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Commentary

Predicting Treatment Outcomes: The Case for Hypoxia Gene Signatures

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Prostate cancer affects a large number of men worldwide: over a million new cases were diagnosed in 2012 (>320,000 in Europe) [1]. The recognised changes in demography (aging) and lifestyle (obesity) of the male population are predicted to give rise to an increase in the incidence of prostate cancer [2]. It is estimated that approximately one in eight men will be diagnosed with prostate cancer and will therefore have to make a choice regarding the best course of treatment of their disease. Most of these men will be candidates for curative treatment with either radical surgery or radiation therapy (external beam, brachytherapy).

Today the selection of a treatment plan for a particular prostate cancer patient is driven by clinical and pathological features defining spectrums of local recurrence risk. The assessment of the risk of recurrence and subsequent prostate-cancer specific mortality is based on a measure of the prostate specific antigen (PSA) level in a blood sample, the scoring of biopsy specimens by a pathologist (Gleason scores) and the estimation of tumour extent within (T) and outside the prostate (regional lymph nodes (N), distant metastases (M)) [3]. This risk classification system is however now challenged, as it is unable to adequately assess the variability in the aggressiveness of newly diagnosed prostate cancer. Personalized medicine through the integration of tumour-specific biological parameters into the decision-making process is anticipated to overcome these challenges and alter the management of prostate cancer patients.

The molecular classification of prostate cancer with microarray and next generation sequencing technologies is under way. Differential analyses of extensive genetic profiles of specimens, using advanced statistical classification methods, such as cluster analysis, have progressed the use of genetic signatures from tumour tissue in providing additional prognostic information [4].

A common feature of solid tumours, including the prostate, the chaotic development of the tumour vasculature compromises the efficient spatial and functional delivery of blood supply to cancer cells. The presence of these hypoxic regions is well recognised as a cause for genomic instability, disease progression and treatment resistance [5]. As a result exploiting hypoxia as a classifier for the molecular characterisation of cancer is an attractive strategy and several molecular signatures have been defined [6–8]. But deriving these signatures requires a stringent work flow that often starts *in vitro*, involves large training and validation patient cohorts and complex computational and statistical tools. In their study, published in *EBioMedicine*, Yang et al. began their analysis in four prostate cancer cell lines and identified 848 genes whose expression was modified under hypoxic conditions [9]. Hypothesising that the *in vitro* genes co-expressing with each other *in vivo* collectively indicate hypoxia, the authors leveraged the TCGA cohort of pre-treatment biopsies to construct an extensive co-expression network and identified 28 hypoxia-regulated genes associated with prognostic outcome. Perhaps reassuring is that ten of these genes were previously reported hypoxia regulated genes.

The personalisation of prostate cancer management relies on the discovery of novel biomarkers predictive of treatment outcomes. This 28-gene signature presents a major step in this direction. Evaluated in both fresh frozen and formalin-fixed-parafilm embedded (FFPE) biopsy specimen, the implementation of this signature in clinical practice should be relatively easy. Its ability to predict biochemical failure following both radical prostatectomy and radiation therapy as well as distant metastasis outcomes will benefit the vast majority of prostate cancer patients. Although associated with a number of outstanding challenges, such as the robustness of the signature in a prospective hypoxia-modifying prostate cancer clinical trial, the stability of these 28 genes across the heterogeneous and ever-changing oxygenation levels of prostate tumours [10], further evaluation of hypoxia signatures as a tool to predicting treatment outcomes in prostate cancer is certainly warranted.

Disclosure

The author declared no conflicts of interest.

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