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Secondary Summary–Gbm

To compliment the TCGA GBM paper, I discussed a recent paper by Will Flavahan, Brad Bernstein, and colleagues that provides a mechanism for oncogene activation through the disruption of insulator boundaries. The primary paper showed that the proneural subtype of GBMs could be characterized by a high number (30 percent of cases) of IDH1 mutations, which in part defined a clinical subtype of this brain cancer. Unlike other hallmark genes that differentiate the GBM classes, IDH1 plays a role in the Citric Acid Cycle. Mutations in these genes often render cells non-viable, so the mechanism for this mutation was largely unknown. In the discussion of the primary paper, the authors note that frequent IDH1 mutations are often observed with an amplified expression of PDGFRA, a better characterized oncogene. The secondary manuscript that I presented provided a mechanism that linked IDH1 and PDGFRA through disrupted cancer topology.

The mechanism of activation is as follows: 1) Mutations in IDH causes the abnormal synthesis and accumulation of 2-Hydroxyglutarate, which is slightly different biochemically than alpha-keto-glutarate, a normal by product of the Citric Acid Cycle. 2) The buildup of 2-Hydroxyglutarate inhibits DNA methyltransferase. 3) Consequently, many location genome-wide in cancers with the IDH1 mutation have distinctive patterns of demethylation that result from the inhibition of this critical enzyme that modulates this epigenetic memory, including a CTCF locus that insulates PDGFRA from an enhancer. 4) This insulator is disrupted, the enhancer is localized to the promoter of PDGFRA, and the gene is activated.

To achieve this insight, the authors profiled primary tissue of IDH1 mutant and non-IDH1 mutant GBMs and performed differential expression and ChIP-Seq analyses. They identified PDGFRA as a candidate that could be affected by a disrupted boundary due to the difference in correlation of a nearby gene as well as differential expression analyses between the IDH1 mutant statuses. Overall, the validate the topological alteration from 3C experiments as well as a CRISPR alteration on the insulator. The authors also introduce 5-aza. as a means of inducing demethylation. Overall, these novel observations of these correlations coupled with very nice functional validation work makes this study an extremely valuable contribution both to GBM biology but also in creating a paradigm to consider the intersection of epigenetic data to characterize complex phenotypes.

Some of the feedback from the presentation suggested that deleting the enhancer using a similar CRISPR/CAS9 construct would have been a nice addition. Moreover, some of the effects genome-wide may not have been as strong as this particular site that was elucidated, which begs the questions 1) do these phenomenon occur systematically in IDH1 (or other cancer) mutants and 2) do normal cells use some modified topological rearrangement, mediated through epigenetics, to achieve specific gene expression programs (and thus specific cellular phenotypes?). Certainly this is an exciting application of an integrated platform for topology, methylation, and TF binding data... one that we can expect to see considered in other cell

systems potentially genome-wide.