Tumor-Host Interactions

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The influence of the tissues surrounding a tumor has been recognized for many years. In 1976, to examine the effect of the environment on tumor growth, rats were treated with a carcinogen to cause mutations. They were then given a drug to inhibit the growth of normal liver cells and part of the liver was removed to provide a strong growth stimulus. Under these conditions, the only cells able to grow were those with mutations that allowed them to avoid the growth inhibitory effect of the drug (i.e. cancer cells). In rats given the carcinogen but not the growth inhibitor, no tumors developed. This experiment suggested that tumors cannot grow when the surrounding tissue is normal; in other words, growth of a tumor from a single mutated cell can only occur when the stromal environment is altered in such a way to allow unrestrained tumor growth.1

Further information on the topics on this page can also be found in most introductory Biology textbooks, a good one is Campbell Biology, 11th edition.2

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- Summary: Tumor-Host Interactions

Conditions Inside a Tumor

Tumors are complex structures containing many different kinds of cells. For many years scientists focused their research on understanding the transformation of normal cells to into neoplastic, or cancer, cells but spent little time studying other cells present within a tumor. However, within the past several years, it has become evident that other components of tumors, including resident non-cancerous cells (fibroblasts, endothelial cells), connective tissue, and extracellular matrix (ECM; components of tissues that provide structural support, such as proteins like collagen) are equally important both in tumor initiation (early development) and progression. Collectively, these components are known as the stroma. Many researchers prefer a broader term, the tumor microenvironment, instead of the stroma, as it encompasses infiltrating cells of the immune system (macrophages, lymphocytes) and cell free molecules (growth factors, proteases), in addition to the more or less permanent stromal components 3 As the role of the tumor environment in cancer has become better understood, researchers are hopeful that novel therapeutic agents can be developed that target not just cancer cells, but the environment around them. Drugs targeting both cancer cells and stromal components may be significantly more effective than those directed solely against cancer cells.

The components of the tumor microenvironment can be grouped into four categories: (1) cancer cells, (2) non-cancer cells, (3) secreted soluble factors, (4) and non-cellular solid material such as the ECM 4. The actual composition of the tumor microenvironment is highly variable, with differences seen between patients and often in different areas of the same tumor. The tumor microenvironment is often altered as the disease progresses; even the percentage of a tumor made up of cancer cells may change 5

Communication between a tumor and its surroundings is very important. Both pro- and anti-tumor interactions occur that act to enhance or block tumor formation/progression. For example, one critical molecule, transforming growth factor beta (TGF-B), is a critical regulator of tumor progression. TGF-B is a potent inhibitor of cell growth and is secreted by multiple cell types within the tumor microenvironment; however, mutations in many advanced carcinomas result in cancer cells that are unaffected by TGF-B (meaning they continue to grow even in the presence of TGF-B). In addition, tumors themselves often secrete TGF-B, which reduces the growth of surrounding normal cells, thus allowing the tumor cells to reproduce rapidly without competition from neighboring cells 3 In this way, tumors continue to grow at the expense of surrounding cells.

The conditions within the tumor microenvironment differ considerably from those in normal tissue. Major changes include:

- Hypoxia (low oxygen levels)
- Low pH (acidic conditions)
- Low glucose levels

In addition, massive cell death occurs, resulting in the release of proteins and other molecules into the surrounding environment. These factors may help or hurt tumor growth.3 Hypoxia results in the generation of oxygen free

radicals which lead to DNA damage (mutation). Mechanisms for repairing this damage are also less efficient under hypoxic conditions. The end result is an increase in the mutation rate and greater variation within the tumor population. Another result is that only those cells with mutations that allow them to survive in harsh conditions will continue to grow and contribute to the tumor 6

Importantly, the conditions within the tumor microenvironment affect more than just cancer cells. The normal cells surrounding a tumor exhibit altered characteristics compared to corresponding cells in normal tissue. These cells also develop mutations, and the tissue is often disorganized compared to normal tissue 5 These abnormal properties might arise in two ways. The conditions of the tumor microenvironment (hypoxia and low pH) may induce mutations, or soluble products (growth factors, cytokines) released from the tumor may alter the genes expressed by stromal cells 3 Interestingly, mutations have been identified in the stroma of non-cancerous tissue collected from breast cancer patients, suggesting that pre-existing genetic alterations in the stroma may provide the foundation for tumor initiation 6Experiments have illustrated the importance of the stroma in tumor development.

Inflammatory Cells and Cancer

The role of the immune system in cancer is a double-edged sword. While there is evidence that a strong immune system can be beneficial, in many cases the immune system clearly **promotes** tumor growth7. For example, patients with weak immune systems (immunosuppressed), have a higher incidence of cancer, but on the other hand, innate immune cells are believed to contribute to tumor formation through the release of molecules that regulate cell growth and migration, and angiogenesis 8. **Innate immune cells,** such as macrophages that do not produce antibodies but are capable of ingesting foreign organisms, are prominent in pre-malignant and malignant tissues. In addition, many cancers (gastric, cervical, colon, liver) are associated with infection and correlate with the *activity* of the normal host immune response. Chronic inflammatory conditions make people more likely to develop certain cancers; for example, patients with Crohn's disease have a higher incidence of colorectal cancer. A greater understanding of the ways by which the inflammatory response initiates cancer may lead to potent new cancer treatments 7.

In other cases, the tumor itself attracts immune cells which can then impact tumor progression. Tumor cell damage and hypoxia attract macrophages from the blood into the tissue surrounding a tumor. In most cases, high tumor associated macrophage (TAM) counts are correlated with reduced survival. Many tumors secrete factors that prevent macrophages from alerting other immune cells to the presence of cancer cells, resulting in an inability of the immune system to recognize the tumor. Macrophages themselves secrete factors that enhance tumor cell proliferation, invasion, and promote angiogenesis. In addition, TAMs release oxygen free radicals and other mutagenic compounds that may create mutations in surrounding cells. The ability of TAMs to stick to tumor cells allows macrophages to carry tumor cells into the circulation and thus aid in the spread of the cancer (metastasis) 9, 6, 8

Learn more about inflammation and cancer.

Learn more about the immune system.

Fibroblasts and Cancer

Fibroblasts are the predominant cells in the stroma. They are responsible for generating the extracellular matrix (ECM) as well as connective tissue. Because each tissue has different requirements, fibroblasts from different organs express different genes. Changes in fibroblast behaviors are associated with tumor progression, mostly due to factors made by the tumor. Fibroblasts begin to express α-SMA (alpha-smooth muscle actin), which allows them to contract. These myofibroblasts are highly proliferative and are surrounded by a dense meshwork of the structural protein collagen. This profile is known as desmoplasia and is often associated with recruitment of immune cells and angiogenesis 10, 8.

Interestingly, although the behavior (phenotype) of fibroblasts is often altered by close proximity to a tumor, in other cases altered fibroblasts have been isolated from patients with no cancer, but who have hereditary predispositions to the disease. This observation suggests that these altered fibroblasts may actually **aid in the development of cancer**11.

How might these cells become oncogenic in the absence of a tumor? Several possibilities exist, including exposure to carcinogens, accumulation of genetic damage due to aging, and hormone imbalances. Molecules present in healing wounds can also alter fibroblasts in such a way that they resemble fibroblasts found near tumors.8

Exosomes

What are exosomes?

Exosomes are tiny, extracellular vesicles (they measure about 30-100 nanometers in diameter) that can carry proteins, lipids, miRNAs, mRNAs, and DNAs from one cell to another 12. By delivering these molecules from site to site, exosomes function as a means of intercellular communication 12, and they can mediate many physiological

and pathological processes 13. They are released from the surface of cells and can be found in the blood, urine, saliva, breast milk, and other bodily fluids 14. When an exosomes fuses with a recipient cell, its molecular cargo can enter the cell and alter the behavior of the that cell 15.

(Diagram depicting the contents of an exosome: Tumor-derived exosomes can carry RNA, DNA, proteins, and lipids. These molecules can stimulate cell proliferation, avoidance of apoptosis, and angiogenesis.)

How are exosomes formed?

Exosomes are regularly released by many different types of cells, including platelets, endothelial cells, blood cells, immune cells, muscle cells, and cancer cells. They are formed when the cellular membrane pinches inward (see figure: 1) to form a small vesicle inside the cell called an endosome (2). This endosome pinches in again (3), forming vesicles (exosomes) inside that endosome within the cell (4). These are referred to as multivesicular bodies (MVBs). When the MVBs fuse with the plasma membrane (5), the exosomes inside are released to the extracellular space, where they can enter the bloodstream and travel to distant sites in the body (6) 16.

What do exosomes have to do with cancer?

Exosomes released from cancer cells can change the structure of tissues to make it easier for cancer to spread (metastasize).

Exosomes were originally thought to function as cellular trashbags: a method for cells to throw away waste and toxins 17. More and more research, however, verifies their roles in cell-to-cell signaling, with implications for tumor progression and metastasis 14.

Although millions of cancer cells are shed from a tumor every day 18, very few of these circulating tumor cells will survive in a turbulent bloodstream, latch on and invade at a new location, and rapidly proliferate. Exosomes can travel from the primary tumor site to distant organs and alter the behavior of cells in the areas where they land. The changes caused by exosomes can make that particular area more suitable for the growth of cancer cells that have left the initial (primary) tumor. The alteration of tissues to make them more easily colonized by circulating tumor cells (CTC) leads to the production of something termed the ‘pre-metastatic niche’. 14, or a microenvironment suitable for cancer cell growth. This is a tissue that does not yet have any metastatic growths, but is ready to receive cancer cells. This is thought to be a very important event in the spread (metastasis) of cancer.

These tiny, molecule-packed vesicles can alter cell behavior at a normal site and can increase the secretion of growth factors, promote angiogenesis (create a blood supply for cancer cells), recruit and “educate” metastasis-promoting cells from the bone marrow to the secondary site 19, suppress the immune system 13, increase inflammation 20, and modify the extracellular matrix to make it easier for cancer cells to settle down 14.

Exosomes have also been implicated in making tumor cells more resistant to chemotherapy 13, specifically by binding to and expelling cancer drugs from tumor cells or by delivering liver enzymes to the tumor cells to aid in drug detoxification 17.

Learn more about the spread of cancer (metastasis).

How can we use exosomes?

Exosomes can be isolated from liquid biopsies and analyzed to monitor cancer development, progression, and treatment response 14. Exosomes contain messenger RNA (mRNA) and proteins from the cells they came from. The set of mRNAs and proteins that exosomes carry serve as a ‘signature’ of the tumor. Exosome contents may be used to predict the future aggressiveness 17, 13 of the cancer.

Exosomes have potential as drug-delivery vehicles. Researchers can make exosomes in the lab and load them up with interfering RNA transcripts that destroy copies of oncogenes (like MAPK1) in the recipient cells. The exosomes could also carry chemotherapy drugs (like doxorubicin), or anti-inflammatory compounds (like curcumin) that could be targeted specifically to the tumor site by matching proteins on the exosome surface with receptors on the surface of tumor cells. Encapsulating anti-cancer compounds in exosomes could also increase their stability in the circulation as they move to the tumor site. The therapeutic exosomes could be administered intravenously (IV) or injected directly into the tumor site 21.

Exosomes are also being looked at as a way of stimulating the immune response against cancer (immunotherapy). Delivering exosomes containing specific miRNAs (short, non-coding sequences of RNA that regulate gene activity) to tumor sites can activate macrophages (cells of the immune system) to fight off the tumor 20.

Dendritic cells are cells of the immune system that consume and process microbes and proteins and show (present) the processed bits (called “antigens”) to T-cells. As a result, those T-cells are activated to kill any invader carrying identical antigens. Exosomes derived from dendritic cells (“DC-Exo”) are being looked at as a way to give tumor cells antigen-presenting abilities 22. The DC-Exo go to the tumor and make the tumor cells present more antigens, which stimulate the body’s T-cells to attack the tumor.

Another way to increase the anti-tumor response is to use exosomes derived from the cancer cells. Tumor-derived exosomes are enriched with antigens from the cancer cells. In mouse models, when dendritic cells are cultured with these exosomes and injected into the mice, survival increases. Presumably, this is because the immune system knows what to ‘look’ for 23.

Eliminating tumor-derived exosomes altogether could also be used as method of cancer treatment 13. The exosomes could either be purified from the blood (via dialysis or a similar process), or drugs could be used to inhibit the production/secretion of exosomes from cancer cells 17.

Matrix Metalloproteinases and Cancer

One of the most critical roles performed by fibroblasts, both in normal and cancer tissue, is the production and remodeling of the extracellular matrix (ECM). Not only does the ECM impart structural support and strength to tissues, it also provides attachment sites for cell surface receptors, and functions as a reservoir of cytokines and other growth factors24 The structure of tumor-associated ECM is abnormal, with loose structure and disorganized collagen fibers25 Matrix metalloproteinases (MMPs) are a large family of enzymes capable of degrading components of the ECM and are critical in maintenance of the ECM. Degradation of the ECM by MMPs releases growth factors, enhances migration, and alters cell:cell and cell:ECM interactions26. Although MMPs can be produced by tumor cells, most are produced by fibroblasts and macrophages, and high levels of MMPs are found at the tumor:stroma interface5. Because MMPs are secreted into the surrounding environment by these cells, they are a good example of the interaction that occurs between a tumor and its environment.

Evidence indicates that MMPs are key players in multiple steps of tumor progression; they promote metastasis, angiogenesis, and even tumor initiation. One of the many paradoxes of MMP activity is that MMPs often have opposing effects depending on the composition of the tumor environment and the nature of MMPs present. For example, MMPs can either promote or inhibit angiogenesis, depending on the molecules they release from the ECM27, 26. Because of their potent effects on tumor formation and metastasis, several clinical trials attempted to use MMP inhibitors as anticancer therapy. However, these trials were soon stopped as patients developed muscle and bone pain, formed connective tissue nodules, and developed joint disorders. These trials highlight the difficulty of targeting molecules critical for the function of multiple tissues27.

Summary: Tumor-Host Interactions

Tumor Microenvironment

- The tumor microenvironment consists of four components:
  - Cancer cells
  - Non-cancer cells
  - Secreted soluble factors
  - Non-cellular, solid material
- The actual composition of the tumor microenvironment is highly variable.

Conditions within the tumor microenvironment

- Low oxygen levels (hypoxia), acidic conditions (low pH), and low sugar (glucose) levels are common conditions in tumors.
- Conditions within the tumor microenvironment affect both cancer cells and normal cells.
- The tissue within and surrounding a tumor is often disorganized.

Inflammatory Cells in Cancer

- The immune system can inhibit or promote tumor growth.
- Many cancers are associated with chronic inflammatory conditions that activate cells of the innate immune system.
- Macrophages secrete factors that enhance tumor cell proliferation, invasion, and promote angiogenesis.

Fibroblasts in Cancer

- Fibroblasts are the predominant cells in the stroma.
- Changes in fibroblast behavior are associated with tumor progression.
- Matrix metalloproteinases (MMPs) produced by fibroblasts degrade the extracellular matrix.
- MMPs are key players in cancer initiation, metastasis, and angiogenesis.

Exosomes and Cancer

- Exosomes are small membrane-covered vessels made by cancer cells and other cells
- Exosomes carry proteins and nucleic acids
- When they travel to distant parts of the body, exosomes can alter the immune response and/or enhance the spread of cancer

Matrix Metalloproteases and the Tumor Microenvironment

The Tumor Stroma and Metastasis

- Seed and Soil hypothesis: given tumor cells (seeds) can only colonize particular distant tissues (soil) that have a suitable growth environment.
- Two key events must occur for site-specific metastasis to occur: 1) formation of a viable landing spot and 2) expression of appropriate genes in the tumor cells.
- Tumor cells may invade foreign tissue but fail to colonize it. The reasons for this are unknown. These cells are considered 'dormant' cancer cells.

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