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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Learning From Gender Disparity: Role of Estrogen Receptor Activation in Coping With Pancreatic Cancer

The gender disparity in cancer is one of the most consistent findings shown in multiple epidemiologic research. Gender not only influences cancer incidence rates but also determines clinical outcomes, and its role is comparable with racial and ethnic disparity in magnitude, and yet is still not fully understood. Recent cancer statistics revealed that men are not only prone to develop cancer but are also likely to die more often compared with women in several different cancer types.[1] According to recent estimates from the International Agency for Research on Cancer, in 2018 there were 243,033 new cases of pancreatic cancer in men (5.5 per 100,000 people) compared with 215,885 in women (4.0 per 100,000 people).[2] Globally, pancreatic cancer is more deadly in men (5.1 per 100,000 people; 226,910 deaths) compared with women (3.8 per 100,000 people; 205,332 deaths) in 2018.[2] These findings indicate that there is something about female sex and their unique hormones that can protect them against this deadly cancer, and yet this aspect of pancreatic cancer has not been investigated extensively before. Over the past few years, researchers have begun to investigate the role of circulating estrogen, progesterone, and testosterone in the genesis and progression of various nonreproductive system cancers.[3-5]

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Natale et al[6] have uncovered a novel mechanism for the protective effects of estrogens in pancreatic cancer. Encouraged by prior findings of a beneficial effect of noncanonical estrogen signaling, which does not act via the well-studied nuclear receptor but rather via a G-protein-coupled estrogen receptor (GPER) in the plasma membrane, in melanoma,[4] they discovered that high GPER expression is associated with improved survival in pancreatic ductal adenocarcinoma (PDAC). Next, they investigated the therapeutic potential of the highly specific GPER agonist G-1 on the growth of PDAC tumor cell lines and found significantly slowed proliferation.

Mechanistically, the authors demonstrated that GPER activation causes a G1-S cell cycle arrest and corresponding decreases in p-RB and c-Myc (Figure 1). C-Myc is a master transcription factor regulator that stimulates proliferation and growth[7] by activating thousands of target genes and is frequently overexpressed in cancer. Through a series of intricate experiments involving mouse model of pancreatic cancer, Natale et al[6] further demonstrated that in vivo administration of GPER agonist G-1 resulted in tumor regression and prolonged survival of the treated mice.[5] Importantly, the response to G-1 did not show any gender differences PDAC mouse model.

Recent emergence of immunotherapy has transformed the cancer treatment paradigm for several cancers, such as melanoma and non–small cell lung cancer. However, current immunotherapies thus far have shown no efficacy in "immunologically cold" cancers, such as PDAC, which are known for their immune-suppressive tumor microenvironment.[8] Clearly, microenvironmental factors dictate the immune infiltration in pancreatic tumors.[9,10] Importantly, Natale et al[6] investigated the therapeutic potential of GPER activation in combination with immune checkpoint inhibitor therapy in mouse model of pancreatic cancer. Their results showed that 2 out of 3 syngeneic PDAC immunocompetent

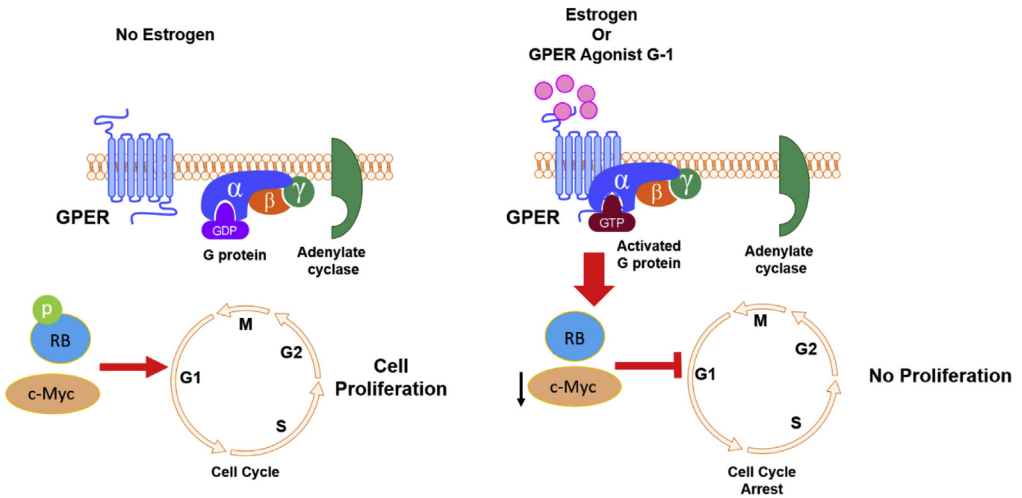

Figure 1. Schematic model depicting mechanisms through which estrogen or GPER agonist G-1 hampers cell proliferation in pancreatic cancer cell.

mouse models responded to G-1/anti PD-1 combination therapy and showed prolonged survival compared with monotherapy. Thus, an intriguing question that arises from this study is why some tumors did not respond to combination therapy? The authors hypothesized that expression of PD-L1 in pancreatic tumors determines the heterogeneous response to G-1/anti PD-1 combination therapy.[6] In situ hybridization showed that responsive tumors have indeed high PD-L1 expression. In contrast, nonresponsive tumors expressed very low levels of PD-L1, indicating potential importance of PD-L1 expression in determining response to GPER activation in combination with immune checkpoint therapy.

In sum, Natale et al[6] provide multiple new insights about the role of gender in PDAC. First, the study highlights the importance of noncanonical estrogen signaling pathway as tumor suppressing in pancreatic cancer. Second, they show that this pathway can be activated by the specific small molecule synthetic GPER agonist, G-1, to inhibit pancreatic cancer cell proliferation. Third, they provide evidence that GPER activation can sensitize PD-L1 expressing pancreatic tumors to immune checkpoint therapy and could thus represent a new treatment modality for PDAC. The therapeutic implications of this observation in developing immunotherapy against pancreatic tumors remain to be evaluated further.

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Conflicts of interest
This author discloses the following: Ashok K. Saluja is one of the inventors of Minnelide, which has been licensed to Minneamrita Therapeutics by the University of Minnesota; and is its cofounder and CSO. Sulagna Banerjee is a consultant of Minneamrita Therapeutics. The other author discloses no conflicts.

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