JCI The Journal of Clinical Investigation

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J Clin Invest. 2012;122(11):3857-3859. https://doi.org/10.1172/JCI65929.

Commentary

The incidence of melanoma — the most aggressive form of skin cancer — is dramatically increasing, while the development of innovative therapeutic strategies continues to be challenging, especially due to a lack of knowledge about the molecular mechanisms underlying melanoma progression as well as antitumor immunity. In this issue of the *JCI*, Yong Lu and colleagues report a central role for Th9 cells in antitumor immunity.

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Amazing IL-9: revealing a new function for an "old" cytokine

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The incidence of melanoma — the most aggressive form of skin cancer — is dramatically increasing, while the development of innovative therapeutic strategies continues to be challenging, especially due to a lack of knowledge about the molecular mechanisms underlying melanoma progression as well as antitumor immunity. In this issue of the *JCI*, Yong Lu and colleagues report a central role for Th9 cells in antitumor immunity.

Pro-inflammatory cytokines have long been regarded as beneficial in robust antitumor immunity. Specifically, cytokines of the common cytokine receptor γ chain family (such as IL-2, IL-15, and IL-21) have been tested for the treatment of melanoma and other tumors in humans (1). However, there is increasing evidence that depending on the individual tumor, inflammation can lead to either favorable or unfavorable clinical prognosis (2, 3). Recent clinical trials utilizing monoclonal antibodies blocking the inhibitory molecules programmed cell death 1 (PD-1) (4) or cytotoxic T lymphocyte–associated protein 4 (CTLA-4) (5) suggest that aggravation of an adaptive immune response is a promising therapeutic strategy for the treatment of melanoma.

During the last two decades the laboratory of Qing Yi has significantly contributed to our current understanding of potential immunotherapies in human malignancies by describing the role of DCs — and particularly T cells — in multiple myeloma.

In this issue of *JCI*, Yong Lu and colleagues from the Yi laboratory elucidate the role of Th9 cells and the γ chain family member IL-9 in a B16 melanoma mouse model, and found that Th9-derived IL-9 inhibited tumor progression (ref. 6 and Figure 1). In addition, Th9 cells induce IL-9–dependent expression of CCL20 in lung epithelial cells, thereby promoting the recruitment of $CD8\alpha^+CCR6^+$ DCs, leading to a strong activation of tumor-reactive $CCR6^+CD8^+$ CTLs. Collectively, the authors demonstrate an IL-9–based antitumor potency of Th9 cells, which is in quality and quantity superior to the immune response steered by Th1 cells. Hereby, the authors corroborate similar data quite recently published by Purwar et al., showing that IL-9–producing Th9 cells substantially inhibit melanoma growth as well as lung carcinoma growth in a murine B16F10 model (7).

IL-9 restrains tumor progression

More than two decades ago, IL-9 was identified as p40 or TCGFIII, and it was functionally characterized as a growth factor for repetitively stimulated T cell lines, but not for naive T cells (8). In addition to its effect on T cells, a mast cell growth-enhancing activity (MEA) was demonstrated, and p40/TCGFIII/MEA was renamed IL-9 (8). Subsequent research proved an essential role for IL-9 in tolerance induction and the pathophysiology of allergic asthma, inflammatory bowl disease, microbial infections, and autoimmunity (8).

In the present study, the authors demonstrate that neutralization of IL-9 in a B16 lung metastasis model resulted in strong tumor growth associated with a significant decrease in the number of $CD4^+$ T cells, $CD8^+$ T cells, $CD8\alpha^+$ DCs, and $CD11b^+$ DCs in the lung. Further analyses demonstrated that Th9 cell–derived IL-9 prevented tumor progression in prophylactic and therapeutic settings. Previous findings

Conflict of interest: The authors have declared that no conflict of interest exists.

Citation for this article: *J Clin Invest.* 2012; 122(11):3857–3859. doi:10.1172/JCI65929.

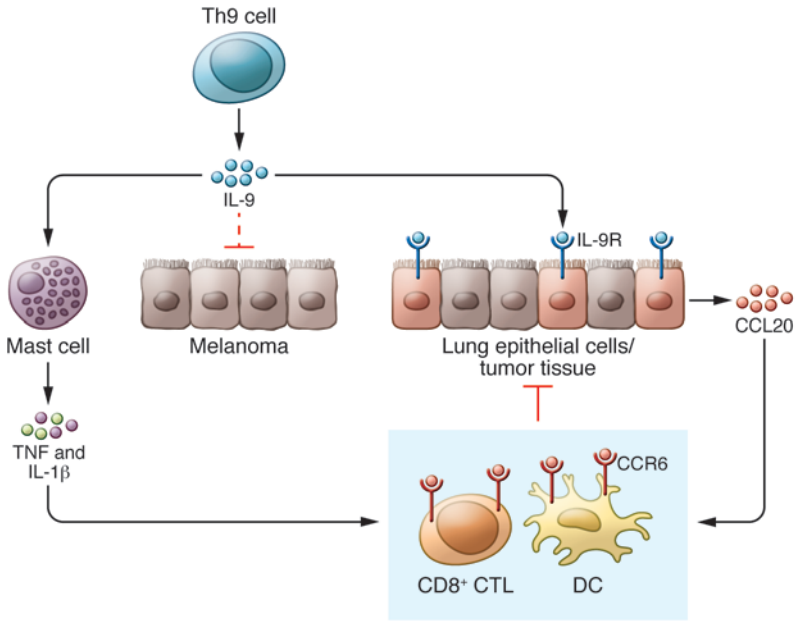

Figure 1
Effector functions of Th9 cells in antitumor immune responses. Th9-derived IL-9 can have direct antitumor effects or can indirectly influence tumor growth by altering immune responses. IL-9 induces the production of CCL20 in lung epithelial cells, which mediates the recruitment of CCR6-expressing DCs and $CD8^+$ CTLs. In addition, the MEA of IL-9 could further potentiate the induction of an adaptive antitumor immune response by providing mast cell–derived IL-1β and TNF-α. IL-9R, IL-9 receptor.

had demonstrated that mutations in the *IL9* gene were associated with a higher incidence of cutaneous malignant melanoma (9). However, by its antiapoptotic properties, IL-9 was also characterized as a growth factor for murine T and B cell lymphomas in vivo (10), and high levels of IL-9 are associated with myeloid malignancies and Hodgkin disease (11).

Since Lu et al. reported no direct cytotoxic effect of IL-9 and Th9 cells on B16 melanoma cells, it can be concluded that depending on the expression of the IL-9 receptor, this cytokine can be either beneficial or detrimental for an effective antitumor immune response.

Th9 cell–derived IL-9 induces CCL20 expression in the tumor tissue

IL-9 was shown to induce asthma-like responses in naive mice, as evidenced by increased serum IgE levels, lung eosinophilia, and airway hyperresponsiveness (12). Consequently, neutralization of IL-9 was shown to attenuate this pathology (13, 14). Th9 cells seem to contribute to allergic diseases by promoting the expression of the Th2-associated chemokines CCL17 and CCL22 (14). Interestingly, Yong Lu and colleagues now provide evidence that Th9 cells induce the expression of the chemokine CCL20 in lung epithelial cells in an IL-9–dependent manner, thus attracting $CCR6^+$ DCs, which eventually elicit an effective antitumor response. Correspondingly, adoptive transfer of Th9 cells into CCR6-deficient mice failed to improve antitumor immunity. IL-9 was also shown to induce CCL20 expression in astrocytes, suggesting a link between IL-9 and the infiltration of $CCR6^+$ Th17 cells into the central nervous system during neuroinflammation (15). Interestingly, it was recently demonstrated that CCL20 could be detected in tuberculous pleural effusion as well as in supernatants of cultured pleural mesothelial cells, suggesting that human Th9 cells also express CCR6 (16).

Th9 cells attract CCR6-expressing DCs into tumor tissue, inducing a robust $CD8^+$ CTL-based antitumor immune response

The role of IL-9 in tumor immunity is far from being fully defined. According to the above cited results, IL-9 obviously plays a rather indirect role, primarily affecting other cell types that ultimately carry out the antitumor immune response. However, it was recently demonstrated that IL-9 promotes the suppressive properties of regulatory T cells protecting the tumor from being attacked by the immune system (17). In the current manuscript, Lu et al. add to these discrepant results by providing strong evidence that Th9 cells attract CCR6-expressing cells, including tumor-reactive $CD8^+$ CTLs and $CD8\alpha^+$ DCs, to tumor tissues to induce robust $CD8^+$ CTL-driven antitumor immune responses. However, no elevation in mast cell infiltration of the lung was observed. Nevertheless, using mast cell–deficient $Kit^{W\text{-}sh}$ sash mice, carrying an inversion mutation upstream of the *c-kit* gene, Purwar et al. very recently demonstrated that mast cells are required for the antitumor effect of IL-9 (7). This is reminiscent of the MEA that was initially described as a characteristic property of IL-9 (8). This activity could potentially play an important role in the initiation of an antitumor immune response since it was demonstrated that mast cells can initiate immediate early inflammation by enhancing activation and migration of DCs, leading to an accelerated $CD8^+$ CTL response (18).

Hence, the results of Lu et al. and Purwar et al. indicate that Th9-derived IL-9 can play an important protective role in tumor immunology by recruiting other cell types (mast cells, DCs, and $CD8^+$ CTLs) that ultimately initiate and maintain an effective antitumor immune response (Figure 1).

Conclusion

The study by Yong Lu and colleagues provides important novel insights on the promotion of an efficient $CD8^+$ CTL-mediated antitumor immune response by Th9-derived IL-9. In this context, the finding that IL-1 considerably enhances IL-9 production (19) shed new light on historical data from Coley and Fehleisen (reviewed in ref. 20). These two researchers realized that the infection of tumor patients with bacteria occasionally led to a regression of the tumor, and they exploited this observation by generating bacterial-based vaccines (*S. pyogenes, S. marcescens*) for the treatment of cancer (20). Fever that was caused by these bacterial

products through the induction of endogenous pyrogenes was thought to play a central role. Later, IL-1 was shown to be a major component of such endogenous pyrogenes, and therefore it can be speculated that the IL-9–potentiating properties of IL-1 represent one of the main antitumor activities of such vaccines. However, IL-9 was also shown to support the growth of tumors that express IL-9 receptors, indicating an ambivalent role of this cytokine in tumor immunology (10, 11). Hence, inflammation and in particular distinct pro-inflammatory cytokines may provoke a Janus-faced response depending on the expression of the respective cytokine receptor by tumor cells. This ambivalence implicitly requires a detailed genetic and immunological characterization of each individual tumor and/or patient to develop personalized innovative therapeutic strategies in cancer immunotherapy.

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Endoplasmic reticulum stress and hypertension — a new paradigm?

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Hypertension occurs in approximately 30% of individuals in Western populations and is known to be a major cause of stroke, heart failure, and myocardial infarction. Despite this, the molecular etiology of hypertension remains poorly understood. In this issue of the *JCI*, Young et al. show that endoplasmic reticulum (ER) stress is an essential signaling event for angiotensin II–induced hypertension in cells of the central nervous system. This provides new insight into the molecular mechanisms that drive hypertension and suggests a potential target for future therapy.

In 1940, Irvine Page described a crystalline substance purified from the reaction of renin and renin activator, which he named angiotonin (1). Simultaneously, Braun-Menendez and coworkers identified a similar substance, which they called hypertensin (2). It is remarkable that three-quarters of a century later, we are still learning the actions of this molecule that ultimately came to be known as angiotensin II. It is now understood that this octapeptide has pleiotropic actions, including promotion of renal tubular sodium reuptake, aldosterone release, vasoconstriction, vascular remodeling, cardiac hypertrophy, cellular oxidative stress, and inflammation. Ongoing research is constantly refining and expanding this list. These actions allow survival during stresses such as dehydration or hemorrhage and have pathological roles in numerous diseases including hypertension and heart failure.

In addition to its peripheral effects, angiotensin II and its related peptides have potent actions on the central nervous system (3). Certain brain nuclei, predominantly in the hypothalamus and the brain stem, possess all of the components of the renin-angiotensin system (RAS) and produce angiotensin peptides locally (4). These nuclei are physically separated from the peripheral RAS by the blood-brain barrier. In addition, circulating angiotensin II can activate specialized regions of the brain that are adjacent to the cerebral ventricles and lack a well-formed blood-brain barrier. These "circumventricular organs" include the subfornical organ (SFO), the median eminence, the organum

Conflict of interest: The authors have declared that no conflict of interest exists.

Citation for this article: *J Clin Invest.* 2012; 122(11):3859–3861. doi:10.1172/JCI65173.