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Opinion Article

Innovative Strategies for Delivery of Immunotherapeutic Agents

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DESCRIPTION

Red Blood Cells (RBCs), traditionally recognized for their oxygen transport function, have recently gained attention for their potential applications in immunotherapy. Beyond their classic physiological role, RBCs exhibit unique biophysical and biochemical properties that make them attractive candidates for modulating immune responses. Their long circulation lifespan, biocompatibility and ability to interact with immune cells provide opportunities for their use as carriers, modulators, or regulators within various therapeutic strategies.

RBCs possess a naturally flexible biconcave shape that facilitates passage through microvasculature and their ability to circulate for up to 120 days. This feature allows RBCs to serve as vehicles for delivering therapeutic agents over prolonged periods. Additionally, the cell membrane of RBCs contains a variety of surface proteins and receptors that can interact with the immune system. These properties have prompted researchers to explore their use in transporting antigens, cytokines, or drugs, potentially influencing immune cell activation, suppression, or targeting.

RBCs can also contribute to immunotherapy through interactions with the mononuclear phagocyte system. Senescent or modified RBCs are naturally cleared by splenic macrophages and this process can be manipulated to direct antigens or drugs to specific immune compartments. By controlling the rate and location of RBC clearance, researchers can influence the activation of macrophages, dendritic cells, and other antigen-presenting cells, potentially enhancing immune responses against targeted antigens.

The biocompatibility of RBCs presents additional advantages. Being autologous, RBCs minimize the risk of immune rejection and reduce adverse reactions commonly associated with synthetic carriers. Even allogeneic RBCs can be processed to reduce immunogenicity, making them versatile platforms for a range of therapeutic interventions. Moreover, RBCs are abundant, easily isolated from blood and amenable to large-scale modification, supporting their feasibility for clinical applications.

Technological advancements have facilitated precise modifications of RBCs for therapeutic purposes. Surface engineering techniques, such as biotin-streptavidin coupling, lipid insertion, or covalent conjugation, allow attachment of antigens, antibodies, or nanoparticles to RBC membranes. Additionally, loading molecules into the RBC cytoplasm through hypotonic dialysis, electroporation, or chemical permeabilization enables controlled delivery of soluble agents. These methodologies support the customization of RBCs for specific immunotherapeutic goals.

Safety considerations are central to the clinical translation of RBC-based therapies. Autologous RBCs reduce the risk of immune-mediated adverse effects, but modifications must preserve cell integrity and functionality. Overloading or extensive surface modification may induce premature clearance, hemolysis, or unintended immune activation. Therefore, optimization of loading strategies, surface chemistry and dosing schedules is critical for achieving therapeutic benefit while maintaining safety.

Regulatory aspects are evolving alongside these technological developments. RBC-based therapies straddle the interface between cell therapy and drug delivery, requiring evaluation of both cellular quality and pharmacological performance. Standardization of RBC isolation, modification and storage procedures will be essential for reproducibility and clinical approval. Preclinical studies must address biodistribution, clearance kinetics, immunogenicity and long-term safety before widespread clinical adoption.

RBC-based strategies may complement existing immunotherapy modalities. For example, combining RBC-carried antigens with checkpoint inhibitors or adoptive T cell therapy could enhance immune activation while reducing systemic toxicity. Similarly, RBC-mediated delivery of immunosuppressive molecules could improve outcomes in autoimmune disease or transplantation. Integration with established treatment regimens requires careful

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evaluation of interactions, dosing and timing to maximize benefit and minimize risks.

The versatility of RBCs offers potential in personalized medicine. Autologous RBCs can be modified with patient-specific antigens or immunomodulators, potentially creating individualized therapeutic approaches. Such strategies could target tumor neoantigens, viral epitopes, or autoantigens, supporting precise immune modulation. Additionally, RBCs may provide a platform for repeated administration without eliciting significant immune rejection, which is advantageous for chronic or long-term therapies.

In conclusion, red blood cells represent a promising platform for diverse applications in immunotherapy. Their long circulation time, biocompatibility and ability to interact with immune cells allow delivery of antigens, drugs, or modulators in a controlled manner. Preclinical studies support the potential of RBC-based strategies in cancer, infectious diseases and autoimmune conditions. Safety, scalability and regulatory considerations remain important for clinical translation and continued research will refine methods to exploit the unique properties of RBCs for therapeutic benefit. With ongoing advancements, RBCs may provide innovative options to modulate the immune system for a variety of clinical indications.