Response prediction using ex vivo PamChip assays for activity-based testing of drug-target interactions in patient-derived tumor lysates

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Abstract

Introduction
In biomarker discovery, the method of correlating a specific molecular profile to a particular clinical response is frequently applied. The profiles are often based on DNA mutations or RNA expression levels. Correlation with clinical response, however, does not imply causation. A complicating factor is the commonly observed low concordance between the transcription of a gene, its expression level as a protein, and its activity. The resulting absence of causative and mechanistic understanding is a bottleneck for the validation and application of useful new biomarkers.

Methods
Here we present a novel approach through which biomarkers are identified using protein activity profiling. At this activity level, where the action is, we are better able to study the consequences of genetic changes and the effect of counteracting drugs. Protein functionality, like kinase activity, can be monitored in patient-derived tissue samples using dynamic peptide microarrays. Moreover, the effect of the drug on these targets can be measured in the same test. The resulting data, presented here, which are information-rich on the drug-target interactions, are a new source to support biomarker discovery. Markers identified in this way are essentially mechanistic markers.

Results
Using dynamic peptide microarrays (PamChips®) comprising multiple phosphotyrosine substrates, kinase activity-based biomarkers were identified predicting the responses to therapy in both pre-clinical patient-derived tumor xenograft (PDTX) models and clinical biopsies. Prediction of response to chemo-radiation therapy was shown in locally advanced rectal carcinoma patients (N=67). In another example, response biomarkers were identified for neo-adjuvant treatment with erlotinib of non-small cell lung cancer (NSCLC) patients (N=28). The drug was included in the test. Also in the third example, now focusing on ERα-positive breast cancer, the drug tamoxifen, was used in generating ex vivo response data from patient-derived tumor tissues (N=15). In this later case, the ERα-tamoxifen interaction was read out on another biochip comprising more than 150 coregulator-derived peptides representing this drug target class’s interactome.

Conclusion
These dynamic PamChip® peptide microarrays provide tools for functional molecular profiling. This method generates new possibilities for identifying response prediction biomarkers by linking the ex vivo drug response to the patient’s clinical response.

New biomarkers: measure where the (drug) action is

PamChip® Dynamic Peptide Microarray technology

Drug testing on Patient’s derived kinases or hormone drug targets

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