Reprogramming Lung Tumor Immunity by Inhibiting C1Q on Tumor-Associated Macrophages (TAMs)

Effective strategies to reprogram immunosuppressive tumor-associated macrophages (TAMs) and overcome resistance to current immunotherapies.

Technology

Dr. Khanna's lab has identified a novel immuno-oncology approach that reprograms tumor-associated macrophages by selectively inhibiting complement component 1q (C1Q), a marker preferentially expressed on nerve- and airway-associated interstitial macrophages (NAMs). Inhibiting C1Q drives a phenotypic shift from an M2-like immunosuppressive state to an M1-like pro-inflammatory, antitumor state.

Unpublished data (manuscript under review) using a syngeneic orthotopic mouse model of lung adenocarcinoma demonstrate that intratumoral delivery of a C1Q inhibitor induces NAM reprogramming, enhances CD8+ T-cell infiltration and activation, and results in significant tumor regression. This macrophage-centric strategy reshapes the tumor microenvironment without directly targeting tumor cells or requiring systemic T-cell activation, providing a promising therapeutic option for immunologically cold tumors or T-cell–excluded cancers.

Notably, NAMs are a transcriptionally distinct lung-resident macrophage population whose abundance correlates with poor progression-free and overall survival in lung cancer patients. Targeting the NAM–C1Q axis through local inhibition or selective depletion reprograms the tumor microenvironment, overcomes immune exclusion, and synergizes with PD-1 blockade to convert non-responders into responders, offering a spatially precise and translationally actionable immunotherapy strategy.

Background

Lung cancer is the leading cause of cancer-related mortality globally, accounting for approximately 1.8 million deaths each year. Although immune checkpoint inhibitors (ICIs) have transformed treatment for subsets of patients, most patients fail to respond or develop resistance. A major contributor is the presence of immunosuppressive TAMs and a tumor microenvironment that inhibits T-cell trafficking and function. NAMs, a specialized macrophage population within the lung, are increasingly recognized as suppressors of antitumor immunity. No current therapies directly target NAMs, highlighting a critical gap. NYU's C1Q-targeting approach represents a first-in-class opportunity to reprogram TAM biology, restore T-cell infiltration, and broaden the efficacy of existing immunotherapies.

Development Stage

C1Q inhibition using commercially available small molecules and nanobodies has been validated in preclinical *in vivo* mouse models of lung cancer. Additionally, polymer-encapsulated

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formulations have further enhanced intratumoral delivery and therapeutic efficacy. Importantly, patient tumor samples from a compassionate use case revealed upregulation of C1Q and NAM gene signatures, supporting the translational relevance of this therapeutic strategy in human lung cancer.

Applications

- **Lung cancer immunotherapy:** Enhance antitumor immune responses by reprogramming TAMs.
- **Combination therapy:** Use alongside PD-1/PD-L1 checkpoint inhibitors to overcome resistance.
- **Adoptive cell therapy development:** Create macrophage-based cell therapies using C1Q inhibition.
- **Drug discovery:** Platform for identifying C1Q inhibitors, C1Q mimetics, or downstream pathway modulators, including CD93 or LAIR-1 signaling.

Advantages

- **Broad disease applicability:** Effective across immunologically cold tumors and checkpoint inhibitor–resistant lung cancers.
- **Mechanism of action:** Macrophage-centered strategy that relieves immune suppression and enables productive T-cell infiltration.
- **Target selectivity:** High differential C1Q expression on tumor-associated NAMs supports a favorable therapeutic window.
- **Flexible modality:** Compatible with small molecules, nanobodies, or nanoparticle-formulated inhibitors for localized delivery.
- **Therapeutic versatility:** Suitable for monotherapy or as a combination approach with checkpoint inhibitors or targeted agents.

Intellectual Property

NYU has filed a U.S. provisional patent application covering methods of treating lung cancer using C1Q inhibitor compositions, including sulconazole and C1Q-specific nanobodies.