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703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

Immune Profiling of Respiratory Syncytial Virus (RSV) for the Development of Targeted Immunotherapy

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Introduction: RSV-associated respiratory viral infections are a major public health problem affecting the immunologically naïve/compromised population. For example, RSV-induced bronchiolitis and pneumonia are the leading cause of hospitalization in infants and young children worldwide, while in adult allogeneic hematopoietic transplant (HCT) recipients the incidence of progression from upper to lower respiratory tract infection (LRTI) is 40-60%, with mortality rates as high as 80%. At the national level, the Fall 2022-Spring 2023 RSV surge translated into a sharp rise in hospitalization rates surpassing last season's respective rate by almost 5-fold (https://www.cdc.gov/rsv/research/rsv-net).
Our group has previously demonstrated the feasibility, safety and clinical efficacy of administering allogeneic ex vivo expanded multivirus-specific T cells (multi-VSTs) as a banked, off-the-shelf product for the treatment of EBV, CMV, BKV, HHV6, AdV and SARS-CoV-2 infections/disease in immunocompromised individuals. Given the RSV-associated morbidity and the paucity of therapeutic agents, we sought to characterize the cellular immune responses to RSV with a view to developing a targeted T-cell therapy product for those at highest risk of severe disease (i.e. HCT recipients, elderly/immunocompromised patients).
Methods: To first identify immunogenic and protective RSV antigens we exposed PBMCs from healthy adult donors to pepmixes (overlapping peptide libraries) spanning the 11 RSV-encoded antigens and found that 7 induced highly reactive T cells. However, Nucleoprotein (N) and Fusion Protein (F) proved to be immunogenic in all donors and were thus advanced for VST manufacturing. We subsequently utilized our optimized VST manufacturing process and culture in a G-Rex device in medium supplemented with activating cytokines to generate RSV-specific VSTs (RSV-STs) with activity against this combination of immunodominant targets.
Results: We achieved a mean 5.2±1-fold expansion (mean±SEM; n=13) of cells that were comprised almost exclusively of CD3+ T cells (94.08±1.15%), with a mixture of cytotoxic (CD8+; 28.91±5.16%) and helper (CD4+; 71.09±5.15%) T cells. These cells had a phenotype consistent with effector function and memory potential, as evidenced by upregulation of the activation markers CD25, CD69, and CD28 and expression of central (CD45RO+/CD62L+) and effector memory markers (CD45RO+/CD62L-) with minimal expression of exhaustion-related markers such as PD1, Tim3 and LAG3.
The anti-viral activity of the expanded cells was confirmed in an IFNγ ELISpot using both stimulating antigens as an immunogen and all lines proved to be reactive against the target antigens (N: 3587±939 SFC/2x10^5; F: 3526±743). As demonstrated by surface and intracellular flow cytometry, the immune response was mediated by both CD4+ and CD8+ T cell subsets through IFNγ/TNFα production and upregulation of activation/costimulatory markers. Reactive cells were polyfunctional and primarily Th1-polarized as evidenced by IFNγ, Granzyme-B, IL-2 and GM-CSF production measured by FluoroSpot and Luminex array. Finally, the expanded cells were able to kill viral pepmix-loaded autologous PHA blasts with minimal/no activity against non-antigen-expressing autologous and allogeneic targets.
Conclusion: Healthy donor-derived RSV-STs are Th1-polarized, polyfunctional and selectively able to kill viral antigen-expressing targets with no auto- or alloreactivity, indicative of their safety for clinical use. A clinical trial evaluating their safety and activity in HCT recipients as part of an off-the-shelf multi-respiratory virus-directed product is currently underway (NCT04933968, https://clinicaltrials.gov).

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