Introduction to metastasis

One of the hallmarks of malignant tumours is the ability of the cancer cell to spread or “metastasize” either to local or distant sites.

Metastases are a highly significant cause of cancer morbidity and are responsible for most cancer deaths.

Metastasis is a multi-step process which requires, first that cells have to detach from a primary tumour, secondly invade local tissues, lymphatics or blood vessels, and thirdly re-establish and re-attach once they have spread into distant sites.

Cells break away from the tumour and may expand through local tissues, and blood vessels or lymphatics.

Tumour cells that spread into lymphatic vessels may become localized in lymph nodes and start to expand and proliferate within the lymph node. Eventually the lymphatic system drains into the blood stream, thereby facilitating metastasis to distant sites via the blood vessels.

An alternative method of metastasis is spread directly via the blood stream to metastasize at distant sites and organs.

For many cancers the development of metastasis either local or distant, may lead to clinically incurable disease. However, this may depend on the tumour type. Some tumours are much more prone to early metastasis than others.

When a cancer is detected at an early stage, prior to the metastasis, it can very commonly be treated successfully, either by local irradiation or by surgical excision resulting in a complete cure.

However, if the cancer is detected only following metastases, in particular blood borne metastases, successful treatment and cure is much less common.

Introduction to metastasis (cont)

The molecular mechanisms which mediate the metastasis of cells from the primary tumour, either by the lymphatics or local blood vessels, remain to be fully delineated, however, it is clear that the process of metastasis consists of a series of specific steps, all of which must be sequentially and successfully undertaken.

For a cancer cell to metastasize it must first shed cells from the primary tumour, which requires that the cancer cell must **first** detach from the parent tumour.

Secondly, the tumour must escape from the local neighbourhood of the primary tumour and establish colonies at distant tissues.

A cell must penetrate and escape across the basal lamina, invade either the draining capillary or the draining lymphatics, and then must initiate and maintain its own growth and either circulate in the lymphatic system, or the blood vessel system, and then adhere to a new site, develop new blood vessels and start to proliferate.

For this to be successfully achieved cancers must be able to survive within the circulation. It is probable that only a few cells in the primary tumour survive in the circulation. Many cancers invade local and connective tissues and cause problems with local recurrences. Much less frequently do cancer cells escape into the circulation and manage to seed in new areas, grow and proliferate.

The cancer cell’s ability to invade, requires that the cell is able to change its subcellular site of attachment and increase its ability to move, i.e. **cell motility.**

Spread of cancer into the lymphatics or blood vessels also requires degradation of the extracellular matrix, resulting in shedding of cells into the circulation either directly, or by the lymphatics.

Introduction to metastasis (cont)

The molecular events, which mediate cancer cells’ ability to form distant or local metastasis, are only recently being characterized by use of specific gene profiling studies. These investigations have analysed the expression of genes in metastatic versus locally invading tumours.

Steps in the Process of Metastasis

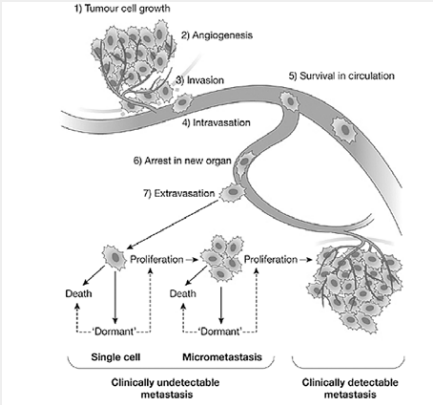


Figure 3.2.2 Steps in the Process of Metastasis. Tumour cells may enter the bloodstream directly by crossing the wall of a blood vessel, as diagrammed here, or, more commonly perhaps, by crossing the wall of a lymphatic vessel that ultimately discharges its contents (lymph) into the bloodstream. Tumour cells that have entered a lymphatic vessel often become trapped in lymph nodes along the way, giving rise to lymph node metastases.

Mechanical factors which regulate deposition

A classical example of a tumour that can develop either local or distant metastasis is breast cancer.

Breast cancer cells may invade either the draining lymphatics, or the local capillaries. If breast cancer cells leave the primary tumour by blood vessels, the cancer cells will drain into the venous system to the heart and then to the capillary beds of the lung (see Figure 2 below). Cancer cells that transit the lung enter the systemic arterial circulation, where they may be transported to distant sites such as the bone or the liver. Alternatively breast cancer cells, which invade the local lymphatics of the primary site, may drain to the local lymph node.

Mechanical factors which regulate deposition (cont)

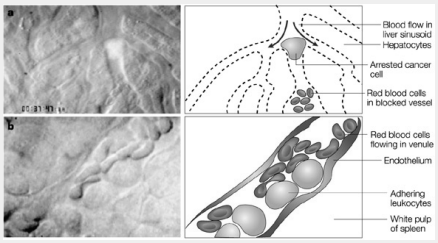
The number of draining lymph nodes, which contain cancer, which are present at the time of diagnosis, can be an important factor in predicting long prognosis. Cancer cells trapped in the lymphatics may grow, invade and expand, and the patient may subsequently present with enlarged lymph nodes. Cells entering the lymphatic system eventually re-enter the blood circulation and the cancer cells are then transported via the blood to distant sites.

Specific mechanical factors may determine the fate of cancer cells after they have left the primary tumour. The site of the primary tumour and its blood flow patterns, which drain the area, may determine in which organ the cancer cells travel to and initially deposit. This may in part explain, for example, that the liver is the primary site of metastasis from colon cancer, however, this does not explain why bone is the primary site for metastasis for breast, or prostate cancer, or why there are often long delays for the appearance of bone metastasis associated with these cancers.

Mechanical factors which regulate deposition (cont)

Data from a number of different experimental models has supported the idea that specific mechanical factors may regulate the delivery of cancer cells into the capillaries (see Figure 3.2.4 below). The relative sizes of cancer cells versus the sizes of capillaries may determine whether the cells arrest, or are efficiently translocated into the circulation. Secondly, it is becoming increasingly apparent that certain organs will preferentially either support, or suppress the growth of specific cancer cell types. This may contribute to whether a circulating cancer cell has the ability to deposit in a specific organ. It is noteworthy that both the lung and liver are extremely efficient in stopping the flow of cancer cells. This may relate to the size of the circulating cancer cells compared to the size of the capillaries in both these organs, which both contain many capillaries of small size approximately between 3 to 8 micron in diameter. These capillaries are designed to facilitate red blood cell passage, which are 7 microns in diameter, but as cancer cells are much larger at 20 microns, the cancer cells are prone to arrest. Arrested cancer cells may undergo adhesion in the precapillary vessels such as portavenules in the liver, and once adhered start to proliferate to form single or multiple metastatic deposits

Cancer and normal cells arrest in the circulation



The Regulation of Metastatic Growth

Factors, which are secreted or localized in specific organs, can determine whether or not a cancer will grow at that site.

For example, one of the reasons why breast or prostate cancer may grow specifically in bone may relate to the presence of local hormones or cytokines, which are secreted or present in the bone matrix, which stimulate the growth of the cancer cell.

These molecules include parathyroid hormone-related protein (PTHRP) and transforming-growth factor b, which are produced by the cancer cells, or are present in the bone environment.

Factors that are specific for the liver have also been identified, such as epidermal growth factor receptor, and transforming growth factor α.

Another gene that has recently been shown to contribute to liver metastasis is the Ras gene. Ras is a small GTP-binding protein that amplifies intracellular signals generated by growth factors.

Ras is commonly mutated in many types of human cancers. Recent studies have shown that cancer micro-metastases occurring in the presence of activated Ras, are much more likely to maintain metastatic growth, than cancers without Ras mutations.

Therefore, the ability of the cancer cell to grow in a specific organ depends both on the environmental factors and cytokines present at that site, the size of the capillaries, the hormones and cytokines synthesized in specific tissues, and also depends on the cancer cell itself, whether it has the ability, size, mechanical features and the genetic defects within its genome which facilitate metastasis.

Cancer dormancy

Metastases can occur long after the initial excision of the primary tumour. Breast cancer and melanoma patients may develop distant metastases, decades after the excision of the primary tumour.

Cancer dormancy (cont)

The molecular mechanisms mediating **cancer dormancy** are unknown, but it is unlikely that it is mediated by continuous slow growth, and more probable that the cancer cell undergoes a period of quiescence, and then for reasons unknown its growth is reactivated.

Cancer dormancy is of clinical importance because if we could identify what regulates cancer dormancy this may be important in terms of therapeutic treatments and response to radiotherapy.

Several studies have suggested that dormancy may relate to the failure of micro-metastasis to develop their own blood vessels. Therefore, the tumour may survive, but cannot expand, because it cannot increase its blood supply.

If these metastases subsequently acquire their own vascular circulation, they may begin to grow and the metastasis may become clinically evident.

An alternative possibility is that solitary cancer cells seed in secondary site, but do not proliferate. These cells may persist for long periods of time without proliferating until later times when, for unknown reasons, these dormant cells may start to proliferate.

Any therapy that has the ability to inhibit the growth and metastasis of cancer cells and limit damage is of clinical importance.

Recent studies have highlighted the development of a novel anti-metastasis therapy, firstly by identifying genes that have been mutated in the cancer cell, which facilitate metastasis, and also by attacking specific targets such as micro-metastases that require vascularization.

Current novel anti-angiogenic (i.e. targeting new blood vessel formation by the cancer) strategies are becoming of increasing importance, as this may regulate the growth and vascularization of metastases.

Lymphatic metastases

A common site for cancers to spread is the draining regional lymph nodes. The molecular mechanisms that facilitate lymphatic spread are unclear. In addition, the role of lymphangiogenesis i.e., the growth of new lymphatics is currently being determined.

Recent clinical and experimental results have identified specific lymphangiogenic factors may play a role in the spread of tumours.

Lymphangiogenic growth factors include vascular and epithelial growth factor VEGFC, and VEGFD and their receptors on the endothelium. These specific endothelial growth factors are secreted as pro-peptides and are subsequently cleaved by proteolysis to form a high infinity ligands that activate their specific receptor and result in the formation of new lymphatic vessels.

VEGFC and VEGFD are growth factors that are synthesized by a significant number of cells and tissues during embryonic life and adult life. These two growth factors bind specific receptors VEGFR2 and VEGFR3. Activation of the VEGFR3 receptor causes lymphangiogenesis, (formation of new lymphatics).

In contrast activation or ligand binding of VEGFR2 promotes a formation of new blood vessels (angiogenesis).

Both VEGFC and VEGFD can induce tumour lymphangiogenesis and specifically direct metastasis into the lymphatic vessels and lymph nodes. Thus these factors may thereby promote the lymphatic spread of human tumours.

Lymphoedema (arm swelling)

One of the significant complications of cancer spread to lymphatic vessels is lymphatic obstruction.

As the lymphatics control the pressure of the interstitial fluid in tissues, the lymphatics transport excess fluid via the lymphatics to eventually return to the venous circulation.

One of the serious complications of metastatic spread to lymph nodes and lymphatic vessels is the blockage of the vessels by the metastatic tumour.

Lymphoedema (arm swelling) (cont)

Oedema is a clinical situation in which swelling develops resulting from blockage of the lymphatic system. This may be a result of impaired lymphatic drainage, due to either inflammatory or cancer mediated obstruction of the lymphatic vessels.

When this occurs due to blockage of the peritoneal drainage, or peritoneal seeding of cancer with cancer cells, this may result in a clinical situation of **"ascites"**, which is the accumulation of fluid in the peritoneal cavity.

In addition, oedema may follow surgical removal of lymphatic vessels or radiotherapy for breast cancer, resulting in arm oedema "lymphoedema".

The current treatment for lymphoedema is by manual lymphatic drainage by compression.

Angiogenesis

An essential requirement for tumour growth and metastasis is the formation of new blood vessels (**angiogenesis**).

As many tumours are rapidly growing, they need to be able to develop ability to provide their own blood supply via the formation of new blood vessels.

Correlations have been shown between patient survival, and the number and degree of vascularization of specific tumour types. A high degree of tumour vascularization may be associated with an increased incidence of tumour metastasis.

The formation of new blood vessels requires the generation and proliferation of endothelial cells, which line the blood vessels, the break down of the extracellular matrix and the migration of endothelial cells.

Specific growth factors such as vasculoendothelial growth factor, heparin binding growth factor, and vascular permeability growth factor, promote the formation of new blood vessels and as a consequence tumour growth.

Angiogenesis (cont)

Angiogenesis has been recognized as a potential target in the treatment of cancer and a number of inhibitors of angiogenesis have been identified and are being currently developed as potential therapeutic strategies.

Such molecules include “Angiostatin”, which is a 38 kilodalton fragment of the plasma protein plasminogen, which has the capacity to suppress the growth of metastasis.

Other methods that are used to control vascularization of tumours include, in certain tumours, the tying off of the blood vessels that supply to the tumour. This depends on the nature of the tumour and has only limited potential as a treatment strategy.

Metastasis to specific sites – Bones

Patients with breast and prostate cancers very commonly develop bone metastasis.

In many instances the patients do not die of cancer at the original or primary site, but rather as a consequence of the metastatic tumour burden, or complications.

Bone metastasis often occurs in cancers, which do not necessarily have a primary aggressive tumour. Metastasis to bone may cause severe unrelenting bone pain, which causes major patient morbidity.

The physiological mechanisms mediating this severe bone pain are unclear. Recent treatment strategies using inhibitors of bone reabsorption have shown promise in terms of relief of bone pain; these include the use of osteoprotegrin (OPG), or the bisphosphonates.

Metastasis to specific sites – Bones (cont)

The latter has now become standard treatment for the treatment of osteoporosis and/or osteolytic lesions associated with diseases such as multiple myeloma. Sites for bone metastases include the load bearing bones, the neck of the femur, or in the vertebra, which may lead to weakening of the bones, resulting in pathological fractures. Other side effects of a bone metastasis include nerve compression, spinal cord compression as a result of vertebral body collapse. Increases in the serum calcium (hypercalcemia) and bone deformity may also complicate bone metastasis.

The effect that the bone metastasis has on the bone will depend on the type of cancer.

In tumours such as breast cancer and multiple myeloma destruction of bone resulting from lytic lesions within the bone, know as “osteolysis” occur. In contrast some tumours, in particular, prostate cancer, may lead to increased synthesis of bone, or “osteoblastic” changes to the bone.

In a latter condition, the osteoblastic lesions results from a synthesis of specific growth factors such as platelet derived growth factor, or endothelium1, which promote new bone formation.

Lytic lesions in the bone, such as those observed in breast cancer are commonly caused by synthesis of parathyroid hormone related peptide (PTHRP), which leads to increased bone resorption (process by which osteoclasts break down the tissue in bones and release the minerals).

Treatment of patients with phosphonates may block bone resorption.

Bisphosphonates are pyrophosphate analogues, which bind with high affinity to mineralised bone surfaces and thereby inhibit the action of bone cells known as osteoclasts which mediate bone resorption.

Physical effects of cancer on the patient

The effects of cancer on the patient can be local or systemic, and may also be specific for particular tumour types.

The physical presence of a tumour can cause major problems when the tumour displaces normal tissue leading to reduced organ function.

The tumour may expand into surrounding areas leading to venous or nerve compression, or may cause blockage of vital passages.

The displacement of normal tissue in contained spaces such as the brain by cancer causes increased pressure not only resulting in pain, but also decreases in brain function.

Cancer cells replace normal brain cells, however they do not carry out the function of normal brain cells as they are in an undifferentiated immature form, resulting in reduced function.

The growth of a tumour can block a vital organ or passage.

For example colon cancers may grow to a significant extent locally so they block the bowel and lead to bowel obstruction in the absence of distant metastasis. In addition tumours may block the normal arterial supply, or venous or lymphatic drainage of tissues or organs leading to significant symptoms.

Cancer also causes nutritional problems in the patient, particularly in cases when the cancer has disseminated, and is often associated with nausea and weight loss.

Changes to tissue metabolism results from the presence of the rapidly proliferating cancer cells, and the secretion of factors such as tumour necrosis factor, interleukins and other cytokines and hormones by malignant cells into the surrounding tissue.

The secretion of these factors can alter tissue metabolism leading to protein metabolism, glucose intolerance, and breakdown of fats.

Physical effects of cancer on the patient (cont)

The breakdown of protein and fats provides the tumour with a sufficient energy source to maintain the high metabolic rate required for successive rounds of cell division.

The high energy consumption by the tumour leads to general weight loss, fatigue, cachexia and susceptibility to infections in the patient.

Cachexia is a profound weight loss associated with cancer, or other disease state.

While cancer is responsible for varying degrees of pain and nausea in the patient, various treatments are often responsible for a significant amount of patient discomfort. Radiation or surgical procedures are pain associated, together with the toxic effects of chemotherapy. Nausea suffered by a cancer patient is most commonly caused by chemotherapeutic treatment, the cancer itself or medications such as antibiotics.

Why people die from cancer

The most common cause of cancer induced death is from metastatic lesions to the liver, brain or bone, or lung, which block a vital passage, or destroy the function of a vital organ.

In brain cancers, patients may not develop metastases but may die from raised intracranial pressure, as the tumour continues to grow in the confined space of the brain within the skull.

Patients with metastatic tumours lose weight, have decreased mobility and increased susceptibility to infection. Patients die from the successive accumulation of these insults.