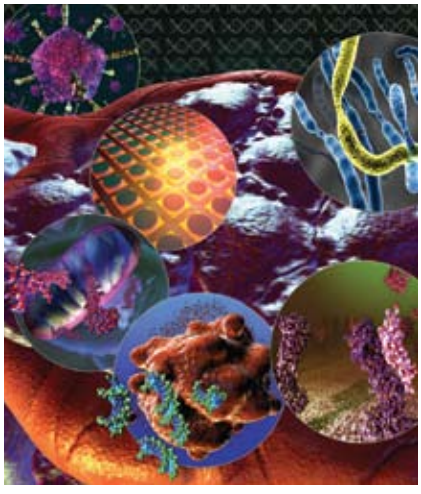

Various biomarkers used to identify vulnerability to therapeutic intervention.

Bringing radiotherapy into the personalized medicine revolution

Bryant Furlow

Personalized medicine—delivery of targeted therapies tailored to individual patients using genetic or other biomarker assays to determine treatment regimens—is importantly advancing clinical oncology. Pharmacogenomic treatment planning uses patient and tumor genetic markers to identify which patients are likely to benefit from a particular chemotherapy. Perhaps most famously, patients with HER2/NEU-positive breast tumors frequently benefit from trastuzumab (Herceptin) therapy, whereas HER2/NEU-negative tumors do not respond to this treatment.

Recent advances allow closer conformation of radiation fields to tumor contours and reduced irradiation of healthy nontarget tissues; however, radiation toxicity remains a common source of morbidity in cancer patients, limiting delivery of potentially curative radiation doses. Patient radiosensitivities and radiation toxicities vary markedly, even among patients receiving identical radiotherapeutic regimens.[1] If biomarkers predictive of radiation toxicity are identified, radiotherapy can enter the personalized medicine revolution, allowing more aggressive treatments for less radiosensitive patients and identifying those highly radiosensitive patients for whom more conservative treatment plans should be devised, thereby improving cure rates while reducing morbidity.

Catherine West, PhD, Professor of Radiation Biology at the University of Manchester School of Medicine in England, described such predictors of patients' intrinsic sensitivities to radiation as "the Holy Grail of radiobiology" in the mid 1990s, and helped pioneer the search for that grail, a field now known as radiogenomics.[2]

Radiogenomics researchers have focused largely on identifying radiation toxicity-associated genetic markers called single-nucleotide polymorphisms (SNPs).[1] "If we know which SNPs confer sensitivity or resistance, we can tailor or personalize radiation treatment," radiation oncologist Barry S. Rosenstein, MD, another radiogenomics pioneer and a professor of radiation oncology and preventive medicine at Mount Sinai School of Medicine in New York, told *Oncology Nurse Advisor*. "We used to ascribe adverse effects to a patient's 'bad luck' and treat (with radiation doses) up to tolerance. In recent years, we've come to appreciate that genetics probably plays a role. Patients come into the clinic with an inherited risk of adverse responses to radiation."

Early radiogenomic research efforts focused on specific candidate genes believed to be involved in DNA damage repair or other processes associated with biologic responses to irradiation. One of many promising SNPs identified this way was the *TGFß1* gene, believed to affect secretion of transforming growth factor ß1 (TGFß1), a cytokine protein implicated in apoptosis (programmed cell death) and fibrosis.[2] Several preliminary studies suggested significant associations between one version of the *TGFß1* gene (referred to as the *-509 TT* or simply *TT genotype*) and late fibrosis risk among patients receiving postmastectomy radiation and rectal bleeding after prostate cancer radiotherapy.[2]

> A genome-wide approach is more likely to discover unknown variants.

Subsequent validation efforts failed to confirm the early promise of the TT genotype as a radiosensitivity biomarker. In 2009 and 2010, radiobiologist and oncologist Christian Nicolaj Andreassen, MD, PhD, of Aarhus University Hospital in Denmark, conducted analyses of data from more than a dozen published studies of *TGFß1*. Andreassen found that stronger findings came from studies with fewer participants, with larger studies' results

clustering around the line of no effect, raising strong suspicions that positive findings had been statistical mirages.[2] Despite the biological plausibility of candidate radiosensitivity SNPs, small single-institution studies were "hampered by inconsistent results and a lack of ability to replicate previous association," Andreassen cautioned.[2]

Researchers were realizing that small studies by local research teams were yielding statistically unreliable false positives. In 2009, Rosenstein and West joined colleagues in Europe and the United States and established the international Radiogenomics Consortium to share biologic samples and patient data, pooling their data to perform statistically powerful analyses to confirm suspected genetic associations with radiosensitivity.[3]

In January 2012, West and coauthors reported disappointing news. No previously reported, biologically plausible SNP associations with patient radiosensitivity could be confirmed in a large validation study of 1,613 radiotherapy patients.[4]

"The effect sizes associated with any SNP were too small to have any clinical relevance individually," said West. "The work highlights the need for large cooperative studies, which are required to detect exactly which SNPs are important. It also highlights the need to move to genome-wide association studies, where there is no assumption about the genes that are important."

TIME TO CAST A WIDER NET

"This is not the 'end' of radiogenomics," Matthew Parliament, MD, Director of Radiation Oncology at the Cross Cancer Institute at the University of Alberta in Edmonton, Canada, told *Oncology Nurse Advisor*. "To paraphrase Churchill, it is the end of the beginning. The model we thought we knew, upon which the choice of candidate genes in pathways such as DNA damage repair, is probably not totally sufficient to explain the phenomenon of radiation injury at the tissue level. A genome-wide gene sequencing approach, as in other population-based studies of complex chronic diseases, is much more likely to discover highly significant, heretofore unknown variants, which may in fact be causative."

> "We're hoping we can carve down to a reasonable number of genetic markers."

Several years ago, Rosenstein's team initiated genome-wide searches for SNPs associated with adverse urinary, sexual function, and rectal effects among prostate cancer patients treated with radiotherapy. Using genetic data for patients from the United States, England, the Netherlands, and Japan, he hopes to narrow down a list of thousands of preliminary associations to a small pool of powerfully predictive SNPs.

"We've taken SNPs with the strongest (preliminary) associations with these three major complications and have created our own customized gene array with 5,000 SNPs," Rosenstein explained. "We've just concluded screening 1,100 prostate cancer patients, using a case/control study approach. Within the next few months, we're hoping to see that of the 5,000 SNPs, there are a much smaller number, 10, 50, or 100 SNPs, that have much stronger associations with the complications we're looking at. We're hoping we can carve it down to a reasonable number of genetic markers that can be used as a predictive assay, not one or a few but a group of markers."

GOING FORWARD

The Radiogenomics Consortium applied for National Institutes of Health (NIH) funding in March 2012. It plans to prospectively enroll 16,000 radiotherapy patients at 12 institutions in the United States and Europe in a study that will use uniform measures of toxicity and establish a radiogenomics data and biobank with blood specimens and detailed information about treatment, dosimetric measurements, and clinical outcomes. "We'll follow them, hopefully for the remainder of their lives," Rosenstein said. "If the funding comes through, we'll start January 1, 2013."

Five years from now, Rosenstein predicts, patients may have their entire genomes sequenced for the cost of a CT scan, with which oncologists can use SNP analysis algorithms to identify a patient's risk of radiation toxicities. "I predict there will be some important discoveries made in this area in the next couple of years," Parliament agreed; "assuming, of course, that researchers share their data with the Radiogenomics Consortium so that large, statistically powerful datasets can address the question." ■

Bryant Furlow is a medical journalist based in Albuquerque, New Mexico.

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