Modulating Immunosuppression in the Intrapleural Space of Malignant Pleural Mesothelioma and Predictive Biomarkers to Guide Treatment Decisions

Raymond M. Wong, PhD*

Two recent articles by Lievense et al. and Chéné et al. highlight a frequently observed characteristic of human solid tumors—local secretion of diverse proteins that likely suppress host antitumor immune responses. These secreted factors, in addition to tumor cell–bound proteins such as programmed death ligand 1 (PD-L1), collectively create a local microenvironment that supports establishment of tumors and their subsequent resistance to immunotherapeutic interventions. In malignant pleural mesothelioma (MPM), these secreted immunosuppressive factors are often detectable in the intrapleural space. An assortment of notable factors have been identified in MPM pleural effusions, including transforming growth factor beta (TGF-β), interleukin-10, chemokine ligand 2 (CCL2) (also called monocyte chemoattractant protein-1), prostaglandin E2, and macrophage colony-stimulating factor. Each of these proteins may have significant roles in facilitating tumor immune evasion through distinct nonoverlapping mechanisms.

These immunosuppressive factors might be produced directly from MPM tissue, from infiltrating immunoregulatory cells (M2 macrophages, T-regulatory cells, myeloid-derived suppressor cells, etc.), or from other proximal tissues in the tumor area. Nevertheless, each factor has a distinct mechanism of action for downregulating antitumor immune responses. For instance, CCL2 may be a principal factor in monocyte recruitment to MPM tissue. MPM-infiltrating monocytes may preferentially differentiate into M2 macrophages, which are generally associated with local immunosuppression. Other factors in the pleural space of patients with MPM, such as TGF-β, could directly suppress T-cell activity and/or induce an immunosuppressive polarization of the local immune response.

Given the complex network of immunosuppressive pathways that are active in MPM, it seems likely that abrogating multiple factors is necessary for maximum clinical effectiveness of immunotherapy for this disease. Indeed, blockade of individual immunosuppressive factors such as TGF-β has not produced strong evidence of clinical benefit in patients with MPM. In other solid tumors such as melanoma, combined blockade of two immune checkpoint pathways (programmed death [PD-1] and cytotoxic T lymphocyte antigen-4) is more effective than either therapy alone. These observation suggest that combining multiple cancer immunotherapies targeting different aspects of the immune system can yield additive/synergistic immune-stimulating activity, thereby conferring enhanced clinical benefit. In MPM, for instance, blockade of immunosuppressive cytokine (e.g., TGF-β and CCL2) in combination with immunomodulatory immunotherapy (e.g., interferon α or interleukin-2) may be a rational strategy to overcome the multiple immune-evasive mechanisms found in this malignancy.

The anatomical location of MPM and the substantial levels of immunosuppressive factors in MPM pleural effusions suggest that the intrapleural space may be an optimal therapeutic intervention site for this disease. Intrapleural delivery increases the local concentration of immunotherapeutic agents within the anatomical region of MPM, possibly improving their therapeutic activity while limiting systemic exposure. Intrapleural immunotherapy (ClinicalTrials.gov identifier NCT01119664) and intrapleural chimeric antigen receptor T-cell immunotherapy are now under way or planned. Positive clinical data on intrapleural immunotherapy using single agents could pave the way for trials of combinatic intrapleural treatments for MPM.

*Corresponding author.
Pacific Mesothelioma Center, Pacific Heart, Lung and Blood Institute Los Angeles, California.
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Address for correspondence: Raymond M. Wong, PhD, Pacific Mesothelioma Center, Pacific Heart, Lung and Blood Institute, 10780 Sans Monica Blvd., Suite 101, Los Angeles, CA 90025. E-mail: rwong@phibl.org
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Although important advancements in cancer immunotherapy have been made, a significant proportion of patients still experience little to no clinical benefit from treatment. There is now a focused effort to study the mutational profile of human tumors with the expressed purpose of elucidating biomarkers that could identify the subset of patients most likely to benefit from immunotherapy. In a recent small clinical trial focusing primarily on colorectal cancer, a defect in DNA mismatch repair appears predictive of clinical response to PD-1 blockade immunotherapy. It is hypothesized that defective mismatch repair in tumors leads to significantly higher somatic mutational load, producing a larger pool of neoantigens for immune recognition. This association between mutational load and clinical response to PD-1 blockade immunotherapy may also apply to additional tumor types, including lung cancer.

Interestingly, a recent review by Hylebos et al. discussed the fact that MPM frequently harbors mutations in four pathways: cell cycle, mitogen-activated protein kinase, phosphoinositide 3-kinase/AKT, and tumor protein 53 (or p53) DNA repair. More detailed analysis of DNA repair defects in MPM, including mismatch repair, is warranted given its predictive significance in other cancers. Such studies might yield crucial knowledge of overall mutational load and concomitant neoantigen levels in MPM. This would advance our understanding of the immunological characteristics of MPM, potentially revealing biomarkers that could guide treatment decisions.

References


