# Ganglioside GM3 as a modulator of cancer cell proliferation mediates enhanced expression of tumor suppressor PTEN

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The simple ganglioside GM3 has been shown to have anti-proliferative effects in several *in vitro* and *in vivo* cancer models. Although the exogenous ganglioside GM3 has an inhibitory effect on cancer cell proliferation, the exact mechanism by which it prevents cell proliferation remains unclear. Previous studies showed that MDM2 is an oncoprotein that controls tumorigenesis through both p53-dependent and p53-independent mechanisms, and tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a dual-specificity phosphatase that antagonizes phosphatidylinositol 3-kinase (PI-3K)/AKT signaling, is capable of blocking MDM2 nuclear translocation and destabilizing the MDM2 protein. Results from our current study show that GM3 treatment dramatically increases cyclin-dependent kinase (CDK) inhibitor (CKI) $p21^{WAF1}$ expression through the accumulation of p53 protein by the PTEN-mediated inhibition of the PI-3K/AKT/MDM2 survival signaling in HCT116 colon cancer cells. Moreover, the data herein clearly show that ganglioside GM3 induces p53-dependent transcriptional activity of $p21^{WAF1}$, as evidenced by the $p21^{WAF1}$ promoter-driven luciferase reporter plasmid (full-length $p21^{WAF1}$ promoter and a construct lacking the p53-binding sites). Additionally, ganglioside GM3 enhances expression of CKI $p27^{kip1}$ through the PTEN-mediated inhibition of the PI-3K/AKT signaling. Furthermore, the down-regulation of the cyclin E and CDK2 was clearly observed in GM3-treated HCT116 cells, but the down-regulation of cyclin D1

and CDK4 was not. On the contrary, suppression of PTEN levels by RNA interference restores the enhanced expression of p53-dependent $p21^{WAF1}$ and p53-independent $p27^{kip1}$ through inactivating the effect of PTEN on PI-3K/AKT signaling modulated by ganglioside GM3. These results suggest that ganglioside GM3-stimulated PTEN expression modulates cell cycle regulatory proteins, thus inhibiting cell growth. We conclude that ganglioside GM3 represents a modulator of cancer cell proliferation and may have potential for use in colorectal cancer therapy.