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Nucleic acid delivery into skin for the treatment of skin disease: Proofs-of-concept, potential impact, and remaining challenges

Michael Zakrewsky, Sunny Kumar, Samir Mitragotri *

Center for Bioengineering and Department of Chemical Engineering, University of California Santa Barbara, Santa Barbara, CA 93106, USA

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ABSTRACT

Nucleic acids (NAs) hold significant potential for the treatment of several diseases. Topical delivery of NAs for the treatment of skin diseases is especially advantageous since it bypasses the challenges associated with systemic administration which suffers from enzymatic degradation, systemic toxicity and lack of targeting to skin. However, the skin's protective barrier function limits the delivery of NAs into skin after topical application. Here, we highlight strategies for enhancing delivery of NAs into skin, and provide evidence that translation of topical NA therapies could have a transformative impact on the treatment of skin diseases.

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1. Introduction

Nucleic acids (NAs) hold great potential for the treatment of various diseases, and there has been a significant amount of both academic as well as commercial interest in a variety of NA-based therapeutics including genes, antisense oligodeoxynucleotides (ODNs), siRNA, aptamers, and CpG oligonucleotides [1–4]. However, translation of these platforms to the clinic has been significantly limited by challenges associated with delivering NAs to the diseased site. Enzymatic degradation in the blood, rapid clearance from systemic circulation, poor bioavailability at the target site, and immunological response have yet to be adequately addressed for the implementation of systemically administered NA therapies [1,4].

Delivery of NAs through the skin offers a potential solution to these issues, especially for the treatment of dermatological diseases (Table 1). The skin is the largest organ of the body, and can provide a pain free and compliant interface for drug delivery [5,6]. Topical delivery of NAs offers several advantages over alternative delivery routes including avoidance of major degradative pathways in the GI tract, avoidance of enzymatic degradation and clearance from the bloodstream, sustained and controlled delivery, reduction in systemic toxicity, the ability to easily observe and treat sites of adverse reactions, and improved patient compliance [6]. Concurrently, it provides a means to directly target the diseased sites for the treatment of dermatological diseases *e.g.* skin cancer, psoriasis, and atopic dermatitis.

Topical delivery of NAs, however, is quite challenging. The challenge originates from the outermost layer of the skin – the stratum corneum (SC) – which serves as a formidable barrier to the entry of topically applied drugs. Nevertheless, significant efforts have been expended over the years to overcome the skin barrier. This review highlights strategies to effectively deliver NAs into the skin. Focus is placed on their applications for the treatment of dermatological diseases. Further, we provide evidence of the transformative impact of topical NA therapies on the treatment of skin diseases. The efforts here highlight significant advances in topical delivery of NAs over the last decade, and aim to guide future technologies and their translation into the clinic.

2. The skin barrier

The outermost layer of skin, the SC, is primarily responsible for its barrier function. The SC is a thin layer only 10–20 μm thick that is made up of corneocytes. Corneocytes are anucleate cells heavily enriched with intracellular keratin filaments. Corneocytes are held together in a "brick and mortar" structure by a lipid matrix composed of ceramides, free fatty acids, and cholesterol. Materials traversing the skin barrier must, therefore, diffuse through the tortuous lipid channels, and/or traverse transcellularly through corneocytes, or enter the skin through hair follicles or sweat ducts (Fig. 1). Transport within the lipid bilayers, however, is the most common mode of passage through the skin. This results in the exclusion of most foreign materials, and more specifically, renders passage of large, hydrophilic molecules (>500 Da and Log $P_{o/w} < 1.5$) such as NAs (typically >> 10,000 Da, Log $P_{o/w} < 0$) to virtually negligible levels without some form of enhancement strategy.

The layer underlying the SC, the epidermis, can also serve as another transport barrier [7]. The epidermis is the first viable tissue layer of the skin where the pathology of several dermatological disorders resides. The epidermis is 50–100 μm thick and is composed primarily of keratinocytes. As keratinocytes migrate upward from deeper

* Corresponding author.
E-mail address: samir@engineering.ucsb.edu (S. Mitragotri).

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Table 1
Advantages of NA topical delivery for the treatment of skin disease.

Advantages of NA topical delivery
• Targeted delivery into skin
• Large surface area for drug application
• Easily observe and excise sites of adverse reaction
• Easily monitor disease progress and adjust treatment
• Needle-free application
• Sustained and controlled delivery
• Avoidance of GI tract
• Limited to negligible systemic toxicity
• Limited to negligible clearance from diseased tissue
• User-friendly application

portions of the epidermis to the SC they gradually begin to keratinize and secrete lipids that eventually form the SC bilayers. This process continues as keratinocytes terminally differentiate into corneocytes and serves to rejuvenate the SC from underneath while the outermost layer of the SC sloughs away. Within the epidermis, keratinocytes are held together by cell–cell tight junctions. In the epidermis, claudin-1, claudin-4, occludin, and zonula occludens-1 are responsible for inhibiting paracellular transport [8]. This makes transport of NAs, other large macromolecules, and drug carriers such as nanoparticles and NA–lipid complexes difficult both vertically, deeper into the skin, as well as laterally from the site of administration to peripheral areas of the skin. For effective treatment, both the SC as well as epidermal transport barriers must be overcome to deliver NAs to all areas of the disease.

3. Methods of transport enhancement

Over the years, a large number of strategies have been devised for perturbing the SC to enhance the delivery of drugs into and through the skin. These strategies can be generally categorized into three main groups: physical, active, and passive methods. The advantages and disadvantages of each class of perturbation methods are summarized in Table 2. Their use for the delivery of NAs is described below.

3.1. NA delivery using physical methods

3.1.1. Microneedles

Intradermal injections are the simplest and most direct method for delivering NAs into the skin. Here, the barrier properties of the SC are overcome completely by injecting NAs directly into the viable tissue layers of the skin. Intradermal injections are typically used for evaluating efficacy of NAs or other cutaneous therapeutics, or as the positive control for evaluating dermal delivery technologies, however, the downsides of intradermal injection for treating skin disease are overwhelming. Needle-phobia is a serious concern for a large number of children as well as adults leading to significant patient non-compliance [9]. Moreover, intradermal injections are limited only to the site of application, and injection into multiple sites during a single administration is challenging. To avoid many of these drawbacks, microneedle arrays have been developed. Microneedle arrays comprise needles that are only 100–700 μm in length (Fig. 2). When placed on the skin, their sharp tips allow easy insertion into the stratum corneum, while the short length ensures adequate penetration into the skin without disrupting nerves in deeper skin tissue. Microneedles have been used extensively for the delivery of NAs. Mikszta *et al.* used microneedle arrays to deliver plasmid DNA encoding a hepatitis B surface antigen for immunization [10], and they showed extensive immunological response in mice. Antibody titers following application of microneedle arrays were significantly higher and less variable than when delivered using either intradermal or intramuscular injection. Chabri *et al.* [11] used microneedles to deliver cationic lipid-DNA complexes (~100 nm diameter) into the skin. Ding *et al.* [12] demonstrated successful immunization of mice with co-administration of diphtheria toxoid and CpG oligonucleotide delivered by microneedle array, and Gonzalez-Gonzalez *et al.* [13] demonstrated effective delivery of anti-luciferase siRNA and gene silencing in luciferase expressing transgenic mice.

3.1.2. Microporation

Microporation is another technique that employs physical disruption of the SC for delivery of large therapeutics or therapeutic carriers. An array of resistive elements can be placed on the skin. An electric current pulsed through the array results in localized ablation of corneocytes in contact with the array [14]. Alternatively, erbium:yttrium–aluminum–garnet (Er: YAG) laser arrays can be used for localized ablation of the SC and epidermis [15]. Similar to microneedle arrays, microporation has gained considerable interest over the last decade. For example, Lee *et al.* [16] used laser microporation to deliver antisense oligonucleotide as well as plasmid DNA into the skin. Delivery of antisense oligonucleotide was enhanced 3–30 fold compared to intact skin *in vitro*. In addition, expression of GFP in nude mice was enhanced 160 fold after application of GFP plasmid DNA. The amount of enhancement correlated with both the laser fluency as well as the size of oligonucleotide. The same group also showed enhanced delivery of siRNA [17]. siRNA delivery into skin was enhanced 3.5 fold and localized mainly in the dermis. Hessenberger *et al.* [18] used laser microporation to deliver CpG oligonucleotides into the skin and successfully protected against immune response to grass pollen in mice. They used the Precise Laser Epidermal System (Pantec Biosolutions) which creates well-defined arrays of micropores in the skin, and allows precise control over the number, density, and depth of the micropores giving the user

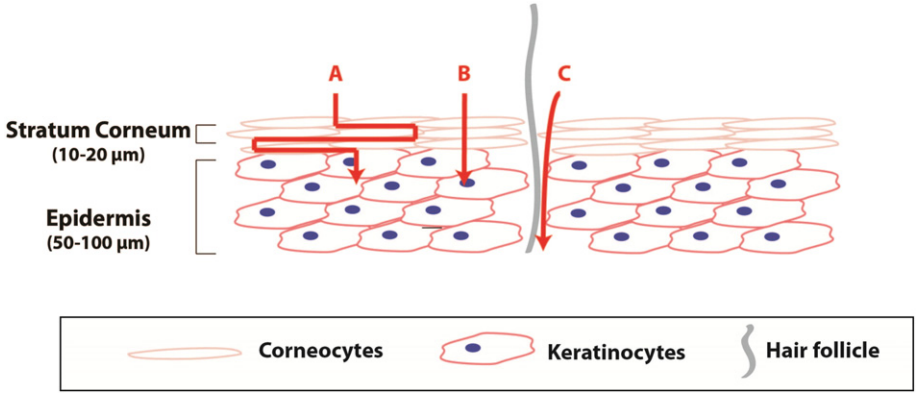

Fig. 1. Transport pathways into the skin. A: Intercellular pathway through lipid bilayers. B: Transcellular pathway through keratin-rich corneocytes. C: Shunt pathway through hair follicles and sweat ducts.

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