Establishment and Characterization of Topotecan Resistant NCI-H460/TPT10 Cells

Lu, Kimberly (School: William A. Shine Great Neck South High School)

Topotecan (TPT) is a chemotherapeutic drug frequently used to treat lung cancer, which is the leading cause of cancer-related death in the US. However, the development of drug resistance in lung tumors remains a major obstacle to successful chemotherapy. Therefore, a better understanding of the underlying mechanisms of TPT resistance is critical. In this study, the first TPT-resistant human non-small cell lung cancer (NSCLC) cell line, NCI-H460/TPT10, was established by culturing parental cells in stepwise increasing doses of TPT. Cell viability assays revealed that NCI-H460/TPT10 cells exhibited a 3470-fold increase in resistance to TPT compared to parental NCI-H460 cells. Western blot analysis and immunofluorescence imaging showed an overexpression of the ABC transporter ABCG2 in NCI-H460/TPT10 cells indicating that ABCG2 was likely to be involved in TPT-resistance by functioning as a drug efflux pump. This was confirmed by low cytosolic accumulation and increased efflux of radioactive [3H]-mitoxantrone (MX), a substitute for TPT, in NCI-H460/TPT10 cells and the reversal of these effects in the presence of ABCG2 inhibitor Ko143. Intracellular accumulation of [3H]-MX in NCI-H460/TPT10 cells was 55% less than that in NCI-H460 cells ($p<0.001$), while the drug efflux function of NCI-H460/TPT10 cells was 13% greater than that in NCI-H460 cells ($p<0.01$). Collectively, these results indicate overexpression of ABCG2 to be one of the major mechanisms of resistance by NSCLC cells to TPT. Moreover, this newly established TPT-resistant NCI-H460/TPT10 cell line serves as a clinically-relevant model for future drug screening and the development of targeted strategies to overcome ABCG2-mediated multidrug resistance in cancers.

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