Nanoparticles in dermatologic surgery

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Nanotechnology is an emerging branch of science that involves the engineering of functional systems on the nanoscale (1-100 nm). Nanotechnology has been used in biomedical and therapeutic agents with the aim of providing novel treatment solutions where small molecule size may be beneficial for modulation of biologic function. Recent investigation in nanomedicine has become increasingly important to cutaneous pathophysiology, such as functional designs directed towards skin cancers and wound healing. This review outlines the application of nanoparticles relevant to dermatologic surgery. (J Am Acad Dermatol 2020;83:1144-9.)

Key words: drug delivery; keratinocyte carcinoma; melanoma; nanoparticles; nanotechnology; surgery.

Nanotechnology is the branch of scientific study that involves particles measured on the scale of 1 billionth of a meter (10^{-9} m). The materials and methods of nanotechnology are used to devise products with novel physiochemical properties that cannot exist under conventional parameters. In particular, nanotechnology has garnered interest in drug delivery, where minute particles are able to more easily penetrate target tissues and bind to target cells.[1] Nanoparticles additionally offer the ability to improve drug solubility, decrease drug metabolism, and decrease drug immunogenicity, thereby potentially reducing dosages and minimizing adverse effects.[2]

NANOPARTICLES

Nanoparticles can be divided into various categories based on their physical and chemical properties. Several of the more common nanoparticle types are described below.

Liposomes

Liposomes are vesicles with an internal aqueous solvent and a phospholipid bilayer. The protective phospholipid exterior allows for increased penetration and the delivery of hydrophilic or hydrophobic contents.[3]

Solid lipid nanoparticles

Solid lipid nanoparticles are colloidal carrier systems composed of a solid, surfactant-stabilized lipid core with a phospholipid coating. Solid lipid nanoparticles represent a new version of lipid emulsion carriers, where liquid lipid is replaced by solid lipid, allowing for small size, large surface area, and high drug-loading capacity.[4]

Dendrimers

Dendrimers are symmetrical molecules with a central core and outwardly radiating tree branch–like extensions. Each successive group of branching units is termed a "generation," all of which are contained within a spherical 3-dimensional morphology. The structure of dendrimers allows for versatile drug delivery, because oligonucleotides can be conjugated to the outward terminals and create multivalent systems.[5]

Fullerenes

Fullerenes are composed of carbon molecules formed into a hollow sphere, ellipsoid, or tube shape. The most well-known fullerene is the Buckminsterfullerene, or buckyball, which is made from 60 carbon atoms arranged into a spherical structure resembling a soccer ball. Fullerenes have generated interest owing to their ability to scavenge free radicals and thereby provide antioxidant effects.[6]

Virosomes

Virosomes use an outer phospholipid membrane that contains functional viral glycoproteins. This viral

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envelope protects against extracellular degradation and allows for fusion with target cells, enabling virosomes to serve as vaccine delivery systems. Virosomes have been used in vaccines against influenza, hepatitis A, hepatitis B, and human papillomavirus.[7]

Metallic nanoparticles

Several metals have been incorporated into nanoparticle designs. Gold is widely studied for its favorable biomedical characteristics, including low toxicity, ease of bioconjugation with a variety of agents, and the ability to ablate tumors through the absorption of near-infrared light.[8] Nanosized particles of zinc oxide and titanium dioxide are used in inorganic sunscreens to reduce their chalky white appearance while maintaining broad-spectrum ultraviolet protection.[9] Silver nanoparticles have been investigated for their antiseptic effects.[10]

CAPSULE SUMMARY

- Nanotechnology—the study of particles sized smaller than 100 nm—is increasingly being investigated for use in dermatologic surgery.
- Current research shows the potential of nanoparticles in influencing treatments for melanoma and keratinocyte carcinoma as well as the development of novel surgical materials.

NANOPARTICLES IN THE TREATMENT OF SKIN CANCER

Nanoparticle drug delivery in the treatment of malignancy is based on the phenomenon of enhanced permeability and retention (EPR). The EPR effect describes the preferential localization of nanoparticles to cancer tissue, which occurs due to a tumor bed's high vascular density, increased permeability, and poor lymphatic drainage.[11] Whereas normal capillaries are lined by a tightly sealed endothelium and abundant pericytes, neoplastic vessels are characterized by an incomplete endothelial layer and poor pericyte coverage. Through the EPR effect, nanodrugs are able to deliver increased active drug payloads to the target tumor with reduced buildup in normal tissue.[12]

Melanoma

Despite the emergence of targeted therapies and immunotherapy, late-stage melanoma continues to be associated with low rates of survival. Nanoparticles hold a promising role in treatment agents through improved drug delivery. Although numerous animal studies have been conducted using nanodrugs in the treatment of melanoma, only recently have these efforts extended to clinical trials in humans.

Nab-paclitaxel (Abraxane; American BioScience, Santa Monica, CA) is a chemotherapeutic agent based on nanoparticle albumin-bound (nab) technology and is currently the most well-studied nanodrug for melanoma. Nab-paclitaxel, which has been approved by the United States Food and Drug Administration (FDA) for breast, lung, and pancreatic cancer, consists of nanosized particles of paclitaxel stabilized with human albumin. In a phase III clinical trial of patients with metastatic melanoma, 529 individuals were randomized to treatment with nab-paclitaxel (n = 264) or dacarbazine (n = 265).[13] Progression-free survival was significantly longer in the nab-paclitaxel group than in the dacarbazine group (4.8 months vs 2.5 months; P = .044). However, the difference in median overall survival did not reach statistical significance (12.6 months vs 10.5 months; P = .271). The most common grade ≥3 treatment-related adverse event with nab-paclitaxel was neuropathy, which occurred in 25% of participants. Of note, neuropathy is also a common, dose-related side effect of traditional paclitaxel treatment.

Nab-paclitaxel has also been studied in combination regimens. A phase II study of nab-paclitaxel combined with carboplatin evaluated responses in 41 chemotherapy-naïve and 35 previously treated patients with advanced melanoma. A response rate of 25.6% was achieved in chemotherapy-naïve patients, although the rate decreased to 8.8% in previously treated patients.[14] A phase I trial examining the combination of nab-paclitaxel, temozolomide, and bcl-2 antisense oligonucleotide (oblimersen) reported an objective response rate of 40.6% was achieved.[15]

Given the rising rates of melanoma and current dearth of highly effective systemic therapies, the need for novel treatments remains paramount. Nanotechnology is likely to become an increasing focus in clinical trials, particularly in conjunction with the growing number of immunotherapy agents, as the search for a therapeutic breakthrough continues.

Keratinocyte carcinoma

The overwhelming majority of skin cancers are categorized as keratinocyte carcinomas (KC), a group consisting of basal cell carcinoma (BCC) and

Abbreviations used:

5-FU:	5-fluorouracil
ALA:	aminolevulinic acid
BCC:	basal cell carcinoma
EPR:	enhanced permeability and retention
FDA:	Food and Drug Administration
KC:	keratinocyte carcinomas
MRSA:	methicillin-resistant *Staphylococcus aureus*
PDT:	photodynamic therapy
PLGA:	polylactic-co-glycolic acid
SCC:	squamous cell carcinoma
SLN:	solid lipid nanoparticle
ZnPc:	zinc phthalocyanine

squamous cell carcinoma (SCC). Current treatment options for localized KC include electrodesiccation and curettage, cryosurgery, topical immunomodulators, photodynamic therapy (PDT), radiotherapy, simple excision, and Mohs micrographic surgery.

Several nanoformulations of PDT photosensitizers have been studied in vitro and in vivo for KC.[16] PDT involves the photonic excitation of a photosensitizer in the presence of ambient oxygen, leading to the formation of reactive oxygen species and the destruction of diseased cells and tissues.[17] Two photosensitizers are available—aminolevulinic acid (ALA) and methyl aminolevulinate. Photosensitizers are topically applied to the treatment area, where the drug is allowed to accumulate within the tumor cells, followed by irradiation with light to activate the photosensitizer.

The hydrophobic nature of ALA leads to decreased uptake in neoplastic cells, which reduces the efficacy of ALA-PDT.[18] Nanoparticles can increase the solubility of hydrophobic drugs, allowing for greater accumulation in the tumor via the EPR effect.[19] In a novel approach, the delivery of ALA using poly(lactic-co-glycolic) acid (PLGA) nanoparticles has been examined through in vitro models of human SCC.[20] The PLGA-ALA nanoparticles were more effective than free ALA in achieving uptake and localization by SCC cells.[20] Building on these in vitro results, researchers studied this PLGA formulation in hairless mice with ultraviolet-induced SCC.[21] Results were consistent with the prior study showing that PDT with PLGA nanoparticles was more effective in treating SCC than PDT with free ALA of the same concentration.[21]

Zinc phthalocyanine (ZnPc) is a photosensitizer that has been investigated in the treatment of SCC.[22] In in vitro studies, ZnPc has been delivered on chitosan/methoxy polyethylene glycol-polylactic acid nanoparticles to study its efficacy in PDT.[23] The nanoparticle formulation increased dose-dependent growth inhibition of cancer cells and produced higher numbers of apoptotic cells and more reactive oxygen species compared with cells treated with free ZnPc.[23]

Nanotechnology has also been investigated in the use of topical immunotherapies, most notably 5-fluorouracil (5-FU). Topical 5-FU is commonly used to treat actinic keratoses and may also be used to treat superficial BCC. The variable success of topical 5-FU has been partly attributed to insufficient drug concentration and poor penetration through the skin.[24]

Several mechanistic studies using animal models with topical 5-FU semisolids have been completed.[25-27] One study observed the drug penetration of a 5-FU nanostructured lipid carrier-based hydrogel into murine skin. Researchers observed an initial burst, followed by a sustained release, leading to increased penetration and retention as well as decreased skin irritation.[26]

Building on the observation that malignant cells demonstrate increased uptake of albumin, the efficacy of nanocomposite spheres of PLGA carrying albumin and 5-FU has been examined in a mouse model.[28] By providing a sustained and controlled release of 5-FU to the target tissue, the nanodrug delivery system demonstrated superior efficacy in arresting tumor growth relative to local 5-FU injections.

The molecular genetics underlying the pathogenesis of BCC have recently become more elucidated, including the central role of the sonic hedgehog pathway.[29] One area of promise is a nanoparticle-encapsulated sonic hedgehog pathway inhibitor that has been studied in hepatocellular carcinoma, although not yet in cutaneous BCC. Through in vitro experiments, the nanoparticle-encapsulated inhibitor of the Gli1 transcription factor exhibited profound tumor growth inhibition and antimetastatic effects against hepatocellular carcinoma.[30]

In addition to their potential therapeutic role, nanoparticles have been explored for their utility in the imaging of SCC. Investigators in one study conjugated gold nanorods to cetuximab—an inhibitor of epidermal growth factor receptor—and delivered the compound topically.[31] Epidermal growth factor receptor is expressed on many tumor cells, particularly in SCC. The authors compared the uptake of these cetuximab-conjugated gold nanorods to nonconjugated control nanoparticles using a murine model of SCC. The conjugated nanorods led to higher contrast imaging and significantly increased pixel intensity (~2.5 times

greater than controls; $P < .05$). In future applications, such technology could provide dermatologic surgeons with real-time imaging of tumor margins during SCC resections.

Overall, the incorporation of nanotechnology in the treatment of KC remains in its preliminary stages and has yet to reach direct clinical application. However, the momentum toward noninvasive therapy options continues to drive its investigation through numerous avenues. In particular, nanoparticles appear poised to impact the development of PDT photosensitizers and topical drug delivery, offering hope for increased efficacy and applicability in superficial KC.

NANOPARTICLES IN SURGICAL MATERIALS

Wound dressings

Numerous nanoparticle formulations have been examined for use in wound healing. Thus far, silver-based materials have provided the most impressive results and are the only nanoparticle-based dressings to receive FDA approval in the treatment of acute and chronic wounds.

Silver nanoparticles demonstrate broad antimicrobial properties, including activity against *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas aeruginosa*.[32,33] In addition, the particles display antifungal and antiviral effects, such as activity against *Candida albicans* and HIV.[34,35]

Despite the antimicrobial benefits of silver products, classic ionic compounds are limited by their inherent cytotoxicity to host cells and tissue. Nanoparticle formulations circumvent this issue by allowing for a slower and more controlled drug release at the wound site.[36] In addition, silver nanoparticle products require less frequent dressing changes compared with ionic silver dressings, thereby decreasing trauma to the wound bed.[37]

Acticoat (Smith & Nephew, St. Petersburg, FL), an FDA-approved dressing for partial-thickness and full-thickness wounds, is the most widely studied nanocrystalline silver dressing. In a multicenter randomized clinical trial of 166 wounds in 98 burn patients, the nanocrystalline silver dressing led to significantly faster healing times than silver sulfadiazine (12.42 days vs 15.79 days; $P = .005$).[38] A recent meta-analysis compared nanocrystalline silver to alternative silver delivery systems (silver sulfadiazine or silver nitrate) in the treatment of superficial and deep partial-thickness burns and found that the nanoparticle design was associated with significantly fewer infections ($P = .005$) and surgical procedures ($P = .00001$) and with shortened hospital stays ($P = .00001$).[39]

Preclinical trials have examined nitric oxide and chitosan nanoparticles in wound treatment. Nitric oxide nanoparticles increased fibroblast migration and collagen deposition in wounded tissue.[40] The same nitric oxide–releasing nanoparticle platform was also used in a mouse model of MRSA-infected wounds, resulting in reduced bacterial burden and accelerated wound healing.[41] Separately, in a mouse model of MRSA-infected wounds, nitric oxide was conjugated to PLGA nanoparticles to create sustained and prolonged release, with results showing strong bactericidal efficacy against MRSA and accelerated wound healing.[42]

Chitosan, a partially deacetylated derivative of chitin, is valued as a tissue-engineering scaffold owing to its biocompatibility, biodegradability, and hydrophilicity. Chitosan has been incorporated into several marketed wound dressings and is now being examined in chemically modified nanofibril formulations, in addition to functioning as a component in some of the above-mentioned formulations.[40,41,43] Future clinical applications are likely to focus on this ability of dressings to serve as drug delivery systems, with the aim of releasing therapeutic agents or growth factors to improve wound healing in vulnerable patient populations (eg, patients with diabetes).

Tissue adhesives

Nanoparticles have been studied for use in tissue adhesives, which can function in addition to or in lieu of sutures and staples.[44] These nanoadhesives have gained attention for their ability to directly bind tissues, thereby improving mechanical strength and possibly reducing postoperative complications such as infection or exuberant tissue reactions. Silica nanoparticles have demonstrated the capacity to bind together polymer gels via a "nanobridging" effect—a function that, without nanoparticles, requires complex chemical reactions.[45] Investigators translated this work into the use of silica nanoparticles to successfully adhere 2 pieces of a calf's liver.[45]

Nanosilver-decorated mesoporous silica nanoparticles have been used to add the antibacterial effects of silver to the concept of nanobridging. In a mouse model of cutaneous wounds, these silver nanoparticle formulations achieved more rapid and efficient skin closure compared with sutures or mesoporous silica nanoparticles that lacked a nanosilver component.[46] Such findings may portend the next generation of nanoadhesives in aesthetic wound healing. Several other studies have corroborated the antibacterial potential of nanoparticles in tissue adhesives.[47-49] These results raise

the possibility that tissue adhesives might serve a dual purpose of wound support and prevention of infection, which would be especially useful, for example, in superficially dehisced wounds requiring reapproximation of their skin edges.

SPECIAL CONSIDERATIONS

At present, the amount of preclinical and in vitro experimentation into nanoparticle formulations vastly outstrips completed clinical trials, leading to a paucity of data on the long-term risks of systemic exposure. In particular, the unique physical properties of nanoparticles raise concern for possible toxicity. Nanoparticles possess greater surface area-to-volume ratios than larger particles, leading to heightened chemical reactivity and biological activity. As such, there exists a theoretical risk that systemic exposure may lead to increased adverse interactions with enzymes and other regulatory proteins or even chromosomal damage and genotoxicity.[50] The FDA remains actively involved in developing analytical tools and procedures to detect such occurrences. Given the unique biodistribution, pharmacokinetics, metabolism, and degradation of nanoparticles, thorough investigation will be needed for each translation into clinical practice.

CONCLUSIONS

Nanoparticles are likely to play an important role in future treatment algorithms for melanoma and KC. Current research supports their ability to adapt to the heterogeneity of cancer cells to enhance intracellular concentrations of chemotherapy agents and, consequently, their targeted cytotoxicity. As such, nanoparticle drug delivery systems represent a promising response to the demand for less invasive and more selective medicine, with a goal of curtailing the widespread cytotoxic effects of current systemic therapies and allowing for improved drug delivery in topical formulations.

In addition, applications of nanotechnology in surgical materials show potential in creating more durable adhesives and more effective wound dressings. These materials could have the ability not only to improve wound healing but also to deliver functional benefits such as robust antimicrobial activity.

With the support of greater clinical studies and experience, nanotechnology represents the possibility of a better, more targeted approach to a wide range of dermatologic surgical problems, potentially impacting the management of acute and chronic wounds and benign and premalignant lesions as well as KCs and their metastases.

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