Molecular Subtypes of Breast Cancer

Breast cancer is a remarkably diverse disease. In terms of gene expression there are multiple different molecular subtypes of breast cancer. Dr. Chuck Perou and his colleagues demonstrated that the way an individual breast cancer behaved was associated with differences in the expression of various genes in the tumor. From the genes in the tissue samples, they selected a subset of 456 genes which they named the “intrinsic” gene subset. This subset contained genes that were significantly different among different breast cancers. Using this subset, they were then able to identify 5 very different molecular subtypes of breast cancer:

- ER-positive/luminal A
- ER-positive/luminal B
- Basal-like
- HER2-positive
- Normal breast

These five molecular subtypes have been confirmed in independent data sets, and importantly, the individual gene expression subtype appears to remain consistent between the original tumor and subsequent metastatic lesions occurring years later. Furthermore, these subtypes are associated with differences in clinical outcome. Sorlie and his colleagues examined a subset of 49 locally advanced breast cancers that had been treated with adriamycin and found that both relapse-free (RFS) and overall survival (OS) differed significantly among the breast cancer subtypes. Luminal A tumors had the longest survival times, the basal-like and HER2+/ER- subtypes had the shortest survival times and the luminal B tumors had intermediate survival times.

Newly developed assays allow investigators to expand on these past findings and be able to more completely describe the precise molecular nature of breast cancer. In a new study published in Nature by the Cancer Genome Atlas Network, investigators studied a diverse set of breast tumors using six different types of technology. Tumor and germline DNA samples were obtained from 825 patients. They found that the ER-positive/Luminal tumors were the most diverse in terms of gene expression, mutations and patient outcomes. Among the HER2-positive tumors, they identified at least 2 types that were clinically different. Among the triple negative tumors (TNBC), about 75% were “basal-like”. Interestingly, the mutations seen in the basal-like and TNBC samples were similar to the mutations and other abnormalities seen in certain ovarian cancers and squamous lung cancers.

These data are extremely important and will hopefully eventually translate into better treatment for patients with breast cancer. They demonstrate a clear move toward discovering the genomic drivers of the various breast cancer subtypes. Breast cancers are not all the same and we are rapidly moving into a new era where different breast cancers will be treated in different ways. These data will inevitably lead to improvements in clinical trial design. Trials will be better designed to specifically target the individual types of breast cancer most likely to benefit from a specific agent. Furthermore, these genomic studies can identify new therapeutic
targets from which novel agents can be developed. The value of a more personalized approach to cancer treatment has already been demonstrated in the setting of early clinical trials. The Clinical Center for Targeted Therapy at MD Anderson recently published very exciting data on the clinical outcomes of patients who were treated with targeted agents matched to the specific molecular abnormalities in their particular tumor. They found that the "matched" patients had a higher overall response rate, longer time to treatment failure and a longer survival compared to patients whose treatment was not matched to any particular molecular abnormality. We are clearly in a very exciting time for breast cancer research.

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