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研究課題名（和文）Clinicopathological characteristics and genomic profiles of RGS1 positive lymphoid neoplasms

研究課題名（英文）Clinicopathological characteristics and genomic profiles of RGS1 positive lymphoid neoplasms

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研究成果の概要（和文）：この研究は、血液がんにおけるRGS1発現についてです。研究は、びまん性大細胞型B細胞リンパ腫、濾胞性リンパ腫、モルトリンパ腫およびその他の小細胞型リンパ腫の分析に焦点を当てています。RGS1の免疫組織化学的発現は変動しました。RGS1の免疫組織化学的発現は予後との関連がありました。びまん性大細胞型B細胞リンパ腫の予後不良に関連する高RGS1免疫組織化学的発現。濾胞性リンパ腫の予後不良にも関連する高RGS1免疫組織化学的発現。RGS1と腫瘍免疫微環境の間の相関関係が作成されました。このほかびまん性大細胞型B細胞リンパ腫遺伝子発現解析をされました。遺伝子発現分析も人工知能で分析されました。

研究成果の学術的意義や社会的意義
RGS1は免疫システムの正しい機能に必要なタンパク質です。 RGS1は免疫系のいくつかの腫瘍であると分析しました。 RGS1がいくつかの腫瘍で可変的に発現されることを見出した。RGS1の発現がいくつかの腫瘍の患者の予後と相関していることを発見しました。 タンパク質発現レベルと遺伝子発現の分析を行いました。 分析は従来型であり、人工知能でもありました。 患者の予後と相関するため、このマーカーは重要です。 リンパ系腫瘍の診断時に、このマーカーをマーカーの診断パネルに含めることができます。 このマーカーは薬物でターゲットにできます。

研究成果の概要（英文）：(1) RGS1 is a protein necessary for the structure of lymphoid tissues.(2) This study focuses on the RGS1 expression in hematological neoplasia, with focus on the analysis of RGS1 in the Diffuse Large B-cell Lymphoma (DLBCL), Follicular Lymphoma (FL), MALT Lymphoma, other small B-cell lymphomas and Hodgkin Lymphoma. The immunohistochemical expression of RGS1 was variable. Immunohistochemical expression of RGS1 was associated with the prognosis of the patients. For example, high RGS1 expression associated with poor prognosis in DLBCL and FL. In addition, a correlation between RGS1 and tumor immune microenvironment was created.(3) The gene expression analysis of Diffuse Large B-cell Lymphoma gene was also performed and the relationship of RGS1 with other relevant clinicopathological markers was assessed.(4) The gene expression analysis was also analyzed by Artificial Intelligence.(5) Immunostaining was also analyzed by Artificial Intelligence.

研究分野：人体病理学

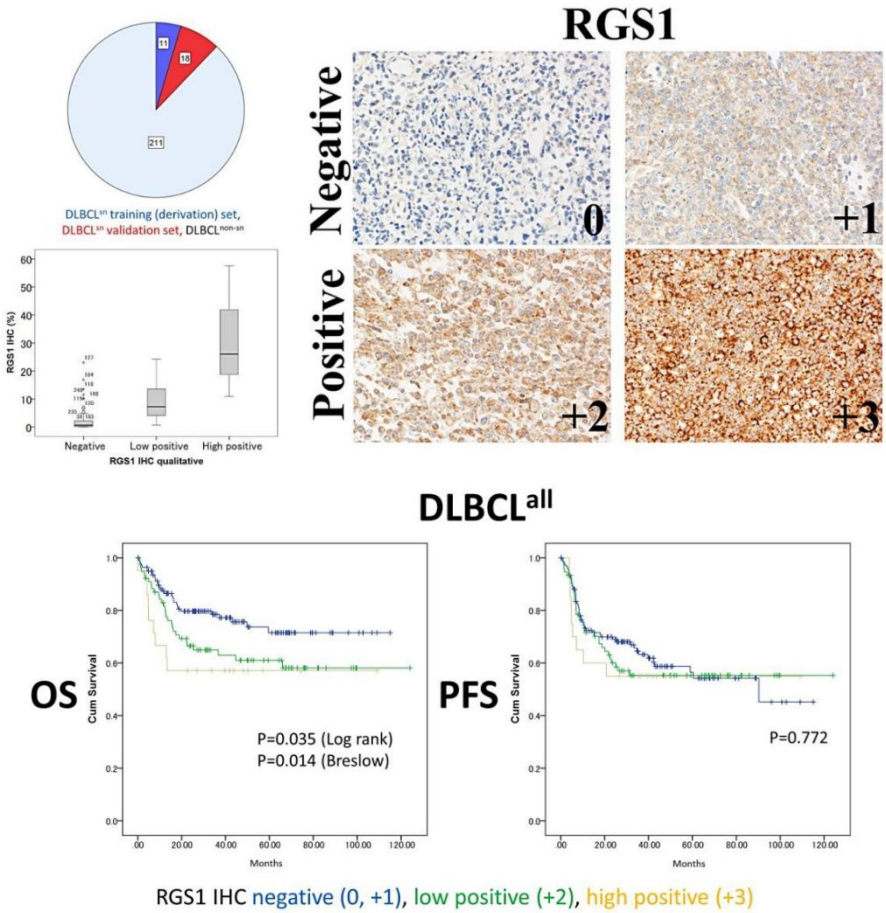
キーワード：RGS1　リンパ腫　血液がん　びまん性大細胞型B細胞リンパ腫　濾胞性リンパ腫　免疫染色　遺伝子発現分析　腫瘍免疫微環境

様　式　C－１９、F－１９－１、Z－１９（共通）

１．研究開始当初の背景

(1) Note of the author: This research report will focus on the results of RGS1 expression in Diffuse Large B-cell Lymphoma and the relationship of RGS1 and other 25 markers. This report will focus on the gene expression data and how artificial intelligence was successfully used to pinpoint the relevant markers, and how other gene expression analysis techniques such as gene set enrichment analysis (GSEA) confirmed the prognostic relevance of the markers. The relevance of this research is that we have also confirmed by immunohistochemistry (protein level) in a Diffuse Large B-cell Lymphoma series and Follicular Lymphoma of Tokai University that high RGS1 expression correlates with a bad prognosis of the Diffuse Large B-cell Lymphoma (DLBCL) patients and with histological transformation of Follicular Lymphoma (FL). In addition, we have also found variable expression of RGS1 in several low-grade B-cell lymphomas as well as Hodgkin Lymphoma. Taken all the data together, we think that RGS1 could be included in the routine diagnosis of lymphoma, as a new biomarker with prognostic value in lymphoma patients, using a simple, quick and inexpensive technique such as the immunohistochemistry.

We analyzed the importance of RGS1 in DLBCL. All the results are shown in the following figure: the RGS1 expression in DLBCL ranges from negative (0, +1) to positive (+2, +3). In a series of 220 cases from Tokai University, we found that a positive expression was associated with an unfavorable prognosis of the patients. Next we aim to identify other biomarkers in DLBCL, and we correlated them with RGS1.



(2) Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lympho-ma (NHL), accounting for approximately 25 percent of NHL cases. DLBCL is curable in approximately half of cases with current therapy, particularly in those who achieve a complete remission with first-line treatment.

(3) The diagnostic category of DLBCL is morpho-logically, genetically, and biologically heterogeneous. In DLBCL NOS there are several identified morphological variants (centroblastic, immunoblastic, anaplastic and others) and two molecular subtypes based on the gene expression profiling (GEP): germinal centre B-cell subtype (GCB) and activated B-cell subtype (ABC), with an additional unclassified subtype. The ABC subtype is associated to a worse prognosis.

(4) The term neural network applies to a loosely related family of models, characterized by a large parameter space and flexible structure, descending from studies of brain functioning. Neural networks are the preferred tool for many predictive data mining applications because of their power, flexibility, and ease of use. Predictive neural networks are particularly useful in applications where the underlying process is complex. Among them, the multilayer perceptron (MLP) procedure produces a predictive model for one or more dependent (target) variables based on the values of the predictor variables.

２．研究の目的

(1) In the project we aimed to identify new gene expression patterns associated to the prognosis of the patients in a large series of DLBCL NOS, that were not previously identified by more conventional statistical approaches. We used the MLP procedure: our target variable was the prognosis of the patients (bad vs. good) and the predictor variables were 54,614 gene expression probes. We identified a signature of 25 genes that was highly associated with the prognosis of the patients and that was independent from the cell of origin molecular subtypes.

(2) In this project we also aimed to correlate the signature of 25 with the expression of RGS1.

３．研究の方法

(1) Subjects of study.

The subjects of study were from an internationally well recognized series of DLBCL NOS, the GSE10846 gene expression omnibus (GEO) series that is comprised of 414 cases. For MLP analysis we selected 100 representative cases that constituted the discovery set. The clinicopathological characteristics of the discovery series were as follows: The male/female ratio was 52/43 (1.2), the mean age was 62-years (median of 66-years, range from 18 to 88,>60 to 75 in 32% and>75 in 22% of the cases), LDH ratio (according to the NCCN-IPI criteria that is used in this series) of≤1 in 39/82 (47.6%),>1 to 3 in 32/82 (39%) and>3 in 11/82 (13.4%); ECOG PS≥2 of 32/94 (33%), Ann Arbor stage III to IV in 61/99 (61.6%) and>1 extranodal sites in 11/93 (11.8%). All cases were DLBCL NOS diagnosed in lymph node biopsies (i.e. nodular cases). According to the cell of origin assessed by GEP, the molecular subtype was GCB in 34/100 (34%), ABC in 49% and unclassified in 17%. The follow up of the patients ranged from 0.01 to 16.8 years, with an average of 2.6 and median of 1.6 years. At the end of the follow up time 53 cases (53%) had died. The 3-year OS was 50.4%, the 5-year was 43.5% and the 10-year was 26.6%. R-CHOP-like therapy was received by 52% of the cases and CHOP-like by 48%. According to the original IPI, the distribution was as follows: low (34.2%), low-intermediate (28.8%), high-intermediate (21.9%) and high (15.1%). In comparison to low/low-intermediate IPI, high-intermediate/high IPI was characterized by worse survival: Hazard Risk=2.881 (95% CI=1.5-5.5), P=0.001. Finally, in comparison to GCB subtype, ABC subtype associated to a worse survival: HR=2.584 (95% CI=1.4-4.9), P=0.004. In conclusion, the characteristics of this discovery series represent a conventional DLBCL series. This human study had been reviewed by the ethics committee of the participating Institutions. Therefore, the investigation conforms with the principles outlined in the Declaration of Helsinki. All persons had given their informed consent prior to their inclusion in the study.

(2) Multilayer perceptron analysis.

MLP analysis on the discovery series was performed using SPSS software following the manufacturer's instructions (IBM® SPSS® Statistics Version 25, IBM, New York, United States) on a desktop workstation with an AMD Ryzen 5 1600 Six-Core Processor 3.20 GHz and 16.0 GB of RAM. One hundred cases were selected from the DLBCL NOS dataset of GSE10846, this discovery set comprised 50 cases associated to poor prognosis and 50 to good prognosis. The samples were classified into a training group (n=70) and a testing group (n=30). All cases were valid for processing and none was excluded. The network had an input layer with 54,614 covariates (number of units) with standardized rescaling method for covariates. The hidden layer number was 1 (with 12 units) and used the hyperbolic tangent activation function. The output layer was characterized by 1 dependent variable (status, survival outcome of dead vs. alive), 2 units, the soft-max activation function and the cross-entropy error function.

(3) Gene expression analysis.

Gene expression analysis was performed as we previously described with the data of the series GSE10846: the gene expression and clinical features datasets were downloaded from the NCBI website, the Gene Expression Omnibus (GEO), series matrix file that used the GPL570 platform: HG-U133 Plus 2 (Affymetrix Human Genome U133 Plus 2.0 Array). The original (quantile-normalized) data was used. In case of duplicated genes an average of all probe sets/records was performed per sample. The gene set enrichment analysis (GSEA) was performed in the discovery series following the Broad Institute software and their instructions as we have recently published]. The GSEA parameters included the gene expression data of the genes previously highlighted in the MLP and as phenotype the status variable (survival outcome of dead vs. alive).For survival analysis the gene expression data was transformed to a prognostic index (also known as risk score) to generate the risk groups. Calculation was performed by multiplying the gene expression values with the estimated beta coefficients from the fitted Cox proportional hazards model. After ranking the samples by their prognostic index, the samples were split into low-risk vs. high-risk groups and low-expression vs. high-expression. In addition, the risk group splitting was also optimized using an algorithm that uses the inner-group p-value in order to identify the best cutoff for survival (i.e. lower P value). Then, conventional survival analysis was performed.

(4) Statistical analysis.

The analysis was performed in R (http://cran.r-project.org) as well as with SPSS software. The criteria for overall survival was the conventional. Survival analysis was performed with Kaplan-Meier and Log rank tests, and Cox regression, method (enter), contrast (indicator) and reference category (first). Hazard ratios/risks (HR) were calculated with Cox regression. The Odds Ratios (OR) with binary logistic regression.

4．研究成果

(1) Multilayer perceptron analysis in the discovery series.

In the discovery series, the samples were distributed in two groups: training set (n=70) and validation set (n=30). The model had an acceptable computation, with a cross entropy error and a percentage of incorrect predictions for the training set and the testing set of 43.2 and 25.7%, and 13.6 and 16.7%, respectively. The classification of the samples for the dependent variable status (death and alive) was good, with a correct percentage between observed and predicted of 74.3% in the training set and 83.3% in the testing set. The sensitivity and specificity were good. The ROC analysis had un area under the curve of 0.8.

The normalized importance of the genes in this model ranged from 1.5% to 100%, with an average of 20.6% and a mean of 18.4%. Using a cutoff for normalized importance of 70% we identified 26 genes that were the most relevant as follows: SFTPC (100% of normalized importance), ARHGAP19 (87.2%), MESDC2 (84.3%), SNN (81.7%), ALDOB (80.7%), C9orf9, SWSAP1, C2orf44, ZSCAN12 and DIP2A (77.5%-75.1%); and ATF6B, CACNA1B, TNFAIP8, RPS23, POLR3H, 237096_at, ENO3, RAB7A, SERPINB8, SZRD1, EMC9, C10orf76, LPXN, KIF23, GGA3 and METTL21A (74.9%-70.3%). The gene name, function and involvement in disease for each of the 26 genes (25 genes as one probe is unmatched) is present in Table 1. In summary, these genes had several functions ranging from signal transduction, protein binding, regulation of apoptosis and antigen presentation, among others. They were more frequently over-expressed in many types of cancer while under-expression was less frequent. These markers were not related between them when testing with the functional module discovery analysis (Flatiron Institute) or by protein-protein interaction analysis (STRING). Of note, an extended additional analysis using STRING managed to find common pathways.

These genes were highlighted in the discovery set by MLP analysis (the genes with normalized importance >70% were selected). The gene data is based on HGNC and Uniprot.

(2) Gene set enrichment analysis in the discovery series.

The GSEA technique was performed to validate the MLP results. GSEA used the same discovery series of the MLP. GSEA determined whether the genes that were highlighted in the MLP showed statistically significant, concordant differences between the patients who died and patients who lived (status variable, also named as phenotype in GSEA software).The GSEA with the 25 genes that were the most relevant (with more normalized importance) showed an enrichment in the phenotype dead. The gene set was

significant at false discovery rate (FDR) <25%. The genes in the core enrichment were: ENO3 (1st), CACNA1B (2nd) and GGA3 (3rd). To improve to power of the analysis (GSEA is sensitive to sets with few genes), the GSEA was repeated using the 100 most relevant genes. This set was also upregulated in the phenotype dead and significant at FDR < 25%. In the core enrichment 20 genes were identified: AKT2 (1st), ZNF550 (2nd), ENO3 (3rd), among others. In summary, by GSEA we confirmed an enrichment, an association of the identified genes of MLP in the group of bad prognoses.

(3) Survival analysis in the validation series.

The set of 25 genes, previously identified in the MLP, were analyzed for prognosis in the validation set of 414 DLBCL cases. By univariate Cox regression analyses we found that high expression of ARHGAP19, MESD, C2orf44(WDCP), DIP2A, CACNA1B, TNFAIP8, POLR3H, ENO3, SERPINB8, SZRD1 (C1orf144), KIF23 and GGA3statistically associated to a poor prognosis of the patients. Conversely, high expression of SFTPC, ZSCAN12, LPXN and METTL21A (TAM119A) associated to good prognosis. In the subsequent multivariate analysis, the genes that kept the prognostic relevance were MESD, TNFAIP8, POLR3H as bad prognosis and ZSCAN12 and LPXN as good prognostic markers.

Using a risk score formula, the survival analysis identified two risk groups (high-risk and low-risk) with different prognosis and different gene expression. Log rank P=8.741E-14, Hazard Ratio=3.2 (95% CI: 2.3-4.4, P=1.77E-12). Of note, when stratified by the molecular groups, this prognosis relevance was kept in each group. Therefore, this prognostic marker set is independent of the cell of origin classification. A functional network association analysis was performed with the 25 markers as a start point. The resulting network was characterized by 693 nodes, 12,082 edges, 34.9 average node degree and a PPI enrichment p-value of 1.0e-16. The molecular function of the network was structural constituent of ribosome, protein binding, RNA polymerase activity, transferase activity and enzyme binding. According to KEGG pathways, the most relevant were ribosome, RNA polymerase, EBV infection, glycolysis and pyrimidine metabolism.

(4) Relationship with known pathogenic markers of DLBCL.

The MLP analysis on the training set was repeated merging the set of 25 genes with a set of known pathogenic markers of DLBCL: MYC, MIK67, TP53, MME (CD10), BCL2, GCET1, MDM2, RGS1, AICDA(AID), PRDM1 (BLIMP1), IRF4 (MUM1), LMO2, BCL6, CDKN2A and FOXP1. The MLP analysis ranked the genes according to their normalized importance for predicting the status of the patients (dead vs. alive). In order of importance, the top 10 genes were as follows: GGA3, ALDOB, CACNA1B, LPXN, MYC, RPS23, MIK67, TP53, MME and ENO3. RGS1 was also identified with a normalized importance of around 21. Subsequently, the same merged set was subjected to GSEA analysis to confirm the direction of the association. In the GSEA output the association towards bad prognosis was confirmed. The genes of the core enrichment, in order of relevance, were IRF4, ENO3, GGA3, AICDA, MYC, BCL2, MKI67, TP53, ALDOB, POLR3H, PRDM1, ERHGAP19, FOXP1and KIF23. A multivariate COX regression analysis (method: backward conditional) of the genes of the core enrichment showed that the most significant genes were ENO3, MYC and BCL2. Finally, survival analysis with log-rank test showed that the group of patients with high expression of those 3 genes (the "triple High group") associated to a marked unfavorable prognosis than the intermediate and triple low expression groups. The function of these genes was also analyzed using a functional network association analysis.

(5) Conclusion.

In conclusion, using a deep learning approach we have identified a set of 25 genes associated to the prognosis of DLBCL, and we have validated their main association to poor prognosis using other techniques such as GSEA, conventional univariate and multivariate survival analysis and a risk score formula approach. To our knowledge, despite that these markers are related to cancer, they are new in the pathological understanding of lymphoma. The prognostic value was independent of the cell-of-origin classification. Therefore, we have identified a set of novel biomarkers related to the prognosis of DLBCL with independence of the molecular subtype classification.

５．主な発表論文等

〔雑誌論文〕　計11件（うち査読付論文　11件／うち国際共著　5件／うちオープンアクセス　5件）

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３．雑誌名 Pathology International	６．最初と最後の頁 1～12
掲載論文のDOI（デジタルオブジェクト識別子） 10.1111/pin.12794	査読の有無 有
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３．雑誌名 Journal of Clinical and Experimental Hematopathology	６．最初と最後の頁 1～16
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2．論文標題 Oncogenic Rag GTPase signalling enhances B cell activation and drives follicular lymphoma sensitive to pharmacological inhibition of mTOR	5．発行年 2019年
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1．著者名 Moriya Keiichi、Kikuti Yara Yukie、Carreras Joaquim、Kondo Yusuke、Shiraiwa Sawako、Nakamura Naoya	4．巻 60
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掲載論文のDOI（デジタルオブジェクト識別子） 10.3960/jslrt.19038	査読の有無 有
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〔図書〕　計0件

〔産業財産権〕

〔その他〕

Research activities of Joaquim Carreras Esteban http://carreras.med.u-tokai.ac.jp/ Under construction

６．研究組織

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