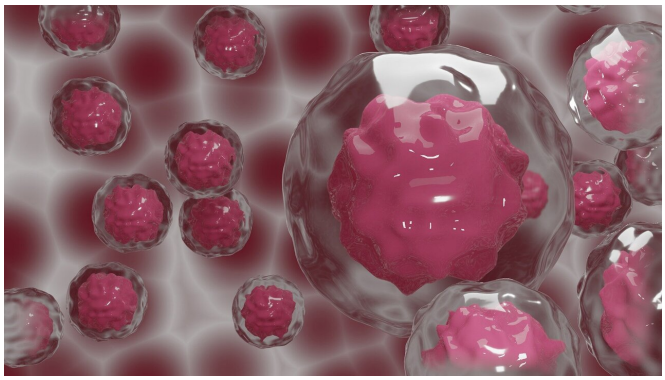
Spontaneous cell fusions amplify genetic diversity within tumors

21 January 2021



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Evolution within groups of tumor cells follows the principles of natural selection, as evolution in pathogenic microbes. That is, the diversity of cellular characteristics within a group leads to differences in the ability of cells to survive and divide, which leads to selection for cells that bear characteristics that are most fit to the malignant environment.

The ability to continuously create a diverse set of new cellular features enables cancers to develop the ability to grow in new tissue environments and to acquire resistance to anti-cancer drugs. The diversity of cell characteristics within groups of cancer cells can be created by a number of well-characterized mechanisms, including small-scale mutations, large-scale genomic changes involving losses, gains and reshuffling of large pieces of DNA, as well as by nongenetic mechanisms that create lasting changes in cellular features.

At the same time, scientists generally believe that cancers lack a powerful and important diversification mechanism available to pathogenic microbes, parasexual recombination, or the ability to exchange and recombine genetic material between different cells. However, in a new article published in *Nature Ecology & Evolution*, Moffitt Cancer Center researchers demonstrate that this belief is wrong and that cancer cells are capable of exchanging and recombining their genetic material with each other through a mechanism mediated by cell fusions.

Why is parasexual recombination important? In its absence, inheritance of genetic information is strictly clonal. As cells divide, the daughter cells inherit the same genetic makeup as their parents, with few modifications due to mutations that accompany cell division. However, many of the features that can give a cell a competitive fitness advantage result from the combined effects of multiple mutations that are not necessarily useful on their own. All of the mutations required for the manifestation of the cell feature need to accumulate in the same cell before their combination can be amplified by selection.

Moreover, as many of the random mutational changes are disadvantageous, mutational burden can decrease cellular fitness over time. Exchange and reshuffling of genetic material through parasexual recombination enables groups of cells to explore combination of mutations that accumulated in different clonal lineages, discovering useful combinations of otherwise inconsequential mutations, while also separating useful mutations from disadvantageous ones. As a result, parasexual recombination can enable groups of cells to adapt to new environments more quickly, while avoiding degeneration.

Spontaneous cell fusions involving cancer cells have been described by many groups before. However, most researchers focused on fusions between cancer and noncancer, where cancer cells could acquire important cell characteristics of their nonmalignant fusion partner cells, such as an increased ability to move and migrate to other locations, thus giving these hybrid cancer cells an

immediate and specific advantage. Another important line of research suggested that virus-caused fusions between two noncancerous cells can lead to a cancer initiation event. However, since spontaneous cell fusions are relatively uncommon, and because hybrid cells formed by fusion of two cancerous cells do not have an immediately obvious advantage over their nonhybrid peers, fusions between cancer cells have been mostly ignored as rare, inconsequential oddities.

However, interest in cancer evolution and the relatively recent discovery of remarkable genetic diversity within the same tumors motivated Moffitt researchers to take a closer look at consequences of fusions between genetically different cancer cells. They started by asking how frequently cancer cells fuse with each other, labeling cancer cells with either red or green fluorescent markers and counting cells that contained both. While these double positive cells were relatively rare, their presence was documented in most of the multiple cancer cell lines that researchers examined. Importantly, viable double positive cells were also observed in experimental tumors, formed by implantation of tumor cells carrying individual markers. While, on average, these hybrid cells were initially less fit than their normal counterparts, they quickly caught up or even exceeded the ability of their parents to divide and move.

Next, the researchers asked what happens to the genomes of the hybrid cells. Initially, cell fusions give rise to cells that combine all of the DNA information from both of the parents. However, instead of retaining genomes within parent-specific chromosomes, the hybrids appeared to recombine them; as the hybrid cells divided, they were randomly losing some of the extra DNA content. This recombination, and an apparently random loss of extra DNA produced remarkable diversification, where the same hybrid cell gave rise to genetically different daughters. These observations were remarkably similar to a mechanism of parasexual recombination, previously reported for some species of pathogenic yeast.

Finally, Moffitt researchers used computer simulations to compare the ability of groups of cancer cells to evolve with and without fusion-mediated recombination, using quantitative parameters observed in the experimental studies. They found that even with low experimentally observed fusion rates, computer simulation populations were evolving much faster in the presence of cell fusion. The impact of cell fusions was strongest in the modeled cancers with highest mutation rates, as fusion mediated recombination amplified diversity created by mutational mechanisms.

The relevance of these findings toward evolution in actual patient tumors still needs to be rigorously examined. Since all cells within a patient originally start from the same genome, there are no markers to discriminate between mutations that originally occurred within the same or different clonal lineages, which makes the task very challenging. Still, occurrence of genetic recombination between donor and recipient genomes was described in case reports of rare new cancers that developed in patients that underwent bone marrow transplantation.

"Given these studies documenting spontaneous cell fusions in human malignancies, we postulate that our results warrant the suspension of the notion that cancer are strictly asexual and may warrant additional testing of the clinical relevance of spontaneous cell fusions," explained Andriy Marusyk, Ph.D., associate member of the Cancer Physiology Department at Moffitt.

This study reflects a unique culture of multidisciplinary collaboration within Moffitt. The work was co-authored by researchers from the Cancer Physiology and Integrated Mathematical Oncology departments with critical contributions from members of the Biostatistics and Bioinformatics and Pathology departments.

More information: Daria Miroshnychenko et al, Spontaneous cell fusions as a mechanism of parasexual recombination in tumour cell populations, *Nature Ecology & Evolution* (2021). DOI: 10.1038/s41559-020-01367-y