Dialogues

How cells' surroundings contribute to cancer

Part of the secret of the cell is outside the cell

A dialogue between Dr. Mina Bissell and Ms. Peggy Devine

The AACR was pleased to have the opportunity recently to bring together cell biologist Mina Bissell, PhD, and advocate Peggy Devine for a dialogue about Bissell's cancer research.

Bissell holds the position of distinguished scientist at Lawrence Berkeley National Laboratory in Berkeley, Calif., where she was the director of the lab's Life Sciences Division for 16 years. A native of Iran, Bissell earned her undergraduate degree in chemistry at Bryn Mawr College in Pennsylvania and Radcliffe College in Cambridge, Mass., and her doctorate in microbiology and molecular genetics at Harvard University. She arrived in Berkeley in 1970 as a postdoctoral fellow. In the late 1970s, Bissell began to explore the idea that an oncogene—a gene that causes tumors in animals and uncontrolled growth in cells in culture—could not in and of itself change a cell from normal to cancerous. She believed that the cells' surroundings, known as its microenvironment, contributed in some way to how cancer occurred. (The microenvironment includes a complex scaffold on which cells grow and develop, called the extracellular matrix.) At the time, other scientists didn't think Bissell's idea made much sense. Today, it is well accepted that the extracellular matrix plays a critical role in how tissues remain normal and that aberrations in—or destruction of—the extracellular matrix can promote or even cause cancer. Bissell's laboratory now uses the mammary gland of mice and humans to study the role that the extracellular matrix plays in normal breast function and in the development of breast cancer.

Devine is the founder, president, and executive director of the Cancer Information and Support Network (CISN). A breast cancer survivor with more than nine years of advocacy experience, Devine took part in the AACR's inaugural Scientist↔Survivor Educational Workshop. Her organization, CISN, works to bridge the gap between the pharmaceutical industry, academia and the public, and to foster public awareness and literacy about the importance of medical research to daily life.

PEGGY DEVINE: Dr. Bissell, your work really drives home for me how important it is for advocates to pay attention to the basic research that scientists like yourself are doing. It's at the bench where some of the most earth-shattering science takes place. And I think it's really critically important that that's understood.

MINA BISSELL: Thank you. I agree, and I'm pleased to have this opportunity to talk with you about our work.

DEVINE: You often speak about the need to understand the microenvironment to understand cancer. What do you mean by that?

BISSELL: The microenvironment is what surrounds a cell. I believe it is critically important to how a cell behaves. Let me demonstrate with some dramatic examples from our research. When I first began to work on animal cells in my postdoctoral years, I learned about a well-known chicken virus, called RSV, which contains the very first cancer gene discovered. Scientists had begun to put this virus into chicken cells in culture [in lab dishes]. When they put these infected cells into animals, they caused tumors. When I began my own laboratory, a postdoctoral fellow, David Dolberg, and I showed that this very virulent cancer gene caused tumors in chicken wings if injected into chickens. But when injected into chicken embryos, the gene would infect the embryo's tissues without disrupting normal development. This shows why context is so important.

When we talk about breast cancer, for example, we usually talk about the epithelial cells—the cells that line the milk duct—because those essentially are the cells that turn into breast tumors. But the epithelial cells are surrounded by other cells and the extracellular matrix in a structure that we refer to as an acinus [pronounced \'a-sɛ-nɛs\].

All of these cells, combined with the growth factors and hormones that circulate in the blood, form the cell's microenvironment. I discussed the importance of microenvironment and extracellular matrix in two articles 25 years ago [in the *International Review of Cytology* and the *Journal of Theoretical Biology*].

Very often when you talk to scientists in cancer research, they equate cancer with one or a few mutations in the genome. But a cell is not an island only responding to itself. The cell is surrounded by all these other things that together make an organ. The breast, for example, is an organ. Even the organs are not islands. The breast talks to the pituitary gland; the heart has a connection to the stomach; the stomach talks to the brain; the brain talks to the musculature, and so on.

DEVINE: Why is this concept important to the work that you do?

BISSELL: What I want to convey is that the unit of function in your body is not the DNA or the nucleus or the cell. It is the entire organ or even the organism itself. And cancer is a problem of an organ or the organism. It's not a problem of a single cell or a few genes. We wrote a review a couple of years ago in *Nature Reviews Cancer* where we

discussed why a tumor is like a newly formed organ, and how it tries to protect itself by constantly evolving.

DEVINE: I've also heard you say that to understand cancer it is important to understand that the phenotype can override the genotype. Can you explain that?

BISSELL: A genotype is what your genes are made of. It is the genetic material you inherit from your parents. [Genes consist of long sequences of DNA.] Every cell in your body—and there are billions of them—has the same genotype. Yet your organs look very different from each other, and perform very different tasks. This is referred to as the phenotype. [In other words, a phenotype is the observable characteristics of an organ or an organism.] For example, the way the mammary gland looks or the way an acinus behaves is referred to as a phenotype. And your nose has a phenotype of a nose, and your eyes have a phenotype of an eye, but the genome—the genes inside of them—are the same.

Your genes can become damaged during your lifetime. You can also be born with a genetic mutation. [An example of a genetic mutation is the mutation in the BRCA genes that increases breast cancer risk.] If you are born with a genetic mutation like BRCA-1 or BRCA-2, then every single cell in your body has that mutation. Yet, you are essentially normal in all organs and functions for years and years. And, if and when you develop tumors, it is only in one or two organs like the breast or ovaries. Your genes can also become damaged and sustain new mutations in some cells and not others during your lifetime. This is because of influences such as what you eat, your internal metabolism, inflammation and the sun's rays.

DEVINE: How does this relate to your cancer research?

BISSELL: Scientists have discovered that when they look at carcinoma in situ, [a non-invasive cluster of cancerous cells, often referred to as a pre-cancer phenotype] the pattern and the aberrations on the chromosome and DNA are very similar to what develops if this pre-cancer goes on to become a cancer.

But in these earliest stages of cancer, the cancer cells don't look that different from normal cells. And the tissue doesn't look that different from other tissue—it still has the epithelial cells and other cells, called myoepithelial cells, in the right order, and it still has the basement membrane [a thin layer of extracellular matrix material that is found in glandular tissues and some other organs]. Yet we now know that even when the cells have the precancerous genotype, they still have a pretty normal phenotype. This says that depending on the context that surrounds these cells, they can behave like a cancer cell or like a normal cell. This also means that we should be able to manipulate the microenvironment to make cells think they are normal.

DEVINE: So a cell can look normal but have genes that already have mutations.

BISSELL: Exactly. We did an experiment with epithelial cells from the mammary gland of a mouse. We found that when we put these cells on a plastic culture [a flat dish], they would forget they were breast cells. But when we put these cells on a three-dimensional extracellular matrix we had created, the cells got reorganized and looked like breast tissue. We found the same thing to be true in humans: Isolated breast cells lost their shape and structure in a flat culture dish, but when we put them in the three-dimensional matrix they would form an acinus and make milk.

And when we did this same experiment with tumor cells from humans—working with my long-time collaborator Ole Petersen of Denmark—we found that if we put the tumor cells on a flat plastic culture, they did not differ much from normal cells in the way they looked. But if you put them in the three-dimensional matrix, they would form a structure that looked very much like a tumor.

DEVINE: So when you changed the microenvironment the cells changed?

BISSELL: That's right. So then we went back and analyzed the cells that became a breast acinus when put in the extracellular matrix. We discovered that they actually already had a number of DNA mutations. Yet when they were put into the three dimensional environment, they understood that they were still normal and they formed an acinus.

Based on this finding, we developed an assay [a test] in 1992 that could distinguish between normal and malignant cells by distinguishing the phenotype, not the genotype. We could have two cells that looked the same in solution or on a flat dish, but when we put them in the three-dimensional matrix, which allows us to see their phenotype, we could see that one went on to form a tumor and the other an acinus.

So then we asked, since we know that there are normal cells that can still remember they are normal even when they have some mutations, is it possible for us to manipulate the microenvironment in a way that would get the tumor cells to think that they are actually normal cells?

DEVINE: How did you explore that?

BISSELL: We looked to see if we could send some [chemical] signal from the microenvironment to the cells. And lo and behold, we found that if we sent the right signal we could make these tumor cells look—and more importantly, act—normal again. They stopped growing. They reorganized. They formed little tiny acini that looked as if they were normal. And when we injected these acini into mice they wouldn't form tumors.

This meant we had changed the tumor phenotype despite the fact that the genotype was still the tumor genotype. Now, how do we know that? Because if we take these structures and analyze their DNA, they are identical to the tumor DNA.

DEVINE: So what would the implication of that be?

BISSELL: Well, first of all, it says that cancer is not a death sentence. And furthermore, it says that if we knew how to treat a specific kind of cancer with additional specific drugs that are related to the tissue the cancer is in, we should be able to either kill the cells, get them to revert or keep them in check.

For example, people who have diabetes keep that in check with insulin. It's the same thing with these tumors. And that's what we are doing with people who have leukemia or lymphoma and are being treated with interferon or retinoic acid. These patients can live for years on these drugs, even though their genome is still a mess.

DEVINE: Another area you have been working on is wounding. What have you learned?

BISSELL: As I mentioned in the beginning of our discussion, we had found that a cancer gene can act one way in the chicken and another way in the chicken embryo. We asked, "Why was this?" We found two important things. One, that wounding could be a co-carcinogen. And two, that the events that occur after wounding are very different in embryos and in adults. In the embryo the wound heals with no scar. In the adult, the adult wound heals with a scar and the scar is all this stuff we talk about—extracellular matrix, loss of the structure—and those events clearly play a role in how tumors develop.

DEVINE: So does this lend credence to the myth that trauma to the breast may trigger breast cancer if other factors are already in place?

BISSELL: I don't know the literature about the breast, per se, but there is a lot of literature about wounding and cancer. That's why people are getting very interested in the relationship between inflammation and cancer. It may not be the wound, but the inflammation that plays a role in contributing to cancer.

DEVINE: So could surgery for cancer affect the cancer's growth?

BISSELL: I think to try and scare people about this is not a good idea because everything is a question of risk and probability, and so if you don't do the surgery, then the chances of you dying is a lot higher than if you do the surgery. On the other hand, we can do the basic research and learn how to reduce the inflammation after surgery and then the patient can benefit both ways.

DEVINE: So, to sum up, how can scientists pull together the research being done on the microenvironment to advance our knowledge of how to treat different types of cancers?

BISSELL: One important message I am trying to give is that the structure and architecture of every organ in your body plays a role in the way that particular organ gets cancer. Cancer is tissue- and organ-specific. And to understand tissue specificity, you also have to understand a lot about why an ovary remembers to be an ovary and why a breast remembers to be a breast. Both the ovary and the breast share exactly the same

genome, and they have many of the same genes expressed [or turned on], but they have it at different ratios, at different locations and therefore are not regulated identically.

That means you have to understand ovarian specificity or breast specificity in order to understand ovarian cancer or breast cancer. There's absolutely no shortcut. The microenvironment of every tissue is different from every other tissue, and that's why the area we have developed and are studying is so important in cancer research.

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