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Center News

Developmental Biology Reveals a Wealth of Vital Information About Cancer

Studying the role that specific genes play in the development of organisms provides important clues on the role of those genes in mature cells, including cancer cells.

"It's an extremely exciting time to be studying developmental biology right now, because things are changing so rapidly," according to MSKCC researcher Kathryn V. Anderson. "The human genome has been sequenced, but we only know about 10 percent of the genes' functions, so it's important to use new approaches to figure out what they do."

MSK biologists Mary K. Baylies (left) and Kathryn V. Anderson study the role of genes during development to determine their functions in mature cells, including cancer cells.

Developmental biology is the study of how an egg and sperm join together to form a single cell, begin dividing, and eventually differentiate into every cell needed to create an adult animal, be it a human, a mouse, or a fruit fly. This research is crucial to understanding cancer, because in order to comprehend what goes wrong in cancer, scientists must first understand how cells develop and grow under normal conditions.

The field of developmental biology is multidisciplinary, drawing from many other areas of research: genetics, because genes encode the proteins that are needed to create every type of cell; cell biology, because developmental biologists study how cells move, change and interact with each other; and biochemistry, because much of developmental biology involves

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the study of cell-signaling pathways, which are cascades of molecules sending messages to each other, both within and between cells.

"In my work, I try to understand the genes that are involved in the decision-making process that all cells go through," said Mary K. Baylies, head of the Laboratory of Molecular Mechanisms of Development. "Cells are constantly making decisions, whether in development, in normal adult cells, or in cancer cells." These decisions include whether to move, divide, change, or die.

The *Drosophila* fruit fly is a popular animal model for genetic and developmental biology research because its genes can be easily altered and because it develops quickly from embryo to adult.

In Dr. Baylies' lab, researchers study the development of muscle cells in *Drosophila* fruit flies, a popular animal model for genetic and developmental research. "Working with the fruit fly allows us to quickly define genes critical to the organism's development and then understand how they function — which means finding not only how the individual gene works but also which other genes work with this gene," Dr. Baylies said. One gene that is key in the development of muscle cells is *twist*. The Twist protein is a transcription factor, which means it binds to other genes in the nucleus of the cell and turns them on or off. Mutations in *twist* in humans have been linked to developmental disorders as well as cancer, in particular rhabdomyosarcomas.

In August, Dr. Baylies' lab published a paper in *Development* that showed that different forms of Twist behave differently in the same cell — one form turns genes on, whereas the other turns genes off. "The decision that the muscle cell makes depends on the delicate balance between these two different forms," said Dr. Baylies. "We now want to know how the amounts of these different forms are regulated. This information then will give us clues about why mutations in *twist* can lead to diseases such as cancer."

Dr. Anderson, head of the Developmental Genetics Laboratory, also works with fruit flies, as well as with mice. She and her colleagues recently published a paper in *Nature* showing that in mice a gene called *open brain* is part of a signaling pathway, called the Sonic hedgehog pathway, which is essential in early development and also plays a role in certain cancers, including basal cell carcinomas and the pediatric tumor medulloblastoma. (*Open brain* gets its literal name from the birth defect that results from its mutation, a neural tube that doesn't fuse together; Sonic hedgehog gets its whimsical name from a video game.)

In further work, Dr. Anderson's lab showed that the *open brain* gene directs the production of the protein Rab 23, which is known to be related to the transport of vesicles, tiny sacs that shuttle materials throughout cells. The researchers were surprised to learn that a vesicle-transport protein could be involved in a signaling pathway, and the discovery provides new avenues for research.

Dr. Anderson's lab also studies the Toll pathway in fruit flies, which is involved in determining cells' eventual fate and in immune response. In reaction to infections, insects make large amounts of chemical peptides that punch holes in bacteria and fungi, but only if Toll pathways are working. Toll pathways have been found in humans and are required for humans to respond to bacterial infection.

Barry M. Gumbiner, head of the Cell Adhesion and Morphogenesis Laboratory, studies two classes of proteins that are related to development, called cadherins and catenins. Cadherins are cell-adhesion molecules. Catenins are signaling molecules that also play a role in adhesion. Dr. Gumbiner carries out much of his research with the frog *Xenopus*.

"Cell adhesion is the mechanism by which cells are held together to form tissues," Dr. Gumbiner said. "By studying this, we hope to meet our long-term goal: to understand the process called morphogenesis, which is how you create the three-

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dimensional architecture of organs out of cells." Cell adhesion is also related to cancer because if cells become less adhesive, they can roam around and become metastatic.

One of the catenins Dr. Gumbiner discovered, ß-catenin, was found to be a player in the Wnt pathway, which regulates cell fate in both embryonic development and the formation of some cancers. A gene called *APC*, which is strongly linked to a hereditary form of colorectal cancer, turns off ß-catenin. When *APC* is lost or inactivated by mutation, ß-catenin levels increase, giving rise to cancer. It is not yet clear how ß-catenin's role in regulating adhesion is related to its role in signaling, a problem being investigated in Dr. Gumbiner's laboratory.

The molecules that control development are the same ones that control cancer.

Dr. Gumbiner uses frogs as a model system because they make it easy to determine the function of a particular gene or protein during development. Unlike a mouse, frog embryos can grow in a dish, and researchers can inject the molecule of interest into the embryo and see within hours or days what the effect is. Dr. Gumbiner found that injecting ß-catenin into a frog egg will cause the embryo to develop two heads, indicating that the molecule plays an important part in very early development.

The study of developmental biology at a cancer center is vital, Dr. Gumbiner pointed out, because the molecules that control development are the same ones that control cancer. And the exchange of knowledge goes two ways: Cancer biologists often uncover new information that contributes to developmental biology. One example is *APC*, which was first found to cause cancer when inactivated and only later found to be involved in development pathways. "In addition," Dr. Gumbiner said, "cancer is a disease of development. To understand how a molecule is involved in cancer and why it's making cells cancerous, you have to understand what the molecule is supposed to do normally."

"One of the advantages of working with embryos," Dr. Anderson said, "is that you can look at the first time these molecules have been required during the life cycle. When you can study how processes unfold in the life cycle of an animal, that's the context that gives these molecules meaning." That molecular meaning is what MSK's developmental biologists are striving to define.