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Contribution of ERK nuclear translocation to cisplatin resistance in ovarian cancer cells

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The clinical use of the anti-cancer drug cisplatin is impaired by the development of resistance against this drug. However, the mechanisms of resistance are not completely understood yet. In this work, the importance of the subcellular localization of ERK1/2 (Extracellular Signal regulated Kinase1/2) for cisplatin resistance in ovarian cancer cells was examined. We studied both EFO27 and A2780 ovarian carcinoma cells and their corresponding cisplatin-resistant variants (EFO27/CDDP and A2780cis) for this purpose. Using MTT test and apoptosis assay (Annexin V-FITC using flow cytometry) we found that inhibition of ERK increased the sensitivity of cisplatin in EFO27 and EFO27/CDDP cells. However, opposite effect was found in A2780 cells. We also investigated translocation of ERK1/2 to nucleus in response to cisplatin by immunofluorescence. Translocation of ERK1/2 to nucleus in response to cisplatin was detected in EFO27 and EFO27/CDDP cells, but no such translocation was detected for A2780 and A2780cis cells. Further, PEA-15 (phosphoprotein enriched in astrocytes), a small protein which inhibits ERK1/2 translocation to nucleus, was used to investigate ERK cytoplasmic sequestration in cisplatin resistance. For this purpose, PEA-15wt, PEA-15AA (nonphosphorylatable form) and PEA-15DD (phosphomimetic form) were overexpressed in A2780cis and EFO27/CDDP cell lines. The overexpression of PEA-15 and its mutated forms showed an increase in sensitivity of EFO27/CDDP cells to cisplatin but a decreased sensitivity of A2780cis cells to cisplatin showing the importance of ERK1/2 localization for cisplatin sensitivity. Therefore, ERK1/2 nuclear translocation could be a good prognostic biomarker to determine cisplatin sensitivity in ovarian cancer as shown at cellular level.

Biography

Shahana Dilruba (S.D.) received her B.Sc. and M.Sc. degree in Biochemistry and Molecular Biology at Dhaka University. Afterwards, she performed a M.Sc. study in Molecular Biotechnology at the University of Bonn. Currently, she is working as a PhD student at the Department of Clinical Pharmacy, Institute of Pharmacy, University of Bonn under the supervision of Prof. Ulrich Jaehde. In her PhD work, she investigates the role of subcellular localization of activated ERK in cisplatin resistance in ovarian cancer cells. This PhD work is funded by Bonn International Graduate School (BIGS) and German Ministry of Education and Research (BMBF).

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