



Surface engineering for lymphocyte programming[☆]



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ABSTRACT

The once nascent field of immunoengineering has recently blossomed to include approaches to deliver and present biomolecules to program diverse populations of lymphocytes to fight disease. Building upon improved understanding of the molecular and physical mechanics of lymphocyte activation, varied strategies for engineering surfaces to activate and deactivate T-Cells, B-Cells and natural killer cells are in preclinical and clinical development. Surfaces have been engineered at the molecular level in terms of the presence of specific biological factors, their arrangement on a surface, and their diffusivity to elicit specific lymphocyte fates. In addition, the physical and mechanical characteristics of the surface including shape, anisotropy, and rigidity of particles for lymphocyte activation have been fine-tuned. Utilizing these strategies, acellular systems have been engineered for the expansion of T-Cells and natural killer cells to clinically relevant levels for cancer therapies as well as engineered to program B-Cells to better combat infectious diseases.

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Contents

1.	Introduction	103
2.	Chemical and biological factors (signal proteins)	105
2.1.	T-cells	105
2.1.1.	Signal 1: cognate antigen presentation	105
2.1.2.	Signal 2: costimulation	106
2.1.3.	Signal 3: soluble factors	106
2.1.4.	Adhesion molecules	106
2.1.5.	Killer aAPCs: T-cell deactivation	106
2.2.	B-cells	106
2.2.1.	Requirements of B-cell/antigen interaction	106
2.2.2.	Particulate systems for B-cell activation.	106
2.3.	Natural killer cells	107
3.	Surface patterning and fluidity	107
3.1.	T-cells	107
3.1.1.	Spatial arrangement of immunological synapse	107
3.1.2.	Surface patterning	107
3.1.3.	Surface fluidity.	107
3.1.4.	Alternative methods to enable receptor clustering	109
3.2.	B-cells	109

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3.2.1.	Surface fluidity	109
4.	Surface area contact	109
4.1.	T-cells	110
4.1.1.	Requirements of APC/T-cell surface area interactions	110
4.1.2.	Particle size as a parameter to control surface area interaction	110
4.1.3.	Particle shape as a parameter to control surface area interaction	110
4.1.4.	Nanotopography as a parameter to control surface area interaction	111
4.2.	B-cells	111
5.	Surface rigidity and mechanical properties	112
5.1.	T-cells	112
5.2.	B-Cells	112
6.	Conclusion	112
	Abbreviations	112
	Acknowledgements	112
	References	113

1. Introduction

The field of drug delivery has in many ways focused on the controlled delivery of soluble biomolecules to tissue types of interest and increasingly to targeted cell types. While this mode of delivery covers many categories of therapeutics, including both small molecule drugs and biologics such as peptides, proteins, and nucleic acids, certain types of biologics require presentation from a surface, rather than soluble presentation, for their desired cellular function. Biomimetic materials, in particular, that aim to mimic the physical, chemical, and biological aspects of natural biological materials for cellular engineering, must take into account this feature of surface presentation.

One of the varied areas of biology where the proper balance of physical, chemical, and biological interactions appears most critical is in the signaling of the immune system. Thus, for the engineering of lymphocytes, surface engineering of biomolecules is key to deliver the proper signals for lymphocyte programming. This review highlights lymphocyte immunoengineering approaches including the components of the necessary chemical and biological signals that engender cellular responses, the required features of the surfaces that best present these signals such as surface fluidity, and the geometric and physical properties of the supporting substrate that also modulate lymphocyte behavior (Fig. 1) (Table 1).

Lymphocytes include T-Cells, B-Cells and natural killer (NK) cells, all of which arise from the common lymphoid progenitor [1]. T-Cells and B-Cells are primarily responsible for the effector functions of the adaptive immune system, while NK cells serve as innate effector cytotoxic lymphocytes. Lymphocyte development begins in the bone marrow during hematopoiesis with lymphocytes migrating to peripheral lymphoid tissue following maturation. In the body, lymphocytes interact with a variety of cell types and signaling molecules that provide the cues necessary to initiate expansion, activation, anergy or cell death. T-Cell interaction with professional antigen presenting cells (pAPC), as well as stromal cells, largely shapes the adaptive immune response to pathogens and plays a role in auto-immunity [1]. pAPCs include dendritic cells, macrophages and to a lesser extent B-Cells that all express the major histocompatibility (MHC) class II molecule to allow presentation of exogenous antigens. B-Cells, in contrast, are capable of interacting with soluble antigen directly, allowing for a varied approach to targeting their response. After the immune system is activated by a specific pathogen and that pathogen is subsequently cleared, some of the pathogen-specific T-Cells and B-Cells become memory cells, ready to respond quickly if the same pathogen is ever seen again in the future. While lymphocytes are the chief cells involved in adaptive immunity and the long-term immunological memory necessary for effective vaccination, this review focuses on lymphocytes in the context of direct programming to elicit primary functions. Much work has been done in the area of vaccine design, although it has often focused on soluble antigen, small molecule

adjuvants and release formulations for optimal temporal stimulation instead of surface engineering, as well as focusing on delivery to dendritic cells rather than to lymphocytes [2,3]. In particular, Purcell et al. provides a good review of the interplay between lymphocytes in response to peptide antigens and their involvement in long term immunity [4] and Irvine et al. provides a good review of nanoparticles for use in vaccines [5].

Modulating the immune system through cellular based systems, particularly for anti-cancer immunotherapies has seen great success in recent trials with therapies targeting the anti-tumor response both through the direct modulation of lymphocytes and through *ex vivo* expansion of dendritic cells. In particular, chimeric antigen receptor (CAR) T-cell therapies for a subset of otherwise non-responsive cancers have seen high levels of efficacy and are in various stages of clinical trials in the USA [6,7]. Most CAR-T-cell therapies rely on adoptive transfer strategies that have certain risks associated with the genetic modulation of T-cells for the purpose and have had adverse events resulting from antigen recognition leading to cytokine storms [8]. In contrast to CAR-T-cell expansion for adoptive transfer, Sipuleucel-T therapy was recently approved for refractory prostate cancer with high efficacy in a subset of patients but carries its own costs and associated risks [9]. For Sipuleucel-T therapy, patient specific *ex vivo* expansion of dendritic cell populations in the presence of immunostimulatory molecules followed by reinfusion had an initial cost-per-patient of \$93,000 in 2010 that has since risen [9]. Many of the challenges associated with these therapies in terms of cost and regulatory hurdles could be overcome with sufficiently effective acellular strategies currently in pre-clinical stages as discussed in this review.

As understanding of these natural systems has advanced, investigators have sought to design artificial systems capable of mimicking and controlling these interactions to shape the lymphocyte response. Moving towards this goal, engineered particle and surface based systems have been designed that can activate a variety of lymphocyte subtypes *in vitro* and *in vivo* for purposes of anti-cancer therapies. Across multiple stages of translation to the clinic, activation of lymphocytes *ex vivo* and *in vivo* have been studied. As the majority of lymphocyte engineering strategies in the past two decades have focused on cancer therapies, engineering of cytotoxic T lymphocytes (CTLs) has arguably advanced the furthest and strategies for genetically engineering T-Cells have already reached the clinic in the form of CAR-T-Cells [10]. Similar in some contexts, cellular based artificial antigen presentation systems have likewise seen significant development [11], but face challenges related to the manufacturing and amplification of dendritic cells or other professional APCs *ex vivo* [12].

Unlike strategies to modify lymphocytes directly such as with CAR T-Cell engineering [13], artificial antigen presenting cells (aAPCs) [14] and surface engineering for lymphocyte modulation function within the domain of activating lymphocytes through their existing molecular

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