

Identifying Therapeutic Targets for IDH-Mutant Brain Tumors

Can single-cell RNA sequencing of IDH-mutant glioma samples help identify cell lineages, phenotypes and microenvironments that would respond to specific therapies?

The heterogeneity between tumors and within a tumor can contribute to the failure of therapy and lead to the progression of cancer. Many factors play a role in this heterogeneity: Cancer cells within a tumor have differences in genotypes and phenotypes, and tumors differ in the composition of their microenvironments. While the genetic signatures of tumors are now fairly easy to discern with the

common strategy of bulk genomic analysis of samples collected from large cohorts, phenotypes and microenvironments are harder to characterize in this manner. Bulk tissue profiles tend to average the diverse cell types within each tumor, masking critical differences in phenotype expression and microenvironments.

Now Mario Suvà, MD, PhD, assistant professor of pathology at Massachusetts General Hospital

Cancer Center and Harvard Medical School, has used single-cell RNA-sequencing techniques to precisely characterize the genetics, cell lineages, phenotypes and microenvironments driving early-stage gliomas that feature a mutation in isocitrate dehydrogenase (IDH). Dr. Suvà and his colleagues were able to use their data to further characterize bulk data from *The Cancer Genome Atlas*. The findings, published in the March 2017 issue of *Science*, may allow them to create therapies that target specific stem cells found in early-stage IDH-mutant gliomas.

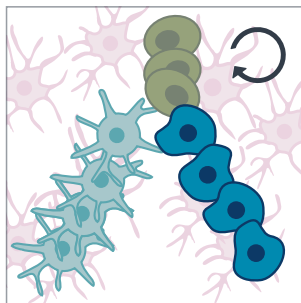
Their methodology also provides a framework for deciphering differences among other classes of human tumors via single-cell RNA sequencing, a powerful but time-sensitive and logistically

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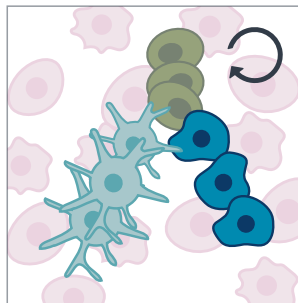
Model for IDH-mutant gliomas and their microenvironments

IDH-mutant gliomas differ in genetics and in the composition of their microenvironment, but they share similar lineages of differentiation and are driven by similar stem cells.

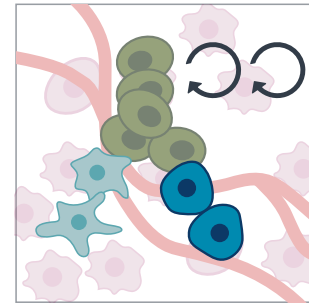
IDH-O (oligodendroglioma)



IDH-A (astrocytoma)

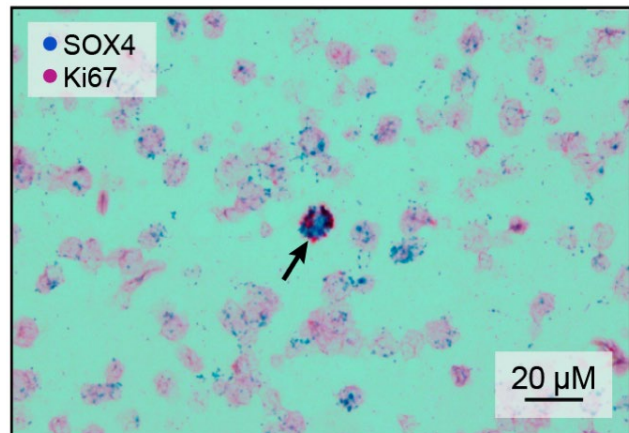
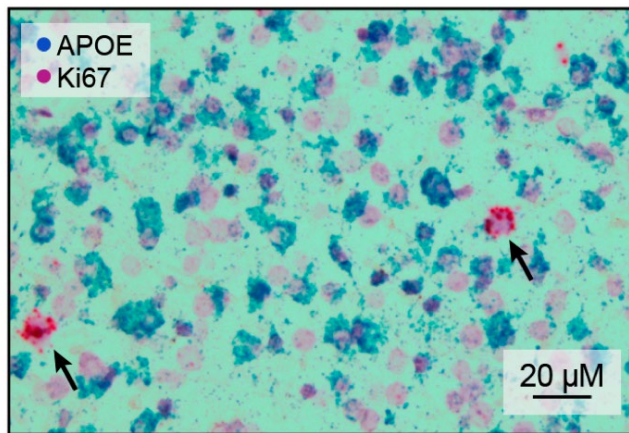


Grade-associated changes



Undifferentiated stem cells drive IDH-mutant gliomas

In situ RNA hybridization shows mutually exclusive expression of the astrocytic differentiation marker APOE (blue) and proliferation marker Ki-67 (red); also shown is the coexpression of the stem cell marker SOX4 (blue) with the proliferation marker Ki-67.



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complicated approach that requires quickly getting viable live samples from the operating room or pathology to Dr. Suvà's lab.

ASTROCYTOMAS AND OLIGODENDROGLIOMAS

IDH-mutant gliomas are hard to study and while they may initially respond to existing therapies, they frequently recur in a more aggressive form. "Modeling the development of these brain tumors has proven very difficult both with cell cultures and animal models," says Dr. Suvà. The only cellular models that have succeeded in culture have come from tumors that were either more advanced or recurrent, and so have accumulated many other genetic events—which made it challenging to study their

early-stage development. "We have a better chance of treating them early on—before they accumulate more genetic anomalies."

Dr. Suvà's research revealed that two genetically distinct IDH-mutant gliomas, known as astrocytomas and oligodendrogliomas, may actually be driven by similar kinds of stem cells and follow similar differentiation programs. This is one step toward resolving a long-standing debate in the field over whether these different types of tumors have a shared origin. The team observed significant differences in the microenvironments of the two different kinds of gliomas, however—specifically, the amounts of immune cells called microglia and macrophages. Astrocytomas

tend to contain higher amounts of microglia and macrophages than oligodendrogliomas do.

In addition, the team found new granularity to these immune cells, as the cell types found in the IDH-mutant gliomas fell along a spectrum: Some were very clearly microglia-like; others clearly macrophage-like; and many had an intermediate profile. The continuum in the phenotypes suggests a certain plasticity—perhaps one cell can acquire the characteristics of another, says Dr. Suvà. "Finding new cell types and cell states is a common feature in the emerging field of single-cell genomics. In this case, it provided new insights into the types of immune cells present." The next step will be to understand

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how these can be manipulated to fight against the tumor.

FROM MODELS TO THERAPIES

Dr. Suvà and his colleagues are now busy building single-cell RNA-sequencing analyses across various types of brain tumors to understand how they resemble each other and how they differ. They are investigating samples from recurrent tumors to see how different treatments affect specific subpopulations of cells in tumors. They are also collaborating with scientists in the field of immunotherapy to design ways to enhance antitumor immunity. And they are developing an approach that would force differentiation of IDH-mutant glioma stem cells into more mature cancer cells—which, in animal models, can eliminate their capacity to start a tumor.



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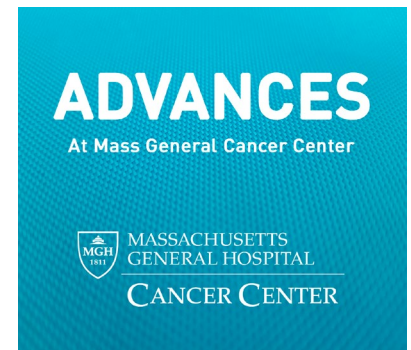
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