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Meeting abstract

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Unfolded protein response is activated by single application of BMP-2

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Introduction

Tumor formation and progression is characterized by a proceeding degeneration of genetic material. As a consequence a growing number of proteins are misfolded and thus accumulate in the lumen of the endoplasmic reticulum and induce the "unfolded protein response" (UPR). Activation of the UPR can cause elimination of cells through apoptosis or a restabilization and therefore cell survival.

We could previously show that chronic and single application of BMP-2 alters distinct subsets of genes in the breast cancer cell line MCF-7. The group of apoptosis-related genes was predominantly regulated after short-term application of BMP-2. The protein kinase R (PKR) exhibited the most prominent BMP-2 dependent regulation.

Materials and methods

In order to verify the array results, we incubated the breast carcinoma cell line MCF-7 with 50 ng/ml or 100 ng/ml BMP-2 and performed real real-time PCR for PKR and selected genes associated with UPR and apoptosis regulation at several time points. The activation of the PKR pathway was analyzed by immunoblotting using phosphor-specific antibodies for PKR and eIF2alpha. UPR is involved in apoptosis regulation. Therefore, the cell cycle status of the cells was studied by FACS analysis using the Cell Cycle Test (Becton Dickinson).

Results

Incubation of MCF-7 cells with BMP-2 induces a 2-fold induction of PKR expression after 24 h independent of the amount of BMP-2 applied. The alterations of PKR expression found on the mRNA level were further investigated on the protein level by western blot analysis. We could show that the BMP-2 dependent up-regulation of PKR mRNA is paralleled by an increase in PKR protein content with a subsequent down-regulation of the total protein content of PKR after 24 hours. Incubation of MCF-7 cells with BMP-2 led to a robust increase of the fraction of phosphorylated PKR after 4 hours suggesting an additional route of BMP-2 dependent regulation of PKR activation. A prominent substrate of PKR is the alpha-subunit of the translation factor eIF2. Phosphorylation of eIF2alpha leads to an inhibition of translation. During incubation of MCF-7 cells with BMP-2 the level of total eIF2alpha is not altered. In contrast, the amount of phosphorylated eIF2alpha is increased in BMP-2 treated MCF-7 cells after 16 h up to 24 h. compared to serum-free controls. Cell cycle analysis revealed a slight reduction of apoptotic cells under the influence of BMP-2 in comparison to controls.

Conclusion

BMP-2 is able to activate the cellular stress response in the breast carcinoma cell line MCF-7 giving a link to a new impact of BMP-2 in tumorigenesis.

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