Mechanism of the tumor suppressive properties of glycodelin

Malignant growth in cancer is characterized by loss of cell differentiation, uncontrolled proliferation and resistance to apoptosis. In some cases it is possible to revert malignant cells back to normal. However, this process is not very well understood. Many of the tumor suppressor genes that protect cells against malignant transformation regulate cell differentiation. Our previous results have shown that glycodelin, a human reproduction-associated glycoprotein, induces morphological differentiation in endometrial adenocarcinoma cells. Concomitantly, these cells exhibit reduced tumor growth in vivo in a preclinical mouse model, suggesting that glycodelin acts as a tumor suppressor. Glycodelin is expressed in differentiated epithelial cells, especially those of reproductive tissues, and is involved in cell recognition both in reproductive and immune systems. It is expressed in normal endometrium, where its expression is regulated by progesterone. In hormone-related cancers, including endometrial cancer, glycodelin expression is reduced and more frequently observed in well-differentiated than in more aggressive less differentiated tumors.

![Diagram of Mechanism of the tumor suppressive properties of glycodelin]

Despite of the evident role of glycodelin in epithelial differentiation and tumor growth suppression, the mechanisms involved in this have not been elucidated. Based on previous studies, mitogen-activated protein kinase (MAPK) signaling pathway is a strong candidate for a mediator of glycodelin-induced differentiation. Thus, we examined the mechanisms mediating the effects of glycodelin on HEC-1B endometrial cancer cells.

We found that glycodelin-induced cell differentiation is associated with repressed activation of protein kinase C delta (PKCδ), which is one of the regulators of the classical MAPK pathway. PKCs are serine/threonine protein kinases, which are activated in several cellular processes and often dysregulated in cancer. PKCδ has also been implicated in pathogenesis of different cancers. However, the functions and effects of PKCδ appears to be cancer- and cell type-specific. Thus, depending on the context it has been found to act both as a tumor promoter and suppressor. Phorbol esters, such as phorbol 12-myristate 13-acetate (PMA) have been found to activate several PKCs. Partially because of this, phorbol esters are...
considered as tumor promoters. Therefore, we tested the effect of PMA and transforming growth factor β (TGFβ) on endometrial cancer cells. TGFβ is an endogenous cancer-associated growth factor, which acts both as tumor promoter and suppressor. Our results suggest that glycodelin makes the cells resistant to the tumor promoting effects of PMA and TGFβ, which is mediated by repressed PKCδ activation. Therefore, it is feasible that previously observed tumor suppressive properties of glycodelin are related to repressed response to tumor growth promoting factors in the tumor microenvironment. These novel results have begun to uncover the mechanisms by which glycodelin reduces cancer cell growth and brings about a less malignant phenotype in cancer cells.

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