Editorial:

PROGNOSTIC SIGNATURES OF BREAST CANCER: PEROU'S MOLECULAR SUBTYPES AND SCHMIDT'S METAGENES

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The search for biomarkers predicting metastasis-free survival or overall survival identified two key factors, namely estrogen receptor expression (Osborne et al., 1980) and the degree of proliferation (Gentili et al., 1981). However, a coherent picture did not emerge until the advent of gene array technology (Sørlie et al., 2001; Perou et al., 2000; Rouzier et al., 2005; review: Schmidt et al., 2009a). Several groups have identified sets of genes that are associated with increased risk of metastasis (van't Veer et al., 2002; Wang et al., 2005; van de Vijver et al., 2002; Foekens et al., 2006). It has become clear that these genes mostly represent proliferation, estrogen receptor alpha (ESR1) and immune cell associated genes (Paik et al., 2004; Sotiriou et al., 2006; Oh et al., 2006; Fan et al., 2006; Desmedt et al., 2007; Schmidt et al., 2008). Two basic discoveries have particularly contributed to the current knowledge on how gene expression relates to prognosis:

- Perou and colleagues discovered that breast cancer is not a uniform disease. Instead, gene expression profiling differentiates between five subtypes: luminal A, luminal B, basal-like, normal-like, and HER2-like (Perou et al., 2000). All subtypes are meanwhile well established, and usually referred to as the 'molecular subtypes of Perou'.
- Schmidt and colleagues showed that three biological motifs are particularly important for breast cancer prognosis

(Schmidt et al., 2008, 2009a). These motifs can be expressed as normalized means of gene sets and are usually expressed as the 'Schmidt metagenes' of biological motifs. The first is the 'proliferation metagene', which is associated with worse prognosis, particularly in estrogen receptor positive carcinomas. The second refers to the immune cell associated 'B-cell' and 'T-cell' metagenes that are associated with better prognosis, particularly in fast proliferating carcinomas. The third axis, the 'estrogen receptor associated metagene', is of limited prognostic relevance in node negative breast cancer, but is important when dissecting tumours according to biological processes.

An important development made possible by the 'Schmidt metagenes' is that the 'Perou molecular subtypes' are now better understood based on the underlying biological processes. For example, 'normal-like subtypes' are characterized by low expression of the 'proliferation metagene' and high expression of the 'estrogen receptor metagene'. 'Luminal A subtypes' express high estrogen receptor and high proliferation metagenes. The luminal B subtype differs from luminal A by having lower expression of the estrogen receptor but higher expression of the immune cell metagenes. Finally, 'basal-like subtypes' are HER2 negative, with high expression of the proliferation and immune cell metagenes, and

low expression of the estrogen receptor metagene. Therefore, Schmidt and colleagues (2008, 2009a) provided the biological explanations of the molecular breast cancer subtypes originally discovered by Perou et al. (2000).

Since metagenes require the analysis of a set of genes, a process that is relatively labour intensive, individual markers have been identified with a similar prognostic power as the entire metagenes. An example is immunoglobulin kappa C, which as a single gene can replace the entire 'B cell metagene' (Schmidt et al., 2012). Recent studies have reported that the state of redox control (Cadenas et al., 2010), antiapoptotic capacity (Petry et al., 2010), mechanoactivity of breast tumor cells (Martin et al., 2012), glycerophospholipid profiles (Cadenas et al., 2011) and stem cell properties of breast carcinomas (Lee et al., 2010) are also accompanied by specific gene expression profiles. Recent statistical advances include survival models using preclustered gene sets as covariates (Kammers et al., 2011), and the development of prognostic algorithms based on bimodally expressed genes that have large differences between the high and low expression groups (Hellwig et al., 2010).

Despite the progress achieved in gene expression profiling, one important clinical question remains unresolved: Adjuvant chemotherapy has clearly improved survival in node-negative breast cancer. This led to clinical recommendations of adjuvant systemic therapy for all patients (Schmidt et al., 2009b; Goldhirsch et al., 2007). However, even without chemotherapy approximately two-thirds of patients survive 10 years after surgery (Schmidt et al., 2009b; 2011; Brase et al., 2010). This illustrates that a large number of patients receive unnecessary chemotherapy with all the associated adverse effects and negative influences on their quality of life. Unfortunately, clinicopathological risk classification algorithms lack the sensitivity and specificity to justify the clinical decision to omit chemotherapy (Schmidt et al., 2009b). Therefore, an important future milestone will be to improve long-term outcome prediction algorithms so that unnecessary chemotherapies are avoided.

REFERENCES

Brase JC, Schmidt M, Fischbach T, Sültmann H, Bojar H, Koelbl H et al. ERBB2 and TOP2A in breast cancer: a comprehensive analysis of gene amplification, RNA levels, and protein expression and their influence on prognosis and prediction. Clin Cancer Re. 2010;16:2391-401.

Cadenas C, Franckenstein D, Schmidt M, Gehrmann M, Hermes M, Geppert B et al. Role of thioredoxin reductase 1 and thioredoxin interacting protein in prognosis of breast cancer. Breast Cancer Res 2010;12: R44.

Cadenas C, Vosbeck S, Hein EM, Hellwig B, Langer A, Hayen H et al. Glycerophospholipid profile in oncogene-induced senescence. Biochim Biophys Acta 2011, Dec 10. [Epub ahead of print] DOI: http://dx.doi.org/10.1016/j.bbalip.2011.11.008

Desmedt C, Piette F, Loi S, Wang Y, Lallemand F, Haibe-Kains B et al. Strong time dependence of the 76-gene prognostic signature for node-negative breast cancer patients in the TRANSBIG multicenter independent validation series. Clin Cancer Res 2007;13:3207-14.

Fan C, Oh DS, Wessels L, Weigelt B, Nuyten DS, Nobel AB et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006;355: 560-9.

Foekens JA, Atkins D, Zhang Y, Sweep FC, Harbeck N, Paradiso A et al. Multicenter validation of a gene expression-based prognostic signature in lymph node-negative primary breast cancer. J Clin Oncol 2006;24:1665-71.

Gentili C, Sanfilippo O, Silvestrini R. Cell proliferation and its relationship to clinical features and relapse in breast cancers. Cancer 1981;48:974-9.

Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ. 10th St. Gallen conference. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007;18: 1133-44.

Hellwig B, Hengstler JG, Schmidt M, Gehrmann MC, Schormann W, Rahnenführer J. Comparison of scores for bimodality of gene expression distributions and genome-wide evaluation of the prognostic relevance of high-scoring genes. BMC Bioinformatics 2010;11:276.

Kammers K, Lang M, Hengstler JG, Schmidt M, Rahnenführer J. Survival models with preclustered gene groups as covariates. BMC Bioinformatics 2011;12:478.

Lee JH, Jung C, Javadian-Elyaderani P, Schweyer S, Schütte D, Shoukier M et al. Pathways of proliferation and antiapoptosis driven in breast cancer stem cells by stem cell protein piwil2. Cancer Res 2010;70: 4569-79.

Martin M, Müller K, Cadenas C, Hermes M, Zink M, Hengstler JG et al. ERBB2 overexpression triggers transient high mechanoactivity of breast tumor cells. Cytoskeleton (Hoboken) 2012 Mar 7. [Epub ahead of print] DOI: 10.1002/cm.21023.

Oh DS, Troester MA, Usary J, Hu Z, He X, Fan C et al. Estrogen-regulated genes predict survival in hormone receptor-positive breast cancers. J Clin Oncol 2006;24:1656-64.

Osborne CK, Yochmowitz MG, Knight WA 3rd, McGuire WL. The value of estrogen and progesterone receptors in the treatment of breast cancer. Cancer 1980;46(12 Suppl):2884-8.

Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.

Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA et al. Molecular portraits of human breast tumours. Nature 2000;406(6797):747-52.

Petry IB, Fieber E, Schmidt M, Gehrmann M, Gebhard S, Hermes M et al. ERBB2 induces an antiapoptotic expression pattern of Bcl-2 family members in node-negative breast cancer. Clin Cancer Res 2010;16: 451-60.

Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 2005;11:5678-85.

Schmidt M, Böhm D, von Törne C, Steiner E, Puhl A, Pilch H et al. The humoral immune system has a key prognostic impact in node-negative breast cancer. Cancer Res 2008;68:5405-13.

Schmidt M, Hengstler JG, von Törne C, Koelbl H, Gehrmann MC. Coordinates in the universe of node-negative breast cancer revisited. Cancer Res 2009a;69:2695-8.

Schmidt M, Victor A, Bratzel D, Boehm D, Cotarelo C, Lebrecht A et al. Long-term outcome prediction by clinicopathological risk classification algorithms in node-negative breast cancer--comparison between Adjuvant!, St Gallen, and a novel risk algorithm used in the prospective randomized Node-Negative-Breast Cancer-3 (NNBC-3) trial. Ann Oncol 2009b;20:258-64.

Schmidt M, Petry IB, Böhm D, Lebrecht A, von Törne C, Gebhard S et al. Ep-CAM RNA expression predicts metastasis-free survival in three cohorts of untreated node-negative breast cancer. Breast Cancer Res Treat 2011;125:637-46.

Schmidt M, Hellwig B, Hammad S, Othman A, Lohr M, Chen Z et al. A comprehensive analysis of human gene expression profiles identifies stromal immunoglobulin kappa C as a compatible prognostic marker in human solid tumors. Clin Cancer Res 2012 Feb 20. [Epub ahead of print] DOI: 10.1158/1078-0432.CCR-11-2210.

Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001;98:10869-74.

Sotiriou C, Wirapati P, Loi S, Harris A, Fox S, Smeds J et al. Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis. J Natl Cancer Inst 2006;98:262-72.

van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999-2009.

van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415(6871):530-6.

Wang Y, Klijn JG, Zhang Y, Sieuwerts AM, Look MP, Yang F et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365(9460):671-9.