Can Stroma Reaction Predict Cancer Lethality?

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Stromal features in carcinomas may provide a relatively consistent means to stratify patients afflicted with solid tumors. Stromal-derived transcriptome signatures can now be used to make predictions about patient survival, suggesting the potential for their clinical application in precision medicine to predict disease progression and emergence of therapeutic resistance. Clin Cancer Res; 19(18); 4905–7. ©2013 AACR.

Stroma–cancer interactions recapitulate highly conserved molecular programs that are active during embryonic development. In response to cancer growth and progression, stromal reactions are believed to be specific and nonrandom and initiate a series of reciprocal chain reactions that modulate cancer progression. In this issue of Clinical Cancer Research, Chen and colleagues have taken a computational approach to determine whether cancer stroma gene expression profiles are able to predict survival of ovarian, lung, colon, and prostate cancer patients. Unlike other groups attempting to define stromal responses to cancer epithelium using less well-defined stromal signatures from cancer cases (1), the group led by Dr. Robert B. West pioneered an approach that involves characterizing gene expression patterns of two relatively pure populations of stromal cells isolated from soft-tissue tumors, the desmoid-type fibromatosis (DTF), and the solitary fibrous tumor (SFT). They tested the hypothesis that DTF and STF molecular signatures offer prognostic insight in differentiating the survival of breast cancer patients. The West group published two earlier articles (2, 3) about their work using datasets from different institutions in which they concluded that patients with breast carcinomas expressing the DTF fibroblastic signature had significantly better prognosis than patients expressing the SFT signature. The current publication is an extension of the previous work in which the authors set out to test another hypothesis, i.e., whether the usefulness of the DTF fibroblastic signature is specific to breast cancer or can be applied to other solid tumors. They analyzed gene expression profiles of five ovary, five lung, two colon, and three prostate cancer microarray datasets, and conducted immunohistochemical (IHC) analyses of two selected stromal biomarkers, osteonectin (SPARC), and versican (CSPG2), with a focus on whether the DTF signature can predict survival in these malignancies. They concluded that, in contrast with breast cancer, the DTF signature predicts worse outcome in ovarian cancer (rather then better outcome in the case of breast carcinoma). In this study, the authors noted that significant variations exist in the publicly available datasets subjected to their statistical analyses. Within five ovarian cancer datasets, one with a smaller number of patients failed to show statistical significance in predicting survival outcomes. Colon cancer datasets were discrepant. One DTF signature dataset showed a correlation with better patient survival. The other showed a correlation with worse survival. Further investigation of a new set of colon cancer tissues using a different technical approach revealed that positive IHC staining for SPARC and CSPG2 as surrogates for the DTF signature predicted worse colon cancer survival.

Overall, the idea of harnessing stromal fibroblastic signatures, rather than epithelial signatures, to predict the progression and survival of cancer patients has received substantial endorsement in the published literature (4, 5). The main reason stromal signatures may elicit greater predictive power in comparison with cancer epithelium is that cancer-associated stroma presumably contains a normal genotype. Stromal reactions in response to cancer epithelium most likely only affect gene expression, not drastic and stochastic disruptions of the genome. Because cancer and stroma coevolve during cancer progression (6, 7), many genes expressed by stroma are also expressed by cancer epithelium (7). A promising opportunity for continuing progress in understanding the clinical significance of stromal signatures is represented in attempts to use this type of information to identify and quantify soluble or cellular blood-based biomarkers. Nevertheless, although Chen and colleagues provide new approaches toward clinical translation of stromal analyses in ovarian cancer using the more homogenous DTF signature, the authors’ conclusion that the “DTF fibroblast signature is a common tumor stroma signature in different types of cancer including ovarian, lung...
and colon carcinomas” may not be fully warranted based on
the findings presented.

The concept that tumor–stroma interactions play key
roles in dictating cancer growth and differentiation origi-
nated from the rich developmental biology literature, which
has shown that local organ development is profoundly
programmed by embryonic connective stromal tissues
(8). In the context of cancer, these interactions are reciprocal
and in tissue recombinant model systems their conse-
quences can be either an acceleration (9) or inhibition
(10) of tumor growth, depending on the composition and
receptor subtypes in the chimeras. Therefore, it is not
surprising that some stromal molecular signatures correlate
positively with survival in one type of cancer but correlate
inversely with that of another tumor type, or are not
correlated at all. The stromal and epithelial composition
of tumors is heterogeneous, comprising a large number of
cell types represented in different proportions and with
different lineage relationships. Their reciprocal interactions
and intrinsic plasticity when interacting with growth factors
and extracellular matrices (Fig. 1) are yet another source of
variability in transcriptomics analyses. It is likely that future
studies will define the molecular features of this heteroge-
nity and apply accordingly the knowledge of mathematical
modeling learned from the analysis of clinical specimens on
an individualized basis for improved prediction of cancer-
or progression-free survival (11).

The disparity in results with the use of different public
datasets could be viewed as a potential barrier for hypoth-
esis testing. The number of patients in each database, the
quality of specimens collected, the experimental proto-
cols used to create such databases, including sample
processing, instrumentation used for gene expression
read-out, and bioinformatics methodology all contribute
to variations in the quality of databases derived from
patient material. In the study by Chen and colleagues,
despite their use of multiple large datasets across several
cancer types, significant disparities were noted in the
predictive models developed, suggesting a lack of uniform-
ity and unknown biases in the datasets. Hence, future
studies must establish rigid criteria for database selection,
incorporating or rejecting datasets using objective criteria
that will increase the chances for prognostic success in a
single patient. This type of study can be further strength-
ened by integrating transcriptome data with analyses of
other molecular targets, such as quantitative protein data
obtained using multiplex technologies. Methods are
emerging allowing expression of proteins to be assessed
quantitatively at the single-cell level using antibodies
linked to quantum-dot nanoparticles with light emission
at specific wavelengths. Because multiplex quantum-dot
labeling technology has been validated by quantitative
reverse-transcription PCR and Western blot (12), we
suggest such technology may be applied together with

Figure 1. Reciprocal tumor–stroma interactions: the
question of cellular heterogeneity and the potential
for prediction of cancer progression and survival.
Although DTF and SFT represent homogeneous,
 fibroblastic tumor stroma, other
cell types, including
 inflammatory/immune cells,
 smooth muscle/myofibroblast,
 endothelium, and adipocytes,
 reside in the cancer-associated
 stromal compartment. This
 stromal element is known
to interact in a reciprocal
manner with mesenchyme,
 epithelium, and stem-like, and
 neuroendocrine cells in the
cancer epithelial compartment.
Novel technologies including
 advanced quantitative
 immunohistochemistry (qIHC)
 and in situ hybridization (qISH)
 methods could enhance the
power of prediction of cancer
progression and lethality.
microarray data for improved power of prediction of cancer patients’ survival. Mass spectrometry–based proteomics technologies are also rapidly advancing and are becoming relevant to clinical medicine. In addition to exon-capture microarray transcriptomics, technologies to record miRNA and long noncoding RNAs are also now available and are being applied to clinical specimens. These additional targets, multiple RNA species representing a majority of the expressed genome as well as new quantitative protein-based methods, will likely increase the power of large datasets to predict more faithfully what lies in store for individual patients with cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: L.W.K. Chung
Development of methodology: L.W.K. Chung
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Writing, review, and/or revision of the manuscript: M.R. Freeman, L.W.K. Chung
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Acknowledgments
The authors thank Dr. Ruoxiang Wang, Department of Medicine, Cedars-Sinai Medical Center, for his contribution of the figure used in this commentary.

Grant Support
This work is supported in part by the National Institutes of Health/National Cancer Institute (NIH/NCI) 2P01CA098912, 1R01CA122602, Prostate Cancer Foundation Challenge Award and Board of Governors Endowed Cancer Research Chair (to L.W.K. Chung) and NIH/NCI R01 CA143777 (to M.R. Freeman).

Received July 3, 2013; accepted July 5, 2013; published OnlineFirst September 5, 2013.

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