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Cells in stiffer tissues are squeezed into mutating more often

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When it comes to cancerous mutations, cells in soft tissues like bone marrow and the brain tend to exhibit fewer irregularities than their stiffer somatic brethren in the lungs or bone. According to researchers at the University of Pennsylvania, this isn't only due to differences between the cells' type and function, but also to the rigid forces of resistance that act on them when they move and divide.

The group's project began with a meta-analysis conducted by Charlotte R. Pfeifer, a Ph.D. student in physics at UPenn, who collated data on somatic mutation rates of different cancers in various organs. Her analysis found that tumors arising in stiff tissues, such as the human lung and bone, tended to exhibit mutation rates and chromosome variations around 100 times higher than those in soft tissues, such as marrow and brain.

"Basically, we hypothesize that stiffer tissues with their denser matrix and smaller constrictions cause more nucleus deformation that damages the nucleus," said Jerome Irianto, a postdoctoral researcher in the lab of Dennis E. Discher, Director of the Physical Sciences in Oncology Center at UPenn. Irianto and his colleagues present their work this week at the Biophysical Society's 60th Annual Meeting in Los Angeles, CA.

To examine this, the researchers had two cancer cell lines - one derived from lung tissue and the other from bone - migrate through thin plastic filters with 3-micrometer pores that are only about one-fifth of the diameter of the nuclei. When the cells migrate and force their way

through the pores over a 24-hour period, they deform and accumulate DNA damage; larger, 8-micrometer pores do not cause such damage.

In further experiments, the researchers expressed in these cells DNA repair proteins that usually diffuse around the DNA to search out breaks. Then they pulled individual nuclei into small pores to mimic the migration and observed what happened by tagging the repair proteins with green fluorescent protein.

"Imagine modeling the DNA as threads in a small cottonball that is squeezed into a small see-through straw. The air that makes the cottonball fluffy will be squeezed out," Irianto said. "We think that such compaction reduces porosity and severely limits the mobility of protein to follow the DNA." This nuclear constriction - with local deficits in DNA repair factors - should reduce the repair rate, and thus increase mutation rates.

"What we are addressing right now is whether this constricted migration with molecular damage and segregation will translate to genomic instability, which is a 'hallmark' of cancer," Irianto said. "Cancer needs to invade to spread, and that invasion could itself cause mutations."

With the support of the newly awarded Physical Sciences Oncology Center at UPenn (PSOC@Penn) by the National Cancer Institute (NIH), Discher's lab will continue to work on new physical aspects of tumor growth.

More information: www.abstractsonline.com/Plan/V … 60-a4fa-88b62feb855b

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