Clinical data and mouse model of lung adenocarcinoma brain metastasis reveal efficacy of anti-PD-1/CTLA-4 therapy and involvement of cytotoxic T lymphocytes

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Abstract

Brain metastasis (BrM) significantly impacts lung adenocarcinoma patients' outcomes. The distinct immune microenvironment in BrM, particularly the role of CD8+ cytotoxic T lymphocytes (CTLs), requires further investigation using clinically relevant models to assess treatment efficacy and mechanisms.

We developed a clinically relevant BrM model by introducing syngeneic mouse lung adenocarcinoma cells into immunocompetent mice via the internal carotid artery. Combined anti-PD-1 and anti-CTLA-4 therapy showed superior efficacy compared to monotherapy, as evaluated by bioluminescence imaging and mouse survival. The efficacy of combined therapy could be primarily attributed to changes in CTL numbers and functionality, assessed by histological and flow cytometric analyses and confirmed by depletion experiment of CTLs.

Using clinical specimens, we performed immunohistological analysis of paired surgically resected BrM and primary lesion specimens from 19 patients. This revealed lower CTL infiltration in the BrM microenvironment compared to primary lesions (median density, 92.9 versus 178.5 cells / mm^2, $p = 0.023$). Despite this difference, higher CTL infiltration in BrM correlated with better prognosis, aligning with previously reported prognostic significance of CTLs in primary tumors.

Our findings in preclinical models and clinical data underscore the critical role of CTLs in BrM. These results suggest that enhancing CTL infiltration into BrM may be a key strategy to improve outcomes in BrM patients.