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Guest editorial:

HIGHLIGHT REPORT: RELEVANCE OF T-CELLS, B-CELLS AND IMMUNE CHECKPOINT FACTORS FOR PROGNOSIS OF BREAST CANCER

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Recently, Anne-Sophie Heimes and colleagues from the University Hospital of Mainz published a study to gain a better understanding of the association of specific immune responses with prognosis in breast cancer (Heimes et al., 2017). Although it is well established that tumor-infiltrating lymphocytes have prognostic and predictive impact, the specific role of individual cell types is still discussed controversially (Schumacher and Schreiber, 2015; Denkert et al., 2010; Salgado et al., 2015; Iglesia et al., 2016; Rody et al., 2009; Mahmoud et al., 2011). To gain a deeper understanding, 197 node-negative breast carcinomas of patients not treated with adjuvant therapy were analyzed for T-cell and B-cell markers based on gene-expression data by immunostaining (Heimes et al., 2017). Moreover, two immune checkpoint markers, PD-1 and CTLA-4, were analyzed. In a multivariate analysis, infiltration of both T-cells and B-cells was significantly associated with better prognosis. Also the immune checkpoint markers showed a significant association with prognosis, independent of the clinical-pathological variables. Particularly interesting results were obtained after analysis of the molecular subtypes HER2+, basal-like (ER-/HER2-), luminal A (ER+, HER2-, AURKA-low) and luminal B (ER+, HER2-, AURKA-high). The prognostic effect of immune cells (T- and B-cells) was strongest in the HER2+ molecular subtype. Major differences were obtained between the other molecular subtypes with T-cells most pronounced in the luminal A, B-cells in the luminal B and the immune regulators in basal-like carcinomas.

The positive prognostic influence of lymphocytic infiltrates has been known for decades (Di Paola et al., 1974; Aaltomaa et al., 1992). While the relevance of T-cells has been accepted since long, the key prognostic impact of the humoral immune system has only been reported in 2008 (Schmidt et al., 2008) and the prognostic role of individual cell types and related factor of influence have been further assessed in several studies (Heimes et al., 2017; Schmidt et al., 2018, 2012; Mattsson et al., 2015; Sicking et al., 2014). The situation remains challenging, since only the presence of T- and B-cells in tumor tissue does not seem to be sufficient to guarantee a favorable prognostic influence. Besides lymphocyte infiltration, further factors seem to be relevant, including the redox status, migration capacity, proliferation and the metabolic microenvironment (Hammad et al., 2016; Cadenas et al., 2010, 2014; Marchan et al., 2017; Hassan et al., 2017; Hellwig et al., 2016; Stock et al., 2015; Stewart et al., 2012). A particularly critical aspect is to consider negative immune regulators, such as CTLA-4 and PD-1. In conclusion, the study of Heimes and colleagues (2017) clearly

shows that the analysis of tumor infiltrating lymphocytes should at least include differentiation between T-cells, B-cells/plasma cells and negative immune regulators, and should independently consider the four molecular subtypes HER2+, basal-like, luminal A and luminal B.

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