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The Role of NF-kB and Bortezomib in Uveal Melanoma

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PURPOSE: Uveal melanoma (UM) is the most common primary intra-ocular malignancy in adults. Despite the high accuracy of clinical diagnosis and advances in local treatment, more than 40% of UM patients will develop metastases that ultimately lead to death. The nuclear factor-kappa B (NF-*k*B) is a dimeric transcription factor related to carcinogenesis by regulating genes involved in apoptosis, cell cycle, differentiation and migration. Bortezomib is a NF-*k*B inhibitor, which received accelerated FDA approval to treat multiple myeloma patients refractory to previous therapies. Although the roles of NF-*k*B in protecting skin melanoma cells from apoptosis and the effects of bortezomib in skin melanoma have received considerable interest recently, the role of NF-*k*B in UM has not yet been studied.
METHODS: Patient medical charts were reviewed to provide the following information: age at date of diagnosis, gender, previous ocular radiation therapy, development of metastasis and date of last medical consultation with clinical status. Histopathological analysis of the specimens with regards to prognostic factors such as cell type, largest tumor dimension, tumor-infiltrating lymphocytes and closed vascular loops was performed. Thirty-one UM specimens were subjected to immunohistochemical analysis with an anti-NF-*k*B monoclonal antibody. Samples were classified as low (+1), moderate (+2) or high (+3) positivity with respect to extent and intensity of staining. The final microscopic classification was defined as low (group 1) if the combination of both extend and intensity of staining was < +5 and high (group 2) if this combination was ³ +5. Four human UM cell lines and one human transformed uveal melanocyte cell line were assayed for proliferative ability under conditions of increasing concentrations of bortezomib.
RESULTS: All cases subjected to immunohistochemistry were found to be NF-*κ*B positive. Seventy-one percent (n = 22) presented with high cytoplasmic and nuclear immunoreactivity. Meanwhile, among lesions with low general immunoreactivity (n = 9), 100% presented with cytoplasmic reactivity while

nuclear staining was absent. Although statistical analysis demonstrated no correlation between NF-κB expression and clinicopathological prognostic factors, interestingly, patients that presented with high expression of NF-κB had a higher cumulative metastasis rate than those with low expression. With regards to proliferation assays, all UM cell lines exposed to bortezomib disclosed a decreased proliferation rate when compared to the control group. **CONCLUSIONS:** The results of this study demonstrated that NF-κB is highly expressed in UM and that bortezomib treatment effectively decreases the proliferation rate of human UM cell lines. Recent advances in the development of drugs that down-regulate NF-κB signalling may therefore provide potential adjuvant modalities to conventional therapies in UM.