(Abstract of Dissertation submitted by Luong Thi My Hanh)

Significance of abnormal 53BP1 expression as a novel molecular pathologic parameter of follicular-shaped B-cell lymphoid lesions in human digestive tract

ヒト消化管濾胞形成 B 細胞性リンパ球病変の新規分子病理学的指標として 53BP1 発現異常は有用である

Luong Thi My Hanh,Katsuya Matsuda, Daisuke Niino, Hirokazu Kurohama, Masahiro Ito, Masahiro Nakashima

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Division of Advanced Preventive Medical Sciences,
Nagasaki University Graduate School of Biomedical Sciences

Supervisor：Professor Masahiro Nakashima MD, PhD

Introduction:

The gastrointestinal (GI) tract is a common site of extranodal malignant lymphomas (MLs) and benign lymphoid lesions (BLs). Pathological diagnosis of MLs using biopsy samples from GI tract, particularly follicular-shaped lymphoid lesions (FLLs), is not always easy because of the small-size cells and insufficient recognizable features. The tumor suppressor p53-binding protein 1 (53BP1), which is a DNA damage response (DDR) molecule, rapidly forms nuclear foci at the site of DNA DSBs in response to ionizing radiation, and has been widely investigated in immunoglobulin class switch recombination of lymphocytes. We previously reported that immunofluorescence (IF) analysis of 53BP1 expression is useful for estimating genomic instability in several tumor tissues. In this study, we furtherly examined the potential of IF-based analysis of 53BP1 expression in differentiating MLs from BLs with biopsy samples from GI tract.

Materials and Methods:

Subjects: We analyzed 107 cases of primary MLs in GI tract, diagnosed at hospitals in Nagasaki between 2008 to 2019. A total 124 cases of inflammatory diseases or non-lymphoid tumors in GI tract were also examined as controls for BLs. All available samples were biopsied, formalin-fixed, and paraffin-embedded tissues. The pathological diagnosis was verified by three experienced pathologists by the diagnostic criteria of 2017 WHO classification.

Analysis for Type of 53BP1 expression*:* Dual IF analyses for 53BP1 and BCL-2, FDC (follicular dendritic cell), γH2AX (γ histone-2AX), or ATM (ataxia telangiectasia mutated, phospho S1981) were performed to determine the types of 53BP1 expression in respective anatomical structures of lymphoid lesions, such as germinal center (GC), mantle-marginal zone (MM), primary follicle (PF), and simple lymphoid accumulation (LA). All signals for 53BP1 expression were measured using the image analysis software, and classified as follows, stable, low DDR, high DDR, large focus, and diffuse, according to our previous reports. The

translocation t(11;18)(q21;q21) by dual-color FISH was also examined to clarify the association between abnormal 53BP1 expression and “high-risk” MALT (mucosa-associated lymphoid tissue) lymphoma.

Results:

The B-cell type MLs included MALT lymphoma, mantle cell lymphoma (MCL), follicular lymphoma grade 1, 2, 3A (FL1, FL2, FL3A) and diffuse large B cell lymphoma (DLBCL). The T-cell type were classified into two groups, such as small- or large-cell size. For 53BP1 expression, most nuclei in BLs showed stable or low DDR type. In contrast, several nuclei in MCL and FL tissues showed abnormal types, such as high DDR, large focus, and diffuse types. Our statistical analysis showed a higher frequency of abnormal types in MLs as compared with BLs ($p< 0.0001$). The logistic regression model with ROC (receiver operating characteristic) curve analysis revealed that the proportion of cells showing abnormal types is a very effective diagnostic parameter for FLLs [AUC (area under the curve), 0.94; CI (95% confidence interval), 0.88–1; cut-off, 27.2%] and for small cell lymphoid lesions (AUC, 0.89; CI, 0.82–0.97; cut-off, 33.6%). The frequency of the abnormal types in MLs decreased significantly with an increasing histological grade of FLs [FL1> FL2> FL3A> DLBCL (linear regression model, $p< 0.0001$). Furthermore, a high frequency of abnormal 53BP1 expression was associated with “high-risk” MALT lymphomas ($p= 0.0145$).

Discussion:

This retrospective study indicates that the frequency of abnormal type 53BP1 expression in FLLs in biopsy specimens from GI tract is an attractive diagnostic test to distinguish MLs from BLs. The logistic regression model with ROC curve revealed that the proportion of cells showing an abnormal type is an effective diagnostic parameter for FLLs and for small cell lymphoid lesions. Furthermore, we found a stepwise decrease in the frequency of abnormal type with FL progression, suggesting the involvement of different DDR machinery impairments in aggressive feature of FLs. Additionally, abnormal types appear to be associated with chromosomal translocation, a parameter of prognosis in gastric MALT lymphoma. Thus, IF-based analysis of 53BP1 expression may be a useful tool for distinguishing MLs from BLs in biopsy samples from the GI system. If it is technically possible to automate the quantification of 53BP1 expression by using a computational image analysis system, our method may be useful for practical diagnosis of FLLs.

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