The genomic landscape of endocrine-resistant metastatic breast cancer

Synopsis

Recent efforts to characterize the genomes of metastatic breast cancers hold promise for deciphering the evolution of the disease through comparative analyses with primary breast cancers. However, these analyses have proven challenging due to the many differences between primaries and metastases including: (1) spatial heterogeneity resulting in discrepancies of tumor representation with primary tumors representing a larger portion of the whole than solitary biopsies of metastases, (2) differences in the microenvironment of the mammary gland and diverse metastatic loci, and (3) temporal heterogeneity and disparities in exposure to the selective pressures of systemic therapy between early and late disease, all of which may independently modify the ongoing natural evolution of the cancer. Recently, advances in computational genomic analyses and the now large repositories of samples with detailed clinical annotation have enabled rational deconvolution of these datasets, revealing insights into the unique drivers of advanced and lethal disease. In particular, large cohorts of patients with exposure to hormonal therapy has enabled the identification of specific genomic alterations that promote resistance to anti-estrogens. This new classification of genomic mechanisms of endocrine resistance has helped uncover the forces that create the underlying hormone dependence of ER+ breast cancer while also revealing new therapeutic targets that may be useful to treat or even prevent resistant disease. In this presentation, we will review the genomic features of endocrine resistant metastatic breast cancer, detail evidence for (or against) specific alterations as likely mechanisms of resistance and describe next steps for clinical utilization of genomic information for the management of this disease.