Prognostic impact of Cytotoxic CD4 T cells (CD4 CTL) in tumor immune microenvironment of breast cancer patients

Kyrillus S. Shohdy¹, Doaa Almeldin¹, Ramy Ghaly¹, Loay Kassem¹, Olivia Pagani²

¹Clinical Oncology Department, Kasr Al Ainy School of Medicine - Cairo University, Cairo, Egypt
²Medical Oncology, HRC -Hôpital Riviera-Chablais - Site de Rennaz, Rennaz, Switzerland

BACKGROUND

CD4 CTLs are a subset of CD4 T cells that infiltrate the tumor immune environment (TIME) and have cytotoxic activity against malignancies. A gene signature defining the CD4 CTLs was recently developed (Cell. 2020;181(7):1612-1625.e13). The prognostic value of CD4 CTLs in breast cancer TIME is unknown.

METHODS

We tested a gene signature that identified the CD4 CTL subset within the T cells basin in the breast cancer TIME and examined its association with breast cancer patients' outcomes.

We extracted the transcriptomic and clinical outcomes of patients with primary breast cancer from the cancer genomic atlas database (TCGA-BRCA).

Z-scores of the five genes defining active CD4 CTL (ABCB1, APBA2, SLAMF7, GPR18, and PEG10) were used to calculate the signature score using principal component analysis (Fig. 1a).

The CD4 CTL signature score was dichotomized into high vs. low scores using the median (0.02).

The abundance of other T-cells populations was estimated using CIBERSORT.

RESULTS

• Transcriptomic and clinical data of 1083 breast cancer patients were retrieved from TCGA-BRCA. The median score of the CD4 CTL-defining gene signature was 0.02 (range -4.45-4.79) (Fig. 1a).

• High signature scores were significantly more frequent in younger patients (< 55 years) (57% vs. 42%, P = 0.001) and invasive duct carcinoma (IDC) (76% vs. 24%, P = 0.008).

• In multivariate analysis, adjusting for age, TNM stage and subtype, high CD4 CTL signature score was significantly associated with better disease-free and overall survival (OS) (hazard ratio (HR): 0.62, 95% Confidence Interval (CI): 0.42-0.96, p = 0.03 and HR: 0.66, 95%CI: 0.43-0.99, p = 0.001), respectively (Fig. 1b,c).

• In a stratified Log-rank survival test, higher score was associated with better OS among advanced T stage (T3-T4) (p = 0.014) and node-positive cohorts (p = 0.016).

• Correlating CD4 CTL with different immune infiltrate fractions showed a significant positive correlation with CD8 T cells (rho = 0.44, p = 0.001) and a significant negative correlation with macrophage M2 cells (rho = -0.45, p<0.001)(Fig. 1d).

CONCLUSIONS

• Cytotoxic CD4 T cell is an emerging prognostic biomarker within the breast cancer immune environment. Further dissection of CD4 CTL activity could carry a predictive signal for immunotherapy in patients with breast cancer.

Figure 1. A) The z-scores of the genes defining the CD4 CTL signature across the TCGA-BRCA cohort. B) Patients with high CD4 CTL were associated with significantly longer disease-free survival and overall survival (C). D) Heatmap of r squared of the correlation of CD4 CTL signature with key immune cells.