From biomarker development towards implementation of multidimensional biomarker panels in a clinical setting

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Editorial

From biomarker development towards implementation of multidimensional biomarker panels in a clinical setting

During decades, sarcomas and cutaneous lymphomas have been among the main paradigms of the importance of multidimensionality in biomarkers assessment. In these tumors, the diagnostic taxonomy and prognostication are based on multidimensional systems, combining phenotypic, immunohistochemical and molecular variables. This is now standard of care for all tumors, however not yet for prediction of treatment response where, with some notable exceptions like in gliomas (Erdem-Eraslan et al., 2013), predictive variables are often used as single-dimensional information. Our progressive insight in the molecular underpinning cancer can only translated into clinical practice if strong validation and quality assurance programs are introduced. Whereas the scientific literature is overwhelmed with proposed prognostic and predictive series of biomarkers, only a few have been validated in prospective studies and have obtained level 1 evidence as a biomarker in the clinical setting. At the protein level, validated immunohistochemical protocol using high quality antibodies should be used to determine absolute quantity of the protein, and not only "qualitative" assessment. This is true for proteins that can be affected by different genetic events, such as reduced or lack of PTEN expression by deletion, mutation or promoter methylation (Ascierto et al., 2013), but also for putative predictive biomarkers like PDL-1 in immunotherapy (Kaplan et al., 2013). Unfortunately, quantitative immunohistochemistry is an oxymoron because of the large number of non-controllable variables in immunohistochemistry. The power of a prognostic or predictive clinical test is as good as the validity of its parameters.

In this special issue of Molecular Oncology attention is given to controllable and uncontrollable variables that affect the accuracy, robustness, and quantitative and qualitative value of molecular tests in oncology in a research setting and in clinical practice. It includes in depth validation criteria for immunohistochemistry in the clinical setting and the use of theranostic antibodies, a critical appraisal of mRNA and miRNA expression analyses in tissue and circulation, a description of the quality control and assurance mechanisms for molecular tests, and a discussion on the critical parameters for quantitative clinical proteomics. A biomarker test can only be implemented in a clinical setting when biomarkers are accurately validated, strict criteria for test performance standards are met (i.e. precision, accuracy, limit of detection), and that a quality assurance mechanism are in place. Because of this stringency, the identification of novel biomarkers in a research setting should adhere to the same strict criteria to allow rapid promotion from the research bench to a clinical testing laboratory. This includes proper validation of antibodies, accurate description of methods, justified used of references and internal standards, and knowledge about the performance of the assay by which a biomarker is measured. There should be no difference in biomarker detection criteria in the research and clinical setting, but many of these parameters are taken for granted in biomarker discovery and initial validation programs.

When identified and measured properly, biomarker signatures provide a wealth of information. Not only as single biomarker or series of markers of the same order (e.g., gene mutations, gene expression, protein expression, or protein modifications), but especially when analyzed in a multidimensional manner: mutation profiles combined with gene and/or protein expression profiles. Comparing these comprehensive molecular portraits of tumors is a statistical challenge because the number of possible different permutations is large and the sample size in general small. However, integrated analyses of co-occurring mutations and protein modifications successfully resulted in the identification of breast cancer subtype specific signaling pathways (Cancer Genome Atlas Network, 2012). The need for the development of multidimensional biomarker panels is in large part driven by the activation of complementary or inhibition of antagonistic pathways as drivers of malignant progression and therapy resistance. Furthermore, the contribution of the tumor microenvironment on tumor progression and therapeutic response cannot be underestimated. Whereas an inflammatory response can be appreciated from a histopathological level, their activity is reflected in tumor cells at the level of gene and protein expression and protein modifications. Furthermore, little is known about the effect of a given mutation on modulation of the cellular response to an inflammatory

stimulus. Whereas chronic inflammation can cause DNA damage due to constant exposure to oxygen radicals, mutations in transformed cells can modulate the inflammatory response. One such example is the polarization of tumor-associated macrophages in GIST, in which the presence of an oncogeneic KIT mutation polarizes macrophages into the protumorigenic M2 phenotype, and that the inhibition of KIT with inhibitor imatinib established a proinflammatory and anti-tumor M1 phenotype (Cavnar et al., 2013). Therefore, thorough understanding of positive and negative regulators of signaling events at the molecular and cellular level, as well as the mechanism that regulate translation and metabolism yields a blue print onto which interacting gene mutations and protein profiles can be mapped. Instead of a purely statistical approach to identify correlations between mutations, expression and post translational modifications, a systems biology approach will contribute to a rational design of biomarker panels that can predict prognosis and therapeutic response. However, these analyses depend on the quality of the starting material, the quality of the molecular profiling data, and correct clinical annotation of the samples in the study: Garbage in, garbage out.

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