Inflammatory Breast Cancer: New Hopes and Many Hurdles

By Karen Rowan

The field of inflammatory breast cancer (IBC) research is rife with enigmas and grim statistics. It is more aggressive and deadly than other breast cancers (see Stat Bite), and the mechanisms driving its rapid progression and metastasis remain unclear. Also perplexing is why the disease disproportionately strikes African American women and women of North African or Middle Eastern descent. Even its name needs deciphering; the typical redness and swelling of the breast seen in IBC that superficially resemble inflammation are actually due to lymph ducts that have been clogged with tumor cells.

But recent findings have begun to unlock IBC's mysteries. The search for molecular markers is revealing the genes at work in this disease, and research is turning up clues to how metastasis may unfold. With new cell lines and animal models in the works, and promising findings in several recent studies, those in the field are hopeful for future insights and therapies.

“We are entering a very exciting time in inflammatory breast cancer and in aggressive cancers in general where we are uncovering brand new targets,” said Sofia Merajver, M.D., Ph.D., codirector of the breast cancer research program at the University of Michigan, Ann Arbor. “They seem to be hugely informative about the behavior of these cells.”

Gene Discovery

IBC, first identified in 1924, is different from other cancers in that it doesn’t form a typical tumor. Instead, the cancer cells form small structures called emboli, composed of a few hundred thousand cells. In other types of cancer, Merajver said, one or two emboli might be present near a tumor, and they usually indicate that the tumor is invading the lymph vessels or blood vessels. But in IBC, these emboli are the cancer, and they are already found mainly in the vessels by the time of diagnosis. The emboli are believed to be the reason that IBC can metastasize so quickly. “When they get to distant sites—the liver, the brain—they get there as large clusters,” said Merajver.

Merajver first began her work on IBC in 1994. At the time, there had been several attempts to find markers of the disease, but none had been found. Researchers knew that IBCs tended to have low expression of estrogen and progesterone receptors, but this was hardly a characteristic feature that could be used to identify the disease or explain its devastating effects. “What we set out to understand,” Merajver said, “is why this tumor progresses so fast and seems metastatic from its inception.” Five years later, she and her colleagues published their first report identifying two genes that are expressed differently by IBC cells than by other cells.

One of these genes encoded a protein called RhoC GTPase, which is overexpressed in IBC. RhoC plays a role in signal transduction from growth factor receptors on the cell surface to the cytoplasm and is involved in the reorganization of the cytoskeleton; it is instrumental in a cell’s motility and its ability to metastasize. The second gene, called WISP3, is a tumor suppressor gene, the expression of which is decreased in IBC.

Later work, led by Celina Kleer, M.D., also at the University of Michigan, showed that RhoC and WISP3 work together. She and colleagues found that neither the overexpression of RhoC nor the decreased expression of WISP3 was sufficient to give rise to the aggressiveness seen in IBC. Instead, the researchers wrote in a 2004 report in Breast Cancer Research that the loss of WISP3 expression seems to lead to the increased expression of RhoC. The mechanisms of this genetic link are still not understood.

Interestingly, a gene that is normally found to have decreased expression in late-stage, non-IBC breast cancers has increased expression in IBC. E-cadherin, which is found on the cell surface in the adherens junctions that hold cells tightly together, decreases as non-IBC cancers progress. The decrease is believed to contribute to metastasis by allowing individual cells to slip away from the tumor mass. But in IBC, Kleer showed that E-cadherin may persist and play a key role in maintaining the structure of the tumor emboli, allowing them to metastasize as entire structures.

And now, researchers at the New York University University Cancer Institute have identified a new gene, called eIF4G1, that may be another possible marker of IBC. Led by Robert Schneider, Ph.D., an associate director at the Institute, and Deborah Silvera, Ph.D., a postdoctoral researcher there, the team analyzed biopsy samples from 37 IBC tumors, 30 non-IBC tumors, and 10 normal breast tissue specimens. They found that eIF4G1 was overexpressed in 80% of the IBC tumors, compared to the control samples. The overexpression of eIF4G1 may explain how IBC cells can maintain high levels of E-cadherin, Schneider said. Other proteins, including a protein called p120 catenin, anchor E-cadherin to the cell surface. The gene Schneider found encodes a protein that allows the translation of p120 catenin. Putatively, if eIF4G1 expression were blocked, p120 catenin could not be translated and E-cadherin could not function.

High levels of eIF4G1 are an excellent drug target because normal cells can get by with very low levels of it, Schneider said. And without eIF4G1, IBC cells may not survive because high levels of it are required for their functioning.

Schneider’s work is important, Merajver said, because it not only identified the eIF4G1 gene, it also explained a possible role of the gene in the progression of IBC. “I think there is a lot of emphasis on markers that give you a barcode, but they don’t tell how the tumors got to where they are,” she said. “It’s like showing up at the scene
of an earthquake and noting down everything that is destroyed. It doesn’t help you understand what caused the earthquake.”

While investigators search for the genetic alterations specific to IBC, a parallel search for the interactions between IBC cells and their stroma is under way. “I think that no matter what type of cancer you’re looking at, genetic markers are only part of the picture,” said Bonnie Sloane, Ph.D., chair of the department of pharmacology at Wayne State University School of Medicine in Detroit.

In recent work, Sloane and her colleagues examined the influence of human monocytes, a type of white blood cell, on IBC cells by growing the two cell types together in culture. They found that coculturing the cells caused the IBC cells to increase their expression of cathepsin B, a protease. In normal cells, cathepsin B exists within the lysosomes, where it is involved in routine protein degradation and turnover. But something goes awry in IBC cells that causes cathepsin to translocate to the cell surface, where it degrades proteins that make the extracellular matrix, a step required for metastasis.

“It’s like a swimmer trying to get through a Jell-O pool by eating his way out,” said Dora Cavallo-Medved, Ph.D., at the University of Windsor in Ontario, who worked with Sloane.

Unfortunately, tumors can change and take advantage of the various classes of proteases, Sloane said. Often, if one protease is inhibited, others can quickly take over its job, which makes figuring out possible drug targets difficult. But cathepsin B is more than just one of the players in this cascade: It may have a key role. Most proteases are produced as inactive enzymes and are activated via proteolytic pathways in which one protease activates others. Because cathepsin
B plays a role in activating other proteases, inhibiting cathepsin inhibits some of the breakdown of the matrix. “But it’s not 100%,” said Cavallo-Medved. “Part of our next goal is to figure out the network of proteases.”

**More Cell Lines?**

IBC researchers say that their work is limited because there are currently only two commercially available cell lines for the disease and one animal model. Moreover, one of the cell lines does not mimic the ability of IBC cells in vivo to invade the vessels in the skin. The reason there are so few cell lines is the relative rarity of IBC, said Cavallo-Medved. To overcome this obstacle, she and Sloane are working with the third lead author on their cathepsin study, Mona Mostafa Mohamed, Ph.D., now a researcher at the University of Cairo in Egypt. Because the incidence of IBC is higher in Egypt, they are hopeful that the additional samples will allow the development of more cell lines.

Massimo Cristofanilli, M.D., associate professor at the University of Texas M.D. Anderson Cancer Center in Houston, is also working on developing IBC cell lines. His group currently has three cell lines in the works and is now trying to describe the characteristics of each line. They are also working on developing an animal model.

At M. D. Anderson, Cristofanilli and others have set up the first clinic in the U.S. devoted specifically to treating patients with IBC. They have also created a registry of tissues from IBC patients and collected about 80 samples last year, believing that the tissues will yield data on stromal interactions that will prove important.

As more cell lines become available, the focus will be on trying to develop coculture models that include IBC cells and other types of cells to better understand the rapid progression of IBC, according to Cavallo-Medved. “Communication between cells promotes the movement of IBC cells towards the lymphatic vessels—that’s really important,” she said. “We are on the cusp of really getting into this disease.”

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