GONADOTROPINS IN THE REGULATION OF CADHERIN-MEDIATED SURVIVAL OF HUMAN OVARIAN SURFACE EPITHELIAL CELLS

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INTRODUCTION. Epithelial ovarian cancer is the most common cause of cancer deaths among women in North America. Our understanding of the development of ovarian cancer depends on knowledge about the biology of its precursor, the human ovarian surface epithelium (OSE), which a single layer of flat-to-cuboidal mesothelium covering the surface of the ovary (reviewed in 1). However, the signaling pathways involved in the regulation of cell death and survival in human OSE are poorly understood. In the past, we have shown that N-cadherin is the prime calcium-dependent cell adhesion molecule that mediates OSE cell-cell interaction (2). In this study, we examined the anti-apoptotic role of N-cadherin in human OSE cultures, defined its regulation by gonadotropins (major regulators of ovarian function), and compared it with the responses of ovarian carcinoma lines.

METHODS. Three SV40 large T antigen (Tag)-transfected human OSE cell lines and two human epithelial ovarian cancer cell lines (OVCAR-3 and SKOV-3) were used in this study. To analyze the survival effect of N-cadherin, OSE cells were treated with EGTA or anti-N-cadherin function blocking antibodies and apoptosis was measured by TUNEL assay. To investigate the possible regulation of N-cadherin by gonadotropins, OSE cells were grown in follicular concentrations of gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone/human chorionic gonadotropin (LH/hCG), and expression of N-cadherin was determined by immunoblotting. To examine the gonadotropin-mediated signaling pathway used to regulate N-cadherin, adenylyl cyclase inhibitor, cAMP analogues, and protein kinase A inhibitors were used.

RESULTS. Our results show that N-cadherin is an important mediator of cell survival in human OSE. Treatment of OSE cells with gonadotropins, FSH and LH/hCG, reduced the amount of
N-cadherin expression with a concomitant induction of apoptosis, and that this effect was mediated by a cAMP/protein kinase A pathway, but not the extracellular-regulated kinase (ERK)-1/2 and protein kinase C cascades (Fig. 1). We further demonstrated that, in contrast to normal human OSE, gonadotropins had no effect on N-cadherin expression and disruption of N-cadherin-mediated cell-cell adhesion did not induce apoptosis in human ovarian carcinoma cell lines (Fig. 2).

**DISCUSSION.** Our present study shows that N-cadherin is intimately involved in determining the fate of normal human OSE. Although normal human OSE depends upon both adhesion and hormonal control for cell survival, malignant OSE cells are independent to these cues. Such loss of responsiveness to environmental influences in the two ovarian cancer cell lines used in this study is an example of autonomy, which is one of the hallmarks of malignancy, and likely relate to survival advantages for the malignant progression of OSE through the inhibition of apoptosis.

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**REFERENCES**
