Driving T cell dysfunction in vitro for rational immunotherapy design

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Background

In the development of anti-PD-1 antibody treatments, desirable responses in some cancer patients, but not others, have limited the potential of this class of therapies. While immunotherapy responses are highly dependent on anti-tumor immunity, the mechanisms of T cell dysfunction have been poorly defined. Therefore, we developed an in vitro system to study T cell responses to chronic antigen exposure and systematically strived to discover novel targets, optimize our therapies and design novel clinical trials, which is an illustrative example of a virtual system capable of translation to a human immunotherapy in Phase II clinical trials. Agenus VISION platform supports smart, streamlined drug discovery and development.

Methods

We developed an in vitro T cell functionality culture system comprising primary T cells and cancer cell lines that interacted through multiple cell surfaces, cytokines, and chemokines. We measured T cell effector functions, protein and RNA expression across states and single cells. Finally, we challenged the system with anti-PD-1 antibodies and assessed T cell function and mechanisms of dysfunction.

Results

T cells in our system then became activated and gradually progressed to a terminally dysfunctional state shown by multiple cancer antigen exposures. T cell functionality is characterized by several antigen responses before steady declining. For each antigen exposure, the system maintained a number of antigen-specific T cell responses that declined over time, with new antigen-specific T cell responses then being recruited into the system. With each antigen exposure, the system maintained a number of antigen-specific T cell responses that declined over time, with new antigen-specific T cell responses then being recruited into the system.

Conclusions

These findings demonstrate the potential of VISION systems to deeply interrogate response and resistance to current and next-generation therapies. The Agenus VISION platform is poised to advance against multifaceted approaches to fighting cancer with immunotherapy.