3rd Annual Town Hall Meeting
Translating Breast Cancer and Environmental Research into Action

Models to Study Mammary Stem Cells

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Dr. Barcellos-Hoff, a radiation biologist, uses mice to study cancer as a disease of organisms. In her presentation to the Town Hall Meeting, she explained that while studying human epithelial cells is certainly interesting and important, by using mice she is able to do experiments that are not possible using human subjects.

The focus of Dr. Barcellos-Hoff's presentation today is on stem cells and how her laboratory is using radiation to study the characteristics and distribution of mammary stem cells.

It is well known that radiation is a carcinogen. From the tragic occurrences of Hiroshima and Nagasaki during World War II, we know that radiation exposures can cause cancer in a wide number of organs, including the breast.

Radiation is not, however, a very efficient carcinogen. After exposure, it takes years to decades for *normal cells* to proceed from the *initiation* of genomic changes to the expansion of the damaged cell population (*promotion*), to *progression*, when the damaged cells escape the barrier of a particular tissue, invade surrounding normal tissues and even migrate to distant sites, i.e., *metastasis.*

The effect of radiation depends on the endpoint you are interested in studying. Radiation can cause molecular damage, such as double-strand breaks in the DNA. It can cause aberrations in the chromosomes and changes in the genome, which is the complete set of genes in an organism. These occurrences can lead to molecular mutations, which over a long period of time lead to cancer at the organism level. Radiation can also cause cell death, which in itself does not cause cancer, but is evidence that significant damage has occurred in the system.

One of the ideas prevalent in biology today is that cancer arises via alterations in the tissue stem cells. Dr. Barcellos-Hoff introduced to the attendees the hypothesis that *cancer* stem cells are a result of carcinogen-induced changes in normal stem cells.

Why is that? Dr. Barcellos-Hoff explained that tissue-specific stem cells, for example, those found in the breast, live the longest. Normal stem cells are particular cells that can self-renew (make another of itself) and give rise to a daughter cell that is able to differentiate into all the cells represented in a specific tissue, including in the mammary gland, ER positive and ER negative cells.

The mammary gland is the perfect system for studying stem cells because it is the only organ that develops after the animal is born. At three weeks of age, under the influence of pubertal hormones, the epithelial duct expands into the mammary gland fat pad like a tree does. It has a primary branch, secondary branches and tertiary branches. And those can further proliferate under the hormones of pregnancy to give rise to milk-producing cells.

How do we know there are stem cells involved in this process? In order to study this in the laboratory, Dr. Barcellos-Hoff referenced the work of K. B. De Ome, who first demonstrated it was possible to create an experimental model in which the target cells (epithelial cells that give rise to cancer) can be manipulated independent of the environment. This model has created opportunities for scientists like Dr. Barcellos-Hoff to test various hypotheses, including the postulation that radiation causes DNA damage, which leads to mutations that give rise to cancer cells.

Using high-content microscopy and computer analysis of microscopic images, Dr. Barcellos-Hoff is currently studying the manner in which mammary stem cells are distributed throughout the system of ducts in the mouse mammary gland, how they are organized, where they are located, and whether they are clustered in a particular fashion or randomly. Recent analyses found that mammary gland stem cell distribution in mice is not random. At the local level, stem cells are preferentially found in large ducts in clusters of two. Globally, stem cells are predominately found near the origin of the tissue at the nipple, where the epithelium begins to bud out and grow to fill the fat pad.

Interestingly, these studies have been supported by studies on human tissue which also showed that human mammary stems cell are not randomly distributed but are predominately found at the junction of medium and large ducts.

By learning more about the location and distribution of mammary stem cells in mice, scientists can now study how alterations in life history (such as number and timing of pregnancies), carcinogenic exposures (such as radiation) and hormonal environments affect stem cell location, distribution and behavior.