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Recent insights into cutaneous immunization: How to vaccinate via the skin

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ABSTRACT

Technologies and strategies for cutaneous vaccination have been evolving significantly during the past decades. Today, there is evidence for increased efficacy of cutaneously delivered vaccines allowing for dose reduction and providing a minimally invasive alternative to traditional vaccination. Considerable progress has been made within the field of well-established cutaneous vaccination strategies: Jet and powder injection technologies, microneedles, microporation technologies, electroporation, sonoporation, and also transdermal and transfollicular vaccine delivery. Due to recent advances, the use of cutaneous vaccination can be expanded from prophylactic vaccination for infectious diseases into therapeutic vaccination for both infectious and non-infectious chronic conditions. This review will provide an insight into immunological processes occurring in the skin and introduce the key innovations of cutaneous vaccination technologies.

1. Introduction

Q2 The skin has been used to induce protective immunity against highly infectious diseases since the very first recorded vaccinations against smallpox in 1796 [1,2]. Jenner's breakthrough eventually lead to the eradication of smallpox by mass vaccination programs, where vaccines were initially administered by subcutaneous (s.c.) inoculation with a lancet and later performed using needle-free jet injectors and bifurcated needles for intradermal (i.d.) vaccine delivery [1,3,4]. Furthermore, bacille Calmette-Guérin (BCG) vaccines have been administered intradermally since the early 1920s to prevent tuberculosis [5–7].

Although the skin has been known for centuries to be an attractive site for immunization, recent developments in needle-free systems have renewed the interest in cutaneous vaccination, here defined as the induction of an immune response upon topical, intradermal, or intraepidermal delivery of a vaccine [8]. This route of immunization, sometimes also referred to as skin vaccination or transcutaneous immunization, takes advantage of the unique immunological features of the skin immune system [9–11]. The two uppermost skin layers, the epidermis and the dermis, have a high density of immunocompetent cells such as Langerhans cells (LCs) and dermal dendritic cells (dDCs) (Fig. 1) [12]. These professional antigen presenting cells (APCs) play an important role in developing adaptive immunity through the processing and presenting of antigen [13,14]. Delivering a vaccine to the skin has been shown to elicit similar or even higher immune responses compared to i.m. injection, even in some cases using lower vaccine doses [15–22]. This could be of special significance for pandemics, when vaccine supply is limited and dose reduction is necessary. By evoking humoral, cellular and, in some cases, mucosal immune responses [23–25], cutaneous vaccination holds the potential to expand the range of applications beyond conventional prophylactic immunization

Abbreviations: APC, professional antigen presenting cell; bGal, beta-galactosidase; CD, cluster of differentiation; CpG, CpG oligodeoxynucleotides; CT, cholera toxin; CTL, cytotoxic T cell; CSSS, cyanoacrylate skin surface stripping; dDC, dermal dendritic cell; DNA, deoxyribonucleic acid; DSJI, disposable syringe jet injector; DT, diphtheria toxoid; EP, transdermal electroporation; EPI, epidermal powder immunization; GAD65, glutamic acid decarboxylase 65; gp120, envelope glycoprotein GP120; HbsAg, hepatitis B surface antigen; HIV-1, human immunodeficiency virus type I; IFN-γ, interferon gamma; Ig, immunoglobulin; IL, interleukin; i.d., intradermal; i.m., intramuscular; i.v., intravenous; JEV E, Japanese encephalitis virus E glycoprotein; LC, Langerhans cell; LT, *Escherichia coli* heat-labile toxin; LTR, local transport region; mAb, monoclonal antibody; MUNJI, multiple use nozzle jet injector; MYR, myristylated peptide; NA, nucleic acid; OVA, ovalbumin; PA 63, *Bacillus anthracis* protective antigen; pDNA, plasmid DNA; Phl p 5, recombinant allergen from *phleum pretense*; rdAd, replication-defective adenovirus; RNA, ribonucleic acid; s.c., subcutaneous; SC, stratum corneum; SDS, sodium lauryl sulfate; SIINFEKL, octapeptide, ovalbumin epitope; SUDJI, single-use disposable jet injector; TCI, transcutaneous immunization; TNF, tumor necrosis factor; TLR, toll-like receptor; TT, tetanus toxoid; UVB, ultraviolet B.

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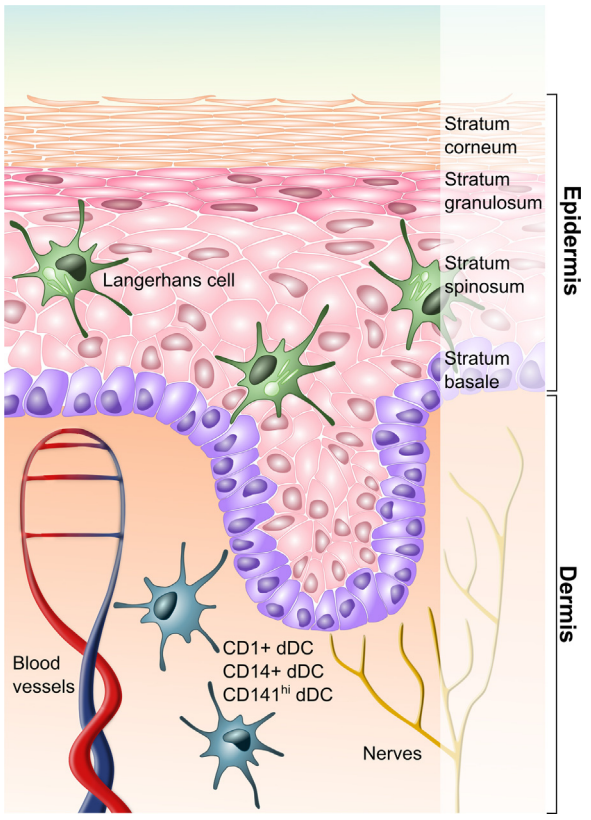

Fig. 1. Professional antigen presenting cells of the superficial skin. Three subsets of professional antigen presenting cells have been identified within the two topmost layers of the skin. Whereas a high density of Langerhans cells (LC) can be found within the epidermis, CD1+ and CD14+ dermal dendritic cells (dDCs) reside in the underlying dermis.

into therapeutic vaccination for cancer and HIV infections [26,27].

The demand for a safe, pain-free and simple alternative to i.d. and i.m. needle injection has led to the development of alternative techniques to deliver vaccines to the skin. Intradermal vaccination, usually performed with needle and syringe, can be regarded as the first approach of cutaneous vaccination. However today, the variety of strategies has been expanded, including conventional i.d. injection, but also needle-free vaccine delivery techniques, stratum corneum-disruptive approaches, and passive targeting strategies [28]. The simplest techniques involve the passive diffusion of protein or DNA vaccines into intact skin or skin pretreated by tape stripping or abrasion of the stratum corneum (SC) [29–34]. Active vaccination approaches deliver the antigen directly to immunocompetent cells either by needle-free jet and powder injection or by creating microchannels or transient cavities in the upper skin layers [35–37]. Such active microporation techniques include the use of microneedles, thermal microporation, radiofrequency ablation, and laser poration, as well as electroporation and sonoporation. Here we will review the latest advances in the field of needle-free cutaneous vaccination with special consideration being given to DNA or RNA vaccines and the use of adjuvants for cutaneous vaccination.

2. Vaccination via the skin

2.1. Antigen presentation

The aim of vaccination is to activate the acquired immune system to induce long-lasting protection against specific pathogens [38]. Upon encountering a pathogen APCs mature and migrate toward draining lymph nodes [13]. By up-regulating antigen-loaded major histocompatibility complexes (MHC) class I and II as well as co-stimulatory surface molecules, mature APCs initiate the proliferation and differentiation of naïve T cells into effector and memory T cells [13,39]. Typically, exogenous antigens are presented via MHC-II complexes to CD4+ T cells, comprising T helper cells (Th cells) and regulatory T cells (Tregs), whereas CD8+ T cells (cytotoxic T cells, CTL) interact with cytosol-derived endogenous antigens loaded onto MHC-I [40,41]. However this segregation of antigen presentation is not complete as distinct subsets of APCs are able to cross-present exogenous antigens via MHC-I to prime CD8+ T cells [42,43]. This cross-priming is expected to play an essential role for eliciting immune responses against tumor or virus-infected cells [42].

In addition to the MHC-restricted presentation of proteins and peptides, APCs are able to process and present non-protein antigens, such as lipids, glycolipids and lipopeptides [44]. Surface molecules of the CD1 family are loaded with lipid antigens via endocytotic pathways [45], subsequently priming killer T cells (NKT cells), which respond by secreting large amounts of Th1 and Th2 cytokines and influencing DC maturation [46,47]. LCs have been found to express large amounts of the group 1 family of CD molecule CD1a and moderate amounts of CD1c [48,49]. However, all identified molecules of group one and two of the CD1 family have been found on dDCs [49,50]. CD1d is the only molecule of the CD1 family that has also been detected in mice [51].

2.2. Acquired immune responses

CD8+ T cells that differentiate and proliferate upon MHC-I interaction into CTLs [41,52] are able to lyse transformed or infected cells through the production of granzymes and perforin [53]. CD4+ T helper cells play a role in modulating a variety of immune responses. This includes cellular, humoral, regulatory and inflammatory responses [54]. B cells may be activated in either a T cell dependent or independent manner [55]. Upon activation naïve B cells differentiate into antibody secreting plasma cells and memory B cells [56].

Four different subsets of T helper cells are known to reside in the skin Th1, Th2, Th17 and Th22 [51]. Promoted by IL-12, non-polarized CD4+ T cells differentiate into Th1 cells, typically secreting interferon-gamma (IFN-γ) and IL-2 [57]. The polarization toward the Th2 subset is enhanced by IL-4 and these cells secrete IL-4, IL-5, IL-10 and IL-13 [57]. While IFN-γ promotes a switch toward IgG2a in mice and stimulates cellular immune responses, IL-4 induces the synthesis of IgG1 and IgE [58]. IL-23 induces the proliferation of Th17 cells that secrete IL-17 and often IL-22 [59,60]. The Th22 subset, which has been identified recently, can be characterized by the secretion of IL-22 and in the absence of IL-17 or IFN-γ [61,62]. Healthy skin harbors approximately 80% mainly Th1-biased effector memory T cells as well as a substantial numbers of central memory and regulatory T cells [63].

2.3. Dendritic cell subsets

While the dendritic cell network in the skin differs between mice and human, some similarities exist. The main dendritic cell subsets that have been identified in mice and human skin are the epidermal Langerhans cells (LCs) and dermal dendritic cells (dDCs). In both species LCs form a continuous network throughout epidermal keratinocytes and can be characterized by their expression of the lectin receptor langerin (CD207) [51,64]. In mice, the dDC population constitutes of dermal resident DCs, namely CD103+ DCs and CD11b+ DCs, as well as migratory LCs [65]. Langerin-negative CD11b+ DCs represent the main dermal dendritic cell subset, (approximately

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