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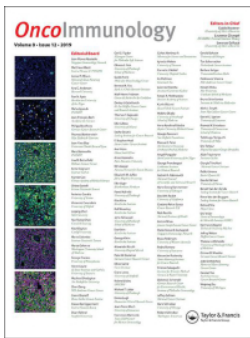
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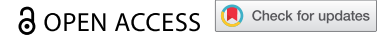


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AUTHOR'S VIEW



Pyridoxal kinase and poly(ADP-ribose) affect the immune microenvironment of locally advanced cancers

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ABSTRACT

Malignant cells adapt to the hostile tumor microenvironment by escaping from, or actively suppressing, anticancer immune responses. In the past, we reported that reduced synthesis of active vitamin B6 (due to downregulation of pyridoxal kinase) or overactivation of poly(ADP-ribose) polymerase confers resistance to chemotherapy with cisplatin. Recently, we found that these prognostically adverse alterations in oncometabolism also correlate with the rarefaction of immune effectors in the tumor bed.

ARTICLE HISTORY

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Tumor microenvironment; immune escape; metabolism; vitamin B; immunotherapy; CD8+ T cells; dendritic cells; survival; cervical cancer; non-small cell lung cancer

The immune system is known to play a major role in cancer immunosurveillance and response to chemotherapy.^{1,2} Recently, immune checkpoint blockade therapy has created a paradigm shift in antineoplastic treatments, highlighting the importance of focusing on the tumor microenvironment. Cancer cell-intrinsic properties, and in particular metabolic features, are known to impact the tumor immune environment.

In the past, we reported that chemotherapy with cisplatin leads to the down-regulation of vitamin B6 activating enzyme pyridoxal kinase (PDXK)³ and the up-regulation of the enzymatic activity of poly(ADP-ribose) (PAR) polymerase 1 (PARP1)⁴ in tumor cells, and that these metabolic alterations affect the prognosis of non-small cell lung cancer (NSCLC) patients.^{5,6} The activity of PARP1 requires a supply of nicotinamide (vitamin B3) adenine dinucleotide. Thus, both of these enzymes participate in vitamin B metabolism.

Recently, we dove further into the mechanisms underlying the interplay between cancer metabolism, immunosurveillance and prognosis,⁷ and investigated the role of these two vitamin B metabolism-related markers on the immune microenvironment.

In locally advanced cervical carcinoma (LACC) patients, for whom cisplatin is still part of the standard of care, we observed that tumor infiltration by CD8⁺ T lymphocytes and DC-LAMP⁺ cells were both associated with an improved prognosis. Tumors scarcely infiltrated by both CD8⁺ and DC-LAMP⁺ cells had a particularly dismal prognosis. We also described

a negative correlation between CD8 density and PAR expression and a positive correlation between DC-LAMP density and PDXK expression in LACC.

These findings were reproduced in a cohort of NSCLC patients, in which the detection of high levels of CD8⁺ or DC-LAMP⁺ cells, were independent prognostic factors, and in which we observed similar associations between PAR and CD8 infiltration (negative correlation) and between PDXK and DC-LAMP (positive correlation). In accordance with these findings, a PAR^{high}/PDXK^{low} status was associated with dismal NSCLC prognosis.

In a final step, we used a heterotopic mouse model of NSCLC, in which we injected Lewis lung cancer (LLC) cells subcutaneously into the flank of C57BL/6 mice. These cells had been previously exposed to increasing concentrations of cisplatin for several weeks and exhibited cisplatin resistance, together with enhanced PARP1 activity, as demonstrated by upregulation of PAR in immunoblot analyses. Immunofluorescence cytometry revealed that tumors formed by PAR^{high} LLC cells exhibited a reduced infiltration by CD8⁺ T lymphocytes as compared to tumors formed by parental LLC cells. In addition, PAR^{high} tumors were less infiltrated by subpopulations of myeloid cells (CD45⁺CD11b⁺Ly6G⁻Ly6C^{low/intermediate}) and activated dendritic cells (CD45⁺CD11c⁺MHCII⁺, non-significant trend).

In essence, in our recent article, we show that two enzymes, PDXK and PARP1, both implicated in the vitamin B metabolism, affect the immune infiltrate in two different malignant diseases, LACC and NSCLC. Our NSCLC mouse

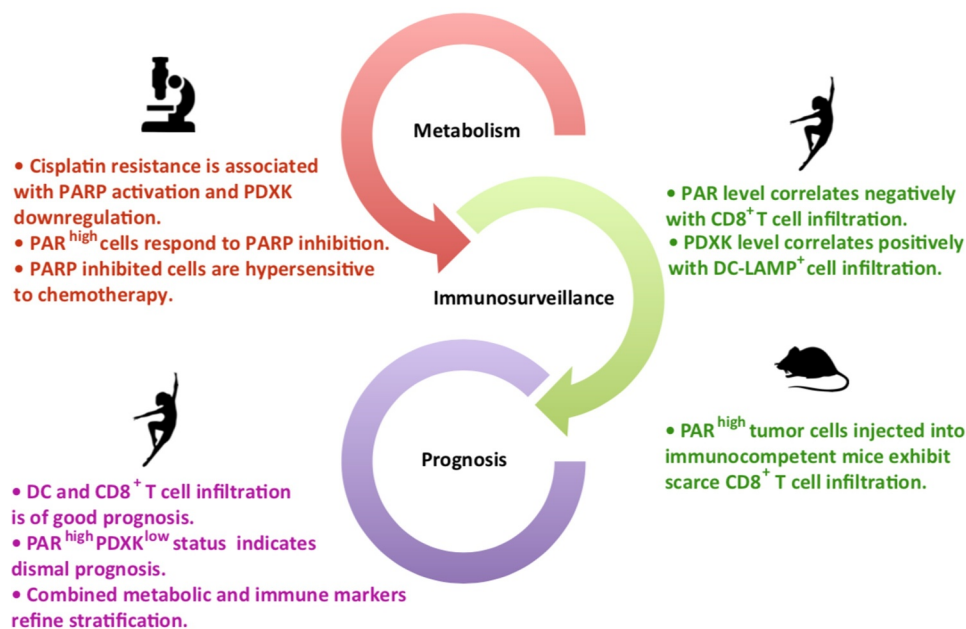


Figure 1. The interplay between oncometabolism, immune infiltrate and prognosis. In non-small cell lung cancer (NSCLC) and locally advanced cervical carcinoma (LACC), PAR level correlates negatively with CD8 T cells infiltration, whereas PDXK level correlates positively with DC-LAMP cells infiltration. Infiltration by each of these cell types is associated with a good prognosis in NSCLC and LACC, whereas PAR^{high}/PDXK^{low} status indicates dismal prognosis. Cisplatin-resistant LLC cells, which exhibit high level of poly (ADP- ribose), form tumors scarcely infiltrated by CD8⁺ T lymphocytes after injection in C57BL/6 mice. Items from this figure are provided for illustrative purposes only.

model supports a causal relationship between these metabolic features and immune tonus, demonstrating that the upregulation of PARP1 activity required for cisplatin resistance leads to a rarefaction of CD8⁺ T cell infiltration, exactly as this is observed in cancer patients. Based on these results, we hypothesize that PARP1 and PDXK activity within tumor cells can modulate the tumor immune environment. Thus, metabolic alterations of cancer cells associated with cisplatin resistance may have an impact on anticancer immunosurveillance (Figure 1).

These findings potentially pave the way for therapeutic interventions. Thus, we previously showed in an orthotopic mouse model of NSCLC that the addition of pyridoxine (phosphorylated by PDXK) to standard cisplatin treatment exhibited hyperadditive therapeutic effects only in the context of an intact immune system.⁸ Additionally, exogenous supply of nicotinamide adenine dinucleotide (NAD), which is consumed by overactivated PARP1, potently stimulates immunosurveillance in the context of hormone-induced breast cancer.⁹ PARP inhibitors are currently being tested in association with immune checkpoint inhibitors (e.g. NCT02571725 and NCT03598270). Our findings, along with others showing an increased infiltration of CD8⁺ T cells after PARP inhibition,¹⁰ support the hypothesis that PARP1 activity and immune infiltration are mechanistically linked, and provide a rationale for such combination therapies.

To conclude, metabolic features of cancer cells, such as PDXK and PAR levels, can impact the immune infiltrate, thereby affecting the clinical course of LACC and NSCLC. Although the interplay between tumor metabolism, immune infiltrate and prognosis remains to be explored and the detailed mechanisms underlying these findings remain to be

discovered, we believe that this area of research has the potential to elucidate new patient-relevant facets of the cancer-immune dialogue.

Disclosure statement

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