Correspondence

The Evolution of Tumor Biology: Seeking a Balance between Gene Expression Profiling and Morphology Studies

To the Editor-in-Chief:

Morphological pathologists (including cytologists) may not be nearly as close to becoming obsolete as the Special Article on expression profiling suggests.¹ There are two reasons. First, steady-state levels of mRNA are but one profile of many measures of "gene expression." Second, even if steady state levels of mRNA were always able to unequivocally distinguish biologically and therapeutically distinctive tumor types, morphologists (including, hopefully, pathologists) will still be needed to understand the larger biological significance of the altered gene expression.

Gene expression—ie, how DNA functions—is regulated at many levels, and cannot be represented simply as a steady-state level of whole cell mRNA. Biologically significant aspects of gene expression that are *not* represented by steady state levels of mRNA include: 1) splicing; 2) regulated export; 3) targeting the mRNA to specific cellular sites; 4) activation of mRNA; 5) mRNA decay; 6) translation; 7) timing of expression relative to other gene products; 8) targeting of nascent proteins to subcellular sites; 9) posttranslational processing of proteins; and 10) protein degradation. There are simply a large number of genes whose function depends little on the steady state levels of their mRNAs. For example, activation of translation and protein degradation regulate the expression of heat shock proteins and cyclins, respectively. To ignore the various levels of gene expression in favor of a simple steady state level of mRNA is to ignore what are certainly emerging novel cell physiologies. In fact, the argument could be raised that gene expression profiling based on steady state levels of mRNA is certainly doomed to be obsolete as we learn more about basic cellular biology!

A more important question cannot be addressed by gene expression profiling: *Why* are there particular gene patterns of gene expression for various tumor types? That

is, how did the evolution of the tumor occur? Consider the following analogy. Evolutionary biologists of the last century used morphology and the study of ecology to construct phylogenetic trees. A modern technique of sequencing the DNA of organisms can also determine evolutionary phylogenies, sometimes more easily or accurately than classic naturalist studies. If the goal were merely to identify a particular bird species, it would be possible to replace ornithologists with molecular chips in which each bird species could be represented by a code of informative nucleotides. But DNA chips cannot offer easy hypotheses for the evolutionary mechanism leading to the emergence of a particular bird species. To derive any information about *how* evolution occurred, the morphologists still hold the trump cards, even if the analysis is sometimes exceedingly difficult.

Likewise, it is possible that gene expression profiling could distinguish a high grade from a low grade squamous intraepithelial lesion, but the actual mechanism for this "microevolutionary event" will likely require a careful consideration of diagnostic morphological features. A more balanced view of the future of gene expression profiling is that it can complement morphology in some cases to help classify tumors, but not generally be able to disclose basic carcinogenic mechanisms. Gene expression profiling based on steady state mRNA levels are also not likely to be able to incorporate newer concepts emerging from cell biologists. It would be a mistake to discourage cancer researchers from seeking the insight of seasoned morphologically-oriented pathologists, or to discourage young pathologists from asking what morphology tells us about the cell biology of cancers.

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References

1. Ladanyi M, Chan WC, Triche TJ, Gerald WL: Expression profiling of human tumors: the end of surgical pathology? *J Mol Diagn* 2001, 3:92–97