GEN Genetic Engineering & Biotechnology News

May 15 2007 (Vol. 27, No. 10)

Feature Article

Probing the Biology of Cancer Stem Cells

AACR Sheds Light on the Microenvironment to Better Target These Cells and Their Pathways

John F. Wong, Ph.D.

Basic research in cancer stem cells erupted over the last couple of years as a result of the growing body of scientific evidence proving that these cells do exist in many cancers. This fervid interest in cancer stem cell research was apparent at the "American Association for Cancer Research (AACR)" meeting held last month in Los Angeles.

The concept of cancer-causing stem cells is not new. John E. Dick, Ph.D., of the University Health Network (www.uhnres.utoronto.ca), made this point during his presentation, conceding that the idea of a cancer stem cell was proposed as far back as the 1930s. During that time, investigators were vigorously debating whether cancer was caused by a foreign agent or arose from an abnormal cell in the body. Interest in this area of cancer research waned, however, until cell culture techniques were developed in the 1950s.

In the 1960s, James Till, Ph.D., and Ernest McCullough, M.D., found a unique stem cell population in the bone marrow that had the capacity to reconstitute blood cells in a lethally irradiated host. Dr. Till and Dr. McCullough subsequently discovered that the transplanted bone marrow-derived cells created individual colonies of red blood cells, white blood cells, and platelets in the spleen of a recipient. They described these cells as colony-forming units with the plasticity to create a variety of different blood cell types, which we now know are hematopoietic stem cells (HSCs).

Hematopoietic System

Dr. Till and Dr. McCullough's findings led to the hematopoietic system and to HSCs becoming the classical model for furthering our understanding of adult stem cells and their ability to morph into distinctly different cellular lineages. Additionally, it was later shown in the 1990s by Dr. Dick and others that leukemias are caused by aberrant HSCs that most likely arise out of mutations in tumor suppressor genes concurrent with epigenetic modifications of the malignant cell's genome.

Particularly, cancer stem cells are able to form tumors, according to Dr. Dick, who demonstrated that these stem cells retain their cancer-initiating property when isolated from a tumor and then serially passaged from one host to another animal host. Dr. Dick noted that it is still unclear whether only one rare type of cancer stem cell in tumors can initiate a tumor or if a heterogeneous subpopulation of stem cells has this capacity.

Similar to normal HSCs and other multipotent adult stem cells, these cancer-initiating cells can self-renew with unlimited proliferative potential. One of the most important characteristic shared by both types of stem cells is the regulation of self-renewal to generate a homogenous population of undifferentiated stem cells. We now know that many of the genes and transcription factors involved in oncogenesis are also involved in the regulation of self-renewal and differentiation of normal stem cells.

Michael F. Clarke, M.D., from the Stanford Institute for Stem Cell Biology and Regenerative Medicine (med.stanford.edu/institutes), stressed that similar to normal stem cells, the cancer stem cell becomes activated while residing in the stem cell niche. Subsequently, through a process of asymmetric cell division, the cancer stem cells can produce a population of transient amplifying progenitors, which eventually differentiate into various tissue-specific cells. It has been suggested that these transient amplifying cells give rise to a heterogeneous population of malignant cells within tumors.

The Microenvironment

Stem cell and cancer biologists are currently investigating the microenvironment of the stem cell niche for its role in maintaining and determining the fate of both normal and cancer stem cells. A plethora of scientific data suggesting that cell-to-cell interaction, cell-to-tissue matrix contact, and the presence of certain factors and signaling molecules together within this stem cell niche/compartment regulate stem cell homeostasis. It now appears that the microenvironment provides the cues that instruct a stem cell to either self-renew or exit the niche and give rise to a subpopulation of progenitor cells.

Mina Bissell, Ph.D., of Lawrence Berkeley National Laboratory (www.lbl.gov), noted that in the context of the microenvironment and particularly the extracellular matrix, these extracellular elements have a profound influence on stem cell survival, proliferation, morphogenesis, differentiation, and cell fate.

From her earlier studies, Dr. Bissell found that the rous sarcoma virus, which causes tumors in chickens, when injected into chicken embryos does not induce tumor formation. On the other hand, if the infected embryonic cells are placed in a culture dish, there is massive transformation and subsequent tumor formation. These experiments provided proof that it is the microenvironment that drives phenotypic expression of oncogenes.

With mammary glands as the organ to study the microenvironment and its role in driving tissue structure and function, Dr. Bissell and her collaborators found that when the cells were grown in tissue cultures over a matrigel substrate, the dissociated cells reorganized

and formed 3-D structures of mammary glands that were similar in function and size to the mammary glands in the body. They subsequently determined that an extracellular matrix (ECM) response element provides external signals that reorganize a cell's chromatin and activates tissue specific genes.

Dr. Bissell also provided data demonstrating that if the breast cells are cultivated on a extracellular matrix deficient in lamin-1, the cells do not form acini-like structures, but instead create tumor-like 3-D structures. If myoepithelial cells are then added to the cell cultures, which are the only cells in the body known to produce lamin-1, the cells reorganize and form a normal acinus phenotype. Despite mutations in a cancer cell's genome, Dr. Bissell provided data illustrating that breast cancer cells could also form normal acini if cultivated in an ECM containing lamin-1.

This organizational process to form either tumors or acini was reversible depending upon whether cancer cells were grown in a 2-D microenvironment (monolayer cultures) or in a 3-D microenvironment with ECMs. From these results, Dr. Bissell proposed that in the context of the microenvironment, "phenotype overrides genotype in normal mammary gland and breast cancer."

3-D Cultures and Spheres

Dr. Bissell's research laid the foundation for our understanding of the microenvironment and the importance of 3-D cell culturing to induce functionality and phenotypic expression in a population of cultivated stem cells.

Ruggero De Maria, M.D., of Fondazione IOM (www.fondazioneiom.it), presented his work on characterizing cancer stem cells from solid tumors. With a cell suspension dissociated from solid human tumors, Dr. De Maria and his research group identified a subpopulation of cells within the tumors. These CD133+ cells isolated from thyroid tumors had unlimited proliferative potential to self-renew. Human tumor cells arising from the xenografts in SCID mice were also tumorogenic. Since these cells gave rise to a heterogeneous population in both cultures and xenografts, the results suggested that Dr. De Maria's group had isolated a subpopulation of CD133+ cancer stem cells.

Dr. De Maria noted that to expand a subpopulation of tumorigenic CD133+ cancer cells, he had to first form spheres in a serum-free media supplemented with EGF and FGF-2. The CD133+ cells derived from spheres were more tumorogenic than the cells grown as a monolayer. Similarly, Dr. De Maria's group also found that CD133+ cells from tumors of both lung and brain glioblastoma produced the same results. In both cases, the CD133+ had to organize first into spheres to retain their tumorigenic property. In glioblastomas, the investigator found that the number of CD133+ isolated from the tumor correlated with prognosis, i.e., the presence of more CD133+ were predicative of poor prognosis for the patient diagnosed with a glioblastoma.

Targeted Therapies

The current therapeutic approach for treating cancers may be rapidly changing as we learn more about the biology of cancer stem cells. With the development of new strategies and drugs that target cancer stem cells, there may come a time when we view the current regimen of surgery, high-dose chemotherapy, and radiation as a crude approach for treating cancer.

It has been suggested that the reasons why these therapies are not very effective in destroying cancer stem cells are because these cancer-initiating cells are usually found in a dormant state within tumors. Since alkylating agents and radiation only kill actively dividing cells, the cancer stem cells could easily evade such cytotoxic therapies.

At the meeting, researchers discussed new strategies that either specifically eliminate cancer stem cells or induce them to differentiate and eventually senesce. There is a high probability that cytotoxic mAbs against the cancer stem cell surface markers such as CD44 and CD133 may prove to be an effective therapeutic approach to eliminate cancer stem cells.

With a rapidly growing interest in cancer stem cells, researchers are actively exploring new approaches to target cancer stem cells and their signaling pathways to prevent them from self-renewing in conjunction with an effort to induce them to differentiate and lose their tumorigenic potential.

As our knowledge in cancer stem cells expands, we can anticipate new and effective drugs becoming available in the near future. By developing drugs that specifically target these rare cancer cells, we may be adding the key component to an oncologist’s armamentarium that finally allows us to cure this insidious disease.
