

of distant metastasis [301]. In this study, increased intensity of CK19 RT-PCR signal, presumably indicating higher numbers of CTCs, was associated with reduced survival. In addition, the detection of CK19 mRNA positive cells in the PB of patients with stage I and II breast cancer before the initiation of any adjuvant treatment was an independent prognostic factor for disease relapse and death [273]. In patients with progressive, locally advanced, and metastatic breast cancer, circulating CK19 positive cells detected by quantitative RT-PCR reflected the changes in disease load [303]. In this study, the trend over a period of months was particularly important. A study using DF3 as molecular marker demonstrated that operative manipulation enhanced cancer cell dissemination [252], indicating that cancer surgery will result in increased shedding of cancer cells into the circulation. Moreover, when CTCs from PB were analyzed before and during therapy for EpCAM, MUC1 and HER2 transcripts, molecular profiling of CTCs could offer superior prognostic information and predictive judgement of therapeutical regimens in the study of Tewes et al [384]. Thus, molecular characterization of CTCs might contribute to improving targeted and more individualized cancer therapies. In this field, important progress has also arisen from the development of an automated enrichment and immunocytochemical detection system for CTCs [177, 385].

In general, however, the metastatic process is grossly inefficient, and the presence of cancer cells in the blood circulation does not necessarily indicate the subsequent appearance of systemic disease [176, 386]. Moreover, it is generally believed that the majority of cancer cells that shed into the blood circulation, are cleared and do not survive in the peripheral circulation, only a very few cancer cells succeeding in establishing secondary tumors [176, 387, 388]. Therefore, there seems to be dissociation between molecular positivity and true metastatic disease, and a more detailed molecular study might give information about the metastatic potential as well as the natural history of CTCs in PB.

### **3. Sensitivity, specificity, and problems in assay**

Several factors may affect the sensitivity and specificity of PCR-based methods. For example, methods of an endpoint analysis to evaluate PCR and RT-PCR products may affect the sensitivity. To date, the majority of studies have used ethidium bromide (EtBr) staining as an endpoint analysis to evaluate these products. However, Southern blot analysis increases the sensitivity compared with EtBr staining [205, 212]. In addition, immunomagnetic bead technology may provide a sensitive and specific means for identifying very small numbers of breast cancer cells in PB [295, 299].

More importantly, as PCR-based methods are up to 100 times more sensitive than conventional methods in detecting micrometastases, this extreme sensitivity confers an inherent disadvantage of producing false positive results [389]. An important cause of false positive results is contamination by carry-over products from the previous PCR amplifications, or contamination by cancer cells or normal epithelial cells. When using epithelial markers, the first blood sample should be discarded to avoid epithelial contamination. For BM aspiration, the skin should be incised before the aspirates are taken. Moreover, the existence of a processed pseudogene or illegitimate transcription of CKs in hematopoietic cells may cause false positive results [259, 390]. Importantly, even a small number of copies of mRNA transcripts presents a problem, not only for CK but for any targeted gene that is expressed at low levels in noncancer cells. One approach to overcome this problem is to develop a quantitative method in which a competitive sequence is used in PCR titration assay, and to introduce an appropriate cut-off value [262, 267, 304]. When using epithelial markers for molecular detection, it must be remembered that the presence of amplified products of these markers is not specific for breast cancer, as other epithelial neoplasms may also produce a positive results. Even benign breast epithelial cells could be mobilized during breast surgery for benign disease [391]. In contrast, false negative results may occur because of the deficient expression of the marker gene in micrometastatic cancer cells. For example, when using CK19, RT-PCR may fail to detect cancer cells that do not express CK19 transcript but rather express one or more of the other CK genes such as CK7, CK8 or CK18 [392]. Therefore, breast cancer specific markers seem to be crucially important for detection of micrometastasis. Given the lack of such breast cancer specific markers, tissue specific markers, including maspin and MGB, seem to be the next choice.

Maspin is homologous with the serine superfamily of protease inhibitors. It is shown to be produced by normal mammary epithelial cells, but its expression is down regulated or absent in breast cancer cells and tissues, suggesting that maspin functions as a tumor suppressor [393]. Two studies have indicated that maspin is useful to detect cancer cells in PB or BM [255, 302]. However, the sensitivity and specificity of maspin has been questioned in other studies [217, 248]. MGB exhibits homology to several secretory epithelial proteins of the uteroglobin gene family, and the human MGB gene is located on 11q13, a region that is amplified in a subset of breast cancer [394]. In non-malignant tissues, expression of MGB is strictly limited to the mammary epithelium, and it is highly expressed in primary breast cancer cells [218, 394, 395]. Moreover, MGB B/MGB2 is a recently cloned member of the uteroglobin gene family that is homologous to the MGB gene [396].

To date, the physiological role of these protein in breast tissue is unknown, as is their involvement in breast tumorigenesis. However, based on their breast cancer association and somewhat unique breast-specific pattern of expression, these proteins appear to be excellent candidates for molecular markers of breast cancer [216, 221, 222, 248, 298, 300, 397].

An ideal molecular marker to detect micrometastasis should be specific to cancer cells and not to normal cells, or to the tissue from which the tumor cell originated. It should not be present in any other cells and tissues than tumor cells. Furthermore, it should be easily detectable with little variance. More importantly, it should be clinically significant. As mentioned above, no single marker evaluated can be used for every breast cancer patient, partly because of heterogeneity of gene expression in cancer cells. Therefore, multi-marker analysis seems to be promising for accurate examination of micrometastasis [214, 222, 223, 248, 266, 309]. Ultimately, microarray analysis will be more effective and may yield more useful data. A study of particular interest demonstrated that complementation of MGB with additional genes including B305D, B311D, B533S, B726P and GABA $\pi$  increased the detection rate [306]. In a similar study using high-sensitivity array analysis of 170 candidate marker genes, cluster analysis identified a group of 12 genes that were elevated in the blood of cancer patients [308]. These genes included SRP19, CD44, TRP-2-8b, maspin, HSIX1, Gro $\alpha$ , myosin light chain, MDM2,  $\beta$ -tubulin, N33, and laminin $\alpha$ 3. Mean expression levels of these genes were elevated in 77% of breast cancer patients, and cluster analysis could correctly classify healthy volunteers and patients.

Thus, molecular methods seem to be useful not only for accurate diagnosis but also for detection of micrometastasis in LN, BM, PB and other body fluids. Potential uses of molecular detection of micrometastasis include: aiding in the selection of patients for earlier treatment for minimal residual disease, improvement of preoperative staging, and monitoring the effectiveness of therapy. Moreover, DNA microarray analysis may allow patient-tailored therapy strategies. A study of particular interest has suggested that gene expression profile will outperform all currently used clinical parameters in predicting disease outcome of breast cancer [168]. These genes consisted of those regulating cell cycle, invasion, metastasis and angiogenesis. However, before these techniques enter routine use in cancer patients, it remains to be evaluated in prospective studies with a large number of patients whether PCR-based methods may provide any diagnostic and prognostic information. For this purpose, sample collection, processing, choice of primers, use of proper controls and meticulous contamination-minimizing techniques should be standardized.

## Conclusion

Recent advances in molecular technology have created the opportunity to understand the biology of breast cancer and the heterogeneous nature of this disease. Ultimately, full awareness of the factors underlying individual differences in cancer etiology and drug response will allow the development of more specific diagnosis and treatment.

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