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Clinical significance of experimentally-derived CTC-specific genes in breast cancer

Emanuela Fina
Fondazione IRCCS Istituto–Nazionale dei Tumori, Italy

Despite recent clinical advances, breast cancer (BC) still represents a considerable health problem, as ~90% of cancer-related deaths are due to metastasis. The spreading of cells to distant organs has been considered the final stage of cancer for decades, but recent data showed that the hematogenous dissemination phase is an early event and that subsets of circulating tumor cells (CTCs) can be detected in blood even when secondary lesions have not been diagnosed. Changes in CTC kinetics assessed using conventional markers may represent advantageous biomarkers compared to standard prognostic factors in some solid tumors, but evidence of the real clinical utility of CTC status in BC is still lacking and ongoing studies are focusing on the molecular features rather than the simple quantification of CTCs. Since CTCs are the seeds of metastasis and on the hypothesis that they have unique molecular features, we compared the transcriptome profile of CTCs isolated from the MDA MB-231 BC xenograft mouse model with those of solid lesions with the aim to identify new metastasis-associated genes and biologically meaningful biomarkers to stratify patients using a CTC based test. We found 474 significantly differentially expressed genes. Among genes up-regulated in CTCs, TFF3 and FADS3 were proved to be involved in some steps of the metastatic cascade using functional assays. Interestingly, the expression status of *TFF1, TFF3* and *ELF3,* but not CTC status alone defined by AdnaTest, allowed identifying BC patients at high risk of relapse or progression in preliminary cohorts. Indeed, patients with TFF3+/CTCs had a significantly shorter progression-free survival compared to those with *TFF3*-/CTCs. The prognostic role of CTC-specific genes will be validated in confirmation studies with other case series, and metastasis assays with mouse models will clarify the role of *TFF3* and *FADS3* in tumor progression and their potential usefulness as therapeutic targets.

emanuela.fina@istitutotumori.mi.it
emanuela1.fina@gmail.com