Gleason Score 7 Prostate Cancers Emerge Through Branched Evolution of Clonal Gleason Pattern 3 and 4.

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Abstract

PURPOSE: 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 directly to Gp4, remain to be established.

EXPERIMENTAL DESIGN: Whole exome sequencing and transcriptome profiling of laser-capture microdissected adjacent Gp3 and cribriform Gp4 were used to determine the relationship between these entities.

RESULTS: Sequencing confirmed that adjacent Gp3 and Gp4 were clonal based on multiple shared genomic alterations. However, large numbers of unique mutations in the Gp3 and Gp4 tumors showed that the Gp4 were not derived directly from the Gp3. 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 support a branched evolution model wherein the Gp3 and Gp4 tumors emerge early from a common precursor and subsequently undergo substantial divergence. 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.

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