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科学研究費助成事業　　研究成果報告書

令和　６ 年　 ６ 月 ２１ 日現在

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研究課題名（和文）悪性リンパ腫におけるT細胞受容体レパトアと免疫微小環境の解析

研究課題名（英文）Analysis of T-cell receptor repertoire and immune microenvironment in malignant lymphoma

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研究者番号：３０８６８６３３

交付決定額（研究期間全体）：（直接経費）　　3,200,000円

研究成果の概要（和文）：免疫プロファイルに基づく予後指標を開発するために、われわれはDLBCLのRNA-seqデータを再解析した。T細胞受容体（TCR）の多様性が低い患者は、多様性が高い患者よりも無増悪期間（PFI）が有意に良好であった。TCR多様性は、CIBERSORT由来の制御性T細胞（Treg）仮想分画と関連した。Treg割合とTCR多様性の組み合わせは、最も短いPFIを有する患者を層別化することに成功した。ロジスティック回帰モデルを用いて、最終的に2つの遺伝子を選択し、Treg分画を説明するスコアリングシステムを開発した。このスコアが低くTCR多様性が高い患者は、他の組み合わせに比べてPFIが非常に短かった。

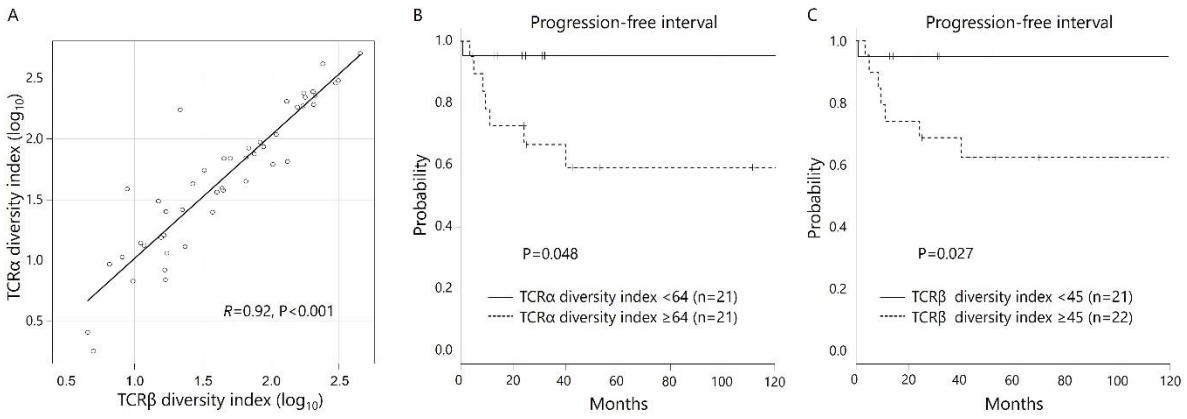
研究成果の学術的意義や社会的意義
DLBCLにおいて、TCRや腫瘍浸潤免疫細胞種を利用した予後予測法を開発した報告はなく、本研究の新規性は高い。TCRレパトアやTregは、単に予後予測だけでなく、腫瘍免疫のメカニズムの理解や、抗腫瘍免疫反応を増強する新しい治療法の開発にとっても極めて重要な知見となり、近い将来、患者における抗腫瘍免疫の回復法の開発に向けて大きく貢献する可能性を秘めている。

研究成果の概要（英文）：To develop prognostic indicators based on immune profiles, we reanalyzed DLBCL RNA-seq data. patients with low T cell receptor (TCR) diversity had significantly better progression free interval (PFI) than those with high diversity. TCR diversity was associated with CIBERSORT-derived regulatory T-cell (Treg) virtual fraction; the combination of Treg fraction and TCR diversity successfully stratified patients with the shortest PFI. Using a logistic regression model, we selected two final genes and developed a scoring system to explain the Treg fraction. Patients with low scores and high TCR diversity had very short PFI compared to the other combinations.

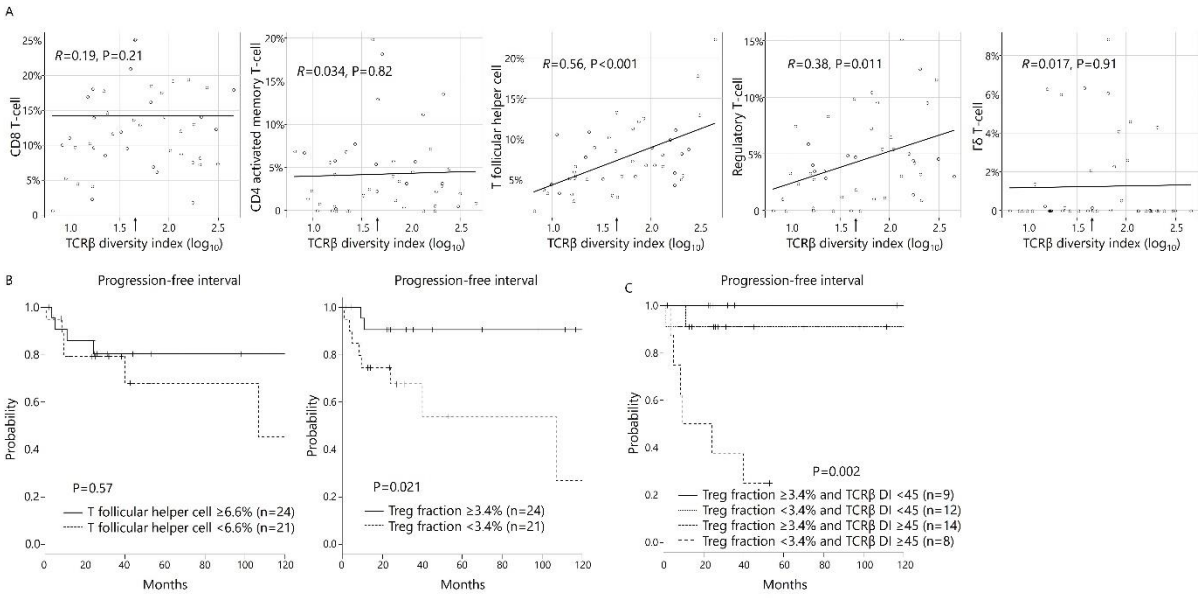
研究分野：腫瘍免疫

キーワード：悪性リンパ腫　腫瘍免疫微小環境　T細胞受容体レパトア

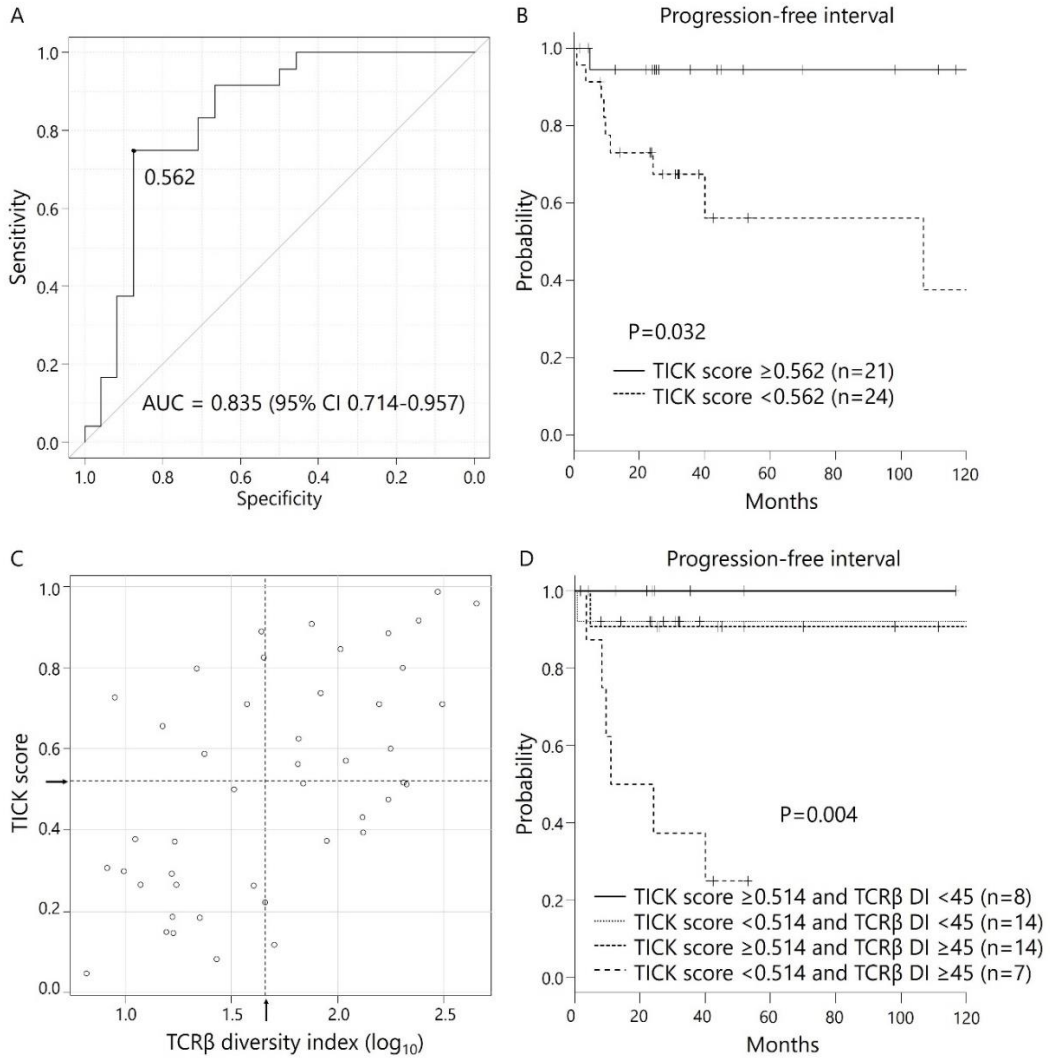
Tumor immune microenvironments have been shown to affect clinical outcomes and therapeutic responses. To develop a prognostic indicator based on immunity profiles, we reanalyzed RNA-seq raw data from diffuse large B-cell lymphoma (DLBCL) in The Cancer Genome Atlas (TCGA), and used earlier large-scale studies in TCGA. Patients with low T-cell receptor (TCR) diversity had significantly better progression-free intervals (PFIs) than those with greater diversity (TCRα: $P = 0.048$, TCRβ: $P = 0.027$). TCR diversity was strongly influenced by the number of sequencing reads, especially in those with narrower diversity. To overcome underestimation of TCR diversity in cases with low TCR sequencing reads, we attempted to combine content percentages of relevant T cell subsets with TCR diversity. TCR diversity was associated with CIBERSORT-derived regulatory T-cell (Treg) virtual fractions. The combination of Treg fraction and TCR diversity successfully stratified patients having the shortest PFIs ($P = 0.002$). As a surrogate for virtual Treg fractions, we sought immune-related factors associated with TCR diversity. Using a logistic regression model, we finally selected ICOS and CD209, and developed a scoring system ("TICK scores") that accounted for virtual Treg fractions (area under ROC curve: 0.835, 95 % CI: 0.714–0.957). Patients with both low TICK scores and high TCR diversity had much shorter PFI than the other combinations ($P = 0.004$). The combination of TCR DI with TICK score/virtual Treg fraction rate could be a useful predictor of DLBCL outcomes.



Patients whose samples were monoclone-predominant for TCR genes had better outcomes. (A) Correlation between TCRα and TCRβ DIs (Spearman rank correlation coefficient analysis). Kaplan–Meier plots of progression-free interval (PFI) by diversity index (DI) for *TCRα* genes (B) and *TCRβ* genes (C). Low DIs correspond to TCR monoclone-predominant tumors. *P* values per log-rank tests.



Correlation of TCRβ DI with CIBERSORT-estimated levels of T-cell subsets, and superior performance to classify clinical outcomes by the combination of TCRβ DI and Treg content rate. (A) Scatter plots of *TCRβ* DI and five T-cell signatures by CIBERSORT scores: CD8 T-cell, CD4 T-cell, follicular helper T-cell, regulatory T-cell, or γδ T-cell (Spearman rank correlation coefficient analysis). Arrows indicate the threshold value of TCRβ DI (45, or 1.65 for logarithm). (B) Kaplan–Meier plots of PFI by CIBERSORT scores for follicular helper T cells and regulatory T cells. *P*-values per log-rank tests. (C) Kaplan–Meier curves of PFI by the combination of CIBERSORT-derived Treg-fraction and TCRβ DI. *P*-values per log-rank tests.



TICK score, and classifier performance of TICK score with TCR diversity. (A) Receiver operating characteristic (ROC) curve by TICK score calculated by levels of ICOS and CD209. (B) Kaplan–Meier curves of PFI by TICK scores. Primary central nervous system lymphoma (3 cases) was excluded from TCGA-DLBCL cohort. (C) Scatter plots of *TCRβ* DI and TICK score. Samples with less than 10 TCR sequence reads (3 cases) were excluded. Arrows indicate the threshold values of TCRβ DI (45 or 1.65 for logarithm) or TICK score (0.562). (D) Kaplan–Meier curves of PFI by the combination of the TICK score and *TCRβ* DI. Samples with less than 10 TCR sequencing reads and primary central nervous system lymphoma (5 samples due to the overlap between the two) were excluded. *P*-values in Kaplan–Meier curves per log-rank tests.

５．主な発表論文等

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〔学会発表〕　計0件

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〔産業財産権〕

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７．科研費を使用して開催した国際研究集会

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８．本研究に関連して実施した国際共同研究の実施状況

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