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A Novel Method for Detecting Lytic Human Herpesvirus 6 in T cell Therapies to Identify Patients at Risk of Encephalitis and Enable Safety Screening of T cell Products

Stanford scientists have developed a method to detect reactivated human herpesvirus 6 (HHV-6) in T cell therapies using genomics technologies, including single-cell sequencing. Detecting lytic herpesvirus 6 in T cell therapies can identify patients at risk of encephalitis and assist in ensuring the safety of T cell products.

Cell therapies have yielded durable clinical benefits for patients with cancer but have been accompanied by unexpected side effects. For instance, approximately 1 in 40-100 patients who undergo CAR T cell therapy suffer from HHV-6 encephalitis. Unexpectedly, the source of the lytic HHV-6 virus can come from the cell therapy itself. Therefore, the detection of lytic HHV-6 in T cell therapies can serve as a diagnostic tool to identify patients at risk of encephalitis and as a safety screening method for T cell products.

Using single-cell sequencing, a rare polyclonal population of HHV-6 'super-expressors' (~1 in 360-10,000 cells) that possess high viral transcription and lytic activity late in chimeric antigen receptor (CAR) T cell culture were identified in vitro. Further, through the reanalysis of single-cell sequencing data from FDA-approved cell therapy products, the presence of CAR+, HHV-6+ super-expressor T cells were detected in vivo. Together, this implicates the T cell therapy as a potential source of lytic HHV-6 reported in multiple clinical trials and has broad implications for the design, screening, and diagnosis of unexpected toxicities in cell therapies.

Stage of Development:

Preclinical - in-vivo data

Applications

- Identification of patients likely to develop HHV-6 encephalitis who receive T cell therapies
- Safety screening autologous and allogenic CAR T cells for HHV6 virus in vitro for HHV-6 via genomics technologies
- Screening of patient samples to detect HHV6 in cells, including the cell therapies, in vivo

Advantages

- In cell therapies, there is no standard / routine screening for HHV-6, so this represents a significant conceptual advance
- Utilizes standard / widely-available tools (experimental and computational) to identify HHV6 expression in cells
- Uses easily-adoptable molecular biology reagents (including genomics tools) and informatics pipelines with custom downstream analyses to confidently call HHV6 expression.

Publications

Lareau, C. A., Yin, Y., Maurer, K., Sandor, K. D., Daniel, B., Yagnik, G., ... & Satpathy, A. T. (2023). <u>Latent human herpesvirus 6 is reactivated in CAR T cells</u>. Nature, 623(7987), 608-615.

Patents

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