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Target growth-driving cells within tumors, not fastest-proliferating cells

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Of the many sub-groups of cells jockeying for supremacy within a cancerous tumor, the most dangerous may not be those that can proliferate the fastest, researchers at Dana-Farber Cancer Institute report in a paper appearing in an advance online publication of the journal *Nature*. The findings have important implications for the treatment of cancer with precision medicines, the study authors explained: Doctors need to ascertain which cell subgroups are truly driving the tumor's growth and metastasis and select drugs that target the critical genes within those cells. It can be a mistake to assume that the largest, most dominant subgroup is the one to be targeted.

"It is well-established that individual tumors are genetically heterogeneous – comprised of multiple subgroups of cancer cells, each with its own genomic signature, or pattern of gene mutations," said the study's senior author, Kornelia Polyak, MD, PhD, of Dana-Farber. "We wanted to explore the factors that allow these subgroups to coexist, and to understand why the subgroup with the greatest proliferative ability does not always take over the tumor."

It has been long assumed that mutations that speed up the proliferation of cancer cells are also responsible for tumor growth. Indeed, when the growth of tumor cells is unchecked (as occurs in lab-grown tumor cells), the subgroup that proliferates fastest should outgrow other subgroups. In actual tumors, however, cell growth is constrained by limited access to environmental factors such as space, nutrients, and oxygen. As a result, tumors often grow much slower than they would under laboratory

conditions. The presence of fast-growing cells does not necessarily cause tumors to enlarge, because their fast growth rates are offset by higher rates of cell death. If a subgroup of cancer cells "figures out" how to change the tumor environment so some of the restraints on tumor growth are removed, that subgroup may have a competitive advantage over other subgroups within the tumor.

To simulate what happens within cancer patients, investigators implanted breast cancer samples in laboratory animals. One set of samples produced tumors that grew very slowly, even though the cells within them were proliferating rapidly, suggesting the tumors were constrained by environmental factors. Researchers used these growth-stunted tumors to generate several subgroups of cancer cells, each of which overproduced a different protein linked to tumor growth.

The investigators then ran a series of tests in which they implanted in mice a single subgroup plus the original cell sample or a mix of several subgroups and observed the growth of the resulting tumors. They found that two of the sub-groups – one overproducing a protein called CCL5, the other overproducing a protein called IL11 – were able to drive tumor growth out of the gridlock.

"Surprisingly, there was no link between a subgroup's ability to drive tumor growth and its competitive expansion within the tumor," remarked Polyak, who is also a Professor of Medicine at Harvard Medical School and an associate at the Broad Institute of MIT and Harvard. The subgroup overproducing IL11 was able to increase tumor growth by relieving environmental constraints, even though the subgroup didn't gain a competitive advantage from this ability, since other subgroups benefited as well. On the other hand, a subgroup that overproduced the protein LOXL3 took over a large share of the tumor but could not increase overall tumor growth. Interestingly, when investigators implanted tumors composed of the IL11 and LOXL3 subgroups, the

tumors grew very fast, but the IL11 subgroup was eventually outcompeted by LOXL3 subgroup, leading to collapse of the tumor as environmental constraints were restored.

Investigators found that when multiple subgroups were present in the same tumor, they interfered with each other's expansion. This suggests that once heterogeneity arises within a tumor, it tends to persist, as it becomes difficult for a single subgroup to take over the tumor, the study authors state. Such co-existence allows interactions between the various subgroups to take place. Indeed, investigators found that when multiple subgroups are present in the same tumors, the tumors grow faster and also become metastatic, which hasn't been observed in tumors composed of any single subgroup.

"The goal of precision therapy for cancer is to kill the subsets of cells that are driving the tumor's growth – even if other subsets are proliferating more robustly," Polyak explained. Targeting the fast-proliferating subsets could actually be harmful, she continued: by removing a competitor, such drugs could assist the growth-driving subsets, thereby enhancing growth of the overall tumor. "We need to be sure we're targeting the actual drivers."

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