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Engineering Dendritic Cells for Immune Modulation: Synthetic Biology Approaches

Geraghty Sauer*

Department of Immunobiology, Hannover Medical School, Hannover, Germany

Introduction

Dendritic cells, as professional antigen-presenting cells, lie at the heart of immune modulation by bridging innate and adaptive immunity. They have the unique capacity to capture, process, and present antigens to T lymphocytes, thereby initiating and shaping immune responses. In health, they maintain tolerance to self-antigens and regulate immune homeostasis, while in disease states, they can trigger robust responses against infections, tumors, or contribute to autoimmunity. Harnessing and manipulating the inherent immunological power of dendritic cells has emerged as a key strategy in immunotherapy, including cancer vaccines, autoimmune suppression, transplant tolerance, and infectious disease control. In recent years, synthetic biology-a multidisciplinary field integrating biology with engineering-has transformed the scope of immune cell manipulation. Synthetic biology enables the design of programmable DCs with enhanced, repressed, or entirely novel immune functions by modifying their genetic circuits, signaling pathways, antigen presentation capabilities, and cytokine profiles. With advances in gene editing tools like CRISPR/Cas9, viral and non-viral delivery systems, modular gene circuits, and synthetic receptors, DC engineering is being revolutionized to create next-generation immunotherapies [1].

Description

Dendritic cells play a central role in controlling T cell responses. In their immature state, DCs patrol tissues for antigens, and upon encountering pathogens or danger signals, they mature and migrate to lymphoid organs to activate naïve T cells. This activation involves three essential signals: antigen presentation via MHC molecules (Signal 1), costimulatory molecules (Signal 2), and cytokine secretion (Signal 3). In the absence of full activation, DCs can induce tolerance through T cell anergy or regulatory T cell (Treg) induction. These unique features make DCs attractive targets for engineering. In cancer, DCs can be reprogrammed to present tumor antigens more efficiently and stimulate Cytotoxic T Lymphocyte (CTL) responses. In autoimmune diseases and transplantation, engineered tolerogenic DCs can promote immune suppression and tissue acceptance. Unlike T cells, which require activation and expansion, DCs can be manipulated ex vivo and used as cellular vaccines or directly modulated in vivo using nanoparticles or gene-editing platforms [2].

Synthetic promoters allow tissue- or signal-specific expression of therapeutic genes in DCs. Gene circuits, composed of regulatory modules, can integrate multiple inputs (e.g., pathogen sensing and inflammation) to produce desired outputs (e.g., IL-12 secretion or checkpoint blockade). Though widely applied in T cells, CARs can be adapted for DCs to enhance antigen uptake or signal transduction. Synthetic Notch (synNotch) receptors in DCs can be engineered to sense specific ligands and trigger tailored transcriptional responses, including cytokine secretion or antigen presentation. Synthetic mRNA can be used to transiently express antigens, transcription factors, or cytokines in DCs without genomic integration, reducing the risk of insertional mutagenesis. mRNA-based vaccines leverage DCs' antigen presentation capabilities and are being widely developed for infectious diseases and cancer [3].

Cancer vaccines using DCs have long been explored, with the goal of presenting tumor antigens and activating CTLs. Synthetic biology enables the development of DCs with enhanced antigen-presenting capabilities, costimulation, and cytokine profiles. DCs can be transfected with tumor-associated antigens (TAAs) using mRNA or DNA vectors, allowing endogenous antigen processing and presentation via MHC-I and MHC-II. Fusion constructs with targeting sequences (e.g., lysosomal-associated membrane protein-1) improve presentation on MHC-II, enhancing CD4+ T cell activation. Co-expression of cytokines like IL-12, GM-CSF, or IFN-β enhances T cell activation and recruitment. Gene circuits can be designed to link pathogen detection with IL-12 secretion, mimicking natural adjuvant effects. CRISPR-mediated deletion of PD-L1 or expression of dominant-negative PD-1 receptors in DCs prevents T cell exhaustion. Combining antigen presentation with checkpoint blockade improves anti-tumor efficacy in preclinical models [4,5].

Conclusion

Synthetic biology has emerged as a transformative approach to engineer dendritic cells for immune modulation, offering unprecedented control over antigen presentation, costimulation, and cytokine production. By leveraging tools such as CRISPR gene editing, mRNA delivery, synthetic promoters, and modular gene circuits, researchers can program DCs to drive immunogenic responses against tumors and infections or induce tolerance in autoimmunity and transplantation. While challenges remain in terms of delivery, stability, and manufacturing, ongoing advances in technology and biology are paving the way for next-generation dendritic cell therapies. As synthetic immunology matures, engineered DCs will become vital components of personalized and precision medicine, enabling tailored immune interventions that are both effective and safe.

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Conflict of Interest

None

***Address for Correspondence:** Geraghty Sauer, Department of Immunobiology, Hannover Medical School, Hannover, Germany; E-mail: geraghtysauer@eri.de*

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