Addressing the Challenges in Solid Tumor Therapy with Base Editing

Introduction

Immunotherapies for the treatment of hematological cancers have been in use for more than 20 years. Such therapies include antibody- and CAR-T cell-based approaches, which have greatly increased survival rates for some patients. The development of effective immunotherapies for solid-tumor cancers, however, has been elusive due to challenges associated with the heterogeneity of solid tumor cells and the tumor microenvironment.

This paper discusses the key challenges in developing immunotherapeutics for solid tumors, ways in which those challenges are being addressed, and how new gene editing technologies hold promise for successful treatments.

Challenges in solid tumor immunotherapy development

Researchers face a few key challenges in their efforts to develop effective immune therapeutics for solid tumor cancers, namely:

- Identifying appropriate target antigens within highly heterogeneous tumor cells
- Overcoming inhospitable tumor microenvironments
- Sustaining therapeutic potency

Target antigens

Identifying appropriate target antigens in solid tumors is much more complex than for liquid tumors. Unlike the uniform expression of the CD19 target in lymphoma and the BCMA target in multiple myeloma, a very limited number of clear targets have been identified for solid tumor cells. Those potential targets that have been identified are typically also expressed on normal cells, presenting another hurdle for researchers seeking a targeted therapy that only acts on tumor cells.

The heterogeneity of solid tumors makes it difficult to identify single targets that will impact an adequate proportion of a tumor's cells. In addition, the surface antigens of solid tumor cells are noted to undergo changes, or even loss, in response to T cells and other stimuli. This inherent and changing heterogeneity makes it imperative that researchers consider multi-target approaches as well as ways to maximize the effectiveness of potential therapies to outpace antigen changes.

Tumor microenvironment

The tumor microenvironment (TME) poses numerous challenges to the development of immune therapies for solid tumors. Immune response-inhibiting activity within the TME of solid tumors commonly includes that of regulatory T-cells (Tregs), anti-inflammatory M2 macrophages, and pro-tumor N2 neutrophils. The tumors themselves activate immune checkpoints that decrease the immune response.

The TME can also be metabolically hostile to immune cells. For example, common tumor conditions, such as low oxygen and high pH levels, dampen lymphocytic activity. Researchers must consider how to work around this hostile environment such that it does not interfere with potential solid tumor therapeutics.

Sustained potency

Immune therapies for solid tumors must be able to maintain their potency while traveling to, and into, the tumor. However, when an immune cell does not encounter its target antigen for some time, it often becomes less active. Researchers are looking for ways to maintain therapeutic potency under such conditions.

Current efforts to overcome these challenges

There are a number of considerations and potential approaches for these challenges.

Tumor types

The solid tumor landscape is complex and varies by cancer type. As individual research teams focus on a specific indication and share their findings, it is critically important to understand the nuanced differences between different cancers. In other words, solid tumors must be evaluated tumor-by-tumor without making assumptions about similarities or differences among tumors. Only then can researchers know how best to apply existing and experimental cell engineering to different tumor types.

One approach to selecting a research focus is to choose an indication based on previously determined parameters. For instance, an indication that has been shown to be responsive to immuno-oncology agents, or is T-cell infiltrated, and so forth. Expanding on existing evidence minimizes the hurdles to getting started in solid tumor research.

Alternate cell types

As noted, the solid tumor landscape is a complex one in which there is no uniformly expressed set of antigens. This has lead researchers to look for other cells types that could be useful as immuno-therapies and in combination therapies. For instance, cell types that can handle the negative TME, or can readily infiltrate solid tumors.

One cell type being considered is the natural killer (NK) cell. NK cells are naturally multivalent – they recognize multiple ligands that are overexpressed by tumor cells and other. Their ligand recognition can be further enhanced with a CAR or bivalent CAR. This NK cell versatility could play a role in addressing the heterogeneity of solid tumors.

iPSC-derived NK (iNK) cells have been shown to help overcome heterogeneity issues between donor and patient-obtained NK cells. iNKs also appear to traffic very well with solid tumors. Other exciting research on alternative cell types for solid tumor therapeutics includes harnessing macrophages (Anderson et al. 2021) and dendritic cells (Sadeghzadeh et al. 2020).

Gene editing

Researchers have been investigating the use of genetic engineering methods to develop CAR-T cells that can successfully infiltrate solid tumors, survive their harsh and immune-suppressive microenvironments, and bind diverse target antigens to elicit the desired response. CRISPR technology has greatly advanced gene editing capabilities in recent years and is still the most commonly used genetic engineering tool. CRISPR-Cas9 has been particularly effective for gene editing thanks to the ability of the Cas9 nuclease to be engineered to target different genes.

Combination strategies

Research into alternative cells types and genetic engineering for solid tumor therapeutics is part of the recognition that combination strategies are going to be important for successful treatments. Effectively tackling heterogeneous solid tumors with challenging TMEs will mean finding new approaches that will readily synergize with other approaches and standards of care.

A combinational approach can also involve non-cellular partners that provide mechanisms not available with cell therapy alone. For instance, to address the challenge of getting immune cells into the tumor, the researcher could add an agent that repolarizes the TME to make it less inhibitory for T cells. There are numerous treatments either approved or in development that could be successfully combined for solid tumor therapeutics. It's important to take this deliberate approach to accurately identify viable combinations.

Limitations of current Gene editing technologies

As useful as first-generation CRISPR-Cas9 has been for gene editing, it has drawbacks that newer technologies are overcoming. The CRISPR-Cas9 mode of action involves making double-stranded breaks (DSB) in the DNA segment targeted for editing. After editing is completed, the DSB are left to be repaired by the cell. This leaves ample opportunity for the erroneous joining of non-homologous ends and the creation of insertions and deletions, all of which can negatively impact the cell and/or gene expression.

Another drawback is the excessive time and costs involved in engineering autologous patient-derived T-cells to form CAR-T cells. This has led researchers to pursue possible allogeneic approaches to CAR-T cell therapeutics. The use of allogeneic cell therapies would require gene editing at multiple locations to create a cell that can avoid being detected by the patient's immune system. Engineering such "stealth" cells would require multiplex editing techniques.

Base editing technologies

New gene editing technologies are being developed at incredibly fast rates. One leading example is the second-generation CRISPR-Cas base editing technology. Base editing uses a partially deactivated Cas9 that "nicks" only one strand of the DNA (Komor, et al. 2016). Because this approach avoids the potential for translocations, it can be used to safely make multiple, simultaneous edits within a single cell.

Base editing technology is being evaluated as a way to develop safe and effective allogeneic CAR-T cell therapies. Its multiplexing capabilities enable the custom-design of stealth cells that are capable of reaching and infiltrating solid tumors. It also enables the targeting of multiple antigens in the highly heterogeneous solid tumors.

From a manufacturing perspective, the high-throughput of base editing technology produces larger batches in less time. This in turn enables all of the required safety and efficacy studies to be efficiently completed from one cell batch.

Conclusion

Researchers have worked for many years to decipher a way to replicate the success of liquid tumor immunotherapeutics for use in solid tumor therapies. The solid tumors themselves have been the biggest obstacle to those efforts. New gene editing technology, especially base editing, is a promising means of delivering safe, effective immunotherapeutics to solid tumors and providing multiplexed antigen targeting. The ultimate goal of all this work is to bring effective therapies to more patients, faster, and at lower cost. Base editing technology is putting that goal well within reach.

References

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