ABSTRACT

Estrogen signalling pathway plays crucial role in carcinogenesis of breast cancer. Estrogen receptor (ER) is a prototypical hormone receptor that upon binding its ligand, estradiol, translocates into the nucleus and turns on target genes related to cellular proliferation and survival. Although estrogen signalling physiologically supports normal breast tissue development, deregulations of this pathway contribute to development of breast tumours that are estrogen receptor dependent.

One of the main obstacles in breast cancer treatment is acquired resistance to common anticancer drugs also known as multidrug resistance (MDR). The switch between chemotherapy responsive to chemotherapy resistant cell phenotype is usually accompanied by increased expression of ABC transporters, special membrane proteins responsible for export of various kinds of commonly used anticancer drugs from the intracellular to extracellular space and is also linked to the existence of cancer stem cells (CSCs). ABC transporters can not only export chemotherapeutic drugs but may modulate tumour microenvironment through the transport of endogenous intracellular substrates such as leukotrienes (LTs), sphingolipids and prostaglandins PGs). This function may also play important role in carcinogenesis.

The aim of the thesis was to compare expression profile of all known human 49 ABC transporters between ER positive MCF7 breast cancer cell line and MCF7 cell line resistant to most commonly used endocrine therapy agent - tamoxifen. Our results show significantly altered expression of several ABC transporters from A family involved mainly in lipid trafficking (*ABCA2*, *ABCA4*, *ABCA5*, *ABCA7*, *ABCA10* and *ABCA12*). We document also higher expression of ABC transporters belonging to the C family (*ABCC5*, *ABCC6*, *ABCC8* and *ABCC10*), one peroxisomal transporter (*ABCD4*) and one mitochondrial transporter (*ABCB10*). Altered expression of two members of F family (*ABCF2* and *ABCF3*) was observed as well.

We also detected significantly higher expression of selected stem cell markers (*ABCG2*, *SOX2*, *CD44*, *CDH2*, *CXCR4)* in tamoxifen resistant cells suggesting that treatment of cells with tamoxifen selects tumour cells that exhibit stem cell properties, supporting the hypothesis that cancer stem cells may contribute to breast cancer therapy failure.

Key words: breast cancer; ABC transporters; tamoxifen; resistance