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Amplification of Notch3 and identification of Notch3 target gene in ovarian cancer

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Abstract

Gene amplification is one of the common mechanisms that activate oncogenes. In this study, we used SNP array to analyze genome-wide DNA copy number alterations in 31 high-grade ovarian serous carcinomas, the most lethal gynecologic neoplastic disease in women. We identified an amplicon at 19p13.12 in 6 (19.5%) of 31 ovarian high-grade serous carcinomas. This amplification was validated by digital karyotyping, quantitative real-time PCR, and dual-color fluorescence *in situ* hybridization (FISH). Furthermore, *Notch3* DNA copy number is positively correlated with Notch3 protein expression based on parallel immunohistochemistry and FISH studies in 111 high-grade tumors. Although several Notch3 downstream genes have been reported, the predominant Notch3-regulated gene(s) in ovarian cancer remains elusive. Based on expression-profiling analysis, we have identified *Pbx1*, a proto-oncogene in hematopoietic malignancy, as a main Notch3 target gene. *Pbx1* expression is transcriptionally regulated by Notch3 activation and Notch3/CSL protein complex directly binds to *Pbx1* promoter segment harboring the CSL binding sequence. The growth-inhibitory effect of gamma-secretase inhibitor could be partially reversed by ectopic *Pbx1* expression. Furthermore, functional studies by *Pbx1* shRNA knockdown demonstrate that *Pbx1* mediates cell proliferation and tumorigenicity. Taken together, the above findings indicate that *Notch3* is amplified in ovarian cancer and *Pbx1* is a direct target gene of *Notch3*. Inactivation of Notch3 and *Pbx1* can be a potential therapeutic approach for ovarian carcinomas.