YALE JOURNAL OF BIOLOGY AND MEDICINE 84 (2011), pp.47-49.

SYMPOSIUM

Advances in Ovarian Cancer Screening

Health and Medicine for Women: A Multidisciplinary, Evidence-Based Review of Mid-Life Health Concerns

Sumayya Ahmad

Yale University School of Medicine, New Haven, Connecticut

Early detection is imperative for improving survival from ovarian cancer, the leading cause of death from gynecological cancer in the United States. At the Health and Medicine for Women continuing medical education (CME†) conference at Yale in September 2010, Dr. Gil Mor, a researcher in the Department of OB/GYN at Yale, presented recent advances on the pathophysiology of ovarian cancer. These advances, and particularly our growing understanding of cancer stem cells, may help overcome the limitations of current ovarian cancer detection and treatment methods.

Ovarian cancer is the leading cause of death due to gynecological cancer in the United States, with an estimated 21,880 new cases and 13,850 deaths predicted in 2010 [1]. The disease often presents with such vague symptoms such as abdominal discomfort, difficulty eating, and feeling full quickly. For this reason, it is called "the disease that whispers." Since adequate screening methodologies are lacking, most women first present with either stage III or IV disease. Stage I disease is associated with a 90 percent cure rate, making early detection methods imperative [2].

There are several reasons for the lack of an effective means of screening for ovarian cancer. First, in order for a cancer to be adequately detected, it must produce a detectable biomarker. This substance should be present in higher quantities in afflicted patients and also must be specific enough for the particular malignancy. To date, the only ovarian cancer-associated biomarker is CA-125. However, estrogen and other hormones can affect the levels of CA-125, leading to many false positives and precluding the widespread use of this biomarker in women with no previous history of cancer [3]. Other proteins are also elevated in ovarian cancer, but none has proven specific and sensitive enough for cancer screening.

To whom all correspondence should be addressed: Sumayya Ahmad, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06511; E-mail: sumayya.ahmad@yale.edu.

†Abbreviations: CME, continuing medical education; VEGF, vascular endothelial growth.

Keywords: ovarian cancer, cancer stem cells, ovarian cancer markers

Second, ovarian cancer seems to break the "rules" of malignancy. Generally, when a neoplasm first develops, a single monoclonal cell accumulates enough mutations that allow it to escape the normal checkpoints for apoptosis and mitosis [4]. This cell produces clonal progeny of the same genotype. Each clone has the possibility to undergo environmentally induced and endogenous mutations that allow the neoplasm to expand and grow [5]. However, in the 1990s, a group of researchers discovered a malignant cell derived from acute myeloid leukemia that was able to recapitulate the original disease after transplantation into mice [6]. This cell type had the surprising potential to both self-renew and produce a new lineage of cells within a malignancy. Dubbed "cancer stem cells," even solid malignancies ranging from prostate to liver cancer have been found to contain them. One of the hallmark features of these cells is that they do not uniformly produce biomarkers that can be used for broad screening, further limiting ovarian cancer detection methods.

Cancer stem cells are thought to cause recurrence after surgery and chemotherapy. In fact, while 80 percent of ovarian cancer cases respond to initial chemotherapy, less than 15 percent remain in remission [7]. Most chemotherapeutic agents target rapidly dividing cells, but since cancer stem cells divide slowly, they are not fully killed by these drugs. Dr. Gil Mor, a researcher in the Department of OB/GYN at Yale, studies which molecular components enable ovarian cancer stem cells to bypass treatment and continue to differentiate. He has discovered a distinct genetic profile that allows them to proliferate despite chemotherapy and promote recurrence of the neoplasm. More specifically, ovarian cancer stem cells presenting the surface antigen CD44 are characterized by constitutive NFκB signaling [8]. Since NFκB has been implicated in cytokine production and inflammation, its constitutive activity could result in a high capacity for cellular repair and proliferation [9].

Dr. Mor and colleagues also have discovered that cancer stem cells have the ability to promote tumor vascularization. Mice injected with CD44+ ovarian cancer stem cells exhibited highly vascularized tumors. When these cells were placed in an *in vitro*, three-dimensional matrigel matrix, which is often used to study endothelial differentiation, they generated vessel-like structures within 24 hours. In contrast, mature, non-stem ovarian cancer cells did not demonstrate significant vessel growth [10]. The same paper also established that cancer stem cell-derived vascular progenitor cells could differentiate into endothelial cells of human origin. The cells grew independently of vascular endothelial growth factor (VEGF), relying instead on IKKβ, an enzyme that activates NFκB [10].

In another study, Szotek and colleagues injected stem cells from genetically engineered mouse ovarian cancer cells (MOVCAR 7 cell line) into the dorsal fat pad of nude mice. Tumors appeared in 3/3 animals at 10 weeks, as compared to no detectable tumors in 0/3 animals injected with non-stem ovarian cancer cells at 10 weeks [11]. However, at 14 weeks, 2/3 mice injected with non-stem cells had detectable tumors. Flow cytometry analysis revealed that the cancer stem cells were less homogenous than the non-cancer stem cell population, suggesting that the former have the potential to initiate tumor growth earlier and with lower numbers.

Another group studied the presence of mitochondrial mutations in ovarian cancer cells. They discovered three nucleotide variations that were highly expressed in the coding regions of epithelial ovarian cells, potentially qualifying as an ovarian stem cell marker [12]. Further analysis revealed that these mitochondrial variations were not found in ovarian cancer stem cell clones. Yet germline mutations were found in these cancer stem cell clones, suggesting that the genetic profiling of these tumors could be error-prone. These findings underscore the difficulties in attempting to find a suitable marker for ovarian cancer.

Although detecting ovarian cancer will likely remain challenging for some time, researchers are much closer to discovering the

reasons for its recurrence and resistance to conventional therapy. With the advancement of research on cancer stem cells, women diagnosed with ovarian cancer in the future hopefully will have a better prognosis than current patients.

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