

Interplay between immune cells in lung cancer: beyond T lymphocytes

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Conclusive evidence has demonstrated that the immune system plays an instrumental role in preventing or promoting the development and progression of lung cancer. Progressively growing tumors escape immune control through a wide variety of mechanism which include: (I) secretion of immunosuppressive factors; (II) expression of immunosuppressive and anti-phagocytic molecules; (III) modulation of local and systemic metabolism; and (IV) recruitment and activation of host immunosuppressive cells that promote tolerance to tumors (1).

To date, most studies in the field of tumor immunology have focused on T cell-mediated adaptive immunity while the contribution of B-cells and humoral responses in cancer pathogenesis has largely been ignored. Therefore, the study by Wang and collaborators (2) represents an important contribution to the field. Using a syngeneic mouse model of lung cancer (C57BL/6J and C57BL/6 congenic CD45.1+ mice), the authors demonstrate that tumor-bearing mice exhibit an increase in the absolute number and percentage of myeloid-derived suppressor cells (Gr-1+CD11b+; MDSCs), both the granulocytic (CD11b+Ly6G+Ly6C^{low}) and the monocytic compartment (CD11b+Ly6G2Ly6C^{high}). Furthermore, new and robust evidence is presented which supports the notion that during tumor progression, MDSCs modulate not only T-cell responses but also the number and function of specific B-cell subtypes via the IL-7 and STAT5 signaling axis. The aim of this editorial is to further discuss the results of the afore-mentioned study in the context of human lung cancer and to provide a conceptual framework

for clinicians to more fully understand the relevance and implications of the study.

One of the advantages of the Lewis lung carcinoma (LLC) model is that tumor cells are immunologically compatible with the host into which they are implanted. Therefore, tumor engraftment was performed in immunocompetent mice, which allowed for immune-tumor interactions to be studied throughout the natural course of the disease. In earlier studies subcutaneous injection of LLC has been used as a relatively easy and reproducible method to evaluate subcutaneous tumor growth and lung metastasis. However, it has been acknowledged that due to microenvironment differences, subcutaneous implantation fails to accurately recapitulate the tumor biology of lung cancer or its response to therapy.

As a result, several methods have been developed to implant LLC cells directly into the lungs of mice (orthotopically). This can be achieved by either intrabronchial or intrathoracic injection into the pleural cavity or the lung parenchyma. Although intravenous and intracardiac injection of LLC cells (as performed in the study under discussion) leads to the rapid development of lung carcinoma in mice, it can be argued that this model is not strictly orthotopic and that it may in fact represent a process of rapid lung metastasis. It is unfortunate that neither *ex vivo* nor *in vivo* measurements of tumor mass in target organs was presented, since it leaves unanswered the question of whether the functional and phenotypical changes in B-cells populations correspond with tumor progression.

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Although mechanistic experiments in murine models are essential to dissect the pathways by which B cells and humoral immunity contribute to lung cancer pathogenesis, it is important to keep in mind that immunological responses in murine models may not be transferable to humans due to intrinsic differences between species. For instance, whereas several studies have demonstrated that IL-7 activation of STAT5 is essential for the development of mouse B-cells and that disruption of this signaling axis results in the arrest of B-cell maturation at the pro-B stage (3), in humans, the regulatory role and timing of IL-7/IL-7Ra/STAT5 signaling during B-cell development remains a largely controversial topic. The classical model of human lymphopoiesis established that IL-7 is required for the proliferation of T-cell progenitors but not for the proliferation of B-cell progenitors. More recently, however, it has been reported that in humans, continuous pSTAT5 response to IL-7 is restricted to a rare population of B cell precursors, in which STAT5 phosphorylation can also be induced by TSLP (4). Furthermore, it has been shown that human B-cell production is increasingly dependent on IL-7Ra signalling which can be provided by IL-7 or TSLP (5). Together, these studies demonstrate that human B lymphopoiesis is affected by IL-7/IL-7Rα signaling, although perhaps to a lesser extent than in mice. This opens up the possibility that IL-7 may indeed affect anti-tumor immunity in humans by modulating not only T-cell but also B-cell responses.

However, there are conflicting reports regarding the effect of IL-7 on tumor growth. Whereas some studies have found that IL-7 can restore the number and function of CD8+ and CD4+ T-cells, others have found that it induces the expression of PD-1 and its ligands (6) and that IL-7R α expression is associated with the immunosuppressive capacity of Tregs.

Similarly, there are studies showing that IL-7 signaling can prevent the apoptosis of human lung cancer cells, induce the epithelial-mesenchymal transition and metastasis of human breast and prostate cancer cells (7). In a large cohort of stage I lung adenocarcinoma patients, Suzuki *et al.* found that tumoral loss interleukin-12 receptor β 2 (IL-12R β 2) and IL-7R overexpression, as well as stromal FoxP3/CD3 ratio, are independent predictors of disease recurrence (8). In a subsequent study, the authors showed that ER α expression is another independent predictor of disease recurrence, which is associated with tumor IL-7R overexpression and FoxP3+T cells infiltration (9).

Clinical trials using IL-7 as a vaccine adjuvant did not

obtain promising results. For instance, in the first human dose-escalation trial, no objective responses were observed when recombinant IL-7 was administered in combination with two melanoma peptides (gp100 and MART-1). Similarly, there was no evidence of clinical activity in patients with non-hematologic malignancies treated with escalating doses of IL-7 or with a vaccine of melanoma cells engineered to express IL-7 (10)

These results are consistent with those of more recent studies showing that in patients with NSCLC, STAT5 expression and phosphorylation is associated with apoptosis inhibition, cell cycle progression, proliferation, invasion, and angiogenesis (11). Future studies could perhaps evaluate the expression and activity of cyclooxygenase-2 (COX-2), since it has been reported that STAT5 stimulates COX-2 expression in NSCLC. COX-2 is involved in the initiation and progress of tumors *in situ* and it is overexpressed in NSCLC, promoting angiogenesis and metastasis and inhibiting apoptosis (12).

The rationale behind assessing STAT5 in NSCLC is based on several reports describing that STAT-mediated pathways induce PD-L1 upregulation and contribute to tumor immune evasion. More specifically, it has been described that STAT3 recruits MDSC and it is related with decrease of immune cell infiltration in different tumors, including NSCLC. Moreover, the inhibition or silencing of STAT3 induces decrease expression of PD-L1 in EGFRmutant and ALK-translocated cell lines (13). Thus, it has been proposed that STAT3 expression can be a potential biomarker of response to immunotherapy.

Myeloid-derived suppressor cells (MDSCs), a heterogeneous cell population of immature myeloid cells with highly immunosuppressive activity, have been shown to modulate various aspects of carcinogenesis including initiation, immune tolerance, progression, metastasis and therapy response. MDSC are comprised of early-stage MDSC (E-MDSC), immature mononuclear cells which are morphologically and phenotypically similar to monocytes (M-MDSC), and immature polymorphonuclear cells which, in turn, are morphologically and phenotypically similar to neutrophils (PMN-MDSC, formerly known as G-MDSC). These populations of MDSCs have become the focus of intense research in recent years (14). Indeed, the presence of different MDSCs populations both in the periphery and within the tumor, has been shown to correlate with poor clinical outcomes in patients with small and non-smallcell lung cancer (14-24). The results of these studies are summarized in Table 1. We have recently reported that

MDSC population	Phenotype	Туре	Main observations	Ref
E-MDSC	Lin-HLA-DR-CD33+CD11b+	NSCLC	Increased in patients, in vitro immunosuppression, ATRA responsive	(25)
MDSC	CD11b+CD15+CD33+	NSCLC	Immunosuppression, poor response to chemotherapy, Shorter PFS	(17)
PMN	CD11b+CD14-CD15+CD33+	NSCLC	Decreased response to chemotherapy	(19)
PMN	CD66b+ Sideward-Scatter high	NSCLC	Increased in patients	(26)
М	CD11b+CD14+CD33+S100A9+	NSCLC	Poor response to chemotherapy and shorter PFS	(23)
PMN	CD11b+CD14-CD33+	-	-	-
Μ	CD14+HLA-DRlow/-	NSCLC	Poor response to chemotherapy, shorter PFS, distant metastases	(16)
PMN	Lin-HLA-DR-CD33+	SCLC	Improved response to vaccination with ATRA- induced MDSCs depletion	(27)
Μ	CD11b+CD14-CD33+	-	-	-
PMN	CD16lowCD11b+CD14-HLA-DR- CD15+CD33+	NSCLC	Increased in patients, correlates with Arg-1 mRNA.	(28)
Μ	CD16lowCD11b+CD14+HLA-DR– CD15+CD33+	-	-	-
MDSC	CD79a+CD11b+CD33+	NSCLC	Increased in patients	(29)
Μ	CD14+CD15+CD11b+CD33+HLA-DR- Lin-	NSCLC	Poor response, reduced PFS and OS	(21)
Μ	CD14+CD15-CD11b+CD33+HLA-DR- Lin-	-	-	-
PMN	CD14-CD15+CD11b+CD33+HLA-DR- Lin-	-	-	-
М	B7-H3+CD14+HLA-DR-/low	NSCLC	Poor prognosis and reduced RFS.	(22)
М	CD14+HLA-DR-/low	SCLC	Reduced OS	(30)
М	CD14+HLA-DRlow/	NSCLC	Incremental with disease stage	(31)
PMN	CD66b+CD14-CD11b+CD15+	NSCLC	Correlated with cvtokine levels and reduced OS	(32)

Table 1 Studies in lung cancer patients evaluating the levels of MDSCs

PFS, progression-free survival; OS, overall survival; RFS, relapse-free survival; ATRA, all-trans retinoic acid; PMN, polymorphonuclear; M, monocytic; E, early-stage; NSCLC, non-small cell lung cancer; MDSC, myeloid-derived suppressor cells.

survival is significantly reduced in NSCLC patients with a high percentage of PMN-MDSCs, particularly among patients with specific cytokine profiles (32,33).

Collectively, the studies discussed thus far provide evidence indicating that comprehensive immunological profiles, that include a characterization of different populations of B-cells, necessary for the rational design and clinical development of novel immunotherapeutic agents. In particular, a large and growing body of literature indicates that agents targeting MDSCs are promising candidates to advance into subsequent stages of clinical development.

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Footnote

Conflicts of Interest: Oscar Arrieta has received honoraria as advisor, participated in speakers' bureau and given expert

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