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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Tools to identify the men with prostate cancer most appropriate for active surveillance?

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A great deal of effort is underway in order to identify those men with prostate cancer felicitous for active surveillance with greater precision than that afforded to us today. In the manuscript by Irshad *et al.* the authors evaluate a novel set of genes associated with senescence and aging as tools that can provide guidance regarding the indolent nature of an individual's prostate cancer with validation using both mRNA and protein analyses. While additional studies are required to understand the full impact of these findings, the innovative approach taken enhances our understanding of distinct phenotypes of prostate cancer.

Much of the controversy regarding the screening and subsequent treatment of localized prostate cancer relates to our current inability to identify individuals most appropriate for active surveillance programs distinguishing them from those that will benefit from more aggressive approaches. While most in the field would agree with the set of patients classified as very low risk prostate cancers,¹ this is a minority of the patients presenting with the disease and some have even suggested that in many of these individuals the designation of 'cancer' may be suboptimal.² A larger percentage of patients present with low to intermediate risk prostate cancer for which the clinical course is less clear. While most of these individuals will not develop progressive disease, current pathological and clinical tools are unable to provide discrimination between these men and those that will progress. A number of biomarkers have and are being developed to provide tools to aid in this clinical distinction.

In the manuscript by Irshad *et al.*³ the goal of the authors is to provide for a panel of genes, i.e., a molecular signature, which can distinguish between men with prostate cancer that can safely forgo treatment and those that would benefit from an interventional therapy. In this manuscript, the authors describe prostate cancers as either indolent, defined by dictionary.com as, 'causing little or no pain; inactive or relatively benign', or aggressive. To accomplish this goal and develop novel and additive markers, the authors focused on the cellular processes of aging and senescence. The rationale behind the selection of markers of senescence and aging relates to these processes as the end stages of cellular growth and therefore expression of these markers may indicate disease that is less aggressive. The study described in this manuscript, initially began with a meta-analysis of genes associated with aging and senescence. This approach centered upon genes associated with aging along with aging-associated diseases. From this analysis, a panel of 377 genes associated with aging and senescence were identified and absent among these were genes associated with cellular proliferation. Genes encoding proteins associated with cellular proliferation as principal components of many of the prognostic tools in use today. With this assembled list, the authors then began to query existing, publicly available data sets from prostate cancer patients to identify those genes that were downregulated in aggressive prostate cancers. Furthermore, the investigators performed an analysis using a mouse model of preinvasive prostate cancer resulting from a germ line loss of function of the *Nkx3.1* homeobox gene. Using tumor tissue obtained from this model, counter to the initial selection as those decreased in aggressive cancers from the 377 genes, they selected a subset that were increased in

this early stage prostate cancer model. The intersection contained 19 genes that were upregulated in the mouse model and also downregulated in the available data related to aggressive prostate cancers.

To validate this 19 gene set, the authors analyzed the publicly available data set by Taylor *et al.*⁴ which contains gene expression data on prostatectomy samples along with a small number of normal adjacent tissues from the same prostates. Although only a small number of the samples from this dataset were high Gleason grade, the authors were able to determine that 18 of the 19 genes that they had brought forward were also found to be downregulated in these cancers. More importantly, the Taylor data set contained a significant number of low Gleason score cancers along with the time to biochemical recurrence (BCR) for these men. The differentiation of those with low Gleason scores that had a long time to BCR versus a short time to BCR provided for the further selection of 14 of the 19 genes being associated with predicting time to BCR in men with low Gleason score prostate cancer. Despite the association of these genes with progression, the set of genes was not able to independently stratify patients utilizing a Kaplan-Meier analysis. Therefore, the authors further focused their gene set and identified three genes out of the 19 selected that in a separate data set were able to distinguish the most indolent from the most aggressive. This three gene panel consisted of FGFR1, a receptor for fibroblast growth factor; PMP22, a glycoprotein that is a substantial constituent of myelin in the nervous system and *CDKN1A*, a cell cycle regulatory gene (p21). The authors then validated this expression data using mRNA and protein analyses and confirmed their discriminatory ability. Most importantly, as

it related to the goals of the authors at the beginning of the study and as it addresses a critical need in the field, the authors examined the ability of these three biomarkers to be detected in prostatic biopsies from men on active surveillance for their prostate cancer. This is a critical experiment that is often not described in investigating the relevance of these types of biomarkers. In the small number of patients that were no longer were suitable for the surveillance program ($n = 14$) compared with a set that did were still suitable for the program 10 years after entry, the initial biopsy from those that failed, had reduced expression of the three biomarkers.

As stated above, there is clearly a need for biomarkers that identify men with prostate cancer that have the form(s) of the disease most appropriate for active surveillance. Despite the onslaught of new biomarkers that

are reported to have this ability, the approach taken by the authors is unique and has revealed markers that are not duplicative of others. The studies outlined in this manuscript have several limitations. Perhaps most striking is the small sample sets that the authors have used to discover and validate their three gene panel. Furthermore, the assay by which these three genes should be evaluated in larger cohorts is not described in the manuscript. Along related lines, if immunohistochemical analysis will be utilized, how will issues such as heterogeneity be handled in the interpretation of data? This work represents a unique and valuable approach to develop and validate biomarkers that address the most important question in the field of prostate cancer. While the ultimate utility of this three biomarker panel will be revealed in further studies, this type of thoughtful approach is certainly of value.

REFERENCES

- 1 Tosoian JJ, JohnBull E, Trock BJ, Landis P, Epstein JI, *et al.* Pathological outcomes in men with low risk and very low risk prostate cancer: implications on the practice of active surveillance. *J Urol* 2013; 190: 1218–22.
- 2 Carter HB, Partin AW, Walsh PC, Trock BJ, Veltri RW, *et al.* Gleason score 6 adenocarcinoma: should it be labeled as cancer? *J Clin Oncol* 2012; 30: 4294–6.
- 3 Irshad S, Bansal M, Castillo-Martin M, Zheng T, Aytes A, *et al.* A molecular signature predictive of indolent prostate cancer. *Sci Transl Med* 2013; 5: 202ra122.
- 4 Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, *et al.* Integrative genomic profiling of human prostate cancer. *Cancer Cell* 2010; 18: 11–22.

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