

Spleen tyrosine kinase expression and its correlation with necrosis and high-risk histopathologic features in retinoblastoma

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To the Editor: Retinoblastoma (RB) is the most common primary malignant intra-ocular tumor in children. It is thought to be initiated in response to biallelic *RB1* inactivation and loss of functional RB protein. Spleen tyrosine kinase (SYK) plays different roles in the regulation of immunomodulatory signaling and cell proliferation in multiple malignancies, indicating either poor or favorable prognosis. A previous study showed that SYK is the fifth most significant gene and the only up-regulated kinase gene in RB according to the results derived from whole-genome sequencing, and SYK is also required for tumor cell survival.^[1] However, the specific role of SYK in RB is still poorly understood. In this study, we examined SYK expression in RB and analyzed its relevance to necrosis and histopathologic high-risk factors (HRFs).

The research protocol was approved by the ethics committee of the Second People's Hospital of Yunnan Province in China. The ethics committee waived the need to obtain informed consent. Formalin-fixed and paraffin-embedded sections of 62 RB eyes (35 males and 27 females, aged 1–14 years), six non-neoplasia lesions (three eyeball atrophy, two endophthalmitis, one cornea perforation), and nine pseudoretinoblastoma,^[2] collected from 2005 to 2016 by the Department of Pathology at the Second People's Hospital of Yunnan Province, were evaluated. All hematoxylin and eosin slides of RB were retrospectively reviewed and examined by microscopy to estimate pathological necrosis and important HRFs. Necrosis was graded as follows: grade 0, no necrosis; grade 1, slight necrosis (less than 30%); grade 2, moderate necrosis (30–75%); grade 3, extensive necrosis (greater than 75%).^[3] Choroidal invasion and invasion of the optic nerve posterior to the lamina cribrosa were considered HRFs, as proposed by both Children's Oncology Group and National Cancer Institute. Formalin-fixed and paraffin-embedded sections were evaluated by immunohistochemical staining of SYK

(1: 100, SYK polyclonal antibody; Santa Cruz Biotechnology, Santa Clara, CA, USA). Immunohistochemical scores were determined using a semi-quantitative method.^[4] The relationships between SYK expression and necrosis as well as HRFs were analyzed by Spearman rank correlation for bivariate analysis with SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

SYK was immunopositive in all RB eyes, but immunonegative in all non-neoplasia lesions and pseudoretinoblastoma eyes [Figure 1]. SYK was strongly immunostained in RB eyes – in the nucleus and cytoplasm of RB cells. Histologically, 30 tumors (48.4%) had 0 HRF (neither optic nerve invasion nor choroidal invasion), 26 tumors (41.9%) had one HRF (either optic nerve invasion or choroidal invasion), and six tumors (9.7%) had two HRFs (both optic nerve invasion and choroidal invasion). There was no correlation between SYK expression and number of HRFs (correlation coefficient: 0.249, $P = 0.051$) in RB. Sixteen (25.8%), 18 (29.0%), 16 (25.8%), and 12 cases (19.4%) had no, slight, moderate, and extensive necrosis, respectively. Negative correlation was observed between SYK expression and necrosis (correlation coefficient: -0.512 , $P < 0.001$).

SYK is expressed in various organs, highest in cells of hematopoietic origins. Our research revealed that SYK was silenced in benign retinas and activated in RB [Figure 1]. SYK was also found to be a good marker for differentiating malignant tumors from benign diseases in the retina. The negative correlation between SYK expression and tumor necrosis suggests that SYK is an important promoter of tumorigenesis in RB. Knockdown of SYK increased cell apoptosis and decreased RB cell viability, as well as activating caspase-3-positive cells in RB.^[1]

Administration of adjunctive chemotherapy in RB depends on HRFs detected by pathologic examination.

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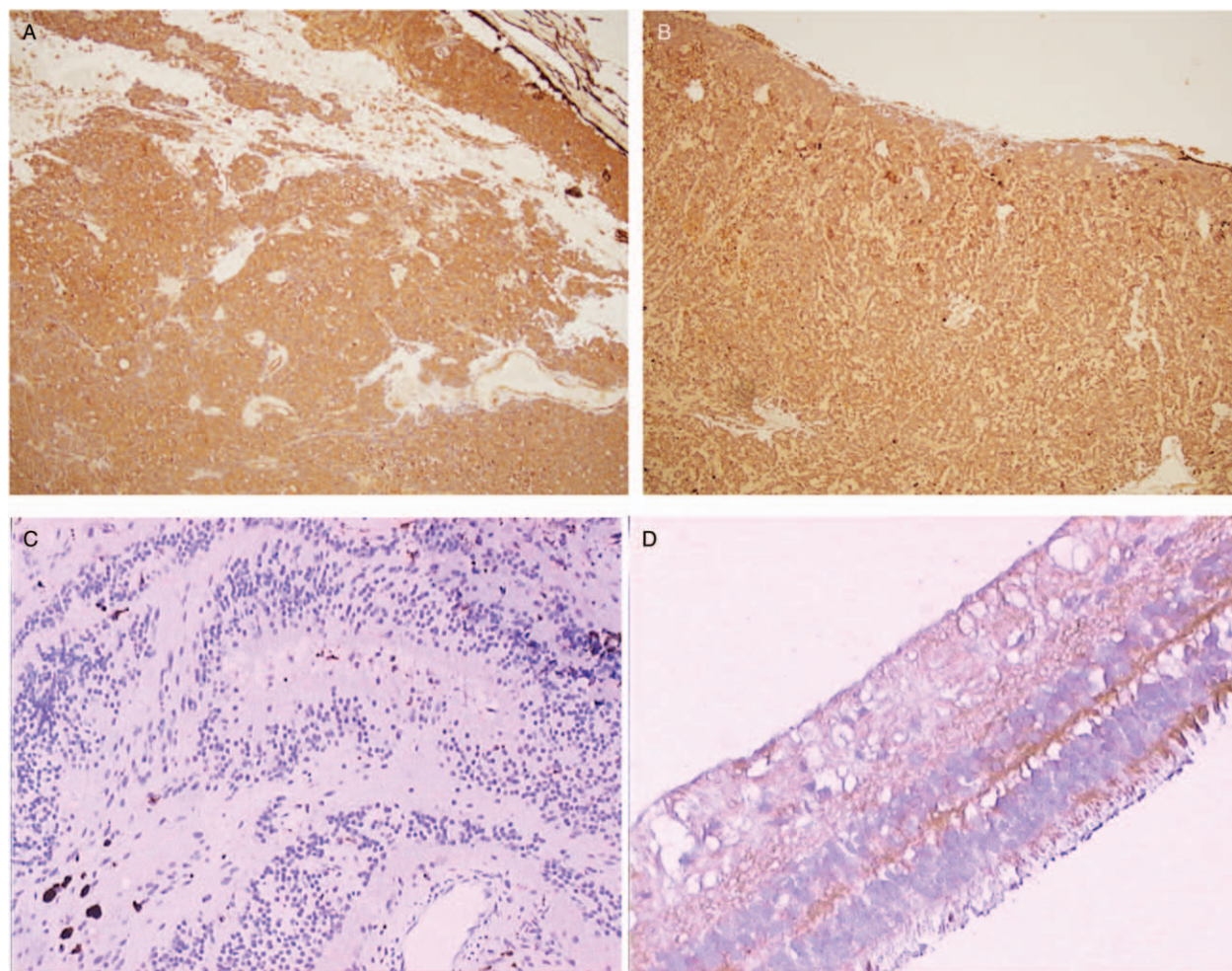


Figure 1: Immunohistochemical staining of SYK in RB. SYK was strongly and extensively stained in two patients with RB (A and B, original magnification $\times 40$), whereas staining was negative in pseudoretinoblastoma (C, a case of toxocariasis, original magnification $\times 200$) and other non-neoplasia lesions (D, a case of cornea perforation, original magnification $\times 200$). SYK: Spleen tyrosine kinase; RB: Retinoblastoma.

Conventional HRFs include extraocular extension, orbital invasion, massive uveal invasion, invasion of the optic nerve posterior to the lamina cribrosa or the line of surgical transection, and anterior segment involvement. The most important HRFs are optic nerve invasion and/or choroidal invasion, which were not correlated with SYK expression in our study.

Pseudoretinoblastoma, which mimics RB with similar symptoms and clinical examination results, is difficult to be detected by clinical and imaging diagnostic techniques.^[2] Our results indicate that SYK may be a useful clinical marker for differentiating these diseases using protein- or gene-based methods.

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Conflicts of interest

None.

References

1. Zhang J, Benavente CA, McEvoy J, Flores-Otero J, Ding L, Chen X, *et al.* A novel retinoblastoma therapy from genomic and epigenetic analyses. *Nature* 2012;481:329–334. doi: 10.1038/nature10733.
2. Yang Y, Sun T, Cao B, Shen H. Pseudoretinoblastoma of 9 enucleated eyes simulating retinoblastoma in 70 enucleated eyes. *Int J Clin Exp Pathol* 2017;10:9475–9481.
3. Kashyap S, Sethi S, Meel R, Pushker N, Sen S, Bajaj MS, *et al.* A histopathologic analysis of eyes primarily enucleated for advanced intraocular retinoblastoma from a developing country. *Arch Pathol Lab Med* 2012;136:190–193. doi: 10.5858/arpa.2010-0759-OA.
4. Axiotis CA, Monteagudo C, Merino MJ, LaPorte N, Neumann RD. Immunohistochemical detection of P-glycoprotein in endometrial adenocarcinoma. *Am J Pathol* 1991;138:799–806.

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