Mutational and expressional analyses of NRF2 and KEAP1 in sarcomas

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ABSTRACT

Aims and background. Nuclear factor erythroid 2-related factor 2 (NRF2) activates expression of cytoprotective proteins such as GCLC and enhances cancer cell survival, whereas KEAP1 inhibits NRF2 by mediating NRF2 degradation. Somatic mutation of NRF2 and KEAP1 genes and loss of KEAP1 expression are detected in many carcinomas and contribute to cancer development. The aim of this study was to see whether mutational and expressional alterations of NRF2 and KEAP1 genes are features of human sarcomas as well.

Methods. We analyzed somatic mutations of NRF2 and KEAP1 genes in 108 sarcoma tissues from malignant fibrous histiocytomas, rhabdomyosarcomas, osteosarcomas, malignant peripheral nerve sheath tumors, leiomyosarcomas, synovial sarcomas, liposarcomas, angiosarcomas, chondrosarcomas and Ewing sarcomas by single-strand conformation polymorphism. Also, we analyzed expressions of NRF2, KEAP1 and GCLC in sarcoma tissues by immunohistochemistry.

Results. Tissue expressions of NRF2 and GCLC were found in 93% and 76% of the sarcomas, respectively, indicating that NRF2 signaling might be activated in most sarcomas. Loss of KEAP1 expression was observed in 24% of the sarcomas, whereas neither NRF2 nor KEAP1 somatic gene mutation was seen in the sarcomas.

Conclusions. Our data suggest a possible activation of the NRF2/KEAP1 system in sarcomas and a possible contribution to cytoprotection of sarcoma cells.

Key words: cytoprotection, expression, KEAP1, mutation, NRF2, sarcoma.

Acknowledgments: The study was supported by the funds from the National Research Foundation (2009-007-1498).

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Received September 26, 2011; accepted December 12, 2011.