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Editorial:

CANCER RESEARCH: FROM PROGNOSTIC GENES TO THERAPEUTIC TARGETS

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In recent years, numerous studies have been performed to identify biomarkers that predict prognosis or response to chemotherapy of carcinomas (Suzuki et al., 2011; Van Schaeybroeck et al., 2011; Micke et al., 2003; Reis-Filho and Pusztai, 2011; Marchan 2012, 2014). Non-small cell lung cancer represents one example where expression profiling was used to successfully identify prognostic signatures (Wigle et al., 2002; Tomida et al., 2004; Roepman et al., 2009; Chen et al., 2007; Larsen et al., 2007; Lu et al., 2006; Guo et al., 2008), with the overall goal to assist in the decision whether patients should receive adjuvant chemotherapy after surgical resection. A recently published meta-analysis based on gene expression microarray data from five lung cancer cohorts (n=860 patients) identified 14 genes as significantly associated with survival (Botling et al., 2013). Using a multiplex real-time PCR-based assay followed by validation on diagnostic paraffin embedded patient tissue, two further studies established gene signatures based on the combination of a few genes that robustly predict prognosis in the clinically-important stage I non-small lung cancer subgroup (Kratz et al., 2012; Wistuba et al., 2013). Gene expression studies have also been performed in breast cancer (review: Schmidt et al., 2009; Hellwig et al., 2010), and most of the identified prognostic genes are proliferation-associated (Schmidt et al., 2008; Siggelkow et al., 2012) or indicate immune cell infiltration (Schmidt et al., 2012; Chen et al., 2012; Godoy et al., 2014). However, redox factors (Cadenas et al., 2010), anti-apoptotic proteins (Petry et al., 2010), and cytoskeletal factors controlling mechanoreactivity and migration (Martin et al., 2012) have also been identified.

A major challenge facing physicians when deciding on the best course of treatment for their patients is the suboptimal accuracy of prognostic markers (Schmidt et al., 2009). For example, in node-negative breast cancer only approximately 30 % of all patients will go on to develop metastasis (Cianfrocca and Goldstein, 2004). However, the majority of patients receive chemotherapy. Therefore, biomarkers are urgently needed that accurately predicts the 70 % of patients who do not require chemotherapy because they will never develop metastasis. Although numerous biomarkers are significantly associated with the risk of metastasis, the accuracy of prediction is not sufficient to convince physicians and patients to waive chemotherapy.

Despite the unsatisfactory situation in predicting prognosis, many scientists have shifted their focus to understand whether the biomarkers identified in expression profiling can be used as therapeutic targets. Ideally, the best candidate genes would be expressed specifically in carcinomas and not in healthy tissues. A further advantage would be that these genes are expressed on the plasma membrane of tumor cells, such as ERBB2 (Brase et al., 2010) or Ep-CAM (Schmidt et al., 2011), making them the good targets for therapeutic antibodies. Such membranous

protein targets were recently described in both pancreatic and non-small cell lung cancer (Wöll et al., 2014; Micke et al., 2014). Claudins, for example are central components of tight junctions that regulate epithelial barrier function, and are frequently deregulated during tumorigenesis (Ding et al., 2013; Kwon, 2013; Runkle and Mu, 2013). Based on gene expression profiles and immunohistochemistry, Micke et al. (2014) identified that claudin 6 and the splice variant 2 of claudin 18, were strongly overexpressed in minor subsets of non-small cell lung cancer patients. In addition, high expression of claudin 6 was associated with worse prognosis. Antibodies against claudin 18.2 showed promising results in clinical phase I/II trials (Schuler et al., 2013) and claudin 6-antibodies have just entered clinical trials for ovarian cancer. Thus, such targeted therapy may present a valuable option, also in selected lung cancer patients. Whether the success story of trastuzumab for ErB2 positive breast carcinomas can be repeated for further membrane proteins that are overexpressed in subsets of carcinomas is high on the watch list of all scientists and physicians in this field of research.

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