Targeting Hematological Cancer Stem Cells (HCSCs) to Enhance Immunotherapy Clinical Decision Making

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Background

HCSCs are malignant cells that drive several characteristics of hematological malignancies, like progression, immune evasion treatment resistance, and recurrence. As a population, they have been challenging to address with conventional interventions due to said characteristics, along with the heterogenicity present amongst malignancy types, patients, and disease stage.

Objective

- To review emerging cellular and molecular immunotherapeutic strategies targeting HCSCs.
- To evaluate HCSCs' potential as precision approaches that advance the personalized treatment of hematological malignancies.

Methodology

Literature indexed in PubMed, Google Scholar and Embase, was investigated in two phases using the keywords:

1. HCSCs, HCSCs pathophysiology/ biology/ role in cancer/ and cancer treatment/ resistance
2. HCSCs mAbs/ cellular therapy/ OVT/ and HSCT/ and cancer vaccines/ immunotherapy.

Results / Discussion

Immunotherapeutic interventions targeting HCSCs can be separated as:

- **Hematopoietic Stem Cell Transplantation (HSCT)**: Autologous and allogeneic HSCT that can induce Graft Versus Tumor (GVT) with physiological stem cells identifying and targeting HCSCs, upon conditioning.
- **Antibodies**: Monoclonal Antibodies (mAbs), Antibody-Drug Conjugates (ADCs), and By-Specific Antibodies have multiple effects, as described in Image A.
- **Cellular Therapies**: Engineered Chimeric Antigen Receptor (CAR)-T cells, **γδ** T cells, Natural Killer (NK) cells and Tumor-Infiltrating Lymphocytes (TILs) capable of enhanced immune surveillance and targeting of HCSCs.
- **Cancer Vaccines**: Antigens like CD123, CD133, and CD44 in the form of peptides or proteins, or on antigen-enriched Dendritic Cells (DC) and CD80-enriched immunostimulatory malignant cells.
- **Oncolytic Virotherapy (OVT)**: Viruses targeting cancer cells can be utilized via mechanisms presented in Image B.

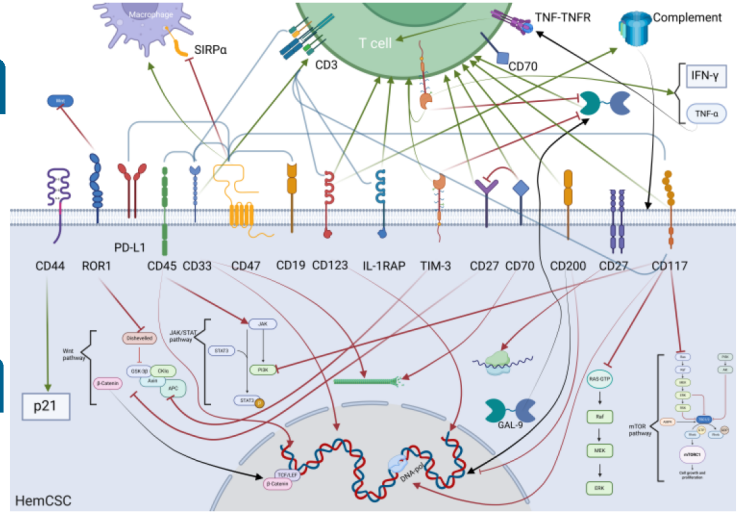


Figure A: Processes related to each antigen's, antibody-mediated, targeting. The green arrows represent upregulation, the red ones inhibition (flat tip for direct inhibition, pointy tip for action of a conjugate's payload) and the black ones the movement of biomolecules. The brackets represent a bispecific antibody targeting the antigens at each end. Graphics by biorender.com

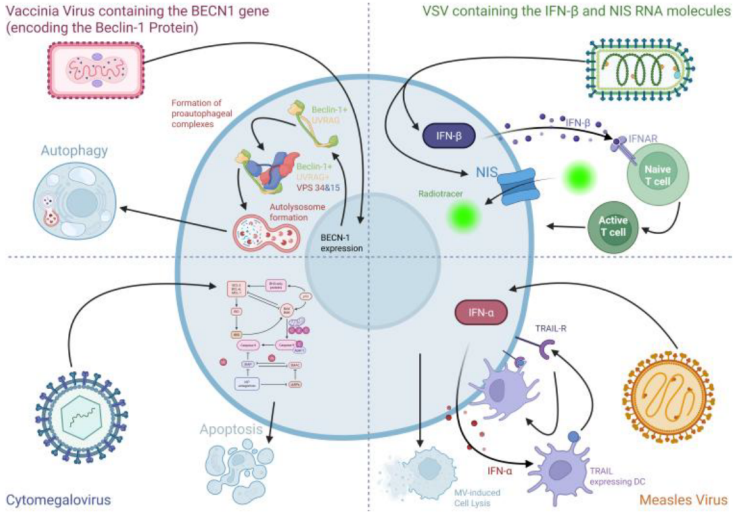


Figure B: Ways HCSC death happens in OVT. VV leads to the formation of autolysosomes. VSV leads to enhanced production of IFN-β, that recruits T cells, and increased NIS-mediated radiotracer uptake. MV causes cell lysis or enhances anti-TRAIL-R expressing HCSC macrophage activity via IFN-α production. CMV initiates caspase-dependent apoptosis. Graphics by biorender.com

Conclusion

Since the first highlighting of the HCSCs' role in hematological oncology, there have been significant strides in their immunotherapeutic targeting. However, many of these have shown promising results, or are in development, only in preclinical and early clinical phases as monotherapies. This is mostly due to HCSCs' challenging nature, primarily their plasticity and immune evasion capabilities. As such, it is suggested that these therapies are applied in a combinational and personalized manner. Hence, modern and future advancements in technologies, therapeutic interventions, regulation and treatment regimens can pave the way to the integration of the proposed treatments into the personalized hematological cancer care.

QR-Code

Scan to access the full publication and the references