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Personalized Implantable Vaccines with Antigen Pre-Activated Macrophages

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Abstract

Implantable vaccines are a major breakthrough in the field of vaccination. Unlike traditional vaccines, implantable vaccines consist of a system allowing natural antigen loading and presentation *in vitro* and further activation of the immune system *in vivo*, while simultaneously overcoming problems such as virulence and side effects of adjuvants. In general, this article is intended as a mini-review to discuss personalized implantable vaccines, as well as their advantages.

Keywords: Vaccine; Silicon scaffolds; Immunology response

Abbreviations

APCs: Antigen Presenting Cells; MHC: Major Histocompatibility Complex; SEM: Scanning Electron Microscopy; SFF: Solid-Free-Form; TCR: T Lymphocyte Receptor

Introduction

Vaccination is an economical and effective weapon for the prevention of infectious diseases. The number of vaccines has increased significantly in the recent decades, but still remains the need to develop vaccines against many diseases such as tuberculosis, malaria or AIDS. In addition there is need to improve safety and effectiveness of existing vaccines.

The development of an immune response lies on the successful antigen presentation by Antigen Presenting Cells (APCs). The traditional view of antigen presentation states that intracellularly synthesized antigens are presented by Major Histocompatibility Complex (MHC) class I molecules and activate CD8+ cytotoxic T (T_c) cells, whereas extracellular antigens are presented by APCs with MHC class II molecules to CD4+T helper (T_H) cells. Extracellular antigens are internalized into phagosomes or endosomes that subsequently mature and undergo a series of molecular changes, such as acidification and fusion with organelles containing degrading enzymes like lysosomes. The generated antigenic peptides are loaded into MHC class II molecules and transported to the cell surface for presentation to CD4+T_H cells [1].

Activation of T_H cells represents one of the most important activities of the immune system since it leads to humoral or cellular immunity as well as tolerance. Thus, T_H will stimulate B cells for specific antibody production or T_c for target cell killing, while the expression of negative surface markers will suppress both types of immunity to ensure homeostasis of the immune system.

Vaccines

Vaccines can no longer guarantee complete protection from any disease [2]. Sometimes protection fails because the host's immune system cannot react adequately or even fail to react. The inability to react is usually the result of clinical factors such diabetes mellitus, steroid use, HIV infection or even age. In addition, there is the case where for genetic reasons an individual is unable to produce antibodies that will recognize a particular factor, such as B-cell deficiency. Even if the host's immune system produces antibodies, the protection may not be sufficient. Immunity can be developed slowly, or antibodies might not completely inhibit the pathogen. But even a slow or weak immunity can moderate the progression of the disease by leading at a lower mortality rate, gentle symptoms and faster recovery.

The road to successful vaccine development, which they can receive authorization for human use is long and difficult. Even vaccines that successfully pass the preparation stages and they receive approval for clinical trials in humans, it is not sure that they will be promoted for wide use. Experience has shown that a vaccine, even if it is effective in the laboratory and in the animals, it doesn't mean that it can prevent the corresponding disease in humans. Some vaccines have very serious complications, and some have even been found to deteriorate the disease they were prepared to prevent. The development of vaccines begins with basic research. Knowledge of the different characteristics of epitopes recognized by T and B cells, has given the ability to design vaccines that will maximize the stimulation of both branches of the immune system. After discovering the mechanisms of antigen processing, the design of vaccines haw started with the use, however, of adjuvants to maximize antigen presentation through MHC class I and II molecules.

Biomimetic scaffolds

The implantable scaffolds consist of biomaterial surfaces with 3D micro and submicron, produced by ultrafast lasers [3]. It has been shown that 3D micro/nano topography and surface chemistry influence the differentiation and migration of macrophages [4,5]. The ultrafast laser structuring technology presents important advantages as it (a) is versatile and independent material (b) is rapid, easily adaptable and scalable through parallel processing and (c) allows the unique possibility for controllable, high resolution features at both micro- and nano- length scales. Additional advantages of laser structuring include high fabrication rate, non-contact interaction, applicability to many types of materials and reproducibility. Furthermore, lasers can be easily incorporated to computer-assisted fabrication systems for complex and customized 3D matrix structure design and

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manufacture. Such systems gave rise to a versatile class of scaffold production techniques which are laser-based Solid-Free-Form (SFF) fabrication techniques. The SFF is essentially a rapid prototyping technique which allows control over macroscopic properties, such as scaffold shape and microscopic internal architecture.

MHC polymorphism in the population leading to apathy

An important issue that must taken into account in vaccine development, is the MHC polymorphism in the population. MHC interacts with the antigen and the T Lymphocyte Receptor (TCR), playing a key role in triggering an immune response. Thus individuals, depending on their MHC, will be able to bind an antigenic epitope with high or low affinity. In the first-generation vaccines, where whole pathogens are used, during the preparation of antigen each individual has the ability to select, upload and present appropriate antigenic peptides that bind high affinity to their own class II and class I MHC proteins. On the contrary, in the second and third generation of vaccines such a possibility is limited due to the limited antigenic epitopes provided to the body, which in some individuals may not effectively bind to the MHC, leading to apathy.

Immuno-adjuvants

The administration of antigen along with adjuvant induces immunity instead of tolerance. Vaccine adjuvants are traditionally defined as chemical compounds or macromolecules that increase immune responses of co-administered antigen with minimal toxicity or long-lasting immunity on their own. Adjuvants like aluminum salts, oil-in-water emulsions, and liposomes facilitate antigen depot and thus presentation by APCs. Other adjuvants like monophosphoryl lipid A, CpG, or poly I: C, activate APCs by binding to Toll-like receptors [6]. All these adjuvants cause inflammation at the site of injection but also have a potential for long term side effects and therefore have not been approved for human use. The most used adjuvant in the clinics is aluminum-based mineral salts (alum) [7] which has a good track record of safety and has been widely used in many licensed vaccines [8]. Although alum adjuvant causes low levels of local inflammation, in some cases of intramuscular injections it was correlated to macrophagic myofasciitis [9]. In addition to the side effects, alum is sensitive to freezing, lyophilization or cold storage which causes a loss of its potency [10]. Alternative vaccine adjuvants that are non-toxic, consistently effective, and easy to handle have been hunted for the past thirty years.

Personalized implantable vaccines

The role of the immune system is to recognize antigens, respond by humoral or cellular reactions, eliminate the foreign stimuli and develop specific memory. The development of immune response against an antigenic stimulus haw been exploited in the context of vaccines that are being developed to prevent or ameliorate the effects of future pathogen infections. In order to avoid virulence, second generation vaccines consisting of defined antigenic peptides or recombinant protein sub-units, need the simultaneous administration of adjuvants to enhance immune responsiveness.

However, adjuvants are responsible for several side-effects. In addition, because of the extended polymorphism of histocompatibility antigens, the selection of specific noninfectious antigenic epitopes might not be effectively presented by all individuals. To overcome these problems, a system allowing natural antigen loading and presentation *in vitro* and further activation of the immune response *in vivo*, was developed.

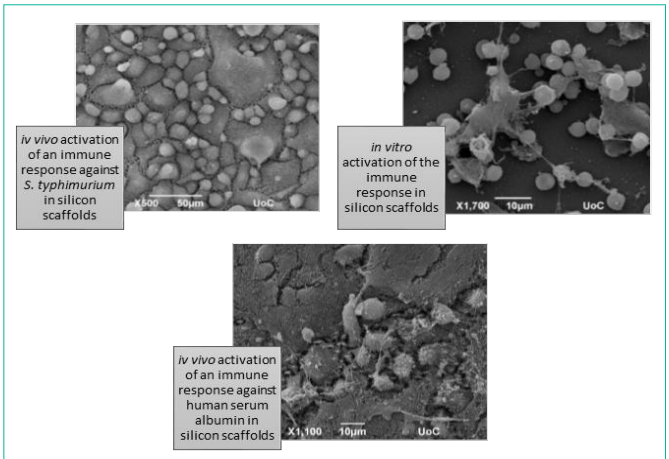

Figure 1: Immune response on silicon scaffolds by SEM.

Such technology leads to personalized implantable vaccines. Thus, pre-activated macrophages naturally seeded with the antigen are being absorbed on implantable surfaces able to stimulate the development of immune response. Such approach eliminates side effects due to the non-specific stimulation of adjuvants, while leaving the natural selection mechanism of antigen loading in antigen presenting cells to choose the right antigenic epitope for each individual. The implantable surfaces proved to play such role consist of 3D micro-textured Si scaffolds fabricated by ultrafast lasers.

Immune response on biomimetic scaffolds

The system of implantable vaccines aims to allow recipient APCs to naturally present antigen epitopes *in vitro* ensuring thus best MHC-antigen complex formation and stimulate immune response upon *in vivo* after implantation.

The best conditions for fulfill the goal of the immune system's activation consisted of the roughness (energy intensity of laser) of the silicon scaffold surface. Surfaces with low roughness (1,68/cm2) were shown to support macrophage growth and after seeding with whole antigen, lymphocyte activation *in vitro*. The combination of *in vitro* and *in vivo* manipulations to develop biomaterials allowing natural antigen-loading and presentation *in vitro* and further activation of the immune response *in vivo*. 3-dimensional laser micro-textured implantable Si-scaffolds supported mouse macrophage adherence, allowed natural seeding with antigens like human serum albumin [11] and Salmonella typhimurium [12] and after implantation, led to the production of specific antibody and inflammatory cytokine production *in vivo*. It is important to be mentioned that antigen-specific antibody production *in vivo*, could be detected even 30 days post implantation. Histology analysis (Figure 1) of implant using Scanning Electron Microscopy (SEM) showed that Si-scaffolds could be stable for a 6-month period. Following such technology, the goal is to develop personalized implantable vaccines stimulating not only humoral but also cellular response against the specific tumor of each individual. Vaccine safety is a serious issue occupying the World Health Organization since vaccine technology was developed. The

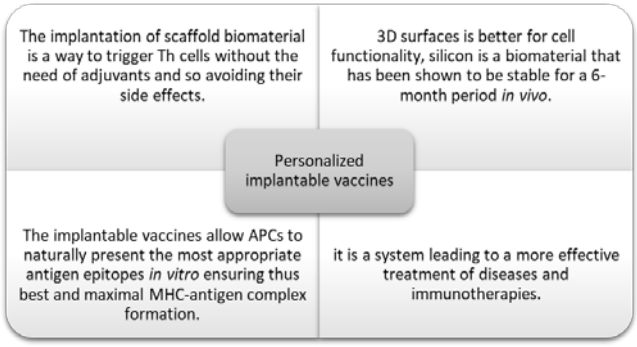

Figure 2: The advantages of personalized implantable vaccines.

use of non-biodegradable implants avoids adjuvant-dependent side effects, while providing the necessary immune stimulation to the host [1].

Implantable vaccine is also a way to trigger T_H cells without the need of adjuvants. During a natural infection the organism develops an immune response in an antigen-dependent manner. Antigens will be immunogenic, if they succeed to be processed and presented by Antigen Presenting Cells (APCs). The development of implantable biomaterial scaffolds with tunable morphology and chemistry had shown that they are able to stimulate the development of a humoral immune response in mice *in vivo*. Such approach represents a personalized vaccination and also it would eliminate all side effects due to the non-specific stimulation of adjuvants due to the ability of the implantation process itself to trigger the initiation of an immune response in the body (Figure 2).

Conclusion

The implantable 3d Si-scaffold with pre-activated APCs is a technology that contributes to the evolution of vaccines. The activation of immune system cells without the need to use additives such as adjuvants is a new chapter in the history of vaccines. This will lead to discharge the organism from pathogenic and infectious agents, as long as it is possible to achieve immune stimulation from the body's own cells.

It is envisaged that these diverse opportunities are offered by bio mimetically shaped substrates will find applications in industry, especially to guide cell proliferation, motility and differentiation, as well as the development of scar tissue and cellular microarrays and the ability to regulate cell adhesion. Also new immunological horizons are being opened, strengthening the natural system to respond and thus lead to a more effective treatment of diseases and immunotherapies.

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