Curcumin Ameliorates the In Vitro Efficacy of Carfilzomib in Human Multiple Myeloma U266 Cells Targeting p53 and NF-κB Pathways

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Multiple myeloma (MM) is a malignant B-cell neoplasm with accumulation of malignant plasma cells in bone marrow. Pharmacological therapy improves response frequency even if with various associated toxicities. The ubiquitin-proteasome pathway is essential for many fundamental cellular processes, including the cell cycle, apoptosis, angiogenesis, and differentiation. Recently, carfilzomib (CFZ), a tetrapeptide epoxyketone-based irreversible proteasome inhibitor, obtained responses in BTZ-resistant MM patients. In recent years, new drugs or drug combinations simultaneously targeting the p53 and NF-κB pathways to combat cancer is evolving as an attractive strategy which could have remarkable therapeutic potential also in MM. Curcumin, a phenolic compound isolated from the plant Curcuma longa, has been discovered to have chemopreventive action for an extensive type of tumors like colon, breast, lung, and esophagus , modulating several transcription factors (including NF-κB), protein kinases and other oncogenic molecules. Herein, we investigated if combination of curcumin with carfilzomib (CFZ) can induce a better cytotoxic effect on in vitro cultured MM cells. The cytotoxic effects of the two compounds, alone or in combination, was investigated on in vitro cultured U266 cells studying the modulation of the p53-p21, NF-κB, and ubiquitin-proteasome pathways. Cell viability data showed that curcumin can significantly ameliorate the cytotoxic effect of CFZ. Furthermore, curcumin addition enhanced CFZ proapoptotic effect. Our results confirmed the induction of p53/p21 axis in anticancer activities of curcumin, effect more pronounced in the CFZ-curcumin tested combinations. Furthermore, CFZ or curcumin decreased NF-κB nuclear levels compared to control. However, curcumin alone was not able to affect proteasome at the tested dose, confirming a different mechanism in NF-κB inhibition involving IκBα phosphorylation. These findings evidence that curcumin can ameliorate the efficacy of CFZ, and lead us to hypothesize that this effect might be useful to optimize CFZ therapy in MM patients.

Keywords: Myeloma, Curcumin, Carfilzomib, NF-κB, p53, proteasome inhibitor.