and structure, has provided an ideal path for cancer cells to enter the circulation for systemic spread. Cai *et al* (22) have documented the importance of angiogenesis both as a mechanism for cancer spread and as new target for cancer treatment. Lymphangiogenesis, the development of new lymphatic vessels, a recognised factor in cancer metastasis, has provided a means for the lymphatic route of metastasis. Lymphangiogenesis is an area, to some degree, behind the progress in angiogenesis research, primarily due to the lack of suitable models, cell lines and limited knowledge of lymphangiogenic factors. However, the past decade has witnessed a dramatic expansion of the knowledge in this area. More lymphangiogenic factors are being identified, namely VEGF-C, VEGF-D, IL-7, and HGF. Together with the availability of primary cultured and established cells of lymphatic endothelial cells, this has provided an unprecedented opportunity for investigation into this important area of research of cancer metastasis. Al-Rawi and Jiang (23) have provided a comprehensive review on the known lymphangiogenic factors.

7. PERSPECTIVE

New targets continue to be identified, an example shown by a recent discovery of the non-immunological role of B7-H3 (24). Methods in identifying new modalities for treating metastasis are increasingly being identified. Anti-angiogenic therapies, targeting proteolytic enzymes, mobilising the immune system in combating the dislocated cancer cells, and taking advantage of the metabolic differences of cancer cells (25) have been attempted with a great deal of success. Perhaps, we are entering an era in which we may hopefully begin to systemically address the most life threatening cause of cancer -"metastasis." This is an exciting time to utilise existing knowledge to forge ahead with the numerous challenges, as well as opportunities facing us, as discussed here and throughout the current issue.

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