

Re:
**Epithelial Inflammation in
Ovarian Cancer**

In the September 1, 1999, issue of the Journal, Ness and Cottreau (1) discuss the role of inflammation in the pathogenesis of ovarian cancer. In reviewing the current literature, they conclude that neither incessant ovulation nor gonadotropin stimulation provides a completely satisfactory explanation for the genesis of ovarian cancer. They suggest that ovarian inflammation, with rapid DNA turnover, oxidative stress, and increased cytokine production, may be an important contributor to the development of ovarian malignancies.

For the past 10 years, we have been studying the role of cytokines in human ovarian cancer biology. We have found that the cytokine network in this tumor is rich in proinflammatory cytokines, growth factors, and chemokines (2-4). Our experiments to date suggest that the proinflammatory cytokine tumour necrosis factor- α (TNF- α) is central to this ovarian cancer microenvironment. TNF- α is expressed in the epithelial tumor islands of ovarian cancer biopsy specimens (the level of expression increasing with tumor grade) and is implicated in the process of ovarian cancer

stromal development and regulation of chemokines and matrix metalloproteinases [(2-6) and references therein]. We also carried out tumor induction experiments in TNF- α deficient mice and found that these mice are resistant to skin carcinogenesis (7). This result provides direct evidence that a proinflammatory cytokine is required for *de novo* carcinogenesis and that TNF- α is important to the early stages of epithelial tumor promotion.

The role of TNF- α in promoting the development of tumor stroma and controlling host and tumor interactions appears to be analogous to its action in inflammatory disease. At some stages of inflammation, TNF- α can cause tissue destruction and necrosis. Similarly, high doses of TNF- α delivered locally to the tumor site cause disruption of the tumor vasculature followed by necrosis. However, lower doses of endogenous TNF- α in the inflammatory microenvironment can promote tissue repair via induction of chemokines and stimulation of fibroblasts and neovasculature. The actions of endogenous TNF- α in cancer are similar, except that TNF- α produced chronically in the tumor does not lead to resolution of the lesion.

Thus, inflammatory cytokines in the tumor microenvironment may not contribute to the genetic damage that initiates the cancer but they may be "a fuel that fans the flames."

Finally, it is possible that inflammatory cytokines are important to the evolution of many different malignancies and not just epithelial ovarian cancer.

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NOTE

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RESPONSE

We appreciate Dr. Balkwill's letter expanding upon our discussion of the role of inflammation in the pathogenesis of ovarian cancer (1). Dr. Balkwill presents a synopsis of data suggesting that cytokines are one type of inflammatory mediator that may potentially initiate or promote ovarian cancer. We have also hypothesized that other mechanisms that come into play in the inflammatory process, including rapid DNA turnover, oxidative stress, and prostaglandins, may play some role in ovarian cancer development. We certainly agree that these mechanisms are not uniquely related to ovarian cancer. Indeed, our

hypothesis drew on the thinking by Ames et al. (2), who suggested that inflammation underlies carcinogenesis in general. Our paper provided specific epidemiologic and some basic biologic support for a relationship between inflammation and ovarian carcinogenesis.

The presence of cytokines, e.g., tumor necrosis factor- α (TNF- α) in already developed ovarian tumors cannot be taken as evidence that cytokines cause ovarian tumors, since tumor development almost surely results in an inflammatory response. However, the fact that mice deficient in TNF- α do not develop skin cancers suggests that, at least for that tumor type, cytokines are important factors in carcinogenesis. We do not believe that any of the experiments to which Dr. Balkwill refers can clearly distinguish between tumor initiation and tumor promotion. Nor does this body of evidence preclude a role for oxidation, genetic damage, etc., in tumor initiation. However, Dr. Balkwill's experiments add fuel to our fire and support our call for further work along this line of inquiry.

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NOTES

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