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Additional studies of the enigmatic Ptch1 protein are likely to unveil novel and illuminating cancer mechanisms.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Applications of Nanoparticles for Treating Cutaneous Infection

Astrid M. Westendorf[1]

Today, nanotechnology is finding applications in medicine. The unique physical and chemical properties of nanoparticles can overcome barriers and allow them to gain access to biological systems. Because of the increasing prevalence of microbial resistance to conventional therapies, the development of novel antimicrobials is imperative. Creating nanotechnology-based drug delivery systems with antibacterial and immunomodulatory activities may lead to novel treatments for cutaneous pathogens.

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Nanotechnology is the design and control of matter that ranges in size from ~1 to 100 nm. The application of nanotechnology to medicine, known as nanomedicine, involves the use of precisely engineered materials in this size range to develop novel therapeutic and diagnostic modalities. The unique physical and chemical properties of nanoparticles, in particular their small size and their high surface-to-volume ratio, can overcome barriers and allow them to gain access to biological molecules and systems. These properties can be used to overcome some of the limitations of conventional therapeutic and diagnostic agents. Therefore, nanoparticles can be engineered to serve as vehicles that carry various therapeutic agents and may be useful in medical applications, including targeted drug delivery, vaccine delivery, antimicrobials, and immunomodulation (Prow *et al.*, 2011; DeLouise, 2012).

Antimicrobial nanoparticles

Several studies have shown that nanoparticles are advantageous in several dermatological applications (Papakostas *et al.*, 2011; DeLouise, 2012). One important application with respect to the increasing frequency of microbiological resistance to conventional therapies is the nanotechnology-based drug delivery with antimicrobial agents.

Acne is a chronic inflammatory disease of the pilosebaceous unit. It results from an androgen-induced increase in the production of sebum, alterations in keratinization, inflammation, and bacterial colonization of hair follicles on the face, neck, chest, and back by *Propionibacterium acnes*. The Gram-positive bacterium *P. acnes* is a ubiquitous member of the skin microbiota and is found in sebaceous follicles located on the face and back of most humans. *P. acnes* is generally regarded as a commensal of the skin, but certain properties suggest that it has a pathogenic role in acne vulgaris. Treatment of acne with antimicrobial agents has been found to be associated with the development of resistance to these agents by *P. acnes,* leading to treatment failure. Because acne often requires long-term treatment with antibiotics, there are concerns that the development of resistance by *P. acnes* may be associated with the development of resistance by other organisms, such as *Staphylococcus aureus* and *S. pneumoniae*. Judicious use of antibiotics is important, especially for a common condition such as

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Clinical Implications

- Encapsulation of antimicrobials into chitosan–alginate nanoparticles contributes to increased efficiency and reduced toxicity during topical treatment.
- Chitosan–alginate nanoparticles allow the delivery of multidrug regimens to combat resistant microbes.

acne. Thus, alternative approaches for the antimicrobial treatment of acne are needed.

Friedman *et al.* (2013) report on the antimicrobial activities of chitosan–alginate nanoparticles. The polysaccharides, alginate and chitosan, are used extensively to develop useful nanoparticles, because of their low toxicity and their biodegradability. Alginate is an anionic polysaccharide derived from brown algae; chitosan is a natural polysaccharide biopolymer derived from chitin, the principal structural component of the crustacean exoskeleton. The antimicrobial properties of chitosan result from its polycationic character, which favors interaction with negatively charged microbial cell walls and cytoplasmic membranes, and thus results in reduced osmotic stability and disruption of those membranes. Friedman *et al.* (2013) demonstrated by electron microscopy that chitosan–alginate nanoparticles induce the disruption of the *P. acnes* cell membrane, thereby providing an antibacterial effect during topical application.

Other nanoparticles, such as uncoated titanium dioxide (TiO_2), possess antibacterial properties because of their photocatalytic action. After UV irradiation, uncoated TiO_2 acts as a photocatalyst and promotes peroxidation of the polyunsaturated phospholipid component of the lipid membrane of prokaryotes, such as bacteria (Tsuang *et al.*, 2008). The most commercialized nanomaterial with antimicrobial activity so far is nanosilver, used not only to coat wound and burn dressings but also to disinfect water. Its antimicrobial effect is presumably the result of mitochondrial toxicity, which results from interaction with thiol groups of internal membrane proteins, and thus causes oxidative stress (Chen and Schluesener, 2008). However, these antibacterial nanoparticles have not been studied for the treatment of acne or the treatment of cutaneous pathogens.

Benzoyl peroxide is a widely used topical agent for acne. It is antiseptic and, in contrast to antibiotics, does not promote bacterial resistance. Although benzoyl peroxide is an effective treatment, at effective doses it is frequently associated with the expected but unwanted adverse event, skin irritation. Friedman *et al.* (2013) demonstrated that encapsulating benzoyl peroxide in alginate–chitosan nanoparticles would enhance its antimicrobial activity against *P. acnes* with less toxicity to eukaryotic cells.

Immunomodulatory nanoparticles

New research has refined our understanding of the immunopathophysiology of acne. Various immune phenomena, including both innate and adaptive immune responses, have been implicated. Cell culture experiments using skin-derived keratinocytes and sebocytes showed that *P. acnes* can trigger an inflammatory response, including the production of several proinflammatory cytokines and chemokines. Pattern recognition receptors of the Toll-like receptor family have been found to be *P. acnes*–responsive receptors (Lee *et al.*, 2010). In addition, a subpopulation of T helper type 1 cells from inflamed acne lesions recognize *P. acnes* antigens (Mouser *et al.*, 2003). Thus, another therapeutic goal in treating acne is a reduction in inflammation. Chitosan has been shown to possess various anti-inflammatory properties, and Friedman *et al.* (2013) have showed that in human monocytes, chitosan–alginate nanoparticles inhibit the *P. acnes*-induced production of IL12p40, a cytokine previously shown to be involved in the inflammatory response in acne. In addition, *P. acnes*-induced production of IL-6 was inhibited in human keratinocytes in the presence of chitosan–alginate nanoparticles.

Topical retinoids are a mainstay in acne treatment. Retinoids reduce dyskeratosis in the pilosebaceous unit, inhibit the formation of microcomedones, and exert anti-inflammatory effects. Among the retinoids, all-*trans* retinoic acid has been shown to be effective in topical treatment of mild to moderate acne. However, the topical use of retinoic acid is commonly followed by a high incidence of adverse effects, such as sensitivity to sunlight, eczematous irritation, and mild to severe erythema. Nanopreparations of acne medications, including formulations containing retinoic acid, offer similar effectiveness and fewer side effects, thus possibly improving patient compliance and treatment outcomes. Castro *et al.* (2011) demonstrated in animal studies that retinoic acid loaded into solid lipid nanoparticles promotes a greater reduction in retinoic acid–induced skin irritation than conventional formulations do, but without reducing the therapeutic efficiency of retinoic acid. To take a step forward, Ridolfi *et al.* (2012) combined the anti-inflammatory activity of retinoic acid and the antimicrobial efficacy of chitosan to produce solid lipid nanoparticles containing retinoic acid and chitosan. These nanoparticles exhibited high encapsulation efficiency, high physical stability during the tested period (1 year), no cytotoxicity to keratinocytes, and high antibacterial activity against *P. acnes* and *S. aureus*, findings suggesting that they may be highly effective in the topical treatment of cutaneous infection.

Taken together, the results of several studies have shown that the use of nanoparticles has advantages in treating many dermatological conditions. Nanoparticle applications facilitate the body's response to foreign pathogens by improving innate and adaptive immune responses, and by increasing the

effectiveness and reducing the adverse effects of antimicrobials and other therapeutic agents. Although these applications are promising, many interesting questions remain to be answered and many challenges remain to be overcome. One important issue is the comparability of the results of *in vitro* and *in vivo* studies: the results of *in vitro* studies do not necessarily predict the outcome of *in vivo* exposure. In addition, there are growing concerns regarding the potential toxicities of materials used to fabricate some particles. Additional studies are needed to improve our understanding of this important field now in development.

CONFLICT OF INTEREST
The author states no conflict of interest.

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Mutant *BRAF*: A Novel Mediator of Microenvironmental Escape in Melanoma?

Keiran S.M. Smalley[1,2]

The acquisition of mutant *BRAF* is an important initiating event for melanoma development, although the process by which transformed melanocytes escape from keratinocyte control and disseminate to other organs is not well understood. Boyd *et al.* (2013) provide evidence that oncogenic *BRAF* contributes to the microenvironmental escape of melanocytes through the downregulation of E-cadherin expression via the transcriptional suppressor Tbx3.

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The earliest stages of melanoma development, in which transformed melanocytes escape the constraints of the local microenvironment and disseminate to lymphatic vessels and distant organs, are still being elucidated. Under normal physiological conditions, melanocytes sit at the basal layer of the epidermis where they interact closely with surrounding keratinocytes at a ratio of about 1:5. Under these circumstances, the two cell types exhibit a close relationship, with melanin pigment (in the form of melanosomes) being actively transported from melanocytes into surrounding keratinocytes. The transfer of melanin to keratinocytes (aka the tanning response) is critical in providing photoprotection to skin and serves to limit the harmful DNA-damaging activity of solar UV radiation (Tran *et al.*, 2008). The process of melanin synthesis and melanosome transport is initiated by signals that emanate from the keratinocytes after the UV-mediated initiation of p53-mediated gene transcription (Tran *et al.*, 2008). This, in turn, leads to the release of α-melanocyte-stimulating hormone from the keratinocytes and the stimulation of melanocortin receptor 1 signaling and melanogenesis in nearby melanocytes. In addition to these events, keratinocytes also control many other aspects of melanocyte behavior, including growth, motility, and differentiation (Haass *et al.*, 2005). This regulation is achieved through a finely balanced signaling network involving direct cell–cell adhesion between melanocytes and keratinocytes, as well as the release of paracrine growth factors. One of the key mediators of melanocyte/keratinocyte interaction is E-cadherin, a calcium-dependent glycoprotein that has important roles in maintaining the cell architecture in epithelial tissues (Haass *et al.*, 2005). Loss of E-cadherin expression is an important step in the majority of epithelial cancers, and it is a prerequisite for dissemination of invasive cells from the initial tumor mass (Kalluri and Weinberg, 2009). Typically, loss of E-cadherin expression is part of a larger dynamic transcriptional program that is frequently observed in cancer cells, called the epithelial-to-mesenchymal transition (EMT). Other features of the EMT include the adoption of a mesenchymal phenotype, increased extracellular matrix deposition and resistance to apoptosis (Kalluri and Weinberg, 2009). Under normal conditions, melanocytes express high levels of E-cadherin (despite being derived from the neural crest) with homotypic E-cadherin-based adhesion

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