The heterogeneous genomic landscape of low-risk prostate cancer

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Background

Adoption of Active Surveillance (AS) is becoming standard of care for men with low risk prostate cancer; however a need exists for tools that go beyond clinical risk factors to assess whether a patient is a good candidate for AS. In this study we compare expression profiles of AS candidates against a higher-risk radical prostatectomy (RP) population to characterize the genomics of clinically low-risk prostate cancer.

Methods

Tumor biopsies from 473 UCSF patients considered potentially suitable for AS (clinical stage ≤T2N0M0, PSA≤10 ng/ml, Gleason 3+3 or low-volume 3+4) were profiled using the Affymetrix Human Exon microarray to generate RNA expression data. These cases were compared to 2043 RP cases previously profiled on the same microarray platform. Scores for 21 published prognostic signatures were calculated and gene-set enrichment analysis (GSEA) pathway genes were summarized to provide levels of patient risk and pathway activity.

Results

Of the 473 AS diagnostic biopsies profiled, 408 (86%) passed quality control and were used for analysis. Based on the average score for 21 prognostic signature risk models, 923 (45%) were classified as low, 724 (35%) as intermediate, and 396 (20%) as high genomic risk (n = 396). Considering only the clinically low-risk patients at diagnosis, 356 (87%) were low, 45 (11%) were intermediate and 7 (2%) were high risk. The Figure shows a heat map of expression comparing the UCSF AS candidates to the higher-risk prostatectomy cases. Genomic risk was positively associated with cell cycle related pathway activity (E2F, G2M, MYC, DNA Repair, mTOR, mitotic spindle, $p<0.001$) and negatively associated with apical junction ($p<0.001$), epithelial-to-mesenchymal transition ($p<0.001$), and androgen receptor signaling ($p<0.05$) pathways. Clustering of patients based on the expression of 36 pathways revealed two main biologic groups corresponding to putative basal and luminal subtypes. Compared to higher risk RP patients, the low risk prostate cancer tumors at diagnosis were more enriched for basal-like tumors (20% vs 33%, $p<0.001$).

Conclusion

Although only 2% of low risk AS candidates have high risk genomic characteristics, very substantial genomic heterogeneity exists in this population, and pathway activation overlaps significantly with higher-risk RP patients. It remains unclear what is the clinical significance of the basal luminal axis in this population and how this information may be used. These results suggest that even in potential AS candidates, genomic profiling could eventually be used to better guide management.

Conflict of Interests

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