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NEWS

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TARGETING IMMUNOSUPPRESSIVE MACROPHAGES OVERCOMES PARP INHIBITOR RESISTANCE IN *BRCA1*-ASSOCIATED TRIPLE-NEGATIVE BREAST CANCER

BRCA1 is a tumor-suppressor gene that encodes proteins involved in the repair of DNA double-strand breaks by way of the homologous recombination repair pathway.[1] *BRCA1* mutations occur in approximately 5% of breast cancer (BC) patients. This mutation renders cells susceptible to chromosomal instability through defective DNA break repair, leading to increased risk of triple-negative BC (TNBC). Two years ago, the FDA approved poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of *BRCA*-associated human epidermal growth factor receptor 2 (HER2)-negative metastatic BC. Approval was based on data from OlympiAD,[2] where response rates and progression-free survival (PFS) were superior to standard chemotherapy.

Mehta et al.[3] published a motivating article in *Nature Cancer* showing the effects of PARP inhibition on macrophages in a preclinical model of *BRCA1*-deficient TNBC. First, they showed in tissue specimens from untreated TNBC patients that tumors with mutated *BRCA1* had significantly more T cells and macrophages than *BRCA*-WT. Furthermore, an extensive characterization of tumor macrophages in a mouse of *BRCA1*-deficient TNBC revealed that macrophage numbers increase further after PARP inhibitor treatment, hence, olaparib modulated the tumor microenvironment. Interestingly, they showed that olaparib treatment drove both pro- and antitumor phenotypes. On the one hand, olaparib induced an up-regulation of CD80 and CD40 and an activation of the stimulator of interferon response CGAMP interactor (*STING*) pathway of macrophages, resulting in an antitumor phenotype. But, on the other hand, a concomitant increase in levels of immune-suppressive markers [programmed death-ligand 1 (PD-L1) and colony-stimulating factor 1 receptor (CSF1R)] and a modulation of macrophage metabolism (switch from glycolysis to lipid metabolism) were observed, which would be related to limit antitumor activity.

Anti-CSF1R therapy has been shown to deplete a subset of macrophages, especially tumor-promoting macrophages. They hypothesized that targeting CSFR1+ macrophages would enhance olaparib activity. To address this premise, they combined anti-CSF1R and olaparib in a *BRCA1*-deficient TNBC mouse model. As they expected, the combination reduced the number of CD206+ and PD-L1+ CSF1R+ protumor macrophages and restored their glycolytic metabolism, which translates to improved response duration and PFS compared with treatment with olaparib alone in preclinical models.

Overall, the manuscript suggests that combining PARP inhibitors with anti-CSF1R therapy reduces immune-suppressive macrophages and overcomes PARP inhibitor resistance in *BRCA1*-deficient TNBC. This could represent a new strategy for anticancer therapy and support how immuno-oncology agents and cytotoxic therapies can be best combined to increase the efficacy of antitumor response.

DNA SENSING IN MISMATCH REPAIR-DEFICIENT TUMOR CELLS IS ESSENTIAL FOR ANTITUMOR IMMUNITY

The DNA mismatch repair deficiency (dMMR) is the initiating event in a wide range of cancer types. It is characterized by high tumor mutational burden (TMB) and high sensitivity to immune checkpoint blockade (ICB). Nevertheless, TMB is not an accurate predictive biomarker, as the objective response rate to anti-programmed cell death protein 1 therapy ranges from 28% to 53%. Preclinical and clinical evidences demonstrated the relevant role of peritumoral pre-existing CD8+ T cells in sensitivity to ICB. T-cell activation promotes antitumor effects by triggering the toll-like receptors or the cyclic GMP-AMP synthase (cGAS)-*STING*-dependent type I interferon (IFN) signal.[4] However, the presence of CD8+ does not always correlate with immunogenic antigens.[5] This is what happens, for instance, in colorectal cancer samples, where ~50% of both microsatellite instability-high (MSI-H) and TMB-high samples present a low level of T-cell infiltration.[6] These data suggest that other functional changes mediated by dMMR may play roles in the ICB response. Thus, additional molecular insights are needed to understand the relation between T-cell infiltration and ICB in dMMR cancers.[7]

In a relevant article published in *Cancer Cell*, Lu et al.[8] try to explain why 50% of dMMR cancers do not benefit from immunotherapy. The authors found that in the absence of treatment, the cGAS-*STING* pathway is constitutively activated in dMMR tumor cells, triggering antitumor immune responses, probably due to the accumulated cytosolic DNA. The loss of cytosolic DNA and IFN signal after MLH1 rescue demonstrates that MLH1 plays dual roles as a tumor suppressor. MLH1 suppresses tumor development by correcting DNA replication biosynthetic errors. Moreover, MLH1 deficiency limits tumor progression by triggering DNA sensing-mediated antitumor immune surveillance. In particular, the loss of MLH1 conducts an uncontrolled DNA excision during DNA repair. The uncontrolled excision causes several molecular alterations that finally activate the cGAS-*STING* pathway, which contributes to tumor control. Interestingly, in a dMMR background, the *STING*-cGAS pathway within tumor cells, but not host cells, is essential for suppressing tumor progression.

The *STING*-cGAS pathway regulates tumor infiltration of CD8+ T cells, while the increased CD8+ T cells disappear in *STING* or cGAS knockout tumors. In their experiments, the authors showed that the reduction of expression of cGAS is common human in dMMR cancer cell lines. The expression level of cGAS is significantly lower in MSI-H human tumor

samples than in microsatellite stable ones, implying an unknown mechanism of negative regulation. By using mouse and human dMMR tumor models, it was possible to see that the impaired cGAS-*STING* pathway in tumor cells confers resistance to ICB therapy. Accordingly, the cGAS/*STING* expression predicts survival of patients with MMR-deficient cancers. Loss of or impaired cGAS-*STING*-IFN pathway might allow dMMR tumors to evade immune rejection, which, besides neoantigens, might be another way of immunoediting. The findings suggest that deficiency of MLH1 and subsequent accumulation of cytosolic DNA activates the cGAS-*STING* pathway, contributing to increased immunity.

Conversely, diminishing this DNA sensing by MLH1 rescue or *STING*/cGAS knockout in tumor cells leads to progressive tumor growth and ICB resistance. For this reason, the cGAS-*STING*-IFN pathway could be an independent biomarker for immunotherapy in patients with dMMR cancers. This study might provide better rationales to try to personalize immunotherapy and opens new horizons for novel combinations.

A PRECISION MEDICINE STRATEGY DEFINING MOLECULAR SUBGROUPS AND PRIORITIZING TREATMENTS ACCORDINGLY IN ADVANCED GASTROESOPHAGEAL ADENOCARCINOMAS

Gastroesophageal adenocarcinoma is characterized by high heterogeneity. This encompasses not only interpatient variability (intertumor heterogeneity), but also variations within the same tumor (intratumor heterogeneity) and temporal dynamic heterogeneity (meaning tumor progression from primary site(s) to recurrent and/or metastatic disease) that could explain treatment failures.[9] Although multiple targeted agents are currently under investigation, so far, only trastuzumab and ramucirumab have demonstrated efficacy in advanced gastroesophageal adenocarcinoma and have a regulatory approval. MSI and Epstein—Barr virus (EBV) subgroups, as well as patients with high expression of PD-L1 could potentially benefit from immunotherapy.[10]

Recently, an inspiring study was published in *Cancer Discovery*.[11] The PANGEA study is based on a challenging personalized medicine approach through a molecular next-generation sequencing diagnosis biomarker's algorithm-based strategy to guide the therapeutics at diagnosis, and up to three treatment lines using monoclonal antibodies combined with optimally sequenced chemotherapy. This study has a novel design: a phase II expansion-platform type II clinical trial,[12] in which therapy is assigned immediately based on a predefined biomarker treatment group in favor of testing a predefined treatment strategy that pools multiple biomarker—drug pairings, ideally with comparison to a biomarker stratified control group. The primary efficacy endpoint of the study was 1-year overall survival (OS).

The study included patients with poor prognosis features such as Eastern Cooperative Oncology Group performance status of 2, signet ring cells, and peritoneal disease (9%, 26%, and 38% of all patients enrolled, respectively). A predefined prioritized biomarker and treatment assignment algorithm was applied at each therapeutic line, entailing eight biologic subgroups with six matched monoclonal antibodies. Remarkably, 68 patients were included in the intention-to-treat analysis, mostly junctional tumors (74%). For this cohort, 1-year estimated survival was 66% and median OS was 15.7 months, meeting the primary efficacy endpoint. All 68 patients received a first-line treatment, 87% received second-line treatment, and 42% received third-line treatment, which is proportionally greater than expected in other Western series.[13] Good disease control rates were achieved in 99%, 72%, and 68% for first-, second-, and third-line treatment, respectively. Interestingly, HER2 amplified patients ($n = 16$) who received chemotherapy plus trastuzumab presented the best outcomes, with a median OS of 25.8 months.

Although the authors remarked on limitations, such as the lack of a control arm as well as the power of the study, this trial provides evidence supporting a 'temporal biomarker therapeutic guide decision'. The study also highlights the weakness of the available predictive biomarkers for checkpoint inhibitors beyond MSI or EBV. The outcome of PANGEA supports a prospective comparison of such personalized treatment strategies in randomized trials.

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