Killing the Queen

Researchers probe the deadly ways of cancer stem cells, hoping to halt the disease

By Alissa Poh

The standard protocol for chemotherapy is to administer the "maximum tolerated dose"—a regimen that's often brutal for patients, yet doesn't always kill their disease. Some cancers don't respond at all; others, too often, will recur.

"We're incredibly good at shrinking tumors, and incredibly bad at curing them," says Richard White, MD, PhD, an oncologist and clinical fellow in the Stem Cell Program at Children's Hospital Boston. "Cancer isn't static; the disease you have on day one is not what you'll have two years down the road. It's like fighting a moving target."

Many scientists are convinced that tumors are formed and fed by a small but critical group of cells known as cancer stem cells. These cells, still poorly defined, can endlessly replace themselves and form other tumor cell types, similar to the stem cells that form different tissues in a developing embryo.

Scott Armstrong, MD, PhD, a pediatric oncologist at Children's and the Dana-Farber Cancer Institute, likens cancer stem cells to queen bees: A hive collapses only if the queen is destroyed; if she isn't, the colony can easily re-form. White makes another analogy. "If you want to get rid of a tree, you could cut off the branches and hope it dies, but it usually won't," he says. "Or you could cut out the root, which will kill the tree. Current chemotherapy removes the branches, not the root."

Research has accelerated dramatically since the first cancer stem cells were identified, about 10 years ago, in a human leukemia. But exactly what a cancer stem cell is or isn't has yet to be defined. "One scientist can mean something different than another in referring to cancer stem cells," says Carla Kim, PhD, another

Illustration: Dan Page

researcher in Children's Stem Cell Program. "Some say they're the cells from which a tumor originates; others think they're specialized cells within a tumor that help maintain it."

Scientists are also debating the true "stemness" of these cells. "Calling them cancer stem cells is confusing, because they don't always come from normal stem cells in the tissue," says Kim. "Sometimes molecules involved only in normal stem cell function are reactivated in cancer cells."

Ultimately, whether or not to hang the "stem" label on these wily cells is less important than figuring out how they help tumors thrive and spread, and how to eliminate or neutralize them. Kim, White, and Armstrong are exploring these questions, looking at three different cancers.

CLARIFYING MELANOMA

Fish tanks fill the room, housing families of tiny zebrafish—some striped, others yellowish, still others genetically engineered as albinos. One breed stands out, looking rather ghost-like as it drifts through the water, its internal organs clearly visible. "That's Casper," says White, pointing at his latest creation.

When not treating cancer patients at the Dana-Farber Cancer Institute, White works in the laboratory of Leonard Zon, MD, director of the Children's Stem Cell Program. He's particularly interested in metastatic disease—the unpredictable, often fatal spread of cancer to another part of the body. "Once you've developed metastatic disease, I generally can't cure you," he says. "I can only delay its progress. That's the paradox of cancer: Shrinking a tumor, and curing one that has spread, seem to be somewhat unrelated. So why is metastatic disease so incurable?"

Zebrafish provide a handy tool for White's studies, which focus on metastatic melanoma, a cancer whose deadliness—patients often live less than a year—makes it a good model for research. Casper's transparent skin allows White to directly observe melanoma's spread. Implanting fluorescent melanomas in Casper's abdomen, and later viewing the fish under a microscope, White observed that some tumor cells quickly break off to

Photo: Patrick Bibbins

RICHARD WHITE, MD, PHD with zebrafish

go elsewhere in its body, almost always heading to the skin. This movement capacity, he notes, is a feature of normal pigment-producing melanocytes in the embryo. The mobility of these tumor cells, at least in melanoma, may be integral to metastasis, he says.

"These cells share certain genetic programs with stem cells; they're inherently mobile and raring to go," White says. "We're trying to find molecules that block this capacity to move." As he finds such compounds, he can test them in Casper and observe how effectively melanoma's spread is checked.

Markus Frank, MD, a researcher in the Transplantation Research Center of Children's and Brigham and Women's Hospital, is also exploring melanoma stem cells. Last January, he and his colleagues reported that these cells have a special protein on their surface, ABCB5, that makes them chemotherapy-resistant. Working with mice bearing human melanomas, they also demonstrated, for the first time, that melanoma stem cells can be targeted for destruction, curbing the cancer. They injected antibodies against ABCB5 into the mice, successfully killing the melanoma stem cells and markedly inhibiting melanoma growth. They now hope to find a way to block ABCB5 that could become a clinical therapy.

"We're taking very different approaches to the same question," White notes. "Markus studies human tissues directly; I first use zebrafish to understand what happens very early in tumor development. From these completely different perspectives, we hope to come up with unifying answers that are relevant to human cancer."

NEW LIGHT ON LUNG CANCER

Although lung cancer is the number one cause of cancer death worldwide, it remains one of the most poorly funded cancers in terms of research, largely because of the lack of survivors and the stigma associated with smoking. "Diagnosed patients often feel very ashamed and are unwilling to speak up, which impacts fundraising," says Kim, who started her lab at Children's two years ago.

Kim is one of the few people in the world who's carved out a niche in lung stem cell research, studying both cancer and normal lung cells. During her postdoctoral fellowship, she was the first to isolate bronchioalveolar stem cells (BASCs), a type of lung stem cell, from adult mice. Kim also found that the most common genetic mutation in lung cancer appears to transform BASCs into the bad guys of adenocarcinoma, a typical and aggressive form of lung cancer.

Kim believes that lung stem cells such as BASCs are involved in the early, undetected stages of adenocarcinoma. This silent period can go on for years, even decades, until the cancer has advanced to a symptomatic stage.

By transplanting lung tumor cells from one mouse to another, Kim has observed that in certain cases, only tumors with BASC-like cells can grow in recipient animals. These cells, she says, may be the stem cells in lung cancer. She's now examining their gene expression profile—which genes are turned on, and which are silenced—to see what makes them different from normal lung stem cells.

"What molecules control these cells, versus the remaining tumor, versus normal lung?" she asks. "If we can answer this, we'll have a better plan to attack lung cancer through new therapies, or combinations of existing ones."

Kim is also searching mouse lungs for other cells, besides BASCs, that have "stem" properties. She genetically tags likely candidates, then injures the lung to see which cell types are involved in repairing the injury, and whether these carry the same genetic tags. She hopes to learn whether normal lung stem cells could be used as a therapy for cystic fibrosis, the defective lungs of premature infants and other pulmonary problems. "There are many broad applications in lung stem cell studies that go beyond cancer," she says.

TARGETING LEUKEMIA STEM CELLS

Scott Armstrong has just spent two weeks on service in Children's oncology unit. He saw more than 30 young patients during that duty, many suffering from leukemia, the most common childhood cancer. These children have abnormally high numbers of immature, dysfunctional white blood cells that crowd out the bone marrow, interfering with its ability to produce healthy blood cells.

Nowadays, most children survive the more common types of leukemia—cure rates are approximately 80 percent. But the same is not true for patients with rare forms of the disease, who may initially go into remission, only to suffer a fatal relapse. Mixed lineage leukemia (MLL) is one such rare example, sharing features of two major childhood blood cancers, acute lymphoblastic leukemia (ALL) and

acute myelogenous leukemia (AML). Armstrong, who studies MLL, believes that cancer stem cells could be at work in initiating relapse, and is keen to find new and better therapies.

Armstrong recently showed that in MLL, certain white blood cell progenitors (which give rise to different types of white blood cells, but don't replicate themselves) inappropriately acquire stem-like, self-renewing qualities. A chromosomal rearrangement causes half of a certain protein in the blood to fuse with a different protein called AF9. When this hybrid protein was directly injected into progenitor cells from mice, it activated genes that made the cells turn cancerous and resemble stem cells.

"The chromosome translocation gives progenitors an ability to copy themselves that they shouldn't have, which eventually results in leukemia," Armstrong explains. "We don't yet know precisely how the hybrid activates this self-renewing program, but we think the activity of a specific enzyme, Dot1, is key, making it a potential therapeutic target."

Although the mechanisms that drive cancer stem cells may take years to map out, even for a single cancer, Armstrong believes that such mapping is possible.

"You can imagine, in the future, having a collection of 30 drugs to attack specific cancer stem cells in specific cancers," he says. "You'd isolate the stem cells, identify the programs controlling their survival, and get the targeted therapy off the shelf."

Photo: Ethan Bickford

CARLA KIM, PHD, investigates lung stem cells.

THE ROAD AHEAD

Scientists don't necessarily agree that all or even most tumors are driven by stem cells; in fact, skeptics argue that every cell has some potential to cause a relapse, not just one group. In certain leukemias, says Armstrong, it seems fairly clear that stem-like cells can initiate relapse, but the origins, characteristics and role of such cells probably vary from cancer to cancer. What scientists are learning is that cancer stem cells are as diverse as cancer itself. And that some tumors, more than others, may be "driven" by such stem cells.

Ultimately, researchers envision two sets of cancer treatments—classic chemotherapy, which shrinks most of a tumor, and new therapies aimed at cancer stem cells. Understanding what makes stem cells tick, and what might make them prone to turn cancerous, is crucial. "It'll help us find new ways to detect, image and treat tumors," says Kim. "Even if we're not directly studying a tumor, we're probably learning things to assist cancer research just by studying stem cell biology."

As scientists like Kim, White, Frank and Armstrong pursue these studies, they see a need to better educate the general public, since there is the potential to equate cancer stem cell research with killing embryos and playing God. Some confusion is understandable, says White, since the terminology used in the stem cell field can sometimes be misleading. Clarifying this murkiness will be important in helping the public understand the research these scientists are doing.

"On the one hand, we're saying we want to use stem cells to cure diseases like Parkinson's and Alzheimer's. And here I am saying, 'Well, stem cells are part of the problem with your cancer; we're going to try killing those cells,'" White says. "In both cases, figuring out how these cells get regulated is the key. The two can't be divorced; they have to be studied together."

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