

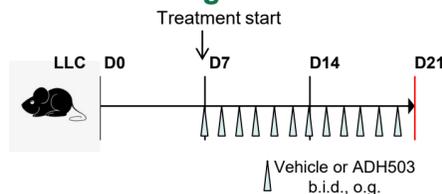
Abstract

A major problem facing cancer therapy is the immune suppression by the tumor and its subsequent escape from the immune response, which is mediated by the tumor microenvironment. Tumors have large numbers of myeloid derived suppressor cells (MDSCs), which suppress the adaptive immune response, increase neo-angiogenesis, and promote tumor survival. GB1275 is a novel small molecule CD11b allosteric modulator. In pancreatic cancer models, GB1275 reduced MDSC infiltration and M2 macrophage polarization leading to tumor growth inhibition. GB1275 is currently in Phase 1/2 clinical development in multiple cancer types. To investigate the impact of CD11b modulation in the context of lung cancer, GB1275 treatment effects on tumor growth and immune infiltrates were assessed in the Lewis Lung Carcinoma (LLC) syngeneic tumor model, propagated in C57BL/6 wild type (WT) mice. Additionally, we developed a transgenic CD11b knock-in (KI) mouse that renders CD11b in a partially active state. CD11b KI mice were engineered to express partially active CD11b by introducing a point mutation at position 332 causing an isoleucine to glycine switch (I332G). We studied LLC tumor growth in CD11b KI mice as an orthogonal approach to test the mechanism of action. Pharmacologic modulation of CD11b with GB1275 significantly reduced LLC tumor growth. Additionally, CD11b KI mice that showed a significant reduction in both the size and the rate of LLC tumor growth, as compared to the WT mice, mimicking treatment effects with GB1275. We found that CD11b modulation by GB1275 is T cell-dependent. Pharmacologic or genetic CD11b modulation significantly reduced CD11b⁺ myeloid cell recruitment, resulted in a phenotypic switch in innate and adaptive immune cells in lung tumors to enhance the adaptive immune response and is a novel strategy against lung cancer.

Background

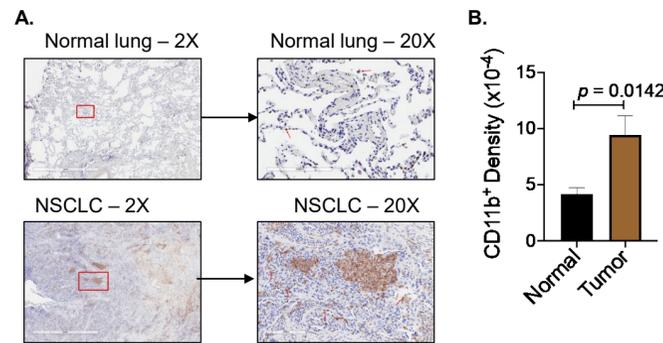
- Lung cancer is the leading cause of cancer-related deaths in the United States. Of the new cancer diagnoses each year, 13% are lung cancers. With an overall 5-year survival rate at 19%, lung cancer patients are sorely in need of new therapeutic options. Non-small cell lung carcinoma (NSCLC) accounts for 85% of all lung cancers.
- Integrin heterodimer CD11b/CD18 (aka Mac-1 or α M β 2) is highly expressed on myeloid cells and plays an important role in recruitment and other biological functions.

Lewis Lung Carcinoma Model

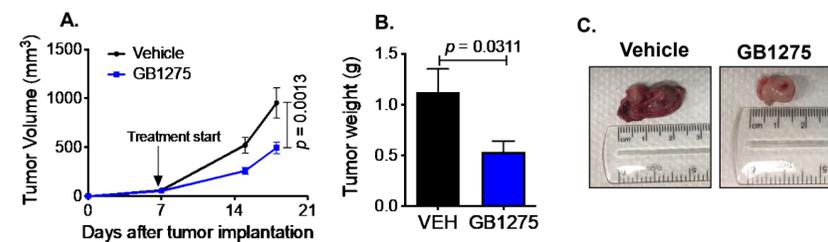


Results

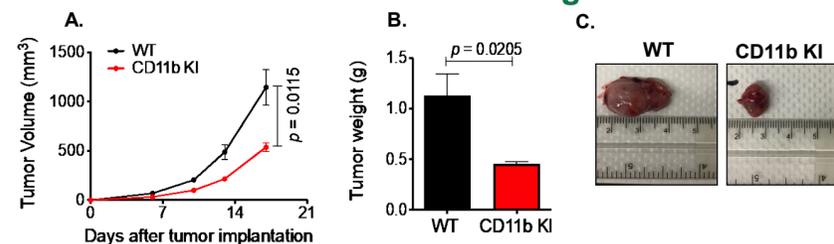
CD11b⁺ cells are abundant in human NSCLC tissues



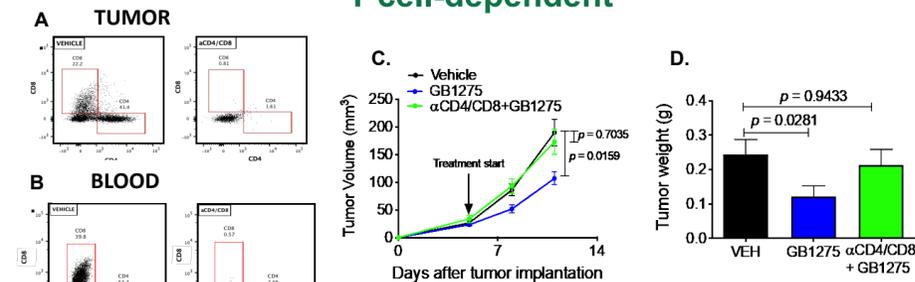
Pharmacologic CD11b modulation delays tumor growth



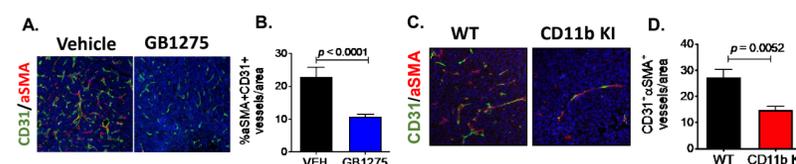
Genetic CD11b modulation in CD11b knock-in mice showed reduced tumor growth



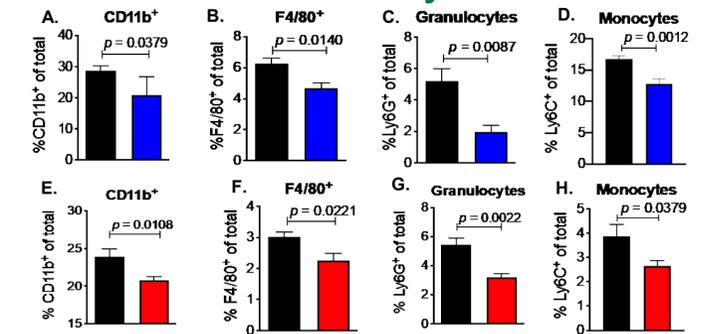
Tumor growth inhibition mediated by CD11b modulation is T cell-dependent



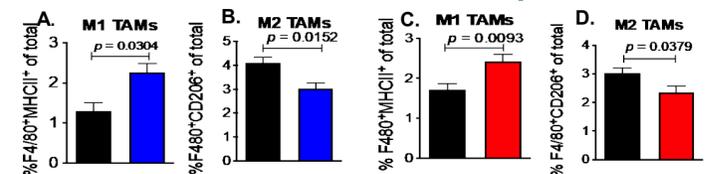
CD11b modulation reduced neo-angiogenesis in LLC tumors



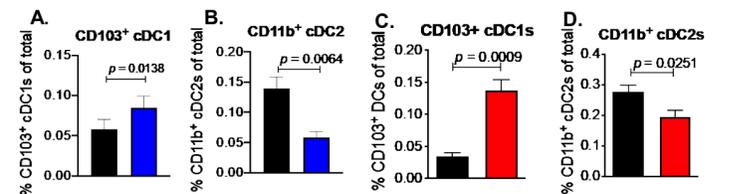
CD11b modulation reduces myeloid cell recruitment



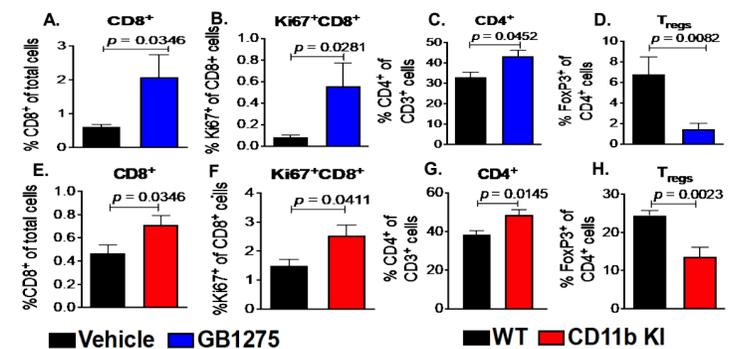
CD11b modulation stimulates M1 polarization



Phenotypic switch in dendritic cells after CD11b modulation



CD11b modulation reduces T cell immune suppression



Conclusions

- CD11b modulation works to slow LLC tumor growth by reducing myeloid cell recruitment, decreasing neo-angiogenesis, and by significantly changing tumor immune profiles.
- Our findings suggest a novel therapeutic strategy against lung cancer via pharmacologic CD11b modulation

