PROSTATE CANCER

Two whole-blood RNA expression signatures for aggressive CRPC

Two distinct whole-blood RNA expression signatures have been identified that can predict the severity of castration-resistant prostate cancer (CRPC), according to two recent reports in *Lancet Oncology*.

In one study, Olmos *et al.* used latent process decomposition (LPD) analysis of mRNA expression data from 64 men with metastatic CRPC and 30 controls (men with clinically indolent cancer under active surveillance) to identify genetic patterns specific for aggressive disease. Unsupervised LPD analyses divided the expression dataset into four groups (LPD1–4), only one of which contained high-risk patients (LPD1). All men in the LPD1 group had CRPC (no controls were included) and this cohort demonstrated poorer overall survival compared with men from LPD2–4 (10.7 months versus 25.6 months). The LPD1 expression signature—whose nine signature genes include *HMBS*, *TMCC2*, *SNCA*, *SLC4A1*, *STOM*, *GABRRAPL2*, *TERF2IP*, *RIOK3*, and *TFDP1*—was also associated with known prognostic markers of CRPC, such as elevated PSA and circulating tumour cells.

In the second stage of the trial, the LPD1 signature was validated in 70 patients with CRPC treated at the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, USA. Overall survival was significantly lower for men who tested positive for LPD1 than for those who tested negative (9.2 months versus 21.6 months), confirming its prognostic utility. “These

data indicate that transcriptomic analyses of noncancer cells in whole blood can associate with outcome,” says lead investigator Johann de Bono.

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Interestingly, seven genes in the LPD1 signature were highly expressed in CD71⁺ early erythroid cells, but not in normal blood cells. When prostate cancer metastasizes to bone, clonogenic tumour cells compete for niches in bone marrow and primitive haemopoietic stem cells are forced into the bloodstream, where they differentiate into CD71⁺ cells. Thus, the LPD1 signature could act as an early marker of bone infiltration. Furthermore, many of the most downregulated genes and pathways in this expression signature are related to B-cell and T-cell function, suggesting that poor prognosis could be related to diminished immune response.

This proposed link between altered immune function and disease severity is supported by a separate trial published concomitantly in the same journal. In this study, Ross *et al.* used a six-gene signature consisting of *ABL2*, *SEMA4D*, *ITGAL*, *C1QA*, *TIMP1*, and *CDKN1A* to separate men with low-risk and high-risk CRPC (7.8 months versus >34.9 months survival). The former three genes have roles in T-cell motility,

antigen surveillance, and T-helper-cell activity, whereas the latter three have been implicated in macrophage production. “Although we have always thought that the host immune response is important, this study suggests that it is a key driver of overall survival,” says William Oh, a Professor at the Tisch Cancer Institute, New York, USA, who led the study. “We believe that this signature can be used both as a prognostic marker and to stratify patients for clinical trials.”

Collectively, the clinical implications of these two studies are significant. “The two datasets from our group and Oh’s group are complimentary,” de Bono remarks. “Together, they suggest that impaired immune function negatively affects outcome for men with advanced prostate cancer.” Furthermore, as blood-based expression profiling is minimally invasive, this approach enables the collection of multiple repeat samples over time. “Whole-blood expression array should be evaluated as a pharmacodynamic marker and possibly also as a predictive biomarker for immune therapy,” recommends de Bono.

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Original articles Olmos, D. *et al.* Prognostic value of blood mRNA expression signatures in castration-resistant prostate cancer: a prospective, two-stage study. *Lancet Oncol.* doi:10.1016/S1470-2045(12)70398-4 | Ross, R. W. *et al.* A whole-blood RNA transcript-based prognostic model in men with castration-resistant prostate cancer: a prospective study. *Lancet Oncol.* doi:10.1016/S1470-2045(12)70263-2.