Cell Communication and Signaling BioMed Central

Meeting abstract

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New bortezomib-based combination therapy for elimination of myeloma cells

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from 12th Joint Meeting of the Signal Transduction Society (STS). Signal Transduction: Receptors, Mediators and Genes
Weimar, Germany. 29–31 October 2008

Published: 26 February 2009

Cell Communication and Signaling 2009, **7**(Suppl 1):A34 doi:10.1186/1478-811X-7-S1-A34

This abstract is available from: http://www.biosignaling.com/content/7/S1/A34

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The clinically approved proteasome inhibitor bortezomib (Bz) represents a promising agent for the therapy of relapsed multiple myeloma. However, long-term remissions are difficult to achieve, in fact myeloma cells often develop secondary resistance to proteasome inhibition. We recently demonstrated that myeloma cells are highly sensitive towards proteasome inhibitors due to their extensive rate of immunoglobulin synthesis, thereby triggering the terminal unfolded protein response (UPR) and apoptosis via endoplasmic reticulum (ER) stress. We want to identify synergistic agents sensitizing myeloma cells towards Bz. The calcium channel blocker verapamil has been shown to inhibit proliferation of leukemia cells and to interfere with multi drug resistance-based drug elimination. Hence, we analysed the effect of Bz together with verapamil on the viability and ER-stress in different human myeloma cell lines. The combination of Bz and verapamil synergistically decreased cell viability of myeloma cell lines by inducing apoptotic and necrotic cell death. Importantly, Bz-mediated activation of major UPR signalling pathways was enhanced by verapamil. The Bz/verapamil treatment also resulted in caspase activation followed by PARP cleavage. NF-kB DNA-binding activity markedly declined in myeloma cells treated with both agents. In contrast to Bz, proteasomal activity was not altered by verapamil. However, the amount of ubiquitinylated proteins in detergent-insoluble fractions was much higher in the presence of Bz/verapamil compared to Bz alone, suggesting increased formation of protein aggregates within the cell. Beside that, verapamil reduced expression of the multi drug resistance protein 1 and impaired drug-efflux in the myeloma cells. We conclude that verapamil increased the pro-apoptotic effect of Bz by inducing additional ER-stress signals along with inhibiting the NF-kB activity and modulating drug transport mechanism. Thus, the combination therapy Bz/verapamil may provide a more effective treatment-strategy for multiple myeloma than the Bz-monotherapy and overcome drug resistance.