Methylated genes as prognostic and predictive markers in breast cancer

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Introduction: Methylation of CpG islands in the promoter regions of genes is a prominent epigenetic silencing mechanism, which can be a driven force in breast cancer progression and/or a cancer’s sensitivity to treatment.

Methods: Using various micro-array-based methodologies, we performed candidate and genome-wide DNA methylation profiling in primary tumors of breast cancer patients and associated differential methylation to disease outcome. We associated DNA methylation of candidate genes with disease recurrence in patients who received adjuvant tamoxifen therapy. And, in two other studies, we associated DNA methylation markers measured in the primary tumor of patients to response of their recurrent disease to respectively endocrine and antracyclin-containing chemotherapy.

Results: (i) DNA methylation of PITX2 was associated with disease recurrence in node-negative patients receiving adjuvant endocrine therapy and in patients not receiving any adjuvant systemic therapy. (ii) DNA methylation markers PSAT1, STMN1, GRIND2, TGFBR2 and S100A2 were associated with first-line tamoxifen therapy response. (iii) The genome-wide discovery revealed various DNA methylation markers associated with anthracyclin-based chemotherapy response. These latter markers were further studied in a cohort of lymph node-positive patients who all received adjuvant antracyclin containing chemotheraphy. Among others, and including again PITX2, BMP4 was identified as the strongest marker for disease progression in this latter cohort.

Conclusion: Specific epigenetic DNA methylation markers associated with clinical outcome have been revealed in patients treated with endocrine or chemotherapy during early stage and recurrent breast cancer.

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Viruses and breast cancer

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Breast cancer is a common malignancy among women, with a lifetime risk of more than 10%. Several risk factors are known, such as age, length of reproductive life, nulliparity, obesity and so on. Unfortunately, no aetiological factor has been identified in human breast cancer, with the exception of the hereditary transmission of some predisposing genes, such as the BRCA genes, accounting for 5-10% of cases. On the other hand, the role of murine mammary tumour virus (MMTV) in the induction of mammary cancer in mice is known and the resulting animal model has given relevant contributions to the understanding of the development of cancer in the human mammary gland. Based on the close relationships between the morphological and biological characteristics of murine and human breast tumours, the existence of a human mammary tumour virus (HMTV) has been speculated upon for many years. The quest for HMTV initially began by using immunochemistry, electron microscopy, serological analysis and, later, molecular methods such as low-stringency hybridization. Unfortunately, none of these methodologies has given conclusive results. Among other factors, the main limitations of these techniques were low sensitivity and an inability to discriminate between human endogenous retroviral sequences (HERV) and MMTV. Ten years ago this problem was overcome by selecting a region of 660 bp of the MMTV envelope gene (MMTV env) that has a low homology to HERVK10 (16%), the prototype human retrovirus and highly similar to MMTV. MMTV-specific primers, located in the 660 bp region, were designed and used to screen a panel of randomly selected samples of human breast cancer by polymerase chain reaction (PCR). A MMTV envelope gene-like sequence (MMTV env-like), 90-98% homologous to the MMTV env, was present in 38% of human infiltrating breast cancer, and in only 2% of normal human breast samples. The same group also found this segment in 66% of the human breast tumours positive for the MMTV env-like sequence, and a significant correlation between the presence of MMTV env-like fragment and expression of laminin receptor, a marker for malignancy and poor prognosis. Our laboratory confirmed these data developing a novel strategy combining a highly sensitive and specific PCR-based method that is simple and reproducible, and an automatic laser-assisted microdissection procedure capable of producing a pure and enriched tumour cell population. Details of our studies and a survey of the literature will be presented and discussed.

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Tumor markers in breast cancer — European group on tumor markers (EGTM) recommendations

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