

## **Gleason score 7 prostate cancers emerge through branched evolution of clonal Gleason pattern 3 and 4**

**Adam G. Sowalsky**<sup>1,2</sup>, Haydn T. Kissick<sup>3,4</sup>, Sean Gerrin<sup>5</sup>, Rachel Schaefer<sup>2</sup>, Zheng Xia<sup>6</sup>, Joshua Russo<sup>2</sup>, M. Simo Arredouani<sup>3</sup>, Glenn J. Bubley<sup>2</sup>, Martin G. Sanda<sup>3,4</sup>, Wei Li<sup>6</sup>, Huihui Ye<sup>5</sup>, Steven P. Balk<sup>2</sup>

**<sup>1</sup>Laboratory of Genitourinary Cancer Pathogenesis, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD**

<sup>2</sup>Division of Hematology and Oncology, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

<sup>3</sup>Division of Urology, Department of Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

<sup>4</sup>Winship Cancer Institute, Department of Urology, Emory University School of Medicine, Atlanta, GA

<sup>5</sup>Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

<sup>6</sup>Division of Biostatistics, Dan L. Duncan Cancer Center and Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX

**Background:** The molecular features that account for the distinct histology and aggressive biological behavior of Gleason pattern 4 (Gp4) versus Gp3 prostate cancer (PCa), and whether Gp3 tumors progress to Gp4, remain to be established.

**Methods and Results:** Whole exome sequencing of laser-capture microdissected adjacent Gp3 and cribriform Gp4 confirmed that they were clonal based on multiple shared genomic alterations. However, larger numbers of unique mutations in the Gp3 and Gp4 tumors show that the Gp4 are not derived directly from the Gp3, and instead support a branched evolution model wherein the Gp3 and Gp4 tumors emerge early from a common precursor and subsequently undergo substantial divergence. Remarkably, the Gp3 tumors retain their indolent appearing morphology despite acquisition of multiple genomic alterations including tumor suppressor losses. Although there were no consistent genomic alterations that distinguished Gp3 from Gp4, pairwise transcriptome analyses identified increased c-Myc and decreased p53 activity in Gp4 versus adjacent clonal Gp3 foci.

**Conclusions:** These findings establish that at least a subset of Gp3 and aggressive Gp4 tumors have a common origin, and that genomic alterations detectable in the Gp3 may distinguish these tumors from truly indolent Gp3. Screening for a panel of these genomic alterations in men who have prostate biopsies showing only Gp3 (Gleason score 6, Gs6) may allow for more precise selection of men who can be safely managed by active surveillance versus those who may benefit from further intervention.

**Conflicts of Interest:** None.

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