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Letter to the Editor

Syk expression patterns differ among B-cell lymphomas

Syk is a non-receptor tyrosine kinase involved in the B-cell receptor (BCR) signaling [1,2], whose main functions include intracellular calcium mobilization, activation of AKT, mitogen-activated protein kinases (MAPKs) and NFκB. Importantly, inhibition of Syk recently appeared a promising therapeutic approach for lymphoid neoplasms [3–6]. Since different cellular localizations with possible different functions have been described for Syk [7,8], we have analyzed these expression patterns across a large series of different subtypes of B-cell lymphomas to further characterize Syk as a therapeutic target.

Formalin-fixed, paraffin-embedded 4 μm thick sections were obtained from 303 clinical samples of lymphoid tissues, which included: 121 diffuse large B-cell lymphomas (DLBCL), 17 MCL, 12 MALT lymphomas, 20 nodal marginal zone lymphomas (nodal MZL), 62 splenic MZL (splenic MZL), 23 follicular lymphomas (FL), 29 Hodgkin's lymphomas (HD), and 19 reactive benign lymphatic tissues (6 tonsils, 13 spleen). For immunohistochemistry, mouse anti-human Syk protein antibody was employed (clone SP147, Spring Bioscience, Fremont, CA, USA), as previously described [3], with the inclusion of proper positive and negative controls.

Syk immunostaining was localized in the cytoplasm and/or in the nucleus, with variations in different cases and among the cells of the same tumor. Four different patterns of Syk expression were identified: an exclusively cytoplasmic localization; an exclusively nuclear localization; a nucleo-cytoplasmic, prevalently nuclear localization; a nucleo-cytoplasmic, prevalently cytoplasmic localization (Fig. 1). Cases were defined as negative when neither nuclear or cytoplasmic signal was present.

The four patterns of Syk localization were find to have a peculiar distribution among different types of lymphoma and lymphoid tissues analyzed. Syk was statistically more frequently detected mainly, or exclusively, in the cytoplasm in DLBCL (87/121, 72% vs 23/121, 19%; $p < 0.001$), splenic MZL (42/62, 68% vs 19/62, 30%; $p = 0.003$) and in reactive spleens (12/13, 92% vs 1/13, 8%; $p = 0.002$). This kinase was significantly found mainly, or exclusively, in the nucleus in MCL (13/17, 77% vs 4/17, 24%; $p = 0.029$). As shown in Fig. 2, a general trend could be observed across histotypes; in fact, the percentage of cases with a mainly cytoplasmic expression

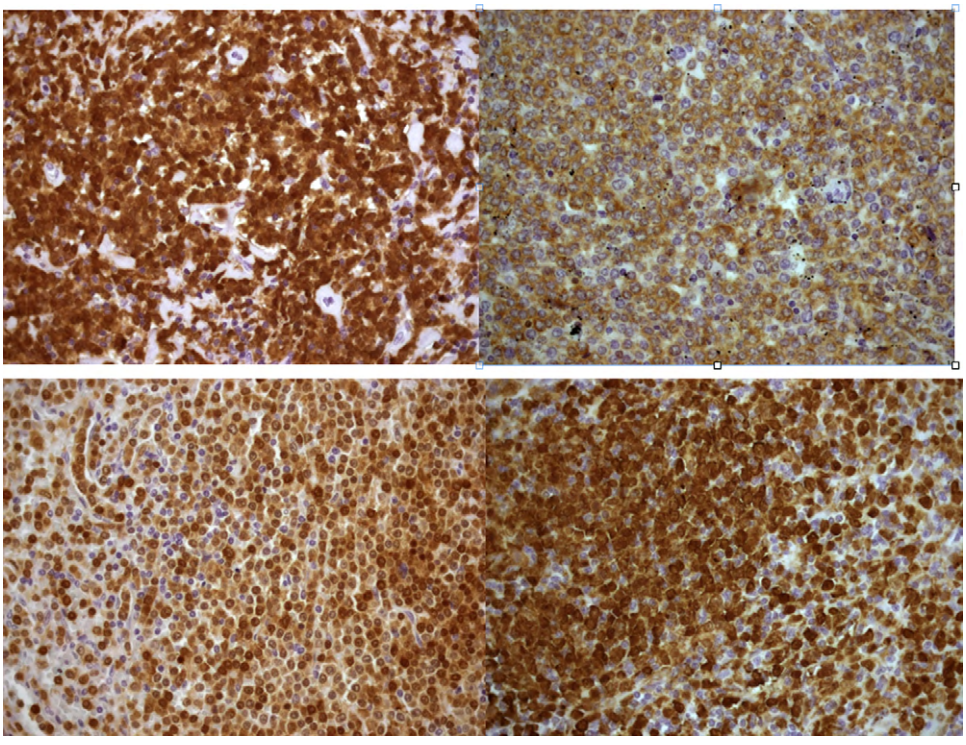

Fig. 1. Example of Syk staining in B-cell lymphomas showing different types of cellular localizations. Upper panel, left: nuclear localization in mantle cell lymphoma. Upper panel, right: cytoplasmic localization in marginal zone lymphoma. Lower panel, left: predominantly cytoplasmic localization in marginal zone lymphoma. Lower panel, right: predominantly nuclear localization in marginal zone lymphoma. All images, original magnification 40×.

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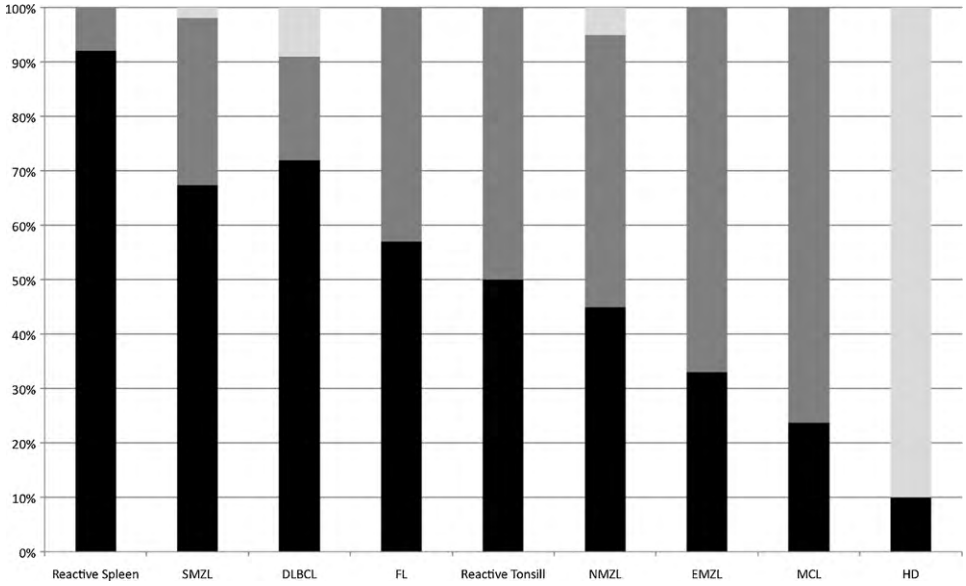

Fig. 2. Pattern of Syk cellular localization by histotype: black (cytoplasmic), dark grey (nuclear), and light grey (no expression).

apparently decreased from reactive spleen, splenic MZL, and DLBCL, through FL, reactive tonsils, nodal MZL and MALT lymphomas, and ultimately to MCL. HD cases were mostly negative for Syk staining.

Our extensive immunohistochemical characterization for the first time better defined sub-cellular localization of Syk in lymphomatous neoplastic cells, since previous reports have shown that Syk kinase can reside both in the nucleus and the cytoplasm of lymphoid and epithelial cells and a nucleo-cytoplasmic traffic of this protein has been proven [7,8]. A relatively strong expression of Syk could be demonstrated in the vast majority of non-Hodgkin lymphoma subtypes, with different patterns of sub-cellular localization. DLBCL, reactive spleen and splenic MZL showed a statistically significant preferential expression of Syk at cytoplasmic level, at a variance with the prevalent nuclear expression observed in MCL. Taken together, these figures point toward a divergent Syk localization in different lymphoma subtypes. Further studies are required to test whether Syk plays its role of kinase when it is mainly present in the cytoplasm and/or as transcription regulator when predominantly resident in the nucleus.

Conflict of interest statement

The authors have no conflict of interest.

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Maurilio Ponzoni
Pathology Unit & Unit of Lymphoid Malignancies, San Raffaele H Scientific Institute, Milan, Italy

Silvia Uccella
Anatomic Pathology Unit, Un. of Insubria, Osp. di Circolo, Varese, Italy

Michael Mian
Andrea Rinaldi
Laboratory of Experimental Oncology and Lymphoma Unit, Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland

Fabio Facchetti
Department of Pathology, University of Brescia, I Servizio di Anatomia Patologica, Spedali Civili di Brescia, Brescia, Italy

Giancarlo Pruneri
Division of Pathology and Laboratory Medicine, European Institute of Oncology, Milan, Italy

Gianluca Gaidano
Division of Hematology, Department of Clinical and Experimental Medicine & Centro Interdisciplinare di Biotecnologie per la Ricerca Medica Applicata, "Amedeo Avogadro" University of Eastern Piedmont, Novara, Italy

Carlo Capella
Anatomic Pathology Unit, Un. of Insubria, Osp. di Circolo, Varese, Italy

Emanuele Zucca
Laboratory of Experimental Oncology and Lymphoma Unit, Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland

Claudio Doglioni
Pathology Unit & Unit of Lymphoid Malignancies, San Raffaele H Scientific Institute, Milan, Italy

Francesco Bertoni*
Laboratory of Experimental Oncology and Lymphoma Unit, Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland

* Corresponding author at: Laboratory of Experimental Oncology, Oncology Institute of Southern Switzerland (IOSI), via Vincenzo Vela 6, 6500 Bellinzona, Switzerland.
Tel.: +41 91 8200 367; fax: +41 91 8200 397.
E-mail address: frbertoni@mac.com
(F. Bertoni)

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