



Epithelial-mesenchymal transition as a potential biomarker for identifying responders to immune checkpoint inhibitor therapy in lung adenocarcinoma

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It is increasingly evident that the immune system plays critical roles in both cancer progression and regression, and it has been a target for anticancer therapies for over a hundred years (1). Until recently, however, attempts at stimulating a *de novo* immune response against tumor cells have met with limited clinical success largely due to immunoinhibitory pathways that downregulate the host immune response against cancer. The discovery of immune checkpoints revealed one of these key immunoinhibitory mechanisms and has led to the development of therapeutic inhibitors that essentially release the brakes on the immune system. The last 5 years has seen a revolution in the treatment of melanoma and non-small cell lung cancer with the regulatory approval of three immune checkpoint inhibitors, ipilimumab which targets the cytotoxic lymphocyte-associated protein 4 (CTLA-4) pathway, and nivolumab and pembrolizumab which target the programmed cell death protein 1 (PD-1) pathway. Several clinical trials have shown that these immune checkpoint inhibitors can induce a durable long-term response and prolong overall survival (2). In addition, they appear to be more tolerable than traditional cytotoxic chemotherapy. However, these benefits are not without major drawbacks as only 20–26% of patients respond to CTLA-4 targeted therapy and fewer than 40% respond to PD-1 targeted agents (2). Moreover, up to 15% of patients can experience severe dose limiting immune related adverse events (2). Thus, there is a critical need to develop strategies to identify patients who are likely to respond to immune checkpoint

inhibitor therapy.

A recent report by Lou and colleagues has taken on the challenge to define patient parameters that would help guide immune checkpoint inhibitor therapy in the setting of non-small cell lung cancer (3). The authors used mRNA expression of 76 genes associated with epithelial-mesenchymal transition (EMT) in lung adenocarcinoma (4) to assign “epithelial” or “mesenchymal” classification to lung adenocarcinoma specimens collected from three independent patient cohorts: the Cancer Genome Atlas (TCGA, n=230), the profiling of resistance patterns and oncogenic signaling pathways in evaluation of cancers of the thorax (PROSPECT, n=152), and the biomarker-integrated approaches of targeted therapy for lung cancer elimination (BATTLE-1, n=57). EMT is an important process in cancer progression and is classically defined as a cell’s transition from an epithelial to mesenchymal state, with the acquisition of properties such as motility and invasiveness (5). However, the role of EMT in the development of an immunosuppressive tumor microenvironment remains unclear. The authors reported that “mesenchymal” tumors were associated with upregulation of the immunoinhibitory components PD-L1, PD-L2, PD-1, TIM-3, B7-H3, BTLA, and CTLA-4 as determined by immunohistochemical and reverse phase protein array methods. They also observed increased infiltration of CD4+FOXP3+ regulatory T cells in “mesenchymal” tumors further supporting an immunosuppressive tumor microenvironment. Additionally, “mesenchymal” tumors demonstrated an inflammatory

phenotype as evidenced by increased CD3+ infiltrates (with CD8+ T cells trending higher), alongside significantly elevated mRNA levels of type 1-associated molecules such as CD80, CD86, 4-1BB, IFN- γ , and CXCL10. The authors conclude that the association between EMT status and an inflammatory tumor microenvironment with elevation of multiple targetable immune checkpoint molecules warrants further investigation of using EMT as a predictive biomarker for immune checkpoint blockade therapy in non-small cell lung cancer.

Although these findings support an association between EMT and immune dysfunction in the tumor microenvironment, it is still unclear whether EMT drives immune dysfunction or vice versa. Overall, the authors discount the utility of PD-L1 expression as a biomarker and instead promote the utilization of EMT markers that also implicate inflammation and immune cell involvement (6,7). In the case of nivolumab treatment, patients with PD-L1 positive tumors appeared more likely to respond to therapy than PD-L1 negative tumors. However, although the response rates were lower, a subset of patients with PD-L1 negative tumors also responded to treatment, suggesting the existence of additional biomarkers to inform immune checkpoint inhibitor eligibility (8). The EMT signature tested by Lou and colleagues appears promising since it also takes into account other immunoinhibitory pathways and the existence of an endogenous, albeit unsuccessful, immune response against tumor cells. Preclinical modeling certainly supports a combined approach of minimizing T cell energy/apoptosis under settings of active immunity in order to enhance therapeutic anti-cancer responses (9). However, the potential utility of designating EMT status to determine immune checkpoint inhibitor administration remains to be determined.

Altogether, the report by Lou and colleagues supports the “mesenchymal” characterization of non-small cell lung adenocarcinoma as a predictive biomarker for tumor microenvironment-derived immune checkpoint and immune-stimulation status. These data are intriguing since it suggests the “mesenchymal” phenotype (with added immunosuppression/inflammation) remains throughout the life-cycle of the disease, although patient longitudinal studies would be required to confirm this observation. These results could also spearhead the development of a much needed selection tool for oncologists in identifying lung cancer patients who are candidates for treatment with immune checkpoint inhibitors. Clinical trial evaluations will be needed to compare patient selection based on

EMT signatures *vs.* other approaches such as expression of PD-L1 alone or with other immunological biomarkers. The finding from these additional studies will determine the extent to which EMT classification could be used as a biomarker to improve outcomes in the treatment of lung cancer patients and, possibly, to guide the treatment of other solid malignancies.

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