PARP1 inhibition elicits immune responses against non-small cell lung cancer

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**ABSTRACT**

High levels of intracellular poly(ADP-ribose) (PAR) resulting from an elevated activity of PAR polymerase-1 (PARP1) correlate with poor infiltration of non-small cell lung cancers by cytotoxic T lymphocytes and dismal patient prognosis. Preclinical experimentation now demonstrates that PARP1 inhibition in cancer cells mediates strong immunostimulatory effects.

First, we created two PAR\textsuperscript{high NSCLC} cell lines (Lewis lung cancer [LLC] and tissue culture number one [TC1]) by selecting them by long-term culture in the presence of low-dose cisplatin (Figure 1a). The resulting PAR\textsuperscript{high NSCLC} cell lines maintained their elevated PAR level even after several months of culture in the absence of cisplatin, likely due to an increased level of spontaneous DNA damage.\textsuperscript{6} PAR\textsuperscript{high NSCLC} cells were cloned to reduce their heterogeneity and then subjected to the knockout (KO) of PARP1 by CRISPR/Cas9 technology, yielding cells that lacked any signs of PAR accumulation (which demonstrates that PARP1 is the sole PARP isofrom generating PAR in these cells) and became sensitive to cisplatin (which demonstrates that PARP1 was indeed responsible for chemotherapy resistance). Of note, PAR\textsuperscript{high NSCLC} cells exhibited strong responses to the cytostatic and cytotoxic effects of niraparib, a specific PARP1 inhibitor which is clinically approved.\textsuperscript{10}

Conversely, PARP1\textsuperscript{KO} cells became resistant to niraparib, as expected (Figure 1b).

Next, we inoculated PAR\textsuperscript{high NSCLC} and PARP1\textsuperscript{KO NSCLC} cells into immunodeficient mice, from which T lymphocytes had been deleted by injection of antibodies specific for CD4 or CD8. PAR\textsuperscript{high NSCLC} and PARP1\textsuperscript{KO NLCC} LLC or TC1 cells indistinguishably formed tumors in these T cell-depleted animals. In sharp contrast, PARP1\textsuperscript{KO TC1} cells failed to develop tumors in immunocompetent histocompatible mice, in conditions in which PAR\textsuperscript{high TC1} cells readily proliferated, forming tumors with similar growth kinetic in immunocompetent and immunodefficient mice. When immunocompetent recipient mice had rejected the inoculation of PARP1\textsuperscript{KO TC1} cells, they subsequently became resistant against PAR\textsuperscript{high TC1} cells implanted into the opposite flank. These findings indicate that PARP1\textsuperscript{KO TC1} cells cause a durable protective anticancer immune response mediated by T cells. We also found that PARP1\textsuperscript{KO LLC} cells came under immunosurveillance. PAR\textsuperscript{high NSCLC} LLC cells similarly grew on T cell-depleted and control
of an anticancer immune response even when the malignant cells lack this target. However, the mechanisms of this immunostimulatory effect remain to be elucidated.

**Disclosure statement**

GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Samsara, Sanofi, Vascage and Vasculos/ Tioma. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio.

**Funding**

GK is supported by the Ligue contre le Cancer (équipe labellisée); Agence Nationale de la Recherche (ANR) – Projets blancs; AMMIGa US23/CNRS UMS3655; Association pour la recherche sur le cancer (ARC); Association "Ruban Rose"; Cancéropôle Ile-de-France; Fondation pour la Recherche Médicale (FRM); a donation by Elior; Equipep Onco-Pheno-Screen; European Joint Programme on Rare Diseases (EJPRD); Gustave Roussey Odyssee, the European Union Horizon 2020 Projects Oncobiome and Crimson; Fondation Carrefour; Institut National du Cancer (INCa); Inserm (HTE); Institut Universitaire de France; LabEx Immuno-Oncology [ANR-18-IDEX-0001]; the Leducq Foundation; a Cancer Research ASPIRE Award from...
the Mark Foundation; the RHU Torino Lumière; Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC Cancer Research and Personalized Medicine (CARPEM). This study contributes to the IdEx Université de Paris ANR-18-IDEX-0001. Al was supported by a fellowship from Institut Thématique Multi-Organisme (ITMO Cancer) du Plan Cancer 2014-2019.

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Data availability statement

This is a commentary on a paper published in Journal for ImunoTherapy of Cancer. All original data are available in this paper.

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