Editorial

CD73: a new biomarker in triple-negative breast cancer

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Triple-negative breast cancer (TNBC) constitute 10–20% of all breast cancers and are characterized by the lack of hormone receptors (estrogen and progesterone receptors) and HER2/neu expression (1). TNBC are not eligible to hormonotherapy and Herceptin/trastuzumab targeted therapy and are generally associated with poor clinical outcome (2). Anthracycline/taxane-based neoadjuvant chemotherapy is the primary systemic treatment but resistance to this treatment is common and the identification of new potential therapeutic molecules is required to improve the outcome of TNBC patients.

CD73 is a glycosylphosphatidylinositol (GPI) anchored cell surface protein encoded by the *NT5E* gene. Accumulating data showed that CD73 is a key molecule that regulates cancer progression (3). As an ectonucleotidase, CD73 is implicated in the purinergic CD39/CD73/adenosine pathway through its capacity to generate adenosine from AMP. Adenosine is an immunosuppressive molecule involved in tumor immune escape over its ability to impair functions of anti-tumor immune effectors. Besides its role in tumor immune escape, some reports brought evidence that CD73 is involved in the control tumor cell proliferation and migration but also angiogenesis and apoptosis, by modulating signaling pathways, like EGFR/Akt, VEGF/Akt pathways and thus CD73 is associated with tumor growth, metastasis and resistance to therapies (3-5). Based on these observations, several studies analyzed CD73 expression in correlation with survival or disease progression in various solid cancers. Remarkably, CD73 appeared now both as a potential prognostic biomarker and a promising target to counteract immunosuppressive tumor microenvironment and favor anti-tumor immune response (6,7).

Based on a recent review of the literature, the prognosis role of CD73 expression in different human solid tumors still remains controversial. Two meta-analyses including 13 and 14 studies with respectively 12,533 and 2,951 patients with solid tumors reported that CD73-high expression is mainly associated with inverse overall survival (OS) and disease-free survival (DFS) (8,9). Other studies in colorectal, gastric, gallbladder and prostate cancers, also identified CD73 as an unfavorable prognostic marker (10-13). Quite the opposite, for epithelial ovarian carcinoma, gastric and bladder cancers and rectal adenocarcinoma, CD73-high expression predicted better prognosis, lower stage and higher degree of differentiation (14-17). In breast cancer, the association of CD73 with long-term survival is still a matter of debate, maybe due to the strong heterogeneity of breast cancers. Supernat *et al.* reported that positive CD73 expression is associated with longer DFS and OS in 136 stage I–III breast cancer patients (18). In contrary, using gene-expression analysis from over 6,000 breast cancer cases, it has been showed that CD73 expression is significantly associated with a poor prognosis, particularly in TNBC (19). This study also revealed that CD73 expression in TNBC patients is associated with an increased resistance to doxorubicin, a commonly used chemotherapy. Interestingly the authors showed that doxorubicin treatment induced CD73 expression on human tumor cell lines *in vitro*. Furthermore, using the AT3-OVA TNBC mouse model, they demonstrated that anti-CD73 antibody treatment enhanced doxorubicin-induced anti-tumor immune response, thus highlighting CD73 as a potential new target in TNBC (19). Monoclonal anti-CD73 antibodies and A2a receptor antagonists are now

entering clinical trials, so it is important to better identify patients most likely to benefit from these new immune-based therapies.

In a recent article, Buisseret *et al*. reported results from a multiparametric analysis on a large cohort of TNBC patients (20). They quantitatively assessed CD73 expression in 122 TNBC samples from the Breast International Group (BIG) 02-98 adjuvant prospective phase III clinical trial that compared the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy in node-positive breast cancers. In this study, based on the expression of CD45, cytokeratin and CD73 by multiplex immunofluorescence, the authors studied the expression of CD73 on tumor cells, stromal cells or immune cells and evaluated its prognostic value. Even through CD73 was expressed in all compartments, they observed a higher expression of CD73 on tumor and immune cells compared to stromal cells. Moreover, higher CD73 expression of tumor and immune cells was observed in patients with massive lymph node invasion (>10 lymph nodes). Increased CD73 expression on tumor cells was correlated with worse survival but no clear association between stromal and immune CD73 expression was found with clinical outcome. In parallel, the authors investigated tumor immune infiltration by performing and analyzing various markers with an algorithm based on cytokeratin and CD45 positivity to determine a CD45+ area relative to the tumor tissue area. Consistent with a previous study, an extent of immune infiltration was associated with better DFS and OS. The analysis of both CD73 expression and CD45+ area revealed a negative correlation between CD73 expression on both tumor and immune cells and the degree of immune infiltration but not with CD73 expression on stromal cells. However, this study did not confirm the previously suggested predictive value of CD73 gene expression of anthracycline-based treatment resistance (19).

The simultaneous investigation of CD73 expression on tumor cells together with tumor immune infiltration degree allowed the authors to identify subgroups of patients with distinct prognosis (20). From this analysis, four phenotypic subgroups of patients were distinguished but only three subgroups in term of clinical outcome. Thus, this retrospective study differentiated patients with an excellent prognosis (high immune infiltration and low CD73 expression) or with a poor prognosis (low immune infiltration and high CD73 expression). Results based on the combined analysis of the two parameters could be of interest to establish new protocols to treat TNBC. First, such analysis would allow to identify patients with both high immune infiltrate and high CD73 expression who should derive benefit from a therapy targeting CD73 either alone or combined with immune checkpoint inhibitors such as anti-PD1, -PDL-1 or -CTLA-4 antibodies to remove the immunosuppressive brake and reinforce a pre-existing immune response. In the case of patients with a low immune infiltration, a combination of CD73-targeting therapy with drugs able to increase tumor infiltration as vaccine or adoptive cell transfer could be a better therapeutic option.

Several inhibitors targeting CD73 or adenosine A2a receptor are currently being evaluated in phase I clinical trials for patients with solid tumors, including TNBC. Preliminary results with adenosine A2a receptor antagonists showed a good tolerance and an increase of tumor infiltrating activated immune cells. Regarding drugs targeting CD73, three clinical trials are on-going using blocking CD73 monoclonal antibodies (BMS-986179, CPI-006 and MEDI9447). Preclinical results obtained with the MEDI9447 antibody described changes in both myeloid and lymphoid infiltrating leukocyte populations within the tumor microenvironment of mouse models (21). Changes included significant alterations in a number of tumor micro-environmental subpopulations, including increases in CD8 effector cells and activated macrophages (21).

Altogether, the results from Buisseret *et al*. highlight the interest to monitor CD73 expression on different cell subtypes and to combine it to other parameters such as the immune infiltration and confirmed its value as biomarker in TNBC. This study provides further support that CD73 expression is associated with a poor prognosis and reduced anti-tumor immunity in human TNBC and that targeting CD73 could be a promising strategy to reprogram the tumor microenvironment in TNBC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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