A breakthrough in understanding the biology and treatment of ovarian cancer

February 21 2012

Researchers at The Pennsylvania State University College of Medicine, Hershey, Pennsylvania have discovered that the presence and integrity of the opioid growth factor receptor (OGFr), which mediates the inhibitory action of opioid growth factor (OGF) on cell proliferation, is a key to understanding the progression and treatment of human ovarian cancer. Transplantation of human ovarian cancer cells that were molecularly engineered to have a reduced expression of OGFr, into immunocompromised mice resulted in ovarian tumors that grew rapidly. This discovery, reported in the February 2012 issue of *Experimental Biology and Medicine,* provides fresh new insights into the pathogenesis and therapy of a lethal cancer that is the fifth leading cause of cancer-related mortality among women in the USA, and has a death rate that is unchanged for over 75 years.

The OGF (also-termed [Met5]-enkephalin)-OGFr axis plays a fundamental role in cancer, development, and cellular renewal by regulating cell proliferation. An important question addressed in this study relates to the requirement of this peptide-receptor system for the progression of carcinogenesis. Human ovarian cancer cell lines that were genetically modified to underexpress OGFr grew far more rapidly in tissue culture than control (empty vector/wildtype) cell lines. Moreover, the addition of OGF to cultures of these genetically modified cells did not respond to the inhibitory peptide and change cell number, indicating that the loss of OGFr interfered with the function of the OGF-OGFr axis with respect to regulating cell proliferation. Immunocompromised mice injected with ovarian cancer cells that had a reduction in OGFr displayed

tumors much earlier than controls, and these tumors grew faster than controls. Putting this information together with knowledge that the pathway for OGF-OGFr regulation of cell proliferation in ovarian cancer is by way of increasing the cyclin-dependent inhibitory kinase proteins p16 and p21, we now can understand that minimizing the quantity of OGFr results in an increase in the number of cells entering the G1/S phase of the cell cycle. This has the net effect of increasing the progression of tumorigenic events. These results reveal the critical nature of OGFr in human ovarian cancer, and that the receptor along with its ligand, OGF, is essential for determining the course of these neoplasias.

The research team was comprised of Dr. Ian S. Zagon, Distinguished University Professor, and Dr. Patricia J. McLaughlin, Professor, along with Dr. Renee N. Donahue in the Department of Neural & Behavioral Sciences. Drs. Zagon and McLaughlin discovered that endogenous opioids serve as growth factors, and have been pioneers in translating their findings from the bench to the bedside. Dr. Zagon states that "Over 75% of women are initially diagnosed with advanced ovarian cancer. Despite excellent initial response to cytoreductive surgery and adjuvant chemotherapy, 65% of these patients relapse within two years. However, only palliative care is available for these patients. With evidence from Phase I and II clinical trials as to the success of OGF for the treatment of advanced pancreatic cancer and knowledge presented herein that the OGF-OGFr axis is a critical determinant of the course of ovarian neoplasia, the present study raises the possibility of using this information to modulate the OGF-OGFr pathway with i) exogenous OGF, ii) imiquimod to upregulate OGFr, and/or iii) low dose naltrexone (LDN) to increase OGF and OGFr, as a therapeutic strategy for ovarian carcinoma." Co-author Dr. McLaughlin adds that "A major problem in ovarian cancer is the need for diagnostic markers - both for early diagnosis and to monitor treatment modalities. Since some of the signaling pathways for OGF-OGFr are known (e.g., karyopherin β, Ran, p16, p21), the components of this system would represent a worthwhile

focus in designing diagnostic assays." Dr. Donahue, who conducted the ovarian cancer studies and its relationship to the OGF-OGFr axis for her doctoral dissertation, states that "Ovarian cancers frequently have a methylation of p16 that is associated with an increased progression of ovarian cancer and a loss of OGFr in ovarian tumors. The diminished expression of OGFr and its repercussions on tumorigenesis, only adds to the concern about the need for information concerning genetic and epigenetic changes that may impact the course of disease and its treatment. Our findings also hold potentially ominous overtones for those individuals taking naltrexone for addictive disorders. The dosage used for treatment of addiction blocks opioid receptors continually. The present findings that diminishing the OGF-OGFr axis by depleting the receptor exacerbates tumorigenesis, could place these patients using naltrexone at risk for accelerating disease processes that involve cell proliferation."

Dr. Steven R. Goodman, Editor-in-Chief of Experimental Biology and Medicine, said "This compelling evidence confirms the absolute requirement for OGFr (and OGF) as a tonically active inhibitory regulatory mechanism in ovarian cancer. As a corollary, amplifying the OGF-OGFr pathway is a novel and highly effective biotherapeutic strategy to suppress the progression of these deadly cancers."

Provided by Society for Experimental Biology and Medicine