Summary

A novel biologically validated method to quantitatively measure activity of oncogenic signal transduction pathways was used to measure in breast cancer intra-tumor signaling pathway heterogeneity and heterogeneity between primary and metastatic tumors, revealing major heterogeneity between primary and metastatic tumors.

Knowledge-based models for quantitative measurement of signal transduction pathway activity

Bayesian computational Models infer signal transduction pathway activity from mRNA expression levels of direct target genes of the pathway-associated transcription factor. Input for the measurement is Affymetrix HG-U133Plus2.0 microarray data or qPCR [Verhaegh et al., Cancer Res 2014;74(11):2806-45]. The network model has three types of nodes: a transcription complex, target genes and probesets. The model describes (i) how the expression of the target genes depends on the activation of the respective transcription complex, and (ii) how probe intensities depend in turn on the expression of the respective target genes.

Methods

Sample set 1: RNA from spatially distinct breast cancer tissue samples: (a) multiple biopsies per resected primary breast cancer; (b) multiple biopsies per primary biopsy block.

Sample set 2: RNA from matched primary and metastatic samples from different organ locations.

Pathway model calibration on one cell type; biological validation on different cell types (examples)

Pathway heterogeneity between primary and metastases; luminal breast cancer

Pathway heterogeneity in log2 odds pathway activity

Intra-tumor pathway heterogeneity

Heterogeneity across pathway activity threshold

Heterogeneity in log2 odds pathway activity

Conclusion

Limited heterogeneity in signal transduction pathway activity was found within a biopsy block, more heterogeneity between quadrants of the whole tumor, and between primary tumor and metastases, as well as between metastases from the same patient.

Heterogeneity was lowest in the ER pathway and in Luminal A tumors; most heterogeneity was found in the PI3K pathway (if oxidative stress was also considered) and in more aggressive breast cancer subtypes between primary and metastasis.

Results suggest that homo-/heterogeneity within a single biopsy is often representative for the whole tumor. Targeted drug treatment of metastatic breast cancer may require analysis of multiple biopsies to choose the most effective drug or drug combination.