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Proliferation of Mammary Epithelial Cells Via RANKL-Id2

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Receptor activator of NF-kB ligand (RANKL) is a key regulator for mammary gland development during pregnancy. RANKL–deficient mice reveal impaired development of lobulo-alveolar mammary structures. Similar mammary gland defects have been reported in mice lacking Id2. Here we report that RANKL induces the proliferation of mammary epithelial cells via Id2. RANKL triggers a marked nuclear translocation of Id2 in mammary epithelial cells, leading to decreased p21 expression. Inhibition of Id2 expression strongly abrogated RANKL-induced epithelial cell growth and down-modulation of p21. An Id2-S5A mutant failed to induce nuclear translocation of Id2 and to inhibit p21-promoter activity after RANKL treatment. *In vivo* studies further demonstrated defective nuclear translocation of Id2, but normal expression of cyclin D1 in mammary epithelial cells of *rankl*$^{-/-}$ mice. Interestingly, p21 expression in *rankl*$^{-/-}$ mammary tissues during pregnancy was significantly increased compared to *rankl*$^{+/-}$mammary tissues. Moreover, RANKL stimulation failed to downregulate p21 expression and induced cell growth in *Id2*$^{-/-}$ mammary epithelial cells. Our results indicate that the inhibitor of helix-loop-helix protein Id2 is critical to control proliferation of mammary epithelial cells in response to RANKL stimulation through the inhibition of p21.