In the Spotlight

Reproductive Sciences
20(9) 1010

DOI: 10.1177/1933719113498571
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A Role for the Stroma in the Fight Against Endometrial Cancer

Endometrial cancer is the most common gynecologic cancer in the United States, with more than 49 000 new cases diagnosed each year leading to about 8000 annual deaths.

Unlike other hormonally regulated carcinomas, which usually respond to the antagonists of steroid receptors, endometrial cancer can be successfully treated through the agonistic actions of the progesterone receptor (PR). Even though progesterone is well tolerated, easily administered, and has minimal side effects, ablative surgery, radiation, and chemotherapy continue to be the leading choices of treatment for endometrial cancer in detriment of the less invasive hormonal therapy. This happens primarily because a subset of patients does not respond well to the hormonal treatment, and those with hormone-sensitive or -resistant disease cannot be prospectively identified. Therefore, there is an urge to discover reliable biomarkers that would enable the physicians to predict the responsiveness of a particular patient to the hormonal treatment in order to avoid more invasive and hard to endure approaches when possible.

As such, Janzen et al aimed to determine the still poorly understood mechanisms and site of action for progesterone in endometrial cancer in hopes of identifying such biomarkers of hormone sensitivity (*Cancer Res.*, June 2013, ahead of print).

Using an in vivo endometrial cancer mouse model driven by clinically relevant genetic changes but dichotomous responses to hormonal therapy, Janzen and colleagues demonstrated that signaling through the stromal PR is necessary and sufficient for progesterone antitumor effects.

The authors observed that endometrial cancers resulting from epithelial loss of PTEN (phosphatase and tensin gene homolog knock out (PTENKO)) were hormone sensitive and showed abundant expression of PR in the stroma. When the PR was deleted in the stroma of these tumors, they were no longer hormone sensitive, indicating that paracrine signaling through the stroma plays a major role in the progesterone therapeutic effects. In addition, when activation of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) was coupled with PTEN loss, it led to an innate progesterone resistance due to methylation of PR in the tumor stroma, which could be overcome by the stromal overexpression of PR

Thus, the results presented by Janzen et al indicate that stromal expression of PR in the tumor microenvironment may become a reliable predicative biomarker for hormonal therapy response. In addition, their findings suggest that epigenetic de-repression of stromal PR may be a potential therapeutic target to sensitize hormone refractory endometrial tumors to progesterone therapy.

Unraveling the Chemotherapy Resistance Mechanisms in Breast and Ovarian Cancers

About 5% to 10% of breast and ovarian cancers are believed to be of familial origin, with inherited mutations in genes such as breast cancer susceptibility genes BRCA1 and BRCA2. In patients with cancer with these mutations, poly(adenine diphosphate-ribose) polymerase (PARP) inhibitors, which are currently in clinical trials, have shown promising results that may make them an efficient alternative to standard chemotherapy treatments.

The PARP inhibitors act by causing selective death through synthetic lethality only in tumor cells where DNA repair by homologous recombination is hampered due to the BRCA1/2 mutations. Nevertheless, some studies indicate that a fraction of the patients with BRCA1/2 mutations end up acquiring resistance to the PARP inhibitors and, therefore, stop responding to this new treatment.

The underlying process to the PARP inhibitors' resistance has not been clearly understood until recently, as a publication in the journal *Cell* (*Cell.* 2013;153(6):1266-1280) by Callen et al shed some light on its molecular mechanisms.

Although studying in detail the role of *53BP1* and its biochemical interactions with different proteins in DNA repair, Callen and colleagues were able to show that *53BP1* mediates productive and mutagenic DNA repair through distinct phosphoprotein interactions. When the *53BP1* interaction with *paired box gene interacting protein (PTIP)* is disrupted through mutations in either of these proteins in BRCA1/2-deficient cells such as the breast and ovarian cell tumors, resistance to PARP inhibitors occurs.

Thus, the results of Callen et al demonstrate that when secondary mutations in proteins such as 53BP1 or PTIP (whose function is to restrain DNA repair) occur, BRCA1/2-deficient tumor cells recover their ability to repair DNA, and the PARP inhibitors stop working.

These findings indicate that in the management of familial breast and ovarian cancers, *53BP1* and *PTIP* genes should also be evaluated prior to deciding on the treatment of choice. Additionally, the study by Callen and colleagues highlights the challenge of considering secondary resistance markers when providing personalized medicine.