IL-6 contributes to the suppression of T and NK cell anti-tumor activity in EGFR-mutant NSCLC

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Introduction

• Patients with NSCLC with activating mutations in epidermal growth factor receptor (EGFR) receive clinical benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs)
• The majority of these patients will acquire resistance which can be mediated by various mechanisms including secondary EGFR mutations such as T790M, MET amplification, or EMT.
• Anti-PD-1/PD-L1 immune checkpoint-blockade demonstrated clinical benefit in NSCLC patients. However, among patients with EGFR-mutant NSCLC, response rates to immunotherapy are minimal.
• Previous studies show that IL-6 is a critical mediator of EGFR-TKI resistance. Thus, we sought to investigate the impact of IL-6 on anti-tumor immunity in EGFR-mutant NSCLC.

Hypothesis

Given the immunosuppressive role of IL-6, we hypothesized that IL-6 in part mediates the immunosuppressive phenotype responsible for EGFR-TKI resistant NSCLC’s marginal response to anti-PD-1/PD-L1 therapy through altering the tumor infiltrating immune cell populations and modulating their cytotoxic potential.

References

3. Lee et al., JAMA Oncology (2018).

Results

Acquired EGFR-TKI resistance is associated with increased levels of IL-6

Depletion of IL-6 increases overall survival and number of infiltrating lymphocytes in EGFR mutant GEMMs

IL-6 suppresses the activation of NK cells in the EGFR-mutant microenvironment

Blockade of IL-6 induces T cell activity in EGFR-mutant NSCLC microenvironment

Conclusion

IL-6 is upregulated in EGFR-mutant NSCLC tumors with acquired resistance to EGFR-TKIs and impairs anti-tumor immunity through suppression of T and NK cell function.

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