Platinum-based chemotherapy inflames the ovarian carcinoma microenvironment through cellular senescence

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ABSTRACT

Epithelial ovarian carcinoma (EOC) is virtually insensitive to immune checkpoint inhibitors (ICIs). Recent findings from an innovative mouse model of EOC demonstrate that senescence induction underlies the increased sensitivity of homologous recombination-defective EOCs to platinum-based chemotherapy as it initiates tumor infiltration by immune effector cells coupled to restored sensitivity to ICIs.

High-grade serous ovarian cancer (HGSOC), the most common form of epithelial ovarian carcinoma (EOC), is the leading cause of death from gynecological malignancies, largely reflecting delayed diagnosis (nonspecific symptoms emerge only when the disease is advanced) and the frequent insurgence of acquired resistance to treatment. The standard-of-care (SOC) management of HGSOC generally consists in debulking surgery followed by induction chemotherapy with a platinum-taxane doublet and maintenance therapy (for platinum-sensitive tumors) with a poly(ADP)-ribose polymerase (PARP) inhibitor. Importantly, sensitivity to platinum-based chemotherapy is largely dictated by homologous recombination (HR) defects that are generally caused by BRCA1 DNA repair associated (BRCA1) or BRCA2 mutations. Of note, HGSOCs bearing BRCA1/2 mutations exhibit a relatively increased antigenic load and improved infiltration by CD8+ cytotoxic T lymphocytes (CTLs). Nonetheless, HGSOCs are poorly responsive to immune checkpoint inhibitors (ICIs) specific to programmed cell death 1 (PD1, best known as PD-1), irrespective of HR status, correlating with a reduced tumor mutational burden (TMB) and a rather immunosuppressed tumor microenvironment (TME) at baseline. Thus, an improved characterization of the molecular mechanisms that govern immunosuppression in the HGSOC microenvironment as well as the identification of clinically actionable strategies to inflame the TME in HGSOC patients are urgently awaited. In preclinical models of lung and pancreatic cancer, the ability of targeted anticancer agents to permanently block the proliferation of malignant cells and induce the secretion of various cytokines and other bioactive factors (i.e., a terminal cell fate commonly known as cellular senescence) has been previously shown to elicit inflammatory responses that are associated with restored tumor infiltration by immune effector cells and increased sensitivity to ICIs. Recently, Paffenholz and collaborators have harnessed an innovative, electroporation-based autochthonous mouse model of HGSOC to demonstrate that senescence induction explains the superior sensitivity of HR-deficient HGSOC to platinum-based chemotherapy as it initiates the recruitment of CD8+ CTLs and natural killer (NK) cells to the TME, ultimately enabling therapeutic responses to PD-1 blockers.

Aware of the considerable limitations imposed by existing genetically engineered mouse models (GEMMs) of HGSOC (cost, limited heterogeneity, ...), Paffenholz and collaborators set out to establish a new syngeneic model of the disease based on direct electroporation of the ovarian tissue, an approach that has concomitantly been pursued by other groups. A variety of alterations commonly detected in human HGSOC were assessed (alone or in combination) for their capacity to drive HGSOC in immunocompetent, female C57BL/6 mice, including Trp53, Rb1, Pten and Brca1 deletion, as well as Mycn overexpression. Complete penetrance was obtained by concomitant Mycn overexpression and Trp53 deletion (MP tumors), which also drove HGSOCs that closely resembled their human counterparts from a histological, genomic, transcriptional, and biological perspective. Concomitant Brca1 deletion (MPB tumors) resulted in neoplasms with increased copy number alterations (CNAs), accrued infiltration of CD4+ and CD8+ T cells, and improved sensitivity to cisplatin-based chemotherapy, thus recapitulating HR-defective HGSOC in humans. Together with recent data from Teng and collaborators, these findings establish electroporation-based carcinogenesis as a convenient model to recapitulate the immunobiology of human HGSOC in immunocompetent mice.

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Of note, cisplatin caused extensive cellular senescence in MPB (but not MP) tumors, correlating with increased secretion of C-C motif chemokine ligand 5 (CCL5), C-X-C motif chemokine ligand 10 (CXCL10) and interleukin 6 (IL6), three prototypical components of the senescence-associated secretory phenotype (SASP). Similar results were obtained by reconstituting human BRCA1-mutant UWB1 HGSOC cells with wild-type BRCA1. Moreover, the retrospective analysis of one HGSOC patient cohort revealed that the neoplasms of individuals responding to treatment exhibited an underrepresentation of genetic signatures for cell cycle progression, coupled to the overrepresentation of signatures for cellular senescence and cytoplasmic DNA sensing. Consistent with this notion, cisplatin caused signs of DNA damage and micronucleation in cultured MPB (but less so MP) cells, correlating with the accrued infiltration of MPB (but not MP) tumors by CD8+ CTLs and NK cells. Importantly, cisplatin-driven CCL5, CXCL10, and IL6 secretion, as well as cisplatin-driven tumor infiltration by immune effector cells, could be abrogated by genetically interfering with the cytosolic DNA sensor cyclic GMP-AMP synthase (CGAS). These data demonstrate that, in the absence of Brca1, cisplatin drives CGAS-dependent senescence in HGSOC cells, which initiates the recruitment of immune effectors to the TME.

In line with abundant preclinical and clinical data demonstrating that ICI sensitivity is largely dictated by tumor infiltration at baseline, MPB (but not MP) tumors treated with cisplatin exhibited increased sensitivity to PD-1, correlating with increased amounts of CD8+ CTLs expressing the effector molecule granzyme B (GZMB) and consequent compensatory expression of the PD-1 ligand CD274 (best known as PD-L1) by malignant and myeloid cells. Importantly, such a therapeutic synergy was fully abrogated by the depletion of CGAS. Thus, CGAS-dependent senescence induction in Brca1−/− HGSOC initiates an inflammatory response that recruits immune effector cells to enable therapeutic ICI efficacy. Similar findings have previously been obtained in other Brca1−/− GEMMs of HGSOC treated with the PARP inhibitor olaparib.

In summary, the findings from Paffenholz and collaborators suggest that the therapeutic induction of senescence by platinum-based chemotherapy (or, at least potently, other CGAS activators such as radiation therapy) may be harnessed to inflame the HGSOC environment in support of restored ICI sensitivity (Figure 1). Early-phase clinical studies testing ICIs along with SOC chemotherapy and PARP inhibitors in patients with HR-deficient HGSOC demonstrated good tolerability and signs of therapeutic efficacy, spurring the initiation of various, randomized Phase III studies. The results of these and other clinical trials testing platinum-based chemotherapy and PARP inhibitors plus immunotherapy in patients with HGSOC are urgently awaited to improve the clinical management of this deadly disease.

**Disclosure statement**

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**Figure 1.** Senescence induction by platinum-based chemotherapy initiates antitumor immunity in HR-deficient HGSOC. In the absence of Brca1, homologous recombination (HR)-deficient high-grade serous ovarian cancer (HGSOC) cells respond to cisplatin-based chemotherapy by undergoing a permanent proliferative arrest coupled to the cyclic GMP-AMP synthase (CGAS)-dependent secretion of multiple cytokines, including C-C motif chemokine ligand 5 (CCL5) and C-X-C motif chemokine ligand 10 (CXCL10). This culminates with the recruitment of CD8+ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells to the tumor microenvironment, which can be therapeutically actioned with immune checkpoint inhibitors.
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