Pan cancer analysis uncovers a molecular link between human adult stem cells and aggressive small cell neuroendocrine cancers from different tissues

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Background
Advancing our understanding of the molecular underpinnings of aggressive malignancies is critical for developing new therapeutics and prognostic signatures. A particularly aggressive cancer phenotype termed small cell neuroendocrine (SCN) can develop *de novo* in most epithelial tissues and can emerge as a treatment resistance mechanism in prostate and lung cancers. Observed lineage plasticity along with altered expression of stem cell transcriptional regulators implies that SCN cancers from different tissues may share a stem-like component.

Methods
A rank-rank hypergeometric overlap algorithm was used to develop gene expression signatures for human stem cell populations. These signatures along with publicly available stem cell signatures were applied to 1) a pan-cancer gene expression dataset consisting of 19 epithelial cancers and 2) gene expression datasets consisting of SCN and non-SCN variants derived from multiple epithelial tissues. We assessed the signatures' abilities to predict survival and their associations with genomic alterations. Immunohistochemistry was performed on prostate cancer xenografts and lung cancer tissue microarrays to validate expression of adult stem cell (ASC) signature associated proteins in SCN cancers. DNA methylation datasets of prostate and lung cancers were mined to identify methylation patterns common to SCN variants. A genome-wide loss-of-function dataset was analyzed to determine the essentiality of methylation regulated genes to SCN cancers.

Results
Gene signatures were generated for human epithelial adult stem cells and other stem cell populations. We found that epithelial cancers generally become enriched for the ASC signature during progression to an advanced, aggressive state. The ASC signature provided prognostic information independent of proliferation or cancer type. The ASC signature was associated with DNA alterations in known oncogenes and genes that influence lineage decisions. Notably, the ASC signature selected for DNA alterations that are enriched in SCN cancers. SCN cancers from different tissues had enhanced activation of the ASC signature compared to other signatures. The ASC signature associated DNMT1 showed higher expression in SCN lung and prostate tissues compared to non-SCN specimens. Analysis of DNA methylation data revealed that SCN prostate and lung cancers share a methylation profile. Combined methylation and signaling activation analyses provided insight into the preferential hypomethylation and activation of developmental regulators in SCN cancers. Gene essentiality analysis supported that a number of these genes may be important for SCN biology.

Conclusions
Our results demonstrate a link between human adult stem cells and aggressive cancers from multiple tissues, notably SCN cancers. Further, our analysis establishes an adult stem cell-based molecular foundation for identifying potential therapeutic targets for aggressive malignancies.

Conflict of Interest
None

Funding Acknowledgements
This work was supported by a Prostate Cancer Foundation Young Investigator Award (to B.A.S.), and an Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research-Hal Gaba Director's Fund for Cancer Stem Cell Research Award (T.G.G. and O.N.W.).