Diagnostic Validation of Genomic Signatures Associated to Invasive Growth and Metastatic Progression of Human Breast Cancer

Renzulli T[(1)], Isella C[(1)], Cantarella D[(1)], Martinoglio B[(1)], Porporato R[(1)], Cimino D[(1)], De Bortoli M[(1)], Sismondi P[(1)], Medico E[(1)]

[(1)] Institute for Cancer Research and Treatment, University of Torino Medical School, Candiolo

Motivation

The major cause of death from human cancer is not the primary tumour, but the development of metastases at distant sites. Metastatic progression can be driven by aberrant activation of the “invasive growth” biological program, triggered in epithelial cells by Hepatocyte Growth Factor (HGF) via the MET tyrosine kinase receptor. To clarify the molecular basis of invasive growth, we previously defined an “invasive growth signature” of over 1000 genes transcriptionally regulated in epithelial cells by HGF. A smaller, 49-gene set was further extracted from this signature as an optimal classifier predicting metastatic progression of breast cancer in published datasets. Such classifier could help defining a subset of breast cancer patients with low risk of metastatic progression that may avoid adjuvant chemotherapy after surgery.

Methods

To confirm the clinical potential of this approach, we analyzed a new set of 76 breast cancer samples obtained at the IRCC, and validated the invasive growth-based classifier together with four published genomic signatures predicting metastatic relapse of breast cancer. The validation was done using two platforms for gene expression analysis: DNA microarrays and quantitative realtime PCR on microfluidic low-density arrays.

Results

Statistical analysis showed that the invasive growth signature has the best classifying performance on both platforms. Interestingly, when all the signatures were used together as a single classifier, the precision in detecting good prognosis patients was further increased. These results confirm the strong biological and clinical significance of the invasive growth genomic signature. Furthermore, the classifier derived from this signature can be successfully merged with other available genomic classifiers and converted into a realtime PCR-based gene expression assay, readily amenable to a clinical-diagnostic use.

Contact : tommaso.renzulli@ircc.it