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# Galactosylceramide-Mediated EGFR Activation in Lipid Rafts: a Mechanism of Drug Resistance in Breast Cancer through AKT Pathway Activation and p53 Down-Regulation

The Epidermal Growth Factor Receptor (EGFR) plays a significant role in developing and progressing various cancers, including breast cancer (BC). Its role in promoting cell proliferation, survival, and metastasis makes it an important target for therapeutic interventions. Despite this, EGFR-directed therapies in BC have faced numerous challenges, primarily due to the complex molecular landscape of the disease and the development of resistance mechanisms. It was shown that one of the mechanisms, driving the drug resistance (DR) of BC cells involves galactosylceramide (GalCer) [1], a glycosphingolipid known for its anti-apoptotic properties [2]. GalCer has been implicated in BC cell DR by downregulating the tumor suppressor p53, a process which simultaneously downregulates the expression of pro-apoptotic TNFSF1B and TNFSF9 and upregulates the expression of Bcl-2, affecting at the same time extrinsic and intrinsic (mitochondrial) apoptotic pathways [1]

In the present study, we show that GalCer downregulates the expression of p53 by inducing the ligand-independent phosphorylation of EGFR in lipid rafts, which causes the activation of the AKT signaling pathway, the central player in cell survival and proliferation, and AKT-dependent increased expression of E3 ubiquitin-protein ligase MDM2. The GalCer-dependent activation of EGFR represents a new mechanism by which glycosphingolipids, regulate EGFR-mediated signaling pathways.

## References

[1] Suchanski J, Reza S, Urbaniak A, Woldanska W, Kocbach B, Ugorski M. Galactosylceramide Upregulates the Expression of the BCL2 Gene and Downregulates the Expression of TNFRSF1B and TNFRSF9 Genes, Acting as an Anti-Apoptotic Molecule in Breast Cancer Cells. Cancers (Basel). 2024 Jan 17;16(2):389 [2]Owczarek TB, Suchanski J, Pula B, Kmiecik AM, Chadalski M, Jethon A, Dziegiel P, Ugorski M. Galactosylceramide affects tumorigenic and metastatic properties of breast cancer cells as an anti-apoptotic molecule. PLoS One. 2013 Dec 31;8(12):e84191

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