Metastasis

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Abstract: Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells. Metastasis is the spread of a cancer from one organ to another organ or place, and the new disease occurrences are generated as metastases. Metastasis is a complex series of steps in which cancer cells leave the original tumor site and migrate to other parts of the body via the bloodstream, the lymphatic system, or by direct extension. To do so, malignant cells break away from the primary tumor and attach to and degrade proteins that make up the surrounding extracellular matrix, which separates the tumor from adjoining tissues. Metastatic cancers may be found at the same time as the primary tumor, or months or years later. When a second tumor is found in a patient that has been treated for cancer in the past, it is more often a metastasis than another primary tumor.
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The human body is made up of trillions of living cells. Normal body cells grow, divide to make new cells, and die in an orderly way. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. The cells used to replace the old cells are stem cells (Ma, et al, 2014).

Normally, the life bodies grow under control by the bodies' biological system. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells.

Cancer cell growth is different from the normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. In most cases the cancer cells form a bulk tissue called tumor. Cancer cells can also move from one location to other tissues that the normal cells do not do and this moving is normally called metastasis. Growing out of control and invading other tissues are what makes a cell a cancer cell.

Cells become cancer cells because of damage of DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA is damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired and not die, but it goes on making new cells same as the cells with damaged DNA. These new cells will all have the same damaged DNA as the first abnormal cell does.

People can inherit damaged DNA, but most often the DNA damage is caused by problem environment. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking or radiation, or chemical pollution, etc, but sometimes there is no clear cause information to be found.

Cancer cells can move to other parts of the human body, where they begin to grow and form new tumor cells that replace normal tissue cells. This process is called metastasis. It happens when the cancer cells get into the bloodstream or lymph vessels of the human body.

No matter where a cancer may spread, it is named based on the place where it started. For example, liver cancer that has spread to the lung is still liver cancer, not lung cancer. Different types of cancer can behave differently, and they grow at different rates and respond to different treatments. That is why people with certain cancers need the treatment that is for the particular kinds of cancer (American Cancer Society, 2014).

Metastasis definition: (1) The process by which cancer spreads from the place at which it first arose as a primary tumor to distant locations in the body. **(2).** The cancer resulting from the spread of the primary tumor. For example, someone with melanoma may have a metastasis in their brain. Metastasis depends on the cancer cells acquiring two separate abilities - increased motility and invasiveness. Cells that metastasize are basically of the same kind as those in the original tumor (Medicinenet, 2013).

Cancer happens after a single cell is progressively genetically damaged to produce cells with uncontrolled proliferation. This uncontrolled proliferation produces a primary heterogeneic tumour. The cells which constitute the tumor eventually undergo metaplasia. After the tumor cells come to rest at another site, they re-penetrate the vessel or walls and continue to multiply, eventually forming another

clinically detectable tumor. This new tumor is known as a metastatic tumor. Some cancer cells acquire the ability to penetrate the walls of lymphatic and/or blood vessels, after which they are able to circulate through the bloodstream to other sites and tissues in the body. This process is known as lymphatic or hematogenous spread. Metastatic tumors are very common in the late stages of cancer. The most common places for the metastases to occur are the lungs, liver, brain, bllod and bone. When tumor cells metastasize, the new tumor is called a secondary or metastatic tumor, and its cells are similar to those in the original tumor. This means, for example, that, if breast cancer metastasizes to the lungs, the secondary tumor is made up of abnormal breast cells, not of abnormal lung cells. The tumor in the lung is then called metastatic breast cancer, not lung cancer.

Metastasis is the spread of a cancer from one organ to another organ or place, and the new disease occurrences are generated as metastases. Metastasis is a complex series of steps in which cancer cells leave the original tumor site and migrate to other parts of the body via the bloodstream, the lymphatic system, or by direct extension. To do so, malignant cells break away from the primary tumor and attach to and degrade proteins that make up the surrounding extracellular matrix, which separates the tumor from adjoining tissues. Metastatic cancers may be found at the same time as the primary tumor, or months or years later. When a second tumor is found in a patient that has been treated for cancer in the past, it is more often a metastasis than another primary tumor. Once a cancer has metastasized, it may still be treated with radiosurgery, chemotherapy, radiation therapy, biological therapy, hormone therapy, surgery, or a combination of these interventions. The choice of treatment depends on a large number of factors, including the type of primary cancer, the size and location of the metastases, the patient's age and general health, and the types of treatments used previously, among others. In patients diagnosed with CUP, it is often still possible to treat the disease even when the primary tumor cannot be located.

Cancer researchers studying the conditions necessary for cancer metastasis have discovered that one of the critical events required is the growth of a new network of blood vessels, called tumor angiogenesis. It has been found that angiogenesis inhibitors would therefore prevent the growth of metastases. Human cells exhibit 3 kinds of motion: collective motility, mesenchymal-type movement, and amoeboid movement. Cancer cells often opportunistically switch between different kinds of motion. Some cancer researchers hope to find treatments that can stop or at least slow down the spread of cancer by somehow blocking some necessary step in one or the other or both kinds of motion. Epigenetic regulation also plays an important role in the metastatic outgrowth of disseminated tumor cells. Metastases display alterations in histone modifications when compared to matching primary tumors. These epigenetic modifications in metastases may allow the proliferation and survival of disseminated tumor cells in distant organs.

There is a propensity for certain tumors to seed in particular organs. This was first discussed as the seed and soil theory by Stephen Paget in 1889. The propensity for a metastatic cell to spread to a particular organ is termed organotropism. For example, prostate cancer usually metastasizes to the bones. In a similar manner, colon cancer has a tendency to metastasize to the liver. Stomach cancer often metastasises to the ovary in women, then it is called a Krukenberg tumor. The somatic mutation theory of metastasis development has not been substantiated in human cancers. Rather, it seems that the genetic state of the primary tumor reflects the ability of that cancer to metastasize. Research comparing gene expression between primary and metastatic adenocarcinomas identified a subset of genes whose expression could distinguish primary tumors from metastatic tumors, dubbed a "metastatic signature.

Cancer cells may spread to lymph nodes near the primary tumor. This is called nodal involvement, positive nodes, or regional disease. Localized spread to regional lymph nodes near the primary tumor is not normally counted as metastasis, although this is a sign of worse prognosis. Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas. The use of immunohistochemistry has permitted pathologists to give an identity to many of these metastases. However, imaging of the indicated area only occasionally reveals a primary. The cells in a metastatic tumor resemble those in the primary tumor. Once the cancerous tissue is examined under a microscope to determine the cell type, a doctor can usually tell whether that type of cell is normally found in the part of the body from which the tissue sample was taken. Expression of this metastatic signature has been correlated with a poor prognosis and has been shown to be consistent in several types of cancer. Prognosis was shown to be worse for individuals whose primary tumors expressed the metastatic signature. Additionally, the expression of these metastatic-associated genes was shown to apply to other cancer types in addition to adenocarcinoma. Metastases of breast cancer, medulloblastoma and prostate cancer all had similar expression patterns of these metastasis-associated genes.

The identification of this metastasis-associated

signature provides promise for identifying cells with metastatic potential within the primary tumor and hope for improving the prognosis of these metastatic-associated cancers. Additionally, by identifying the genes whose expression is changed in metastasis offers potential targets to inhibit metastasis. Treatment and survival is determined, to a great extent, by whether or not a cancer remains localized or spreads to other locations in the body. If the cancer metastasizes to other tissues or organs, it usually dramatically decreases a patient's likelihood of survival. However, there are some cancers - such as some forms of leukemia, a cancer of the blood, or malignancies in the brain - that can kill without spreading at all. The treatment options currently available are rarely able to cure metastatic cancer, though some tumors, such as testicular cancer and thyroid cancer, are usually still curable (Wikipedia, 2014).

The spread of cancer usually happens through one or more of the following steps: (1) **Cancer cells invade nearby healthy cells.** When the healthy cell is taken over, it too can replicate more abnormal cells; (2) **Cancer cells penetrate into the circulatory or lymph system.** Cancer cells travel through the walls of nearby lymph vessels or blood vessels; (3) **Migration through circulation.** Cancer cells are carried by the lymph system and the bloodstream to other parts of the body; (4) **Cancer cells lodge in capillaries.** Cancer cells stop moving as they are lodged in capillaries at a distant location and divide and migrate into the surrounding tissue; (5) **New small tumors grow.** Cancer cells form small tumors at the new location (National Breast Cancer Foundation, 2014).

The following is a brief description of where certain cancers are most likely to spread:

Bladder: Bladder cancer tends to stay in the same area and grow into nearby tissues such as the pelvic wall. It can also spread to the lungs, liver, and bone.

Brain: Brain tumors rarely spread outside the brain. They mainly grow within the brain and sometimes into the spinal cord.

Breast: Breast cancer most commonly spreads to the bones, but also can spread to the liver, lungs, and brain. As the cancer progresses, it may affect any organ. It can also spread to the skin of the chest.

Cervix: Cancer of the cervix tends to grow near where it started, into the vagina and uterus and then other parts of the pelvis, such as the rectum and bladder. It can also grow into the bones and nerves of the spine, and spread to the liver, lungs, and bones.

Colon and rectum: The most common sites for colon or rectal cancer spread are the liver and lungs. These cancers may also spread to nearly any other organ, including the bones and brain. Rectal cancer can also spread within in the pelvis, where the cancer started. This can be painful because it often grows into nerves and bones in this area.

Esophagus: Esophageal cancer mostly grows near where it started. As it progresses, it may grow into nearby organs or major blood vessels, which can make it hard to treat.

Kidney: Kidney cancer can grow where it started and invade nearby tissues. It can grow from the kidney into the large vein that drains the blood from the kidney. From there it can grow into a large vein that empties into the heart. It can also grow from the kidney into the adrenal gland, which sits on top of the kidney. When it spreads, the lungs and bones are the most common sites.

Leukemia: Because they are already in the blood, leukemias can be considered to have spread throughout the body when they are diagnosed. They can progress by filling the bone marrow with leukemia cells. The normal bone marrow is replaced and cannot make new blood cells. Some leukemias may spread outside the blood and into the fluid that surrounds the brain and spinal cord. Tumors made up of leukemia cells can also occur in the skin or in other parts of the body, but this is not common. In some types of leukemia, the cancer cells collect in the spleen, causing it to become large. Less often, leukemia cells settle in the liver, causing it to enlarge. In one type of leukemia, the cells deposit in the gums, so that they become red and swollen.

Liver: Liver cancer doesn't often spread outside the liver. It tends to grow throughout the liver as it becomes advanced. If it does spread, it's most often to the lungs or bones.

Lung: Lung cancer can spread to almost any organ of the body, but most often it will spread to the adrenal glands, liver, bones, or brain. It can also spread to the other lung.

Lymphoma: Lymphoma can affect any part of the body. While most start in the lymph nodes, spleen, and/or bone marrow, some start in lymph tissue in the stomach, intestines, or even the eye socket. Lymphomas can spread within the lymph system to distant parts of the body. Less often, they spread outside the lymph system to other organs, such as the lungs, liver, or bone. Lymphomas can affect the brain and spinal cord, either initially or as spread to the fluid and tissues surrounding the brain and spinal cord. This is called lymphomatous meningitis.

Melanoma: Melanoma can spread anywhere in the body. It first tends to go to lymph nodes near where it started, but then can spread to the brain, lungs, liver, and bones. It can also spread to other areas of skin.

Mouth and throat: Cancers of the mouth, throat,

or nasal passages tend to stay in the same area. When they spread, it's usually to the lungs. Less often they may spread to the liver or bones.

Multiple myeloma: Multiple myeloma can cause tumors called plasmacytomas. These tumors can spread to the bones anywhere in the body, but they rarely spread to other organs.

Ovary: Ovarian cancer most often spreads to the lining of the abdomen and pelvis, and organs in the pelvis and belly. It can cause a build-up of fluid and swelling in the abdomen. It can also spread to the outer lining of the lungs and cause fluid to build up there. As it becomes more advanced, it may spread to the lung and liver, or, rarely, to the brain or skin.

Pancreas: Pancreatic cancer mainly stays in the abdomen. It tends to grow into nearby tissues and may spread to the liver or other nearby organs. It can also spread to the lungs.

Prostate: Advanced prostate cancer most often goes to the bones. Much less often, it will spread to other organs, including the lungs and liver.

Stomach: Stomach cancer tends to spread to nearby tissues and stay within the abdomen. It may also spread to the liver or distant lymph nodes. Spread to the lungs, bones, and brain is less common.

Uterus: Cancer that starts in the uterus can grow into the vagina as well as nearby tissues in the pelvis. It also commonly spreads to the peritoneum and the omentum. Other sites of cancer spread include the liver, lungs, and, less often, bones.

Cancer cells often break away from the main tumor and travel through the blood and/or lymph system, but they don't always settle in and start new tumors. Most of the time, the cells that broke away die. When cancer does spread to other organs and start to form new tumors, it's because of certain genetic changes in the cells that scientists are now starting to understand. Someday, doctors may be able to tell if a person's cancer is the type that will spread to other organs by looking for these genetic changes. Research is also focusing on treatments that block or target these genetic changes so the cancer cells can't spread and grow.

Bladder cancers are divided into several types based how their cells look under a microscope. Different types can respond differently to treatments. Transitional cell carcinoma. This is by far the most common type of bladder cancer. More than 9 out of 10 bladder cancers are this type. The cells from transitional cell carcinomas (TCCs) look like the urothelial cells that line the inside of the bladder.

Urothelial cells also line other parts of the urinary tract, such as the lining of the kidneys, the ureters, and the urethra, so TCCs can also occur in these places. In fact, patients with bladder cancer sometimes have other tumors in the lining of the kidneys, ureters, or urethra. If someone has a cancer in one part of their urinary system, the entire urinary tract needs to be checked for tumors.

Renal cell carcinoma (RCC), also known as renal cell cancer or renal cell adenocarcinoma, is by far the most common type of kidney cancer. About 9 out of 10 kidney cancers are renal cell carcinomas.

Although RCC usually grows as a single tumor within a kidney, sometimes there are 2 or more tumors in one kidney or even tumors in both kidneys at the same time. There are several subtypes of RCC, based mainly on how the cancer cells look under a microscope. Knowing the subtype of RCC can be a factor in deciding treatment and can also help your doctor determine if your cancer might be due to an inherited genetic syndrome. The diagnosis of cancer in a child or teenager can be a devastating blow to parents and other family members who love the child. Cancer creates an instant crisis in the family.

Upon arriving in a distant organ, a metastatic tumor can grow and form, what is called, a secondary tumor or metastatic lesion. We know less about this process than the previous steps. While a tumor, by definition, can grow almost indefinitely, the growth in the primary tumor site is not always identical to growth elsewhere. In the primary tumor site, growth may have been aided by specific factors in the matrix or by interactions with specific neighboring cell types. When a tumor arrives in a new organ, it has to establish new interactions with the local tissue (Hebert, 2014).

The process of metastasis formation is very inefficient process but leads to the majority of deaths associated with cancer. This is because the number of cells that leave a tumor can be in the millions per day. Even if only a small fraction of the cells that leave a tumor are able to survive to form a new tumor, the large number of attempts means that a distant growth is likely to occur at some point.

Liver metastases are common in many types of cancer, especially those of the GI tract, breast, lung, and pancreas. The first symptoms of metastases are usually nonspecific; they are sometimes the first symptoms of the primary cancer. Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. Diagnosis is usually supported by an imaging test, most often ultrasonography, spiral CT with contrast, or MRI with contrast. Treatment usually involves palliative chemotherapy. Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. If metastases are suspected, liver function tests are often done, but results are usually not specific for the diagnosis. Alkaline phosphatase, γ-glutamyl

transpeptidase, and sometimes LDH typically increase earlier or to a greater degree than do other test results; aminotransferase levels vary. Imaging tests have good sensitivity and specificity. Ultrasonography is usually helpful, but CT with contrast or MRI with contrast is often more accurate to a state of self-renewal (Herrine, 2014).

Bone marrow transplants have been done for more than 50 years and are widely used in many hospitals, providing a life saving treatment for cancer and other diseases including leukemia, anemia, and immune disorders. However, the stem cell at the end of the bone provide the useful opportunities to give these human blood stem cells their superior regenerative abilities (Ma and Young, 2014).

Treatment for metastatic cancer aims to slow the growth or spread of the cancer. Treatment depends on the type of cancer, where it started, the size and location of the metastasis, and other factors. Typically, metastatic cancer requires systemic therapy, or medications given by mouth or injected into the bloodstream to reach cancer cells throughout the body, such as chemotherapy or hormone therapy. Other treatments may include biological therapy, radiation therapy, surgery, or a combination of these. Even if the cancer has stopped responding to treatment, many therapies can ease side effects and improve quality of life. Palliative treatments, which may be the same treatments used to treat cancer, aim to relieve symptoms and side effects. At Cancer Treatment Center of America (CTCA), we provide personalized treatment plans using advanced technologies to target advanced and complex cancers, combined with integrative oncology services to improve quality of life. We offer specialized treatment programs for cancers that spread to the brain, bone, liver and other areas (Cancer Treatment Centers of America, 2014).

Certain gene may cause cancer metastasis. Such as, a gene associated with poor-prognosis breast cancer has been identified by genomic profiling studies that may point to a new therapeutic target, investigators here reported. According to a report, a study found that a gene called metadherin (MTDH) may cause some breast cancers to spread to distant locations in the body. MTDH also may cause some breast cancers to stop responding to chemotherapy. Other research has found that one or more genes are associated with a poor prognosis for some breast cancers. MTDH is one of these genes. The study reviewed here looked at how some of these genes acted in human breast cancer tissue that was put into mice. Breast cancer tissue with an active MTDH gene spread to distant locations seven times more than breast cancers with an inactive MTDH gene. The other genes looked at in this study didn't seem to affect breast cancer spread. It's thought that the MTDH gene affects about 30% to 40% of all breast cancers. Researchers aren't sure how an active MTDH gene influences the spread of breast cancer or chemotherapy resistance. While encouraging, these results are early results. The research was done on human tissue implanted in mice. More research is needed to understand how the MTDH gene affects breast cancer. Still, this research can offer clues to how breast cancer spreads and responds to treatment. In the future, researchers may discover therapies that target and block the MTDH gene, which may help treat breast cancer. Stay tuned to Breastcancer.org for the latest news on research that may lead to better ways to prevent, diagnose, and treat breast cancer (Breastcancer.org, 2009).

A gene that makes breast cancer tumors more likely to resist chemotherapy and to spread to other organs has been identified by a team of New Jersey researchers. When activated, it helps the tumor cells stick tightly to blood vessels in distant organs and makes them resistant to chemotherapy drugs traditionally used to treat breast cancer, according to researchers from Princeton University and the Cancer Institute of New Jersey. Their study was published in the journal Cancer Cell. With more than 180,000 women a year hearing the dreaded diagnosis of breast cancer, the potential benefit of the research is great. It could lead to the development of a test to screen for the gene in breast tumors and medication to block the gene's activity. A medication would not only help prevent metastases to distant organs, but enable chemotherapy to benefit more women, helping to prevent recurrences of breast cancer. Breast cancer is the leading cause of cancer death in women, claiming 40,000 lives a year in the United States. More than 90 percent of those deaths result not from tumors in the breast, but from those that have spread to other organs – most commonly the bones, lungs, liver and brain. The newly identified gene – called Metadherin, or MTDH – was found in 30 percent to 40 percent of the tumor samples examined. The gene also appears to play a role in prostate cancer metastases (Washburn, 2014).

Life is unique in the known universe, which is in a diversity of forms ranging from bacteria to human. The life organisms exist in everywhere of the earth. The first forms of life on earth spontaneously arose out of a preexisting prebiotic chemical soup (Ma and Cherng, 2005).

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