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Galactosylceramide (GalCer) acts as an anti-apoptotic molecule and increases the resistance of breast cancer cells to microenvironmental stressors and anti-cancer drugs

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Our clinical and experimental data strongly suggest that UDP- galactose:ceramide galactosyl transferase (UGT8) is a significant index of tumor aggressiveness and a potential marker for the prognostic evaluation of lung metastases in breast cancer (Dziegiel et al., 2010; Owczarek et al., 2013). Recently, we show that increased tumorigenicity and metastatic potential of breast cancer cells overexpressing UGT8 and GalCer is due to their increased resistance to apoptosis which is triggered by multiple factors. Such cells were insensitive to different types of cellular stress found in tumor microenvironment as hypoxia and free radicals. Additionally, accumulation of GalCer in breast cancer cells was associated with their higher resistance to such anti-cancer drugs as doxorubicin and etoposide. Therefore, we speculate that GalCer facilitates the survival of breast cancer cells in a hostile tumor microenvironment and is involved in multidrug-resistance (MDR) of cancer cells. The quantification of ceramide in breast cancer cells revealed that anti-apoptotic effects of GalCer are not associated with decreased levels of pro-apoptotic ceramide by its conversion to GalCer, suggesting that ceramide glycosylation is not a major mechanism ensuring resistance of breast cancer cells to apoptosis. Instead, we propose that the key anti-apoptotic molecule in breast cancer cells is GalCer by itself, since its conversion to sulfatide is directly associated with their increased sensitivity to hypoxia and doxorubicin. Interestingly, gene expression profiling revealed statistically significant down-regulation of pro-apoptotic TNFRSF1B, TNFRS9 and up-regulation of anti-apoptotic BCL2 in breast cancer cells with high expression of GalCer. These data suggest that GalCer can affect the expression of apoptosis-related genes on the level of transcription. However, the direct molecular mechanisms by which GalCer regulates apoptotic gene expression is still under investigation. In summary, this talk will highlight the importance of glycolipid rheostat in cancer progression.

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