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Evolving Role of Exosomes in Plastic and Reconstructive Surgery and Dermatology

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Summary: Exosomes, or extracellular vesicles, represent the latest cell-free addition to the regenerative medicine toolkit. In vitro preclinical studies have demonstrated the safety and efficacy of exosomes, which vary based on source and biomanufacturing, for a myriad of potential therapeutic applications relevant to skin and soft tissue reconstruction. Primary search was performed in September 2021 on the MEDLINE database via PubMed and Ovid, with focus on articles about therapeutic application of exosomes or extracellular vesicles. In total, 130 articles met criteria for applicability, including early-stage clinical trials, preclinical research studies with in vivo application, and articles applicable to plastic and reconstructive surgery and dermatology. Most studies used animal models of human disease processes, using either animal donor cells to isolate exosomes, or human donor cells in animal models. Exosome technology has catapulted as an acellular therapeutic vehicle with off-the-shelf accessibility. These features eliminate prior threshold for broad adoption of regenerative cell-based therapies into surgical and medical practice. To date, there are no exosome products approved by the US Food and Drug Administration. This review highlights exosomes as the new frontier in regenerative medicine and outlines its preclinical therapeutic applications for cutaneous repair and restoration.
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INTRODUCTION

Exosomes, or extracellular vesicles (EVs), are formed by the endosomal system and function through paracrine (cell-to-cell) signaling after release into the extracellular space (Fig. 1). The cell-of-origin influences its composition and offers both diagnostic and therapeutic potential. Exosomes are packaged with tetraspanin surface markers to drive cell entry in tandem with various RNA, miRNA, siRNA, cytokines, and enzymes that are encased in a lipid bilayer membrane to prevent extracellular degradation. Exosome formation begins with maturation of early endosomes to multivesicular bodies followed by invagination of the endosomal membrane. Nanoscale size of exosomes allows for diffusion throughout tissues. Biological macromolecules can be trafficked and loaded into exosomes of endogenous cells, including proteins (eg, growth factors and enzymes) and nucleic acids (eg, mRNA and miRNA).[1] These macromolecules convey a biological effect on the recipient cell type via agonistic and/or antagonistic signaling.

As endogenous exosome cargo reflects parent cell type and function, it is important to consider the exosome source when characterizing inner cargo. Each exosome-based therapeutic requires individual characterization for clinical translation[2,3] When considering exosomes for therapeutic use, it is important to positively identify proteins contributing to the mechanism of action. In the authors' experience, identification of antioxidant enzymes and proangiogenic cytokines contained within platelet exosomes have been essential for their therapeutic utility.[4] Efforts to standardize exosome manufacturing purity, potency, and batch consistency are warranted to eliminate dose-to-dose variability and realize their full therapeutic potential (Fig. 2).

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METHODS

Primary search was performed in September 2021 on the MEDLINE database via PubMed and Ovid with focus on articles about clinical application of exosomes or EVs. Medical Subject Headlines were used, including the terms "exosome," "multivesicular body," "extracellular vesicle," and "clinical application" (authors involved in search: I.M. and E.E.W.). Primary search resulted in 1280 articles. These results were filtered for clinical trials within the last 10 years. Article titles and abstracts were screened for applicability including clinical trials, studies with in vivo application, and articles applicable to plastic and reconstructive surgery and dermatology. In total, 130 articles met the criteria and were summarized. Screened articles were variable in design, methods, execution, and results. There remains a paucity of data on therapeutic interventions in human clinical trials. Most studies utilized animal models of human disease processes, using either animal donor cells to isolate exosomes, or human donor cells in animal models. (**See table, Supplemental Digital Content 1,** which displays descriptive summaries of included studies on EVs. These studies provide comparative analysis of regenerative outcomes from preclinical and clinical analysis of acellular treatments in 2D cell culture, mouse, rat or human models. **http://links.lww.com/PRSGO/D428**.)

Wound Healing

Wound management remains a mainstay of surgical practice. Exosomes offer a new frontier in wound care, including chronic nonhealing wounds and scar improvement. Exosome-mediated intercellular communication influences many functions within the skin and has been demonstrated to have a role in chronic inflammatory skin disorders.[3] For example, adipose-derived mesenchymal stem cell (MSC) EVs are implicated in mechanisms of wound healing, including enhanced collagen production,[5] angiogenesis,[6] cellular proliferation and migration,[7] skin barrier repair, reduced inflammation, and extracellular matrix remodeling.[8]

Takeaways

Question: What is the evidence behind emerging exosome therapy?

Findings: Across 130 publications in our PubMed review of the literature, the type of exosome can greatly vary based on source (eg, mesenchymal stem cells or platelets), and exosome isolation method. The types and success rates in early preclinical models varied based on disease condition. Evidence on therapeutic use is sparse due to lack of Food and Drug Administration approval to date.

Meaning: Exosome therapy is an emerging area of regenerative medicine that offers potential to restore skin structure and function. Clinical studies are in progress for validation.

MSC exosomes and associated miRNAs have an important role in migration and proliferation of fibroblasts and endothelial cells throughout the stages of cutaneous regeneration.[9] Certain umbilical cord MSC exosomes were found to suppress myofibroblast differentiation by inhibiting TGF-β/SMAD2 during wound healing.[10] Skin treated with MSC exosomes resulted in improved reepithelization, collagen maturation, myofibroblast formation, and reduced scarring from burn injuries.[11,12] Topical adipose MSC exosomes following fractional CO_2 laser for facial acne scarring demonstrated efficacy. In a prospective, randomized, double-blinded study, 25 patients received multiple laser treatments followed by posttreatment regimen of adipose MSC exosomes on one side of the face, and control gel on the contralateral side. Exosome-treated sides demonstrated significantly greater improvement in échelle d'évaluation clinique des cicatrices d'acné (ECCA) acne scarring grade, compared with controls. They also demonstrated milder erythema and shorter posttreatment recovery.[13] Platelet exosomes as a topical postprocedure skincare have demonstrated reduction in post-CO_2 laser crusting, erythema, and

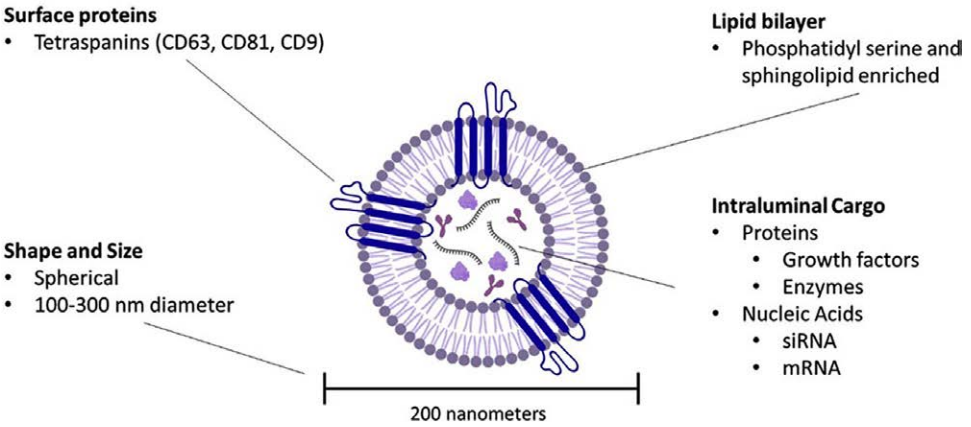

Fig. 1. Key components of exosome structure. Exosomes are composed of a lipid bilayer shell decorated with transmembrane and surface proteins. Biomolecular cargo (eg, proteins and nucleic acids) are selectively loaded into the intraluminal space for extracellular trafficking. siRNA: small interference RNA; mRNA: messenger RNA.

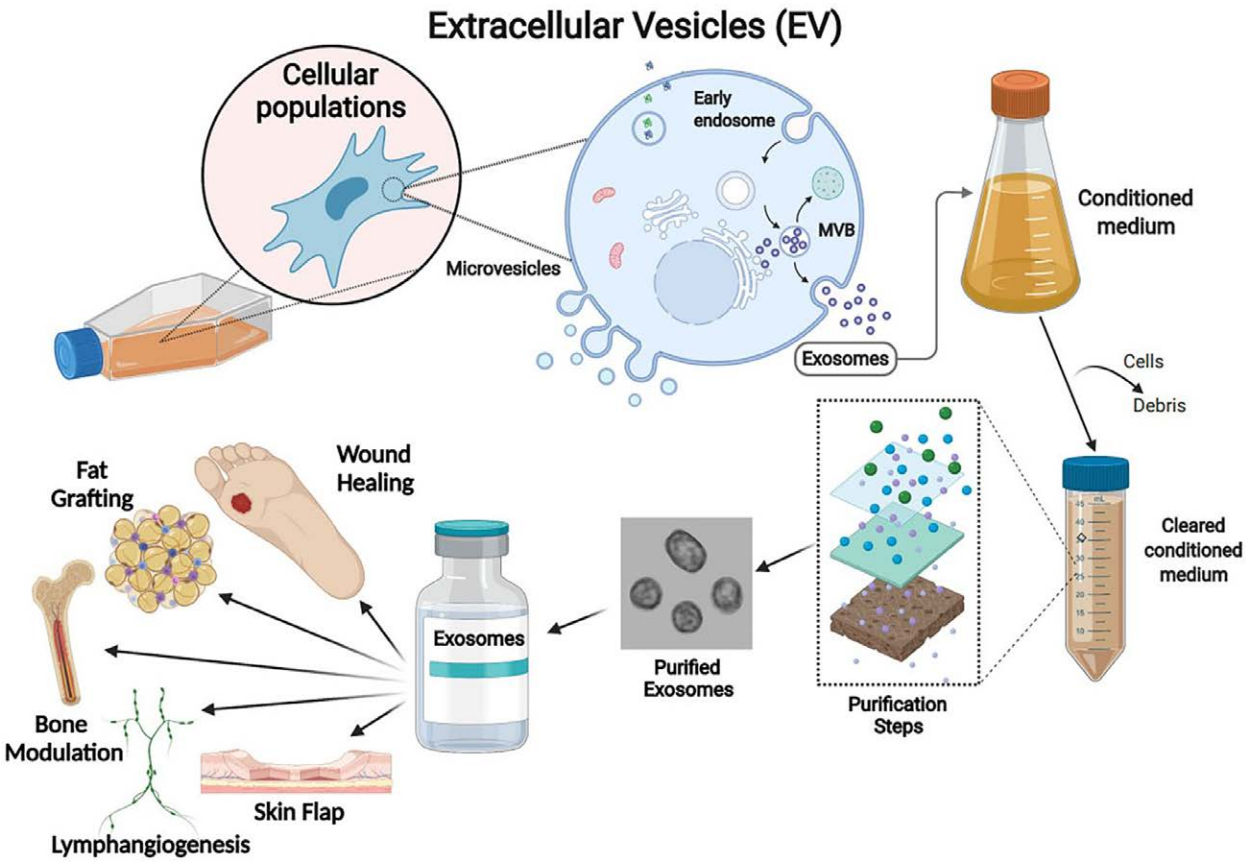

Fig. 2. Overview of extracellular vesicles. Extracellular vesicles, specifically exosomes, are carriers of biomarkers that can vary based on their origin, composition, purpose, and methods of isolation. A detailed understanding of isolation and analysis methods is required to allow the use of exosomes in the clinical setting for wound healing, fat grafting, bone modulation, lymphangiogenesis, and skin flap reconstruction.

recovery.[14] Furthermore, a murine wound model with human adipose MSC exosomes had improved healing via upregulation of lncRNA H19, miR-19b, and SOX9 axis.[15] Human bone marrow MSC exosomes stimulated with magnetic nanoparticles and a static magnetic field (mag-BMSC-Exo) accelerated wound healing, narrower scar width, and increased angiogenesis.[16] Epidermal stem cell-derived exosomes improved rate of wound healing and reduced scar formation in a rat model by downregulating TGF-β1 by downstream effects on myofibroblast differentiation and reduced expression in dermal fibroblasts.[17] Human bone marrow MSCs and engineered synthetic exosome-like liposomes improved wound healing in mice through increased blood vessel density in granulation tissue.[18] Another study showed dose-dependent improvement in wound closure on full thickness rat wounds with human amniotic fluid MSC exosomes with improved collagen organization.[5] Na et al showed improved wound healing closure with upregulation of MMP-1, extracellular matrix proteins, and type I collagen.[19] Human bone marrow MSC–cultured media injected intraperitoneally to rats with burn wounds demonstrated increased epidermal and dermal volume, as well as reduced inflammatory cells.[20]

Chronic wounds remain a challenge; hyperglycemia, chronic vascular changes, biofilm formation and increased oxidative stress contribute to decreased potential for wound healing. Enhanced wound healing was documented in polyvalent exosomes purified from apheresis platelets (PEP), driving angiogenic and wound healing events in a rabbit ischemic wound model.[21] This study highlights the key mechanisms by which exosomes contribute to soft tissue healing, including antioxidant activity, induction of mitogenesis, induction of angiogenesis, and immune modulation.

Exosomes retain characteristics from their cell-of-origin and undergo changes in cargo due to external factors, including metabolic stress. This offers another avenue to tailor them for a specific therapeutic goal. Approaches for mass exosome scalability toward customized therapeutic targets will be instrumental in advancing the utility of regenerative biotherapies for wound healing.

Fat Grafting

Numerous clinical studies demonstrated the positive effects of fat grafting[22] on recipient tissues from volumizing to improving skin quality in the setting of radiation, burns,[23] and scars.[24] Fat grafting has unpredictable

retention rates due to graft resorption as related to local ischemia,[25] processing, and factors such as body mass index[26] and tissue handling and processing. Attempts to improve graft survival led to the introduction of cell-assisted lipotransfer, improving graft retention for small volumes.[27] This concept was based on the principle that fat grafts enriched with adipose MSCs would improve graft survival through neovascularization and tissue regeneration via paracrine signaling, creating a suitable microenvironment for cell survival. Heterogenous cell populations within adipose stromal vascular fraction contribute variably during the process of neovascularization and are not yet fully elucidated.[28] A paradigm shift from cell-assisted lipotransfer to understanding the adipose MSC secretome is underway, and exosomes are at the forefront. Cell-based therapies are limited by risk of uncontrolled differentiation, hence the interest in cell-free and storage-friendly alternatives.

As a cell-free alternative, adipose MSC exosomes have been used in fat grafting to promote neovascularization and enhance graft survival.[29] Mice fat grafted and treated with either hypoxia or normoxia-derived exosomes showed improved neovascularization in the hypoxia-derived group via upregulation of VEGF/VEGF-R and ANG-1/Tie2.[30] A 2021 systematic review showed higher graft retention rates in EV-enriched fat grafts compared with untreated groups. Graft retention rates were similar following EV and MSC treatment,[31] although MSC EVs resulted in reduced inflammation, earlier revascularization, and improved fat graft integrity.[32] Han et al evaluated grafted fat in mice in four quadrants, with each quadrant treated differently. Grafts treated with hypoxic preconditioned adipose MSC exosomes were evaluated by laser Doppler for neovascularization. Hypoxic preconditioned adipose MSC exosomes and normal conditioned exosomes had significantly higher weight than control groups; hypoxic adipose MSC exosomes superseded normoxia conditioned exosomes at 8 weeks. Exosome groups had less fat necrosis, more homogenous lipocytes, and increased perfusion,[32] suggesting that therapeutic effector of stem cells is its exosomal paracrine output. Exosome therapy optimization may preclude the need for stem cell-based therapy as a modality to achieve optimal outcomes.

Flap Viability

Exosomes offer a new modulating factor to increase proangiogenic gene expression, increasing vascularization of free tissue transfer. Superficial inferior epigastric vessel flaps elevated on rats were ligated for 6 hours to produce an ischemia-reperfusion flap model. Following ischemia, flaps were injected with H_2O_2-preconditioned adipose MSC exosomes, normal adipose MSC exosomes, or controls. Flap survival and capillary density were significantly increased with decreased apoptosis and inflammation in the H_2O_2-preconditioned exosomes as compared with other methods.[33] Pectoral skin flaps elevated on the right long thoracic artery were then subject to three hours ischemia then injected with adipose MSC exosomes with IL-6 expression. The experimental group had a smaller inflammatory area and increased epithelialization and skin appendages as compared with the control group. IL-6 silenced models showed decreased flap recovery.[33] Xiong et al used a prefabricated artificial dermal flap, which are prone to necrosis due to poor vascularization; adipose MSC and adipose MSC-exosome treatment significantly increased flap thickness and collagen as compared with human foreskin fibroblast cells (HFF) and HFF-exosome groups.[34] Tetraspanin structure of exosomes facilitate cellular entry and foster rapid induction of antioxidant, immunomodulatory, and pro-vasculogenic events. Exosome-mediated flap viability provides a unique roadmap for critical pathways required to tailor exosome-based therapies.

Nerve Regeneration

Peripheral nerve injuries can be life-altering events, often with limited reconstructive options and less-than-ideal outcomes. Multiple in vivo studies have demonstrated improved nerve regeneration in exosome-treated animals modeling peripheral nerve injury. Rau et al isolated exosomes from interscapular brown fat of mice and purified in adipose MSC media in the presence or absence of the immunosuppressive nerve enhancing drug (FK506). Nerve injury, as modeled by sciatic nerve compression in mice, was treated with topical adipose MSC exosomes and assessed for regenerative capacity. adipose MSC exosomes without FK506 versus adipose MSC exosomes pretreated with FK506 had similar nerve regeneration including significantly larger nerve fiber width, axonal width, fiber area, myelin area, and total fiber area.[35] Sciatic nerve injury models in rats were randomized into various treatment groups: graft conduit, graft conduit with control exosomes, graft conduit with exosomes with neurotrophic factor 3 (NT3), and autologous grafting. Engineered exosomes with NT3 graft conduit produced mRNA in stem cells and significantly promoted nerve regeneration and improve functional recovery of gastrocnemius muscles as compared with control.[36] In another study, unilateral 10-mm sciatic nerve defects in rats were reversed. Specifically, rats were randomized to autograft, autograft with fibrin glue, and autograft with fibrin glue impregnated with a platelet-derived exosomal product (PEP). Isometric tetanic force and axonal diameter was significantly improved in the exosome-treated group. GAP43, a cytoplasmic nervous tissue protein, had significant upregulation in the treatment group.[37] In a similar peripheral nerve injury rat model, bone marrow MSC exosomes were injected into rat gastrocnemius muscle at different doses and evaluated for sciatic nerve function, latency of thermal pain, number, and diameter of regenerated fibers distal to the injury. Treatment groups had a significant increase in peripheral nerve diameter and regeneration of myelinated nerve fibers, superior latency of thermal pain, and improved gait. There was also a dose-related effect between the number and diameter of regenerated myelinated fibers; however, it did not correlate with improved functional regeneration.[38] Bucan et al evaluated exosomes on neurite outgrowth using a similar sciatic nerve injury model in rats. Adipose MSCs harvested from rats were injected proximal and distal to the site of injury.

The exosome treatment group demonstrated increased number and branching points but did not reach significance compared with control. The exosome group had a larger number of regenerated fibers (40% higher) compared with control.[39]

Bone Modulation

Exosomal-induced bone regeneration is another new frontier in regenerative medicine with the potential to revolutionize the approach to bone reconstruction. As with standard paracrine signaling, MSC exosomes can be signaled and mediated towards osteoblastic differentiation. Osteoblasts are further directed to increase proliferation and synthesis of pro-osteogenic factors responsible for new bone formation. Tendon injuries also face similar challenges. Huang et al injected bone marrow MSC-derived exosomes into rats that underwent rotator cuff reconstruction. Exosome-treated rats had increased angiogenesis and breaking load, which exhibited improved tendon-bone growth.[40] Ren et al recently showed that platelet-derived purified exosomes (PEP) in a rodent model of rotator cuff (supraspinatus tendon) injury accelerated tendon-bone healing. Qin et al created two 5-mm calvarial defects in rats; one treated with control hydrogel, and the other treated with extracellular vesicle hydrogel. EV-treated wound defects, as evaluated by microCT, demonstrated significant increase in bone formation via upregulation of miR-196a, with downstream effects on ALP, OCN, OPN, and Runx2.[41] In addition, studies of multiple myeloma have demonstrated preferential osteoblast and osteoclastic activity by exosome signaling. In contrast to soft tissue regeneration, bone formation has unique prerequisites to drive progenitors towards an osteogenic program. Effective bone-forming exosomes mandate selection and priming of ideal packaging cellular system as well as upregulation of key signaling elements to efficiently drive these molecular events.

Lymphangiogenesis

Lymphedema continues to be a significant postsurgical problem despite breakthroughs in surgical treatments. Lymphangiogenesis plays a vital role in tumor progression in cancer. Exosome-derived noncoding RNAs mediate posttranscriptional regulation and affect gene expression. Formation of new lymphatic vessels facilitates tumor spread in mice. Lymphatic enlargement increases the diameter of lymphatic vessels and facilitates nodal metastasis. Vascular endothelial growth factor (VEGF) pathways are considered the primary signaling mediators in lymphangiogenesis and lymphatic remodeling.[42] Melanoma-derived exosomes facilitate lymphatic remodeling that creates a pro-metastatic microenvironment.[43] The ability to monitor lymphangiogenesis markers, and the future potential of therapeutic targets to modify lymphatics could change our approach from cancer to regeneration.

Biomarkers and Other Applications

Exosomes have been widely studied as biomarkers for various disease processes, from cognitive disorders to malignancies. A systematic review encompassing 921 breast cancer patients in 11 studies showed association of exosomal biomarkers and relation to tumor recurrence, distant organ metastasis, and chemotherapy resistance with expression of certain exosomal proteins.[44] A similar systematic review and meta-analysis on solid tumor exosome biomarkers, which pooled data from 28 studies with 4017 patients with solid tumors, including breast cancer, showed a 0.74 sensitivity and 0.81 specificity for solid tumors; urinary system tumor exosomes had higher diagnostic power.[45] A meta-analysis of differential exosomal miRNA expression and prognosis of cancer patients showed that high exosomal miR-21 expression was associated with poor overall survival. Furthermore, miR-21, miR-451a, miR-1290, and miR-638 strongly predicted prognosis in solid tumors and possibly to treatment response.[46] Ono et al demonstrated metastatic breast cancer suppression in a murine model via an exosome-mediated overexpression of miR-23b, as well as a decreased resistance to doclitaxel.[47] High circulating levels of EV-associated-TGFβ3 correlated with poor response to chemoradiation therapy in head and neck squamous cell carcinoma. Head and neck squamous cell cancers were sensitized to chemotherapy in vitro by silencing TGFβ3.[48] Numerous studies look at biomarkers for cognitive impairment and Alzheimer disease,[49–53] malignancies,[54,55] coagulopathy associated with cancer cell-derived exosomes,[56] graft and transplant,[57,58] and diabetic nephropathy.[59] Other disease processes have been studied in regard to their effect on exosomal production.[60]

Exosome Production and Stability

Exosome source and production conditions are important for evaluated EV therapeutics. EVs reflect phenotype and condition of their derived cells, including cargo and downstream effect.

The field gained an appreciation for the utility of MSC-derived EVs throughout the rapid adoption of MSCs as a therapeutic approach within the last two decades.[61] MSCs have been used extensively in clinical studies, although cGMP scale-up of MSC cultures has proven difficult to achieve at the scale required to support clinical efforts.[62] Culture systems produce heterogenous MSC populations within systems and lot-to-lot variability.

Well-characterized cell lines and validated cell culture systems can mitigate heterogeneity.

Using robust quality control assays to release the final EV product is important; however, their development has proven challenging.[63] The International Society for Extracellular Vesicles provides guidance on types of characterization and assays that may be appropriate for EV-based products.[64] Additional characterization of surface marker decoration and cargo identification allows for the link between exosome particle and EV. Surface marker and cargo profiles provide a link to parent cell type and help confirm target population isolation. From a functional standpoint, potency assays linked to mechanism are important to verify product stability. Most importantly, lot-to-lot consistency should be demonstrated.

Several methods have been developed for storage and preservation of isolated exosomes. Storage conditions in

a refrigerated liquid state (2˚C–8˚C) and frozen (−20˚C) or ultracold (−80˚C) conditions have shown altered exosome structure, leading to degradation.[65,66] Further, the need for frozen or ultracold storage and transport render distribution and administration challenging. Generating a stabilized, lyophilized powder containing isolated exosomes provides a room temperature-stable final drug product preserving exosome integrity and stability (Rion, Inc., data on file).

DISCUSSION

Exosomes are an exciting new frontier in regenerative medicine and surgery with exponential growth in basic and translational research. Exosome technology offers an acellular, off-the-shelf, stable, therapeutic option for the modern surgical toolkit. There are over 200 registered studies on ClinicalTrials.gov concerning exosomes as of September 2021.[67] Yet, to date, there are no Food and Drug Administration–approved exosome therapies for clinical indications. Exosomes have thus far avoided ethical and logistical barriers that have limited the actualization of stem cell therapies. As the medical community witnessed the hype associated with stem cell tourism, caution must be executed to avoid this path for exosome technology.[68] As therapeutic targets and manufacturing requirements can be sufficiently defined in nonliving biologics, the hope for this new nanomedicine is that regenerative medicine practitioners will adopt an evidence-based approach to realize the benefit.

Current literature shows promise for plastic and reconstructive surgery and dermatology applications, including skin care[69] and cutaneous wound healing[70] (eg, chronic diabetic wounds), bone regeneration, flap viability, and nerve regeneration. Enhancing exosome properties can meet patient needs beyond the one-size-fits-all application to complex problems faced by today's plastic surgeons and dermatologists. Indeed, it is important to recognize the risk with exosome therapy based on source, such as the high risk of chromosomal changes in MSC cultures that can underpin a pro-oncogenic exosome when derived from MSCs in culture for numerous cell-doubling events.[71] Additional Food and Drug Administration–regulated studies for safety and efficacy are needed to develop regulatory guidelines. Much remains to be elucidated before realizing the reality of exosome therapy. Today, we recognize that the foundational research has burgeoned and demonstrates an exciting addition to the reconstructive and cosmetic elevator of plastic surgery and dermatology.

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DISCLOSURES

Dr. Rohrich receives instrument royalties from Eriem Surgical, Inc., and book royalties from Thieme Medical Publishing; is a clinical and research study expert for Allergan, Inc., Galderma, and MTF Biologics and a medical monitor for Merz North America; and owns Medical Seminars of Texas, LLC. Dr. Behfar is the founder and on the board of directors for Rion, Inc. Dr. Paradise is an employee of Rion, Inc. Dr. Wyles is consultant for Rion, Inc. Dr. McGraw and Erin Wilson have no financial interest to declare in relation to the content of this article.The authors have no financial interest to declare in relation to the content of this article.

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