

ADVANCES IN GYNECOLOGY



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Ovarian Cancer: Overcoming Obstacles to Immunotherapy

The promise of immunotherapy is altering how many cancers are perceived and treated, but it has so far eluded the treatment for some of the more aggressive malignancies, including ovarian cancer. “The same therapeutic approaches for ovarian cancer have been used for the last 40 years, but survival for patients with metastatic ovarian cancer, which is the most common stage at which it is diagnosed, has not substantially improved,” says **Juan R. Cubillos-Ruiz, PhD**, Assistant Professor of Microbiology and Immunology in Obstetrics and Gynecology at Weill Cornell Medicine.



Dr. Eloise Chapman-Davis and Dr. Juan R. Cubillos-Ruiz

Not Your Average Immunosuppression

For the past decade, Dr. Cubillos-Ruiz has focused his scientific career on understanding why the immune system is unable to control this cancer. “While immunotherapy is eliciting remarkable responses against some tumor types, the same immune-based approaches are not working well in ovarian cancer or other cancers that are more aggressive,” says Dr. Cubillos-Ruiz. “These tumors, especially in ovarian and pancreatic cancer, are extremely immunosuppressive. They have evolved

multiple mechanisms to cripple immune cell functions, inhibiting the capacity of the immune system to eliminate the cancer cells. For example, while checkpoint blockade inhibitors for metastatic melanoma induce significant responses in 30-40% of patients, the same strategy is partly effective only in 10% of metastatic ovarian cancer patients.”

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Promoting a Comprehensive Approach to Gynecologic Cancers

“Now is an exciting time for gynecologic oncology,” says **Jason D. Wright, MD**, Chief of the Division of Gynecologic Oncology in the Department of Obstetrics & Gynecology at NewYork-Presbyterian/Columbia University Medical Center.

“More than any other time in the past, we have the ability to extend lives and offer the hope of cure for women diagnosed with these cancers. Gynecologic oncologists – unlike other cancer specialists – provide medical management and perform oncologic surgeries, thereby enabling women to benefit from a single source of care, from diagnosis to treatment to recovery and survival,” says Dr. Wright, who has established a comprehensive program in gynecologic oncology and surgery at Columbia. Under Dr. Wright’s leadership, the Columbia program has launched a number of

initiatives that medically and emotionally support a patient’s course of care and is pursuing a number of important research endeavors.

Precision Medicine The growth of precision medicine in the cancer arena has informed the therapeutic approach for patients who seek out care in the Division of Gynecologic Oncology. “While this precision medicine approach has been used more commonly for other cancer types, it is in its infancy in gynecologic cancers,” says Dr. Wright. “At Columbia, genomic analysis is now a routine part of our care, with patients undergoing a thorough genomic analysis to identify specific DNA changes. We then pair the findings with potential new drugs that may target the abnormalities identified.”

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Ovarian Cancer: Overcoming Obstacles to Immunotherapy *(continued from page 1)*

In light of the shortcomings of current immunotherapeutic approaches for these more aggressive tumors, Dr. Cubillos-Ruiz and his research group have been analyzing what transpires in tumors from ovarian cancer patients. “We are profiling and interrogating the function of those immune cells inside the tumor to understand why they are able to infiltrate the tumor, but not function,” he explains. “What we have found is that they enter into an adverse, very hostile microenvironment in which nutrients are lacking. There’s little glucose. There’s also hypoxia, pH stress, and oxidative stress. We found that this combination of harsh environmental conditions provokes accumulation of misfolded proteins in the endoplasmic reticulum [ER] of infiltrating immune cells, thereby inducing a cellular state called ‘ER stress.’ During this process, the IRE1 α -XBP1 signaling pathway of the unfolded protein response is aberrantly activated and this ultimately inhibits the development of an effective anti-tumor immune response.”

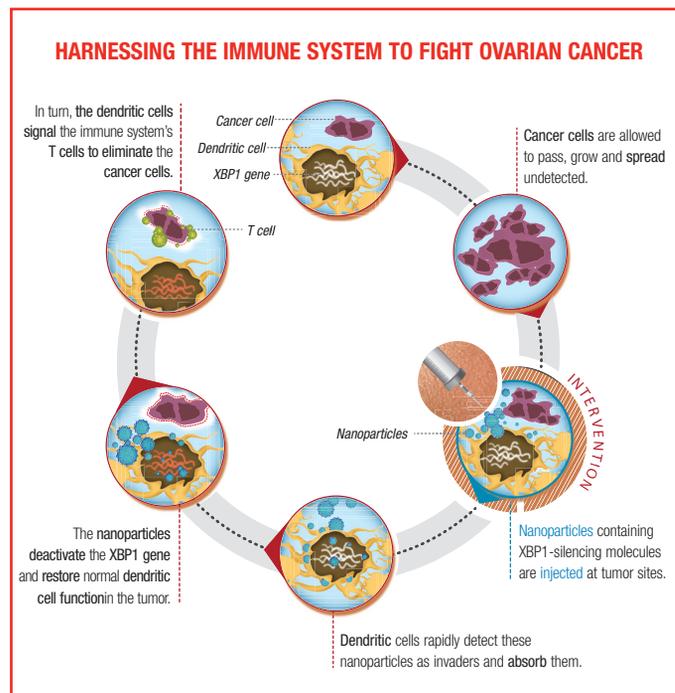
Cancer cells are known to exploit the IRE1 α -XBP1 arm of the ER stress response to efficiently adjust their protein-folding capacity and ensure survival under hostile tumor microenvironmental conditions, says Dr. Cubillos-Ruiz. “However, we found that dendritic cells residing in the ovarian cancer microenvironment also experience severe ER stress and demonstrate persistent activation of the IRE1 α -XBP1 pathway. The unfolded protein response should be intermittent, activating and then shutting down. It should be very specific in terms of time and strength. But the problem is that when this pathway is persistently activated it causes immune cell dysfunction. We call this event ‘abnormal ER stress responses’ because the pathway is trying to correct and improve the folding of the proteins, but at the same time is inducing collateral damage in the immune cells.”

Dr. Cubillos-Ruiz and his colleagues turned their investigation to mouse models of ovarian cancer. Making use of elegant genetic systems developed in the lab, they were able to specifically abrogate the IRE1 α -XBP1 pathway in immune cells. “We developed ovarian cancers in mice devoid of ER stress sensors specifically in immune cells to determine what would happen with disease progression in this context,” says Dr. Cubillos-Ruiz. “The immune cells were still able to enter the tumor, but by turning off the genes encoding either IRE1 α or XBP1, they did not react to the inhospitable environment. Because they lacked those stress sensors they were refractory to conditions that otherwise would inhibit their function, providing them with a more potent, enhanced anti-tumoral function.”

Importantly, Dr. Cubillos-Ruiz notes, he and his research team were able to confirm the mechanistic and functional findings found in the mouse model using human samples from ovarian cancer patients. “We wanted to make sure that this new process was also taking place in freshly isolated human specimens, and we demonstrated that the ER stress response pathway was indeed active in the immune cells that infiltrated human ovarian tumor cells as well.”

Transitioning to Therapeutic Mechanisms

Having described how the previously unrecognized process of ER stress disrupting metabolic homeostasis and antigen-presenting capacity in dendritic cells, Dr. Cubillos-Ruiz and his team now had what they needed to begin pursuing therapeutic implications. “In our first approach we are developing small molecule inhibitors for ER stress sensor,” he says. “These small molecule inhibitors will bind the sensor, IRE1 α , *in vivo*, in the tumor, and will prevent their activation.



Dendritic cells act as the first line of defense against threats like cancer. Ovarian tumors suppress these powerful immune cells by abnormally activating the XBP1 protein. (Courtesy of Dr. Juan R. Cubillos-Ruiz)

We hope that treatment with these inhibitors would mimic what we found in our gene-deficient animals – if the immune cells can’t sense ER stress, they can function better. We are now trying to devise first-in-class drugs that can inhibit the IRE1 α -XBP1 pathway in both cancer cells and dendritic cells, which would sensitize the cancer to treatment and restore an immune response against it.”

Their second approach involves nanoparticles that encapsulate small interfering RNA. Dr. Cubillos-Ruiz and his team tested a strategy in which mice were injected with nanoparticles he developed. These microscopic polymers encapsulate nucleic acids that can silence the genes encoding IRE1 α or XBP1. Dendritic cells in the tumor detect the nanoparticles as invaders and ingest them. Once inside, the nanoparticles deliver the molecule that turns IRE1 α -XBP1 signaling off, allowing dendritic cells to instruct the immune system to attack the cancer. “The nanoparticles act like a Trojan Horse, releasing the payload that will turn off the pathway,” he says.

Plans for future approaches also include genome editing. Now that the research team had demonstrated proof of concept in preclinical experiments, their hope is to actually test this in the clinical arena. “By dissecting the tumors surgically removed from patients, we could isolate antigens that are ovarian cancer-specific,” he says. “At the same time, we would obtain peripheral blood and differentiate the monocytes *in vitro* into dendritic cells. If dendritic cells do not present cancer cell antigens to T cells, the T cells cannot kill the tumor. So what we want to do is exploit new genome-editing tools to delete XBP1 or IRE1 α in the lab and then transfer these gene-modified or gene-edited dendritic cells back into the patient. The process is called adoptive immunotherapy. Our hypothesis is that dendritic cells that no longer have XBP1 or IRE1 α would function better in the cancer host.”

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Promoting a Comprehensive Approach to Gynecologic Cancers (continued from page 1)

Minimally Invasive Surgery “One of the major developments that we’ve seen in gynecologic surgery over the last decade is the availability of minimally invasive surgery,” notes Dr. Wright, who has extensive training in the latest surgical modalities, including minimally invasive and robotic surgery, as well as extended pelvic resections and pelvic reconstructive surgery. “Whenever possible we try to use a minimally invasive surgical approach, which is now common practice for both uterine and cervical cancers and for the evaluation of ovarian masses. This has been one of the real breakthroughs in gynecologic cancer surgery over the last several years.”

In 2014, a popular minimally invasive procedure – laparoscopic electric power morcellation used for hysterectomy and myomectomy – became the center of attention when the FDA issued an alert based on data that showed the procedure posed a risk of spreading unsuspected cancerous tissue, notably uterine sarcomas, beyond the uterus. The number of minimally invasive gynecologic cancer surgeries with electric power morcellators declined dramatically and the number of open gynecologic cancer surgeries rose. It was likely expected that with an increase in open, invasive techniques, perioperative complications would also increase.

Dr. Wright and colleagues at Columbia soon began a national conversation on electric power morcellation based on a number of outcomes studies they conducted, including the first large-scale study to look at trends in the route of hysterectomy, use of electric power morcellators, and prevalence of abnormal pathology before and after the FDA’s guidance announcement. Led by Dr. Wright, researchers examined a database of more than 200,000 women, ages 18 to 95 years, who underwent all types of hysterectomies at more than 500 hospitals. The wide-ranging review showed that the “prevalence of uterine cancer, endometrial hyperplasia, other gynecologic cancers, and uterine tumors of indeterminate behavior in women who underwent morcellation was unchanged.” Additionally, despite the increase in abdominal hysterectomies, concern over a concomitant increase in the rate of major perioperative complications was unfounded.

“Fortunately we didn’t see an increase in the complication rate, which is reassuring,” says Dr. Wright, “and with a morbidity profile of minimally invasive hysterectomy that is superior to abdominal hysterectomy, minimally invasive procedures should be chosen whenever feasible.”

According to Dr. Wright, the FDA warnings might have resulted in a lower prevalence of cancer among women who underwent morcellation due to greater scrutiny on patient selection, and continued caution is needed to limit the inadvertent morcellation of uterine pathology.

Fertility Preservation Dr. Wright and his Columbia colleagues have also been at the forefront of fertility conserving surgery to preserve the ovaries in women with uterine cancer and the uterus in women with cervical cancer. Many of these techniques and strategies have been developed and studied at Columbia and are now being used nationwide. A recent population-based analysis led by Dr. Wright on trends in the use and safety of ovarian conservation in young women with early-stage endometrial cancer undergoing hysterectomy found that ovarian conservation does not adversely affect survival for women with early stage endometrial cancer. However, despite this, the majority of young women with endometrial cancer still undergo oophorectomy at the time of surgery.



Dr. Jason D. Wright

“Age, stage, and tumor grade are important factors associated with the decision to offer ovarian conservation,” notes Dr. Wright in the study discussion. “In the context of prior work, our data suggests that ovarian preservation is a reasonable option in some young women with endometrial cancer. For premenopausal women, the risks of long-term estrogen deprivation may outweigh the oncologic benefits of oophorectomy, and individualized risk assessments may help drive this decision for both the patient and provider.”

Survivorship “One of the great successes in our field is that we have better treatments resulting in a higher cure rate,” says Dr. Wright. “But even for those women who are not cured, we’re often able to turn their cancers into a chronic disease. Consequently, we are observing a lot more of the after-effects of treatments, which can be so complex. A key component of our survivorship program addresses issues related to post-treatment recovery and ongoing well-being. We help our patients manage the toxicities associated with chemotherapy, radiation, and/or surgery. And we help them move forward.”

An integrated medicine program provides patients undergoing treatment with access to massage, acupuncture, and other healing modalities, and a woman-to-woman peer support group brings together women with the same gynecologic cancer.

Ongoing research studies are being conducted by faculty to characterize symptoms, complaints, and concerns that patients identify as important to them. They are also conducting a prospective study looking at the financial impact of cancer treatment on patients and their families.

“I am honored to be able to treat my patients,” says Dr. Wright. “I am always learning from them and inspired by their courage.”

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Ovarian Cancer: Overcoming Obstacles to Immunotherapy *(continued from page 2)*

Closing in on Clinical Applications

Eloise Chapman-Davis, MD, is a specialist in gynecologic cancers in the Department of Obstetrics and Gynecology at New York Presbyterian/Weill Cornell Medical Center. Her passion in bringing advanced medical care to the underserved around the world and patients at home complements Dr. Cubillos-Ruiz's aspirations to translate his work at the bench into clinical applications, ultimately providing treatment options for ovarian cancer in an area of oncology that to date has had little reason for optimism.

Drs. Cubillos-Ruiz and Chapman-Davis, joined by pathologist Cathleen Matrai, MD, were recently awarded a grant by Colleen's Dream Foundation to define the role of XBP1 expression as a potentially crucial biomarker in the treatment of ovarian cancer tumors. Their research builds on their discovery that IRE1 α -XBP1 signaling plays a major tumorigenic and immunosuppressive role in ovarian cancer.

The investigators will analyze tumor specimens from 200 ovarian cancer patients in a retrospective study, quantifying the expression levels of XBP1 in each of the patient's tumor samples, then correlating their results to existing patient data with the aim of understanding the protein's effect in disease progression and therapy engagement. They also hope to establish a new system that reveals which patients are better candidates to receive treatments that target XBP1 and other immunotherapies. "Our goal is to identify biomarkers that could be able to help predict response or resistance to treatment with standard cytotoxic drugs," notes Dr. Chapman-Davis. "The ultimate goal is to be able to create an immune-based scoring system to identify specific patients more likely to be affected. And then, hopefully, we will be able to utilize them to direct treatment with immunotherapy in conjunction with conventional chemotherapeutics."

Dr. Chapman-Davis emphasizes that the big unknown is identifying which patients with ovarian cancer are going to be the

most receptive to the new immunotherapies that are becoming available. "Our goal is to determine novel immunotherapeutic approaches for treating ovarian cancer, but before we can utilize some of those novel approaches, we need to know which patients will benefit," she says. "The problem with ovarian cancer is that while we do a good job of getting patients up-front therapies that can put them into remission, the majority will have a recurrence in a short period of time. And, once they recur, you basically lose your chance for a cure. We're trying to change ovarian cancer into a chronic disease rather than a death sentence."

The challenge is further complicated by preexisting levels of immune dysfunction in patients who are already undergoing treatment for ovarian cancer. "There is a lot of data looking at ways to evaluate T-cell function, T-cell regulation, and tumor infiltration patterns," notes Dr. Chapman-Davis. "Through this retrospective study, we are trying to see if we can develop a pattern in patients who show variance of expression of XBP1 and link that to their clinical data. Identifying specific features about a particular patient's immune profile may help direct patient treatment options and increase the chances that a patient would accept the immunotherapy."

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