Disregarded drivers of diversity within tumors

The past decades of cancer research have uncovered the staggering extent and widespread prevalence of intratumor heterogeneity, which refers to the differences between the genomes of cells in a tumor. In theory, each cancer arises from a single cell, but by the time of diagnosis, several genetically distinct “clones” of cells can be detected. Greater genetic heterogeneity means a greater likelihood that some clones may resist treatment, or have a superior capacity to migrate or invade surrounding tissue. Diversity within tumors is thus responsible for treatment failure, disease recurrence and spread. From the tumor’s perspective, such a state of high diversity allows it to successfully overcome all sorts of challenges, including the onslaught of different therapies, and is thus an “ideal destination”.

In their article entitled “Turning the headlights on novel cancer biomarkers: Inspection of mechanics underlying intratumor heterogeneity”, the authors use the lens of ecology to examine the mechanisms that give rise to a multitude of genetically distinct cellular clones in a tumor-each armed with its own set of traits and special skills. They focus on two key contributors to this clinical scourge-namely, centrosome amplification and rate of tumor cell division. An excess of a subcellular organelle called a centrosome has been long postulated to contribute to aggressive cancer. While normal cells only carry one or two copies of centrosomes per cell, malignant cells often carry many more copies. Studies have shown that excess centrosomes disrupt the normal architecture of tissues and contribute to making tumors more invasive. Ironically, these “supernumerary” centrosomes could lead to grave problems during cell division as they may cause the cell to assemble a mitotic spindle with far too many spindle poles-which is a potentially lethal situation. But cancer cells cleverly cluster their extra centrosomes into two groups during cell division, assemble a spindle with two poles and thus evade cell death. The presence of too many centrosomes however poses yet another problem as each chromosome may find itself attaching to more than one spindle pole during mitosis. Consequently, centrosome clustering during mitosis leads to a low level of whole chromosome mis-segregation, termed “chromosomal Instability” wherein daughter cells may end up either lacking a chromosome or with an extra chromosome. These abnormal chromosome numbers cause daughter cells to become different from their parents and from each other, with this difference becoming greater with each successive cycle of cell division. Thus extra centrosomes are major “drivers” of diversity. On the other hand, the rate of cell cycling in the tumor, also termed mitotic propensity, provides the “engine power” for tumor evolution-the speedier the cell cycling kinetics, the faster the tumor evolves new and potentially more dangerous characteristics. Thus, a tumor utilizes the vehicle of chromosomal instability, chauffeured by excess centrosomes and powered by rapid cell division, to reach its destination of extensive diversity. It logically follows that rather than battling a tumor’s numerous, superiorly evolved clones, it might be more prudent to target the very mechanisms that generate this diversity, as early as possible in the tumor’s life.

Both mitotic propensity and centrosome amplification are amenable to quantitation via inexpensive and simple tissue-based assays, very similar to those routinely performed in pathology

laboratories. Tumor profiling for these prognostic biomarkers and studies aimed at their rigorous clinical validation could yield a robust measure of the heterogeneity in tumors and the “risk” posed by this diversity. This article urges the inclusion of these hitherto overlooked “beacons of risk” for assessing how aggressive a tumor is, for selecting the most optimal therapy for each patient and for investigating new combinatorial drug regimens to improve patients’ outcomes.

Publication

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