Arid5a: A Missing Link between EMT and Tumoral Immune Resistance

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Epithelial-to-mesenchymal transition (EMT) endows tumor cells with the ability to invade and migrate, and to suppress antitumor immunity. In this issue, Parajuli and colleagues report that EMT tumors often express the RNA-binding protein AT-rich interactive domain 5a (Arid5a), which they find stabilizes the mRNAs encoding indoleamine 2,3 dioxygenase (IDO1) and CCL2. As a new link between EMT and tumoral immune resistance, Arid5a represents a therapeutic target of interest.

See related article by Parajuli et al., p. 862 (4).

Epithelial-to-mesenchymal transition (EMT) is a phenotypic switch that leads epithelial cells to acquire a spindle shape and an invasive migration capacity while losing anchorage and polarity. This developmental process can be hijacked by tumor cells, which thereby acquire the capacity to migrate out of a primary tumor and initiate the metastatic process. Cardinal features of EMT are the loss of E-cadherin expression and the acquisition of N-cadherin and vimentin expression. These changes are mediated by a number of EMT-associated transcription factors (EMT-TF). The contribution of EMT to cancer progression, metastatic dissemination, and therapy resistance is well described (1). Increasingly, evidence indicates that EMT causes tumor cells to acquire not only invasion and migration capacity, but also immunosuppressive properties. For example, an EMT signature is associated with resistance to immunotherapy in human melanoma (2). The exact mechanisms underpinning the interplay between EMT and immunosuppression are just beginning to emerge. They involve increased expression of chemokines able to recruit immunosuppressive cells such as myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg), and tumor-associated macrophages. Despite evidence that expression of these chemokines can be partly controlled by EMT-TF, we are lacking a full mechanistic understanding of the immunosuppressive pathways associated with EMT.

Besides transcription, gene expression is also regulated at the post-transcriptional level, through RNA-binding proteins that modulate mRNA stability or translation. Arid5a is one such protein. It binds to a stem-loop in the 3′ untranslated region (UTR) of some mRNAs, thereby preventing binding of Regnase-1, which would otherwise degrade these mRNAs (3). Initially found to stabilize *Il6* mRNA, Arid5a also stabilizes mRNA encoding other inflammatory molecules, such as Stat3, T-bet and Ox40. Arid5a expression is triggered during inflammation, and it contributes to the pathogeny of septic shock and other inflammatory processes by stabilizing the mRNAs of key proinflammatory factors (3). Little is known, however, about the role of Arid5A in antitumor immunity.

In this issue, Parajuli and colleagues uncover a link between Arid5a and EMT-associated immunosuppression (4). They first observe higher expression of Arid5a in human and murine pancreatic tumor lines with EMT features as compared to non-EMT lines. Strikingly, they further report that tumor cells knocked out for Arid5a produce smaller tumors in immunocompetent—but not in immunodeficient—mice, and that the knockout tumors contain more effector $CD8^+$ T cells, fewer Tregs, and fewer MDSCs as compared with wild-type tumors. This indicates that Arid5a allows tumors to resist immune rejection. The authors link this to Arid5a binding to and stabilizing the mRNAs encoding IDO1 and CCL2. IDO1 can locally degrade tryptophan into kynurenine, thereby impairing proliferation of effector T cells and favoring Treg differentiation (5). By stabilizing *Ido1* mRNA, Arid5a increases IDO1 expression and local immunosuppression. Likewise, Arid5a increases CCL2 expression by stabilizing its mRNA, thereby favoring the recruitment of MDSCs to the tumor. These observations, in both a pancreatic (KPC) and a colorectal (MC38) tumor model, make a clear link between EMT, Arid5a, and tumoral immune resistance. Parajuli and colleagues corroborate these observations with analyses of human tumor transcriptomic data, showing positive correlations between *ARID5A* and *CCL2* expression in colorectal cancer, and between *ARID5A, IDO1*, and poor prognosis in pancreatic cancer.

In addition to providing new mechanistic insights into the production of immunosuppressive factors by tumor cells undergoing EMT, these findings identify Arid5a as a key immunoregulatory node that may represent an interesting target for immunotherapy.

Author's Disclosures

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