Bursts of Chromosome Changes Drive TNBC

Recent research suggests that complex genomic rearrangements in triple-negative breast cancer (TNBC) cells occur through a “Big Bang” model—early, short bursts of copy number aberrations (CNA), or chromosome changes, rather than progressive accumulation over time (Nat Genet 2016 Aug 15 [Epub ahead of print]). The study was carried out at The University of Texas MD Anderson Cancer Center in Houston.

“The prevailing model is that of gradual copy number evolution, in which tumors become aneuploid and increasingly malignant as they acquire CNAs one by one,” says senior author Nicholas Navin, PhD. “It’s an idea that’s ubiquitous in textbooks, but our results challenge this paradigm and support punctuated copy number evolution [PCNE] instead.”

Navin’s team examined 1,000 tumor cells from each of 12 patients with untreated TNBC, using highly multiplexed single-nucleus sequencing, a technique they developed. “This allowed us to sequence the genomes of multiple single cells simultaneously, which greatly reduced the overall cost,” he explains.

The group identified one to three highly clonal subpopulations of cells in each tumor and observed that cells within each subpopulation had very similar copy number profiles. The clones were also largely identical across all 12 tumors, typically varying by only a couple of chromosome regions, while others such as TNBC are quite genomically stable.”

TNBC’s lack of intratumoral heterogeneity is favorable for clinical diagnostics,Navin says, because a pathologist may not need to biopsy multiple regions of a patient’s tumor to obtain its copy number profile. Potential drugs against key amplifications in TNBC, such as CCND3 and MYC, should also be able to effectively eradicate most, if not all, of the tumor cells.

Navin’s group is now collaborating with others to probe the mechanistic basis of PCNE. They’re also exploring preliminary data that suggests this model of tumor evolution may operate in other subtypes of breast cancer, along with colon, prostate, liver, and lung cancers. –Alissa Poh