The role of interleukin-10 in the progression of human papillomavirus-associated lung carcinoma

Wen-Wei Sung1,2 and Huei Lee2,3,*

1School of Medicine; Chung Shan Medical University; Taichung, Taiwan; 2Institute of Medicine; Chung Shan Medical University; Taichung, Taiwan; 3Graduate Institute of Cancer Biology and Drug Discovery; Taipei Medical University; Taipei, Taiwan

Keywords: CIP2A, HPV, IL-10, IL-10R, lung cancer

The secretion of interleukin-10 by both malignant and immune cells promotes the progression of lung tumors, hence negatively impacting on patient prognosis. As interleukin-10 mediates oncogenic effects through the PI3K/AKT signaling pathway, PI3K/AKT inhibitors might sensitize cancer cells to chemotherapy, thus favoring tumor regression and improving disease outcome.

Lung cancer is the leading cause of cancer-related deaths in the world, and the overall 5-y survival rate of patients affected by this malignancy is only 14% to 17%. Cigarette smoking is widely considered as the major cause of lung cancer, since more than 85% of Caucasian lung cancer patients are smokers.1 However, approximately 50% of lung cancer patients in Taiwan never smoked. Interestingly, infection by human papillomavirus (HPV) type 16 or 18 has been detected in lung cancer biopsies and is suspected to play a role in lung oncogenesis, at least in Taiwan.2 Such a high HPV infection rate reflects the possibility that immunological defects might play an important role in the development of lung cancer, especially among Taiwanese women who never smoked.

Interleukin-10 (IL-10) is predominately secreted by immune cells including macrophages, T lymphocytes, and natural killer (killer) NK cells, and constitutes a major determinant of viral clearance vs. persistent infection.3,4 The precise effects of IL-10 on tumor progression remain matter of debate, as IL-10 has been shown to play both oncosuppressive and oncogenic roles in virus-associated human cancers.4,5 In fact, our preliminary data indicated that lung tumors bearing high HPV16/18 genome copy numbers also exhibit a robust expression of IL-10 (at the mRNA level). A large body of studies demonstrates that IL-10 secreted from immune cells is associated with the progression of neoplasms including large B-cell lymphoma, T-cell non-Hodgkin lymphoma, myeloma as well as breast, lung, gastric, colorectal and prostate carcinoma.6 Serum IL-10 levels were found to be significantly higher in HPV+ patients as well as in individuals bearing cervical intraepithelial neoplasia (CIN) than in HPV- healthy subjects. Therefore, IL-10 may play a role in the development of HPV-associated cervical neoplasms by favoring HPV persistence.

Elevated IL-10 levels were frequently observed in the blood and tumor tissue of advanced stage cancer patients.6 Additionally, robust IL-10 expression was associated with poor disease outcome in HPV-infected cervical and oropharyngeal cancer patients.7 Therefore, we expected that circulating IL-10 might not only originate from immune cells but also from HPV+ malignant cells. In line with this hypothesis, the circulating levels of IL-10 were found to be higher in lung cancer patients than in healthy individuals.6 Moreover, patients with metastatic disease had significantly higher serum IL-10 levels than patients with early stage lesions.6 Of note, a significant elevation in the circulating levels of IL-10 was observed in patients who failed to respond to chemotherapy (exhibiting progressive disease) as compared with patients undergoing complete responses, partial responses, or disease stabilization.6

We have previously demonstrated that the IL10 haplotype, impacting IL-10 expression levels, is associated with disease outcome among lung cancer patients.8 Such haplotypes corresponded to polymorphisms of the IL10 promoter region, notably -1082A > G, -819C > T, and -592C > A. Thus, neoplastic lesions from patients with the IL10 non-ATA haplotype (-1082G, -819C and -592C) expressed higher IL10 mRNA levels than the mRNA levels were infiltrated by lower amounts of lymphocytes than tumors from individuals with the IL10 ATA haplotype (-1082A, -819T, and -592A).8 As expected, the IL10 non-ATA haplotype was associated with poor survival and increased relapse rate as compared with the IL10 ATA haplotype.8 In addition, we were able to demonstrate that malignant cells suppress the antitumor effects of T cells via IL-10 (at least in vitro), a phenomenon

*Correspondence to: Huei Lee; Email: hl@tmu.edu.tw
Submitted: 07/17/13; Accepted: 07/23/13
Citation: Sung W-W, Lee H. The role of interleukin-10 in the progression of human papillomavirus-associated lung carcinoma. OncoImmunology 2013;2:e25854; http://dx.doi.org/10.4161/onci.25854

www.landesbioscience.com OncoImmunology e25854-1

AUTHOR’S VIEW
that can be reversed by the neutralization of IL-10 with specific antibodies. These results support the hypothesis that IL-10 expression by tumor cells may promote the progression of lung carcinoma.\(^8\)

These findings prompted us to investigate the role of IL-10 in HPV-associated lung cancer. Although the contribution of IL-10 to the evasion of immune responses by malignant cells has been extensively studied, the role of IL-10 in tumorigenesis itself remains enigmatic. IL-10 is well known to favor immune escape by inhibiting the antitumor activity of tumor-infiltrating macrophages as well as the cytotoxicity of tumor-specific T cells, and by blocks the presentation of tumor-associated antigens by antigen-presenting cells.\(^3,4\) In addition, IL-10 is considered as an autocrine growth factor not only for immune cells, but also for malignant cells of various types, including melanoma, gastric carcinoma, and thyroid cancer cells.\(^5\) Apparently at odds with these observations, other studies have shown that IL-10 potently inhibits the growth and metastatic dissemination of colorectal carcinoma, breast cancer, and melanoma.\(^6\) Moreover, the administration of IL-10 elicits tumor-specific immune responses in murine models. Collectively, these results indicate that IL-10 may play a dual role in tumor progression, prompting us to explore whether IL-10 expressed by tumor cells might sustain the progression of lung neoplasms (Fig. 1).

Our mechanistic studies indicate that IL-10 is upregulated by the HPV E6 oncoprotein and acts as an autocrine factor that not only promotes the proliferation of malignant cells, but also anchorage-independent growth and invasiveness.\(^10\) Furthermore, we found that (in the context of HPV infections) the transcription of IL10 is predominantly regulated by the E6-dependent phosphorylation of cAMP responsive element binding protein 1 (CREB1) and CCAAT/enhancer binding protein β (C/EBPβ), which stimulate the production of IL-10 at the transcriptional level. IL-10 secreted by malignant cells stimulates an autocrine loop relying on the IL-10 receptor (IL-10R). In addition, by binding to IL-10R expressed by immune cells, IL-10 may imbalance Th1 vs. Th2 tumor-specific immune responses. Cumulatively, these effects favor tumor progression.

**References**

1. Cokkinides V, Bandi P, McMahon C, Jemal A, Glynn T, Ward E. Tobacco control in the United States—recent progress and opportunities. CA Cancer J Clin 2009; 59:352-65; PMID:19897839; http://dx.doi.org/10.3322/caac.20037

2. Cheng YW, Chiu HL, Shue GT, Hsieh LL, Chen JT, Chen CT, et al. The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. Cancer Res 2001; 61:2799-803; PMID:11306446

3. Moore KW, de Waal Malefyt R, Coffman RL, O’Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001; 19:683-765; PMID:11244951; http://dx.doi.org/10.1146/annurev.immunol.19.1.683

4. Brooks DG, Tiitinen MJ, Edelmann KH, Teyton L, McGavern DB, Oldstone MB. Interleukin-10 determines viral clearance or persistence in vivo. Nat Med 2006; 12:1301-9; PMID:17041596; http://dx.doi.org/10.1038/nm1492

5. Zheng LM, Ojcius DM, Garaud F, Roth C, Maxwell E, Li Z, et al. Serum interleukin-10 levels as a prognostic factor in advanced non-small cell lung cancer patients. Chest 2000; 117:365-73; PMID:10609676; http://dx.doi.org/10.1084/jem.184.2.579

6. De Vita F, Oriduata M, Galizia G, Romanò C, Roscigno A, Lieto E, et al. Serum interleukin-10 levels as a prognostic factor in advanced non-small cell lung cancer patients. Chest 2000; 117:365-73; PMID:10609676; http://dx.doi.org/10.1084/jem.184.2.579

**Disclosure of Potential Conflicts of Interest**

The authors declare no conflicts of interest.
7. Chuang CY, Sung WW, Wang L, Lin WL, Yeh KT, Su MC, et al. Differential impact of IL-10 expression on survival and relapse between HPV16-positive and -negative oral squamous cell carcinomas. PLoS One 2012; 7:e47541; PMID:23118878; http://dx.doi.org/10.1371/journal.pone.0047541

8. Wang YC, Sung WW, Wu TC, Wang L, Chien WP, Cheng YW, et al. Interleukin-10 haplotype may predict survival and relapse in resected non-small cell lung cancer. PLoS One 2012; 7:e39525; PMID:22848356; http://dx.doi.org/10.1371/journal.pone.0039525

9. Todaro M, Zerilli M, Ricci-Vitiani L, Bini M, Perez Alea M, Maria Florena A, et al. Autocrine production of interleukin-4 and interleukin-10 is required for survival and growth of thyroid cancer cells. Cancer Res 2006; 66:1491-9; PMID:16452205; http://dx.doi.org/10.1158/0008-5472.CAN-05-2514

10. Sung WW, Wang YC, Lin PL, Cheng YW, Chen CY, Wu TC, et al. IL-10 Promotes tumor aggressiveness via upregulation of CIP2A transcription in lung adenocarcinoma. Clin Cancer Res 2013; Forthcoming; PMID:23743567; http://dx.doi.org/10.1158/1078-0432.CCR-12-3439