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POSTER ABSTRACTS

622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

The Activation Status of RSK2, but Not PDPK1 and AKT, Associates with the Prognosis of Diffuse Large B Cell Lymphoma

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B-cell lymphoma (BCL) is the most common hematologic malignancy with various genetically and molecularly distinct subtypes. Although the prognosis of most BCL subtypes has been dramatically improved by the advances of disease subtype-directed, molecularly targeted therapies, some patients remain incurable with currently available therapeutics. We previously identified that a serine/threonine kinase 3-phosphoinositide-dependent kinase-1 (PDPK1) and its major downstream substrate serine/threonine kinases, AKT and RSK2, play pivotal roles in the pathophysiology of multiple myeloma and mantle cell lymphoma (MCL) (Chinen Y, Cancer Res 2014; Shimura Y, Mol Cancer Ther 2012; Matsumura-Kimoto Y, Cancer Med 2020). In particular, we found the crucial roles of the constitutive activation of the N-terminal kinase domain (NTKD) of RSK2 in cell survival, resistance to apoptosis, and cell proliferation of myeloma cells and MCL cells. However, the activation status of PDPK1, AKT, and RSK2-NTKD and their impacts on prognosis have yet to be comprehensively investigated in various subtypes of BCLs. To answer this, we here investigated the activation status of PDPK1, AKT, and RSK2-NTKD and their prognostic impacts in two major subtypes of BCLs, diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL). To evaluate the activation status of the three kinases in DLBCL and FL, we performed the immunohistochemical analyses to characterize the expression profiles of phosphorylated (p)-PDPK1, p-AKT, and p-RSK2-NTKD in tumor-biopsied samples from 277 pts with DLBCL and 121 patients (pts) with FL diagnosed between 2010 and 2022 at our institution, and the expression levels of three target kinases were classified into four categories; negative (0), weak (1), moderate (2), and strong (3). As a result, in DLBCL, p-PDPK1, p-AKT, and p-RSK2 were positive in 98%, 68%, and 100%, respectively. More precisely, p-PDPK1 was 0-1 in 160 (59%) and 2-3 in 111 (41%). p-AKT was 0-1 in 225 (82%), and 2-3 in 48 (18%). p-RSK2 was 1 in 177 (65%), and 2-3 in 96 (35%). OS was significantly shorter in patients with moderate/strong expression (2-3) of p-RSK2 than those with weak expression (1) of p-RSK2 (5-year OS rate 52% vs. 73%, $P<0.01$), and, importantly, p-RSK2 status was identified as the independent prognostic factor by the multivariate analysis evaluating p-RSK2 expression and elements included in the International Prognostic Index as variables (HR 1.6, $P=0.03$). In addition, the prognostic relevance of RSK2 activity was evident in non-GCB type DLBCL but not GCB type DLBCL. In FL, p-PDPK1, p-AKT, and p-RSK2 were positive in 76%, 53%, and 69%, respectively. More precisely, p-PDPK1 status was 0-1 in 94 (89%) and 2-3 in 11 (10%), p-AKT status was 0-1 in 81 (77%) and 2-3 in 24 (23%)), and p-RSK2 was 0-1 in 67 (64%), and 2-3 in 38 (36%). In contrast to the case with DLBCL, the OS of FL was not associated with the activation status of p-PDPK1, p-AKT, and p-RSK2. In conclusion, the present analysis suggests the functional involvement of p-RSK2 activity and the role of future therapeutic targeting, especially in DLBCL, especially in high-risk non-GCB subtype.

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