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Differentiation-inducing factor-1 suppresses breast cancer cell proliferation by reducing STAT3-mediated cyclin D1 expression

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Differentiation-inducing factor-1 (DIF-1) identified from *Dictyostelium* inhibits the proliferation of various cancer cells. However, the precise mechanism of DIF-1's action remains undetermined. Here, we investigated whether DIF-1 prevents tumor growth *in vivo* and how DIF-1 inhibits cell proliferation using breast cancer MCF-7 and 4T1 cells.
First, we performed experiments using cancer model mice made by injecting the cells into mammary fat pad. Oral administration of DIF-1 significantly suppressed the primary tumor growth without adverse effects.
DIF-1 strongly suppressed the proliferation of MCF-7 and 4T1 cells reducing the expression levels of STAT3 and cyclin D1. S3I-201, a STAT3 inhibitor, and the siRNA for STAT3 reduced cyclin D1 and inhibited cell proliferation, indicating that the reduction of cyclin D1 was caused by the reduction of STAT3. In MCF-7 cells, DIF-1 did not reduce STAT3 mRNA or promote STAT3 protein degradation, suggesting that DIF-1 inhibited STAT3 protein synthesis. We revealed that DIF-1 inhibited the phosphorylation (activation) of $p70^{S6K}$/$p85^{S6K}$. Inhibition of $p70^{S6K}$/$p85^{S6K}$ using rapamycin, an mTOR inhibitor, also reduced the expressions of STAT3 and cyclin D1.
In conclusion, DIF-1 exhibits anti-proliferative effect by reducing STAT3-mediated cyclin D1 in breast cancer cells. The inhibition of STAT3 by DIF-1 was caused by the suppression of protein synthesis through the inhibition of $p70^{S6K}$/$p85^{S6K}$. Our findings suggest that a novel anti-cancer agent against breast cancer could be developed using DIF -1 as a lead compound.