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Cancers: Solid Tumor

Research is a dynamic activity that creates new ideas. It provides a forum for generating observations and testing why they occur. Because people and their diseases are so diverse, clinical trials are the ONLY WAY it is possible to test whether new ideas about how to diagnose or treat human disease will work. But the process of taking research from bench to bedside is a lengthy one and demands not only vision but also years of teamwork and dedication on the part of scientists, physicians and patients. This document presents basic information about solid tumours and frames the context for the discussion that follows about how stem cells are being used to treat solid tumours and how lessons learned from cancer stem cell research may help to fight cancer recurrence. Readers may also wish to peruse additional web resources or speak with their physicians for more information about this condition.

About Solid Tumours

Cancer Basics

Cancer is the name we give to a mass of cells that grows in an abnormal, unregulated way and that ultimately overwhelms a body system or organ. People often use the word ‘cancer’ interchangeably with ‘tumour’, but in fact they are not the same. A ‘tumour’ refers to any abnormal growth of cells and can be harmless or dangerous. A harmless tumour is called benign and does not contain cancerous cells whereas a dangerous tumour is called malignant (meaning inherently ‘bad’) because it contains cancerous cells.

Tumours are called ‘solid’ or ‘liquid’ based on where in the body they grow. More than 80 per cent of all cancers are caused by solid tumours that grow as a mass of cells in particular organ, tissue or gland. The common sites are breast, lung, prostate, and colon, and examples of other sites are brain, uterus, pancreas, skin, and liver. In contrast, liquid tumours, such as leukemia, develop in the blood and can travel to any part of the body (some of these are covered in the Blood Disorders section).

Solid tumours are further divided into carcinomas, sarcomas or lymphomas, according to the cell types that are involved. For example, tumours that develop in skin cells or cells lining or covering the internal organs are called carcinomas whereas sarcomas develop in bone, cartilage, fat, muscle, blood vessels or connective tissue. Tumours of the lymphatic system that develop in mature immune system cells are called lymphomas. Brain tumours generally do not fall into these categories, as they may arise from cell types exclusively found in the brain.

If solid tumours are benign (harmless) and stay in their place of origin, they can generally be removed and pose no long-term threat. However, solid tumours that have acquired aggressive properties are able to spread (metastasize) via the blood or lymphatic (immune) systems to another part of the body. Once cancers metastasize the prognosis for the patient becomes poor, but why some tumours metastasize and others do not is still a mystery.

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Causes, risk factors and staging

There are too many different types of solid tumours to discuss the particular causes and risk factors for each. Instead, the information that follows presents the causes, risk factors and staging of cancer in general.

Cancer can run in families, but as far as we know only the minority of cases (5-10 per cent) are caused by an altered gene that is inherited. The abnormal growth, invasive properties and treatment resistance of the other 90-95 per cent of cases are also thought to be caused by abnormalities in genes or in how the way genes are regulated; but these abnormalities are acquired, not inherited and hence are unique to the developing tumour. Such abnormalities may affect many aspects of cell behaviour including the control of expression of other genes (epigenetic regulators).

The genetic changes that cause the formation of a particular cancer are not to be confused with factors that affect the risk of cancer development. Risk factors can be subdivided into those that can be altered and those that cannot. Examples of lifestyle factors that appear to affect the risk of cancer include smoking, exercise, weight, and alcohol use. Examples of risk factors that are not modifiable include age, gender, and family history. While there is sometimes a correlation between the type of cancer and exposure to certain toxins (such as lung cancer and smoking), most of the time the cause of cancer remains a mystery.

Although many cancers seem to appear abruptly, most actually grow slowly and remain without symptoms for several years. As a result they may go undetected until they are fairly well advanced or are picked up by chance. A cancer that has acquired aggressive properties, however, can seem to appear out of nowhere and cause death within months. Unfortunately, very little is known about the biologies that explain these different behaviours and outcomes.

Staging is an important part of cancer diagnosis because it can be used to guide therapeutic decisions based on historical experience of particular outcomes after different treatments. In the TNM system of staging, the combination of the tumour size (T), the number of lymph nodes involved (N) and whether metastases are detectable (M) provides details which place the overall stage of the cancer at 0, I, II, III or IV. Some cancers also have particular cell surface receptors that give them a growth advantage, and knowing the receptor status can provide an even more in-depth assessment of the cancer's stage. In addition to staging factors, the likely outcome (or prognosis), may also be affected by the age, and health status of an individual.

Treatment

The standard of care underpinning the modern treatment of solid tumours includes surgery, radiation, and chemotherapy. Surgery is the most effective treatment of choice for tumours that are localized and operable, the success of which is measured by the complete removal of the tumour and confirmation that the tissue edges surrounding the tumour are free of cancer cells. Radiation is often used to shrink a tumour prior to its surgical removal, and is also administered in hope of preventing tumours from recurring. Chemotherapy, often used in combination with radiation or surgery, is a form of system-wide drug administration that is used to kill cancer cells and prolong life.

Although chemotherapy and radiation treatments offer definite benefits to cancer patients, they are nevertheless toxic, debilitating and sometimes lethal to patients, either in the short or long term. Efforts to mitigate these side effects have led to the development of more targeted therapies such as immunotherapy. This strategy works by exposing tumour cells to potent immunological agents that either suppress tumour development or tag tumour cells with specific beacons that trigger the immune system to attack the tumour. Cell-based immunotherapies involve infusing into the patient particular subsets of immune system cells (either from a donor or recipient) that will fight and kill tumour cells, or boost the supply of cells depleted by toxic standard of care regimens. The most common type of cell therapy is a hematopoietic stem cell transplant and it is discussed in more detail below.

When tumours vigorously spread throughout the body there is little hope that they will be removable by surgery, and they often develop properties that make them quite resistant to cytotoxic therapies, such as chemotherapy. Although technological advancements continue to refine the mainstay of treatment approaches, and newer approaches are being tested – targeted therapies, cancer vaccines, cytokine-based therapies, and molecular testing – the majority of metastatic solid tumours remain incurable.

Stem Cell Network
Réseau de cellules souches

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How are stem cells helping in the battle against solid tumours?

The current application of stem cells to treat solid tumours revolves around two basic approaches: transplanting hematopoietic stem cells, and learning about cancer stem cells. Hematopoietic stem cell transplants (HSCTs) have been used for many years with the express purpose of re-supplying blood cells in patients who have received cytotoxic agents (usually chemotherapy or radiation) as part of their cancer treatment plan. The much newer, and exploding field of cancer stem cell research aims to understand how cancer stem cells are involved in tumour formation and metastasis, and how to target them to prevent relapse in patients. These two fields are discussed in more detail below.

History of hematopoietic stem cell transplantation (HSCT)

Hematopoietic (blood) stem cells, also called HSCs for short, have the longest history of clinical use dating back to the 1950s when the first hematopoietic stem cell transplant (HSCT) was performed in an attempt to cure a lethal form of leukemia. The premise was to wipe out the leukemic cells and normal bone marrow with radiation and then to transplant normal hematopoietic stem cells to rebuild the blood system. In the 20-year, steep learning curve that followed the early trials, scientists learned the importance of finding the best donor-recipient match, and how to mitigate graft versus host disease and other complications arising from the transplant procedure.

Scientists have applied this knowledge to the treatment of other blood disorders as well as solid tumours. The primary benefit to adding HSCT to cancer therapy is that chemotherapy and radiation regimens are toxic. These agents result in the death of all fast-growing cells, so while they are effective against dividing tumour cells, they also destroy other rapidly-dividing cells in the body, including bone marrow and blood cells. Hematopoietic stem cell transplants are now routinely administered as an adjuvant therapy to rebuild the blood supply after patients with solid tumours undergo chemotherapy or radiation treatments. Despite the success of this combination therapy, upwards of 50 per cent of patients are still not cured of their disease. In addition to the problem of graft versus host disease and infectious complications, some researchers theorize that a small population of stem cells called ‘cancer stem cells’, that are resistant to radiation and chemotherapy treatments, may be responsible for new tumour growth causing relapse and failure of the initial treatment success.

Autologous versus allogeneic HSCT

There are two transplant methods for HSCT: autologous (stem cells originate from the patient) and allogeneic (stem cells originate from a donor). In either case, the stem cells harvested may undergo manipulation in the laboratory prior to being transplanted. The advantage of using autologous HSCT is that there is no possibility of the graft being rejected and therefore no need to include immunosuppressive drugs in the cancer treatment regimen. However, not all patients are candidates for this approach for a variety of reasons that may include age, weak health, or bone marrow disorders. In such cases, allogeneic stem cells transplants from donors, who may or may not be related to the patient, have proven benefits. Although the ideal strategy is to ‘match’ a donor graft as precisely as possible to the recipient’s constitution, most matches are imprecise and the transplant procedure will require the addition of prolonged use of immunosuppressive drugs to control graft versus host disease (GVHD). In GVHD, the transplanted donor immune cells (in the Graft) see the cells in the patient (in the Host) as foreign and mount a vigorous response to attack them – hence the name GVHD. This can happen very quickly (acute) or over a longer period of time (chronic). The manifestations – skin rashes, diarrhea, inflammation of the membranes lining the digestive tract, destruction of the liver and lungs – account for the majority of deaths following allogeneic stem cell transplantation.

Allogeneic stem cell transplants – graft versus tumour effect

Despite the possibility of causing GVHD, donor immune cells from an allogeneic hematopoietic stem cell transplant also have the ability to kill tumour cells in the recipient. This phenomenon is commonly known as a graft versus tumour (GVT) effect and is an important way that allogeneic transplants can attack solid tumours. In fact, allogeneic stem cell transplantation in combination with reduced intensity chemotherapy has been successful in decreasing relapse rates in some solid tumours, such as breast and kidney. However, achieving a balance between GVHD and GVT is tricky and there are still many transplant-related deaths. These can be offset somewhat by trying to find the best bone marrow donor-recipient match, but in only 25 per cent of cases does the allogeneic HSCT come from a

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sibling, with the remainder of patients having to rely on bone marrow or cord blood banks for allogeneic transplants from unrelated donors.

Autologous HSCT for solid tumours

Patients with solid tumours may also receive transplants of their own (autologous) stem cells. For this strategy patients have their own stem cells collected and banked prior to undergoing intensive chemotherapy, after which time their own stem cells are transplanted back to rebuild the battered blood supply. This approach is particularly useful for very young children. In their case, radiation is out of the question because it would damage the developing brain, and so their hematopoietic stem cells are harvested and re-infused following a super aggressive dose of chemotherapy. This approach is standard of care for children with a variety of different solid tumours of the brain (medulloblastoma, neuroblastoma), bone (Ewing sarcoma) and B or T immune system cells (lymphoma), and has been shown to increase survival rates in children with these types of cancer.

Research and clinical directions

Hematopoietic stem cells

Allogeneic hematopoietic stem cell transplantation for metastatic tumours

The need to find better therapies that target metastatic tumours is clear when one examines the statistics of cancer death: in only 10 per cent of cases are deaths attributed to the primary tumour while in 90 per cent of cases the main cause of death is attributed to metastasis: the spread of the primary tumour to distant sites throughout the body. Years of research and clinical trials in metastatic breast cancer paved the way for researchers to test whether allogeneic stem cell transplantation could benefit other metastatic tumours, including esophageal, stomach, colon, rectal, liver, pancreas, lung, breast, prostate, bone, and kidney. Today, clinical trials are underway to test this approach in patients who do not respond to standard therapy. Rather than subjecting patients to intensive chemotherapy or radiation, they receive what is called a ‘mini-transplant’ of peripheral blood stem cells (containing hematopoietic stem cells) from a brother or sister. Intense immunosuppressive drugs are administered in an attempt to reduce transplant-related side effects and to help the grafted stem cells and lymphocytes to thrive. These types of studies hope to assess whether the lymphocytes in the donor transplant will be able to successfully attack the tumour and extend the life of patients or even cure them.

Hematopoietic stem cell transplants and cancer vaccines

Although chemotherapy in combination with HSCT can lead to remission of high- risk cancers, there is still a high incidence of relapse and the side effects take a heavy toll on patients. In an effort to address this, some researchers have been experimenting with cancer vaccines that target tumour cells or proteins. The cancer vaccines can be made against a patient’s tumour or donor tumour material. The theory is that vaccinating patients after they have received HSCT could kick start the immune system to attack any cancer cells that have remained after high dose chemotherapy. This approach is very much still at the experimental stage, but there are ongoing pilot studies in patients with different solid tumours, including brain cancer (neuroblastoma), bone cancer (Ewing’s sarcoma) and kidney cancer (Wilm’s tumour).

Future sources of hematopoietic stem cell transplants

As the number of people with solid tumours increases due to the aging population, so too will the demand for hematopoietic stem cell transplants to buffer the toxic effects of chemotherapy and radiation. While transplant registries around the world have worked nothing short of miracles in terms of matching donor-recipient bone marrow, there continues to be a dearth of suitable donor material. Attempts to address this shortage, have led researchers to question whether other types of stem cells could be viable sources of hematopoietic stem cell transplants.

One possibility is umbilical cord blood. It is home to a variety of different types of stem cells, including hematopoietic stem cells, and has been validated through clinical trials for allogeneic stem cell transplantation. The main advantages

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with cord blood are that it is easy to obtain without risk to the donors, there is less chance of transmitting infectious viruses, and there are no ethical issues associated with its use. Although the practice of using cord blood transplants as a source of hematopoietic stem cells has saved countless lives for whom no matched bone marrow is available, the major limitation is that there are only enough stem cells per cord to treat a child or very small adult. So while there is less graft versus host disease as compared with bone marrow transplants, there is also slower engraftment because of low stem cell numbers. For cord blood stem cell transplants to become a more widespread application, this problem must be overcome. On the laboratory front, scientists are working with growth factors and signaling pathways that promote self-renewal and expansion of stem cells. In the clinical setting, researchers are boosting the numbers by doing double cord blood transplants and by testing whether different routes of injection or molecules that regulate stem cell homing can help to improve engraftment. Researchers are also investigating whether cord blood stem cells could be directly differentiated into specialized cells called dendritic cells that could trigger T cells of the immune system to attack solid tumours.

Another example of directed differentiation applies to induced pluripotent stem cells. These revolutionary, man-made cells were created by Dr. Shinya Yamanaka in 2006. Yamanaka managed to turn back the clock on adult skin cells and reprogram them to a younger, embryonic-like state. The cells are called ‘pluripotent’ because they are no longer locked into making only one cell type but instead can produce a variety of different cell types. (In Latin, ‘pluripotent’ means ‘very many’ and ‘having power’.) In the short years since the technology was first developed, scientists now have methods in place for directly differentiating skin-derived iPS cells into a variety of of specialized cells, including brain, heart and hematopoietic stem cells. But a significant amount of work needs to be done before hematopoietic stem cells made from iPS technology can be used on the frontlines for patient care. As a start, researchers are first testing whether human HSCs derived from induced pluripotent stem cells could be used for treating congenital blood disorders, such as anemia and thalassemia, in animal models of disease. These pre-clinical studies are underway but proving that there is a long-lasting effect has yet to be demonstrated.

Cancer Stem cells

The concept that cancers are propagated by a small subset of cells with stem cell properties has existed for more than a century. This concept is extremely important. It implies that this minority of cells must be eliminated to achieve long-lasting cures, but their rarity makes them very difficult to identify and study. In the past 30 years, three major technological advances have been invaluable for advancing the field of cancer research. Cell sorting techniques developed in the 1980s provided a means to purify normal stem cells, and methodological improvements in the 10 years that followed facilitated the isolation and characterization of cancer stem cells. A critical contribution to the field has been the creation of mice that lack an immune system and thus can serve as long-term hosts for primary sources of malignant human cells. Another advance has been the development of methods for separating different subsets of cells without killing them, so they can then be tested for their ability to generate a tumour in a transplanted immunodeficient mouse.

In 1994, Canadian scientist John Dick identified a small population of tumour-initiating cells that could generate human leukemia in transplanted mice. This discovery paved the way for the subsequent identification of tumour-initiating cells, dubbed ‘cancer stem cells’, in other types of solid tumours found throughout the body including breast cancer (2003), brain cancer (2004), prostate cancer (2005), colon cancer (2006), colorectal cancer (2007), head and neck cancer (2008), melanoma (2008), lung cancer (2008), ovarian cancer (2008), kidney cancer (2009), and skin cancer (2012). Interestingly, there is now growing evidence that the cells that can generate new tumours are not necessarily normal stem cells that have become cancerous, but may represent “later” cell types that have reactivated stem cell properties. In addition, the situation in cancers is complicated by the fact that they are continuously evolving into more aggressive cells.

As a pre-requisite to developing therapies targeted at cancer stem cells, many questions must first be answered. What role do they play in metastatic tumours? What is the molecular machinery that gives a cancer cell, “stem cell” properties? And what distinguishes cancer stem cells from the normal cells of the same tissue? What molecules and pathways can keep cancer stem cells quiet (non-dividing) but still alive, and which ones unleash the capacity to proliferate uncontrollably? And how does the cancer stem cell genome (all of a person’s DNA) affect the type of tumour that grows from it? These are just a few of the many questions being asked by researchers who are intent on finding strategies to target cancer stem cells effectively. Some of the ways in which they are going about answering these questions are discussed below.

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The hunt for cancer stem cell biomarkers

Scientists rely entirely on patients, surgeons and pathologists for obtaining tumour tissue for their experiments. In the laboratory, they separate and sort the tumour tissue into different fractions based on staining patterns, growth ability, enzyme activity, and a gamut of cell surface biomarkers that distinguish the cells. Biomarkers are particularly useful because they have allowed researchers to sort tumour cells into different fractions and test which fraction is able to form tumours in recipient mice. This approach has led to the identification of cancer stem cell biomarkers for a variety of tumours, including breast, brain, skin, head and neck, prostate, pancreas, colon, lung, liver, ovarian and bone. But while these biomarkers can be used to identify cancer stem cells, they may not be useful as therapeutic targets because they are often also present on normal tissue. High priority is being given to finding unique cancer stem cell biomarkers that can not only further purify cancer stem cells, but also identify cancers that have the highest risk of recurrence and metastasis, and serve as targets for new cancer therapies.

Understanding recurrence

As recently as 15 years ago, the prevailing view was that all cancerous cells within a tumour were all equally capable of being cancerous. However, lessons learned from research about leukemia dispelled this notion and paved the way for understanding that cells within a solid tumour vary in the way they look, divide and function. The model currently favoured describes cancers as being arranged in a hierarchy, with cancer stem cells placed at the root of the tumour, producing all the different types of cells within a tumour and carrying with them the ability to form new tumours in immune deficient mice. The bulk of cells within a tumour do not retain the ability to form new tumours, and taken together the clinical relevance of this research is that if cancers stem cells are pegged as the root cause of disease then traditional anti-cancer therapies which attack the bulk of the tumour will not be effective against recurrence. This has been corroborated by showing that cancer stem cells are particularly resistant to chemotherapy and radiation, which makes it very difficult to completely eradicate residual disease in cancer patients. Cancer stem cells also have additional properties which could lead to metastasis, including motility and invasiveness. One very important finding is that the characteristics and frequency of stem cells can change within the same patient as a solid tumour progresses. To understand the impact of this better, researchers are hoping to do longitudinal studies in patients to obtain cancerous cells at all the different stages (diagnosis, relapse prior to treatment, after treatment, relapse after treatment).

Targeting cancer stem cells: the niche and epigenetics

If cancer stem cells are truly responsible for initiating tumour growth, metastasis, drug resistance and relapse, then targeting them becomes arguably one of the most important efforts for treating patients. The best way to get to this point is to understand as much as possible about cancer stem cells.

We know that researchers are trying to identify the biomarkers that distinguish cancer stem cells from other cells and that could act as targets for therapy. They are also developing new tumour models by using fresh tumour samples to create cancer stem cell lines. These will help them to study cancer and test new drugs in a dish. Understanding the microenvironment, or niche, within the body that sustains cancer stem cells is also critical. As for normal cells, the cancer stem cell niche is composed of multiple components, some cellular, some structural and some chemical. To understand the interactions that create the niche and support cancer stem cells, researchers are setting up model cancer stem cell niches, and these will be used as testing grounds for new cancer drugs.

The field of epigenomics has exploded onto the scene in the past 10 years, and it is providing a novel venue for tackling cancer stem cells. The ‘epigenome’ refers to non-DNA elements, such as how DNA is packaged and chemically marked, that affect how genes are expressed. To use a modern day metaphor, the epigenome can be thought of as the ‘software package’ that allows the DNA ‘hard drive’ to reach optimum levels when driving cell behaviour. Scientists have learned that almost all tumours have genetic mutations that impact the epigenome software, and that a complex interplay between the genome (DNA) and epigenome is what drives every patient’s cancer. They propose that it might be easier to reprogram the epigenomic software than the DNA hardware, and this theory is being tested in early trials of patients with various solid tumours (T cell lymphoma, ovarian cancer, lung cancer and breast cancer). The drugs being used to reprogram the epigenome were originally developed as chemotherapy drugs, but serendipitously researchers found out that they also target the epigenome and can reprogram tumour cells at doses that are much

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lower and less toxic than when the drugs are used for conventional chemotherapy.

The challenge of heterogeneity

The way forward is littered with numerous challenges, the least of which is tumour heterogeneity (variation). From an experimental perspective, it is no easy task to capture the dynamic nature of cancer. Many of the modern experimental tools sample cancer in a way that provides only a single snapshot of the tumour in space and time. This approach does not account for the evolving nature of the tumour, both as it would naturally occur in a person and also in response to therapies that may select for drug resistant or more aggressive cancer cells. There is also tremendous variation within the solid tumours among different patients (intertumour variation), and even within solid tumours samples from the same patient (intratumour variation). It may not come as so great a surprise to find that the same type of solid tumour could differ between two people, but it is rather shocking to learn that there is a lot of variation in a tumour within one person. The concept of intratumour heterogeneity has been elegantly described in recent studies on breast, pancreas, kidney and brain cancer, where genetic analyses of single biopsies or numerous biopsies taken from various locations within an organ show remarkable genetic variation. To compound the complexity, the genetic variation changes in biopsies taken over time, suggesting that the most prognostic cancer cells may not even be detectable at the point of diagnosis. These observations have enormous implications for understanding cancer development, metastasis, and relapse, but they also pave the way for researchers to exploit tumour heterogeneity to create novel therapies for cancer patients.

Web Resources

Readers may wish to peruse the recommended sites or review the selected reading list below for more information about the application of stem cells to treat solid tumours.

- Canadian Cancer Society: http://www.cancer.ca/
- National Cancer Institute: http://www.cancer.gov/
- NCIC Clinical Trials Group: https://www.ctg.queensu.ca/
- Ontario Institute for Cancer Research: http://oicr.on.ca/

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