A robust blood gene expression-based prognostic model for castration-resistant prostate cancer.

Castration-resistant prostate cancer (CRPC) is associated with wide variations in survival. Recent studies of whole blood mRNA expression-based biomarkers strongly predicted survival but the genes used in these biomarker models were non-overlapping and their relationship was unknown. We developed a biomarker model for CRPC that is robust, but also captures underlying biological processes that drive prostate cancer lethality. Using three independent cohorts of CRPC patients, we developed an integrative genomic approach for understanding the biological processes underlying genes associated with cancer progression, constructed a novel four-gene model that captured these changes, and compared the performance of the new model with existing gene models and other clinical parameters. Our analysis revealed striking patterns of myeloid- and lymphoid-specific distribution of genes that were differentially expressed in whole blood mRNA profiles: up-regulated genes in patients with worse survival were overexpressed in myeloid cells, whereas down-regulated genes were noted in lymphocytes. A resulting novel four-gene model showed significant prognostic power independent of known clinical
predictors in two independent datasets totaling 90 patients with CRPC, and was superior to the two existing gene models. Whole blood mRNA profiling provides clinically relevant information in patients with CRPC. Integrative genomic analysis revealed patterns of differential mRNA expression with changes in gene expression in immune cell components which robustly predicted the survival of CRPC patients. The next step would be validation in a cohort of suitable size to quantify the prognostic improvement by the gene score upon the standard set of clinical parameters.