#2506 Transcriptomic profiling of circulating T lymphocytes predicts response to neoadjuvant therapy in patients with early breast cancer

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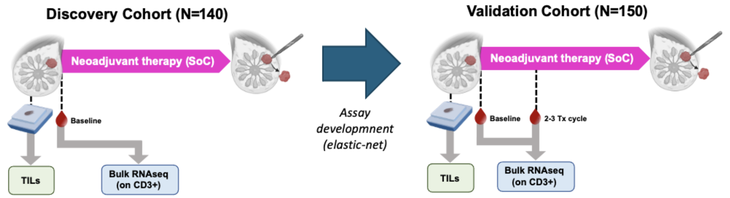
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BACKGROUND

In early breast cancer (eBC), anti-tumor immunity is a key determinant of response to neoadjuvant therapy (NAT). Circulating immune cells may offer a non-invasive means to monitor immune response during NAT, providing complementary information to tumor infiltrating lymphocytes (TILs). On this basis, we designed a study to develop a blood-based immune assay to predict the likelihood of pCR in patients with HER2+ and triple-negative (TN) eBC undergoing NAT. We hypothesize that transcriptomic profiling of circulating T cells will yield a reliable, reproducible, and scalable assay to assess systemic immune reactivity and predict pCR in aggressive BC subtypes

STUDY DESIGN AND METHODS

Study design. Assay development will use a retrospective multicentric Discovery cohort with baseline blood samples only. Subsequent validation will employ a prospective multicentric Validation cohort with blood collection at both baseline and after 2-3 cycles of NAT to assess the dynamic immune response. Both cohorts will be derived from two ongoing translational studies (IRIS and SenNEOAD studies, respectively) conducted at 7 European Institutions.



Methods. Baseline circulating T cells were collected from 75 eBC patients treated at our institution between 2021–2023. The cohort included 39 HER2+ cases treated with NAT plus single (n=13) or dual HER2 blockade (n=26), and 36 triple-negative cases treated with NAT alone (n=17) or NAT plus pembrolizumab (n=19). Circulating CD3+ T cells were isolated from PBMCs using magnetic beads. mRNA extraction and library preparation was performed using standard Illumina protocols. Gene expression analysis was performed using Significance Analysis for Microarrays (SAM), univariate and multivariate logistic regressions, as appropriate

RESULTS

Overall, 43 of 75 patients (57%) achieved a pCR. Circulating T cells from patients achieving a pCR showed higher expression in genes of the heat/shock and stress response, which are typical of an activated phenotype (i.e. HSPA1A, HSPH1), higher expression of genes associated with interferon pathway and inflammatory response (i.e. TNF, EGR1), and higher expression in proliferative genes (i.e. CDKN1A). By contrast, genes encoding for negative regulators of cytokine signaling (CISH, SOCS3) and metabolic reprogramming (ACACB, MYC, CPT1B) were significantly downregulated in the pCR group (Figure 1). Notably, expression of diverse T-cell receptor (TCR) repertoire genes correlated with reduced pCR rates. To determine whether this reflected polyclonal expansion, we calculated TCR evenness—a metric quantifying the equality of TCR gene expression distribution. High TCR evenness, indicative of polyclonal T-cell populations, was significantly associated with decreased pCR (OR: 0.1, 95% CI: 0.01–0.43; p=0.024). Stratification by median TCR evenness effectively discriminated patients with significantly different pCR rates (Figure 2). This predictive value persisted after multivariate adjustment for age, tumor stage, and eBC subtype, both for continuous evenness and dichotomized subgroups (Figures 3–4).

Figure 1. Volcano plot of downregulated and upregulated genes in circulating T cells of patients with pCR (SAM analysis)z

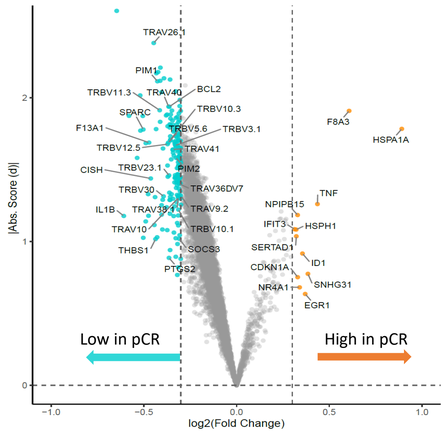


Figure 2. pCR rates according to TCR evenness groups (univariate logistic regression)

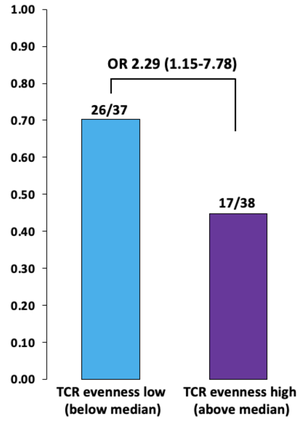


Figure 3. Forest plot showing the association between TCR evenness and pCR adjusted for BC subtype, stage, and age

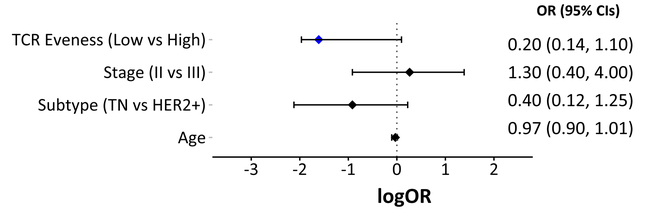
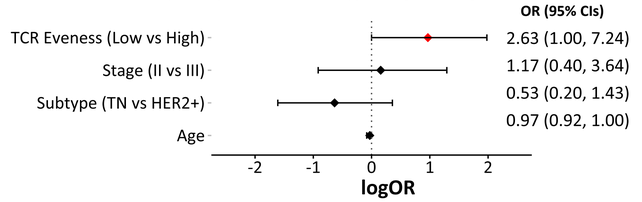


Figure 4. Forest plot showing the association between TCR evenness groups and pCR adjusted for BC subtype, stage, and age



CONCLUSIONS

These results indicate that systemic immune activity carries predictive information in breast cancer and that the predictive relevance of tissue-based immune biomarkers can be recapitulated in blood, supporting the feasibility of a blood-based immune assay.

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