THE IMPACT OF BETA-BLOCKERS ON MULTIPLE MYELOMA CELL SURVIVAL

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Objectives

Stress has been shown to associate with adverse clinical outcomes in cancer. Stress hormones, norepinephrine and epinephrine, bind and activate adrenergic receptors (ADRB1 and ADRB2) and regulate key functions in cancer initiation and progression. The use of anti-adrenergic beta-blockers demonstrated promising therapeutic responses in cancer patients (Hwa et al. 2017). However, the effect and underlying pathways of adrenergic signaling and beta-blockers in Multiple Myeloma (MM) is not well defined.

In this study, we aim to investigate the anti-tumoral effects of both selective and non-selective beta-blockers in MM cells. In addition, the underlying mechanisms and the combination with standard-of-care agents will be studied as well.

Methods

The anti-tumor effect of three different beta-blockers propranolol, bisoprolol and ICI 118.551 was determined with Cell Titer Glo assay and AnnexinV-7AAD staining. The effects on viability and apoptosis were studied on human MM cell lines (LP1, OPM2, ANBL6 and XG2), human bone marrow stromal cells (HS5), mouse 5T33MM cells, primary mouse bone marrow stromal cells and freshly isolated human bone marrow patient samples. The ADRB expression of cell lines was examined by qRT-PCR and western blot. Patient cohorts TT2-TT3-MMRF were used to correlate ADRB expression and survival. Statistical analyses were performed with GraphPad Prism 6.0. Each experiment was performed at least 4 times. Differences between variables were assessed by Mann-Whitney U test (two groups) and One-way ANOVA (multiple groups) with p values less than 0.05 considered as statistically significant.

Results

The beta-2 adrenergic receptor, also known as ADRB2, was highly expressed in human MM cell lines LP1 and XG2. Among the three beta-blockers, propranolol significantly induced apoptosis in MM cells and ADRB2 was significantly decreased after propranolol treatment. Stromal cells treated with propranolol were highly resistant and showed a protective effect. In vitro, propranolol affected myeloma cell metabolism by increasing hexokinase II and decreasing Glut1. We found that combination of propranolol and standard-of-care agents bortezomib and melphalan significantly induced apoptosis of 5T33MM cells.

In patient cohorts ADRB2 expression was detected in different immune cells in particular CD3. In the MMRF patient cohort, we observed that a high ADRB2 expression was correlated with a poor overall survival and progression free survival in myeloma patients.

Conclusion

Propranolol is a widely used beta-blocker that decreased viability in MM cells and altered MM metabolism. The use of propranolol in combination with standard-of-care agents is a promising therapeutic strategy. In the future, we aim to study the combination of propranolol and bortezomib in vivo in the 5TMM model. Effects on the tumor cells as well as the immune microenvironment will be investigated.