

Hypothesis

A Mechanism for Cox-2 Inhibitor Anti-Inflammatory Activity in Chemoprevention of Epithelial Cancers

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Epidemiological and experimental data support the use of non-steroidal anti-inflammatory drugs, including specific inhibitors of cyclooxygenase 2 (Cox-2), as chemopreventive agents in a number of epithelial cancers, including colon, mammary, esophageal, lung, and oral cavity (1). There is also evidence to suggest that nonsteroidal anti-inflammatory drugs may be chemopreventive against ovarian cancer, because regular, long-term use of aspirin reduces the risk of ovarian cancer (2, 3) and the Scandinavian Cancer Registry data supports an inverse association between the use of nonsteroidal anti-inflammatory drugs and ovarian cancer (4). In general, it has been suggested that the inhibitors limit Cox-2-catalyzed production of prostaglandins, which may affect cell proliferation, apoptosis, anti-inflammatory responses, and angiogenesis (5, 6). On the basis of our recent observations in ovarian cancers (7), we propose here a new mechanism for the chemopreventive activity of Cox-2 inhibitors in epithelial cancers, related to the integrity of the epithelial basement membrane.

The well-understood biological function of Cox-2 in ovarian physiology provides a window of opportunity to explore the possible mechanism for its role in carcinogenesis. In the normal premenopausal ovary, the gonadotropin luteinizing hormone (LH) induces Cox-2 expression after the preovulatory phase of follicular maturation (8). Cox-2 induction signals the initiation of the ovulatory phase, an inflammatory-like biological process (9), and, indeed, Cox-2 is required for ovulation, because mice null for Cox-2 fail to ovulate (10), and Cox-2 inhibitors prevent ovulation (11). In humans, there is evidence that Cox-2 inhibition delays and suppresses ovulation (12, 13). Moreover, prostaglandins, the products of Cox-2 activation, are believed to activate collagenase and proteolysis and decrease the synthesis of the basement membrane components in both ovarian granulosa and surface epithelial cells (14). Finally, the basement membranes of the ovarian surface and follicular wall are lost, and the surface epithelial cells detach at the site of rupture (15).

A recent study of preneoplastic lesions of human ovarian tumors suggests that the collagen IV- and laminin-containing

basement membrane of the ovarian surface epithelium is lost before morphological transformation of the epithelial cells (7). Both increased proteolysis and decreased synthesis of the basement membrane components by the surface epithelial cells contribute to this loss, which may dramatically alter the biology of the epithelial cells, because the basement membrane is known to profoundly influence gene expression, cell contact signaling, and positional organization of the epithelial cells (16). Indeed, a recent study shows that degradation and removal of mammary epithelial basement membrane by transgenic expression of matrilysin (MMP-7) promotes mammary tumorigenicity of the transgenic mice (17). It can be reasoned that, without an intact basement membrane, the surface epithelium represents a precursor lesion, and subsequent genetic and epigenetic changes will lead to overt neoplastic transformation and tumorigenicity. This transient loss of basement membrane resembles the change in the ovarian surface that occurs during ovulation. It also provides a cellular mechanism for the gonadotropin hypothesis of ovarian cancer (18), which postulates that pituitary gonadotropins stimulate the ovarian surface epithelial cells and induce cell transformation. The frequent placement of the surface epithelium in such a precursor state by repeated gonadotropin stimulation and subsequent Cox-2-induced changes would increase the risk of a subpopulation (the cancer-prone cells that have accumulated genetic mutations) to transform. This hypothesis is consistent with epidemiological data that the incidence/risk of ovarian cancer increases dramatically and peaks 10–20 years after menopause, when ovulation has ceased but plasma gonadotropins remain elevated. The high gonadotropins may stimulate ovulation-like loss of basement membrane but without the actual ovulatory rupture. We would suggest, moreover, the implication of this mechanism provides support for the use of Cox-2 inhibitors in preventing ovarian cancer. By inhibiting Cox-2, the loss of the basement membrane of the ovarian surface epithelium may be lessened, and neoplastic transformation of the ovarian surface epithelial cells may be reduced.

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