Stromal Therapy: The Next Step in Ovarian Cancer Treatment

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Among gynecologic cancers, ovarian cancer is the leading cause of death in the United States. Unfortunately, over two thirds of ovarian cancer cases are diagnosed at a late stage, when peritoneal dissemination of the ovarian cancer cells has already taken place (1). Understanding the molecular events that support the survival and implantation of disseminated ovarian cancer cells can provide urgently needed strategies for early detection, prevention, and intervention. It has long been suspected that cancer is a product of the tumor–host microenvironment (2). The single-layer ovarian surface epithelium, the presumed progenitor of ovarian cancer cells, lies adjacent to the basement membrane and may be in constant communication with the underlying ovarian stroma, which is on its basal side, and the peritoneal microenvironment, which is on its apical side. We can hypothesize that a homoeostatic feedback circuit exists that promotes the survival of the ovarian surface epithelium only if these cells are attached to the proper substratum and receive the correct signals from the ovarian stroma. Thus, if non-neoplastic ovarian epithelial cells are desquamated into the peritoneum, the communication circuit is broken, and the ovarian cells would fail to implant, or grow as ascites. By contrast, neoplastic ovarian cancer cells may survive because they co-opt or disregard host-derived molecular signals. In this scenario, the host is a necessary participant in, and perhaps an unwilling facilitator of, the neoplastic process. Here the peritoneal microenvironment provides both motive and opportunity to shed malignant cells through its rich support surfaces, which release pro-invasive and pro-angiogenic cytokines and other cellular components.

In this issue of the Journal, Huang et al. (3) provide direct evidence that the host contributes critical molecules that promote the solid and liquid growth of xenografted human ovarian cancer cells [Huang et al. (3), Table 1]. In a landmark experiment, the authors implanted human ovarian carcinoma cells into the peritoneal cavities of genetically modified nude mice. The mice lacked the gene for a critical metalloproteinase, matrix metalloproteinase-9 (MMP-9), that is known to be involved in stroma–host communication, such as those involved in angiogenesis (4,5). Numerous therapeutics have targeted the matrix metalloproteinase family with mixed success at the levels of efficacy and toxicity (6,7). These first-generation metalloproteinase inhibitors have targeted the active site of the enzyme(s), and some agents have MMP-subclass selectivity. Early work with the first agent to be tested, batimastat (BB-94), an agent that inhibits both MMP-2 and MMP-9, showed interesting intraperitoneal activity in ovarian cancer xenografts (i.e., a reduction in ascitic tumor growth with less effect on the solid tumor) (10). Advancing batimastat and the second-generation agent, marimastat, to the clinic has yielded few hints of efficacy (11). The next logical therapeutic target suggested by the results reported by Huang et al. is the peritoneal macrophage, which is a rich source of pro-angiogenic and pro-invasive agents in addition to MMP-9 (12). Selective inhibition of macrophage activity may be a promising direction. However, one important biologic role of macrophages may be to prevent intraperitoneal disease complications, such as adhesions and bowel obstruction that require surgery, which is a non infrequent event in women with ovarian cancer. This leaves the third logical therapeutic target, the interaction between the tumor and the stroma. Continuing research into the mechanisms underlying the observation presented in the work of Huang and colleagues will likely yield a stromal therapy approach that can be sensitive and specific to the interaction between the peritoneal macrophage and solid and ascitic ovarian cancer.

REFERENCES


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