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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 cytopretection of sarcoma cells.

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

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