Therapeutic values of engineered immune cells: a precision-guided weapon

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Immune cell genetic engineering mainly includes cellular receptor engineering with high safety and specificity by logic circuit and switch control, genome engineering with high efficacy and consistency by genetic knockin/knockout, and payload co-engineering with high efficacy by deliver therapeutic proteins (Irvine et al. 2022). Engineered immune cells are becoming one of the most important alternatives in rebalance of systemic defense functions, strength of protective capacity of pathogens, and therapy for cancer cells. A number of target genes can be transferred to immune cells through the homology-directed repair with or without DNA templates. With rapid development of delivery systems like natural or biosynthetic carriers and gene editing like CRISPRs, engineered immune cells have become more clinically applicable, efficient, and immunocompetent. Simultaneously, target-specific and essential factors are being identified and modified to improve the efficacy of target gene delivery and cell therapies. By genome-wide knockout screening, Nyberg et al. (2023) identified an assistant factor (QA2) to promote the infection efficacy of the synthetic adeno-associated virus (Ark313) with a high transduction efficiency in murine T cells. Such biosynthetic carriers have a broad potential in preclinical and clinical application for gene deliveries, with less possible toxicities and high targeting efficiencies. Sworder et al. (2023) evaluated the efficacy of the autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel in patients with relapsed/refractory large B cell lymphoma and predicted the outcome, by profiling circulating tumor DNA, cell-free CAR19 retroviral fragments, and cell-free T cell receptor rearrangements which enabled integration of tumor and both engineered and non-engineered T cell effector-mediated factors. Engineered immune cells with genome wide CRISPR knockout screens may act as a molecular target mode for uncovering genetic regulators of biological responses to pathogen infections, drug actions, and microenvironmental changes. The current Editorial briefly overviews the latest development of immune cell engineering and calls special attention to the therapeutic effects and

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potential toxicities of engineered immune cells for clinical application.

One of the important issues is the dynamic alterations of engineered immune cell identities and phenomes, which vary before and after engineering, implanting, and interacting with other cells. Cell identities are a complex biological phenomic profile, dependent upon the measurement, living microenvironment, and gene modification. Liu et al. (2022) categorized single-cell sequencing-based cell subset identities into specific, associated, and reference gene panels, by defining the repeated expression rate of each gene in various gene panels for cell subset identities. It is important to profile alterations of genes, proteins, and morphological and function phenomes in engineered immune cells. Phenomic characteristics of engineered immune cells can be influenced by gene editing and modification per se, surrounding resident cells, pathogens, inflammatory factors, and pathological cells (e.g., damaged cells, tumor cells, and other immune cells) within the microenvironment. The implantation of engineered immune cells changed molecular phenomes of target cells directly or indirectly and thus altered the sensitivity of targeted cells to therapy and the gene expression of engineered cells by the reaction force from targeted tumor cells. Sworder et al (2023) found that CAR19-engineered T cells-targeted somatic tumor cell reshaping could reactively influence CAR19 T cell proliferation capacity, sensitivity to extracellular changes, and microenvironmental profiles, to improve the efficacy of engineered cells and the quality of precision medicine. The quality of engineered immune cells is monitored by the formation of target gene-specific functions and cell identities, length of engineered gene sequence, and the amount of double-stranded DNA repair temple.

It is important to recognize the impacts and value of engineered immune cells, including their effects on cell development and evolution, spatiotemporal re-distribution, cell–cell communication, and survival. Cell engineering, as part of synthetic biology, refreshes multiple networks and interactions in intracellular metabolism, regulation, and signaling. The engineered immune cells can be generated by inducing differentiation from stem cells engineered with CAR, forming the ready-for-use CAR immune cells for anticancer immunotherapy with molecular characteristics and identities as well as cytotoxic capacities against cancer cells with target gene expressions.

The efficiency and efficacy of target gene function can be indirectly improved by the modification of target gene-specific regulatory genes, which promote or suppress the expression of upstream limiting factors. Dai et al. (2023) presented an innovative engineering system with high editing efficiency and high-throughput knock-in by combining Cas12a/Cpf1 mRNA with pooled adeno-associated viruses. This is a new alternative to perform the editing of multi-genes simultaneously, precisely, efficiently, and in large quantities. Such system can be used in various subsets of T cells, increase cell critical capacities of proliferation, stem-like properties, and memory, as well as be translated into clinical therapies for blood malignancies and solid tumors.

Cell engineering is an example of crossing sciences and technologies, and the engineering combination of multi-functional targets improves the specificity, sensitivity, and efficacy of anti-tumor therapy. Engineered cells integrated with other technologies, e.g., nanoparticles, liposomes, photo-controlling, can efficiently deliver target genes, drugs, and activating factors. Tichet et al. (2023) integrated anti-PD-1 against the immuno-stimulatory IL-2 cytokine variant (IL2v) by precisely guiding the transfer of IL2v to PD-1^{+} T cells in the tumor microenvironment. This combination improved the cancer cell selection and sensitivity to checkpoints and engineered cells, accelerated the infiltration of stem-like CD8^{+} T cells, slowed down the speed of cancer cell progression and metastasis, and prolonged the survival duration. Multi-genes-based engineering can be a new alternative of immunotherapies for cancer patients with high resistance, malignancy, and metastatic potential. To improve the therapeutic efficacy of engineered immune cells, engineered T cells were live-tracked and co-cultured with patient-derived solid-tumor organoids (Dekkers et al. 2023). Such innovation provides potential to increase metabolic sensitivities, biological capacities, and cytotoxic effects of engineered immune cells, although the standardization and repeatability of preparation processes need to be furthermore defined. This is a new therapeutic strategy within precision medicine or individualized medicine, to design and select patient-, disease-, and severity-specific and sensitive engineered immune cells for solid tumors. In comparison with dynamic mutations-monitored or spatial omics-proposed therapeutic strategies (Qian et al. 2020; Wu et al. 2022),

the combination of live-tracked engineered immune cells with patient-specific organoids is expected to show more specific efficiency.

In conclusion, with the rapid development of bio-engineering technologies, the quality and quantity of target gene delivery systems are being efficiently improved for engineering immune cells. Phenomes and identities of engineered cells should be further dynamically clarified before and after engineering and implanting. The combination of engineered target genes, delivery platforms/systems, spatializations, and temporalizations provides new alternatives for precise immunotherapy, although numbers of challenges are to be overcome, including efficacy and specificity of various solid tumors, repeatability of engineered cell tracking and monitoring, long-term efficacy, toxicity, and acquired resistance. Thus, there is an urgent need to comprehensively evaluate molecular mechanisms of cytotoxic effects for therapeutical and toxicological profiles of engineered immune cells.

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