Scientific journal of Material Science & Engineering
ISSN 2688-5379

Hypothesis Open Access

Delivery of doped mesoporous bioactive glass nanoparticles and adipose-derived stem cells via electrospun nanofibrous silk fibroin membrane to accelerate chronic wound healing by enhancing angiogenesis

Ali Nosrati[1], Reza Aramideh Khouy[2], Mohammad Khodaei[3], Mehdi Banitalebi-Dehkordi[4], Korosh Ashrafi-Dehkordi[4], Zohreh Alizadeh[5, 6], Hamed Nosrati[7*]

[1] School of Mechanical Engineering, College of Engineering, University of Tehran, Tehran, Iran
[2] Department of Virology, Iran University of Medical Sciences, Tehran, Iran
[3] Department of Materials Science and Engineering, Golpayegan University of Technology, Golpayegan, 8771765651, Iran
[4] Department of Molecular Medicine, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran
[5] Department of Anatomy, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[6] Endometrium and Endometriosis Research Center, Hamadan University of Medical Sciences, Iran
[7] Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran

***Corresponding Author: Dr. Hamed Nosrati,** Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran.
E-mail: hamednosratibio@gmail.com, **Tel:** +989365643274

Citation: Delivery of doped mesoporous bioactive glass nanoparticles and adipose-derived stem cells via electrospun nanofibrous silk fibroin membrane to accelerate chronic wound healing by enhancing angiogenesis. Sci J Mat Sci & Eng.2020; 2(2); 01-08.

Submitted: 07 October 2020; **Approved:** 10 October 2020; **Published:** 12 October 2020

ABSTRACT

One of the most challenging problems in skin tissue engineering is the development of functional vascularized networks in wounded tissues. In this regard, improving angiogenesis is considered to be effective for the regeneration of the skin during wound healing. Therefore, different strategies have been developed to induce angiogenesis in skin tissue engineering. Using stem cells and delivery of angiogenic nanomaterials via a biocompatible scaffold are examples of these strategies. Adipose-derived stem cells could not only differentiate into endothelial and epithelial cells under appropriate conditions, but could also secrete angiogenic growth factors such as vascular endothelial growth factor, basic fibroblast growth factor and hepatocyte growth factor that induce angiogenesis in ischemia injury models. Bioglass nanoparticles are potent nanobiomaterials to improve angiogenesis in chronic wound healing. Because the wound healing process depends on the quality of newly formed blood vessels, recent interest in bioglass nanoparticles has increased dramatically. Adding some of the metallic ions (e.g., Co2+, Cu2+, Eu3+, Mg2+ and Nb5+) to the structure of bioglass nanoparticles could enhance their angiogenic properties. We purpose that delivery of doped mesoporous bioactive glass nanoparticles and adipose-derived stem cells via electrospun nanofibrous silk fibroin membrane as a scaffold would improve chronic wound healing by enhancing angiogenesis.

Keywords: Doped bioactive glass, adipose-derived stem cells, silk fibroin, chronic wound, wound healing

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Background

Skin is known as the body's largest organ and also the first defensive barrier against foreign agents and microbial invasions. It also retains body fluids, controls temperature, and detects external stimuli. Thus, when the skin is severely damaged, human health and life will be at risk. Chronic wounds often have severe scarring and inflammation, and it takes up to three months to heal (1). In recent years, different strategies have been developed for the treatment and healing of chronic wounds. The most successful clinical strategy is skin autograft, which is considered the gold standard for wound treatment. Despite all of the advantages of this method, including the lack of immunogenicity, there are limitations. Slow rate of dermis regeneration, pain, hair regeneration and pigmentation disturbance are reported post-surgery problems at the donor site. Therefore, alternative approaches are needed to overcome these issues (2, 3).

One of the strategies is to use engineered structures, such as engineered scaffolds with or without cells that can imitate the extracellular matrix (ECM) of the native tissue. Such scaffolds could provide a suitable microstructure similar to the ECM for cells to proliferate, migrate and differentiate (4). Various elements and factors, such as ions, nanoparticles and growth factors, could be incorporated into these scaffolds to give them advantages such as angiogenic properties (5).

Wound healing is a complex multi-step process. In the first step, a clot plugs the wounded site. The repair and regeneration of the area would then continue with the formation of granulation tissue due to the introduction of fibroblasts, capillaries and immune cells into the clot. The edge of the wound would be aggregated and the epidermal layer would cover the surface of the wound (6). Angiogenesis plays a critical role in this process. In brief, angiogenesis implies the formation of new capillaries from pre-existing vessels to create a complex network of blood vessels. Angiogenesis at the wound site provides more nutrition through blood flow and improves the healing process. Many strategies to improve skin regeneration are based on stimulating and promoting angiogenesis (7).

Hypothesis

It is assumed that adipose-derived stem cells (ADSCs) delivered via electrospun nanofibrous silk fibroin membrane may have the potential to proliferate efficiently and differentiate into different cells such as epithelial and endothelial cells in the presence of doped bioactive glass nanoparticles (BG-NPs). Doped BG-NPs could also stimulate the production of various angiogenic cytokines that lead to angiogenesis. In addition, an incorporated nanofibrous scaffold could offer numerous benefits for the delivery of stem cells to the wounded area, as it provides a framework to support their regenerative capacity. Therefore, local delivery of ADSCs via an incorporated nanofibrous electrospun membrane with angiogenic properties could effectively accelerate the process of chronic wound healing by improving angiogenesis and re-epithelialization.

Evaluation of the hypothesis

Differentiation of ADSCs

ADSCs have shown many interesting advantages over other available stem cells. They are abundant and could easily be isolated from liposuction aspirates and cultured in vitro. They also maintain multipotent differentiation potential with aging. Many studies have shown the potential of ADSCs for differentiation in tissue engineering and regenerative medicine applications (8, 9). A number of studies have demonstrated that ADSCs provide a potent source for bone regeneration (10, 11). An investigation by Cowan et al. showed in vivo osteogenic capability of apatite-coated PLGA scaffolds seeded with ADSCs to heal critical-size mouse calvarial defects. The results revealed the differentiation of ADSCs into osteoblasts resulting in significant intramembranous bone formation after 2 weeks of implantation (12). Furthermore, some studies have shown that ADSCs could be a cell source for cornea regeneration due to their differentiation into corneal endothelial-like cells and functional keratocytes (13). Other studies have demonstrated the capacity of ADSCs to differentiate into other lineages, including chodrogenic, myogenic, epithelial, endothelial, etc., under appropriate conditions (14-18). We highlight the point whether ADSCs can improve wound healing by differentiating into epithelial and endothelial cells.

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A study conducted by Cao et al. revealed that ADSCs expressed endothelial markers in the presence of vascular endothelial growth factor (VEGF) in vitro, while ADSCs could differentiate into endothelial cells and play a role in angiogenesis in responding to local signals (19). Another related study by Lu et al. indicated that ADSCs improve the blood supply of skin flaps through differentiation into endothelial cells (20). It has also been shown that the multipotent ADSCs population tends to be closely associated to the perivascular cells (21). Endothelial cells differentiated from ADSCs may play a critical role in the formation of new vessels to ensure the enhanced viability of ischemia tissues.

All-trans-retinoic acid has been demonstrated to induce cytokeratin-18 expression in ADSCs and to almost abolish vimentin expression, indicating that ADSCs also have epithelial potential (22). Further studies by Yan et al. showed the differentiation of ADSCs into epithelial cells in the presence of epithelial growth factor (EGF), fibroblast growth factor (FGF) and all-trans-retinoic acid in the epithelial differentiation culture medium (23). It is therefore possible, based on the studies mentioned above, that ADSCs have the potential to be induced into epithelial and endothelial cells under appropriate conditions.

Angiogenesis of ADSCs

One of the evidence supporting the idea of angiogenic capacity of ADSCs is their potential to differentiate into endothelial cells, as discussed earlier. Apart from being able to differentiate into other cell types, ADSCs secrete angiogenic growth factors, including VEGF, basic fibroblast growth factor-2 (bFGF) and hepatocyte growth factor (HGF) (24-26). VEGF is the most significant angiogenesis stimulating factor. The main role of VEGF is to stabilize the vascular system through the development of new blood vessels networks (27). bFGF is one of the most studied cytokines in angiogenesis investigations. As a result of its effects on smooth muscle and endothelial cells, bFGF stimulates angiogenesis as well as its function as a chemo-attractant and aids in the proliferation of fibroblasts and epithelial cells (28). It also has a critical function in the self-renewal of ADSCs (29). Folkman and Klagsbrum reported in vitro proliferation of endothelial cells treated with bFGF in 1987 (30). In vivo angiogenic properties of bFGF were then studied by different researchers in chick embryo chorioallantoic membranes (CAM) and rodent corneas (31, 32). bFGF also has an indirect role in inducing angiogenesis by enhancing VEGF expression (33). HGF is another important endothelial growth factor with mitogenic and angiogenic effects (34). Cai et al. have demonstrated that Suppression of HGF production impairs the ability of ADSCs to improve ischemic tissue re-vascularization (35).

In conclusion, the results of these related studies may support the angiogenic role of ADSCs due to the secretion of angiogenic growth factors.

Doped mesoporous BG-NPs angiogenic properties

BG is a series of designed silica-based glasses where the 3D SiO2 network is modified by adding CaO, Na2O and P2O5. By mixing the different ratios of these four oxides, various BGs have been produced. Additional oxides or ions may also be used to improve specific therapeutic function (36).

In recent years, BG-NPs have been widely studied for potential applications in the fields of tissue engineering and regenerative medicine due to their ability to improve angiogenesis and osteogenesis (37, 38). Doped mesoporous BG-NPs have attracted a great deal of interest, as their ion dissolution products have been recognized to enhance angiogenesis, which plays a critical role in wound healing process. In this respect, the basic composition of BGs has been modified using additives or dopants, usually metallic ions such as Zn2+, Co2+, Cu2+, Mg2+, Ag+, Sr2+, and F–. The presence of these metallic ions in the BG structure is an important factor making them angiogenesis stimulators, antibacterial agents, and anti-inflammatory agents (39) (Fig. 1).

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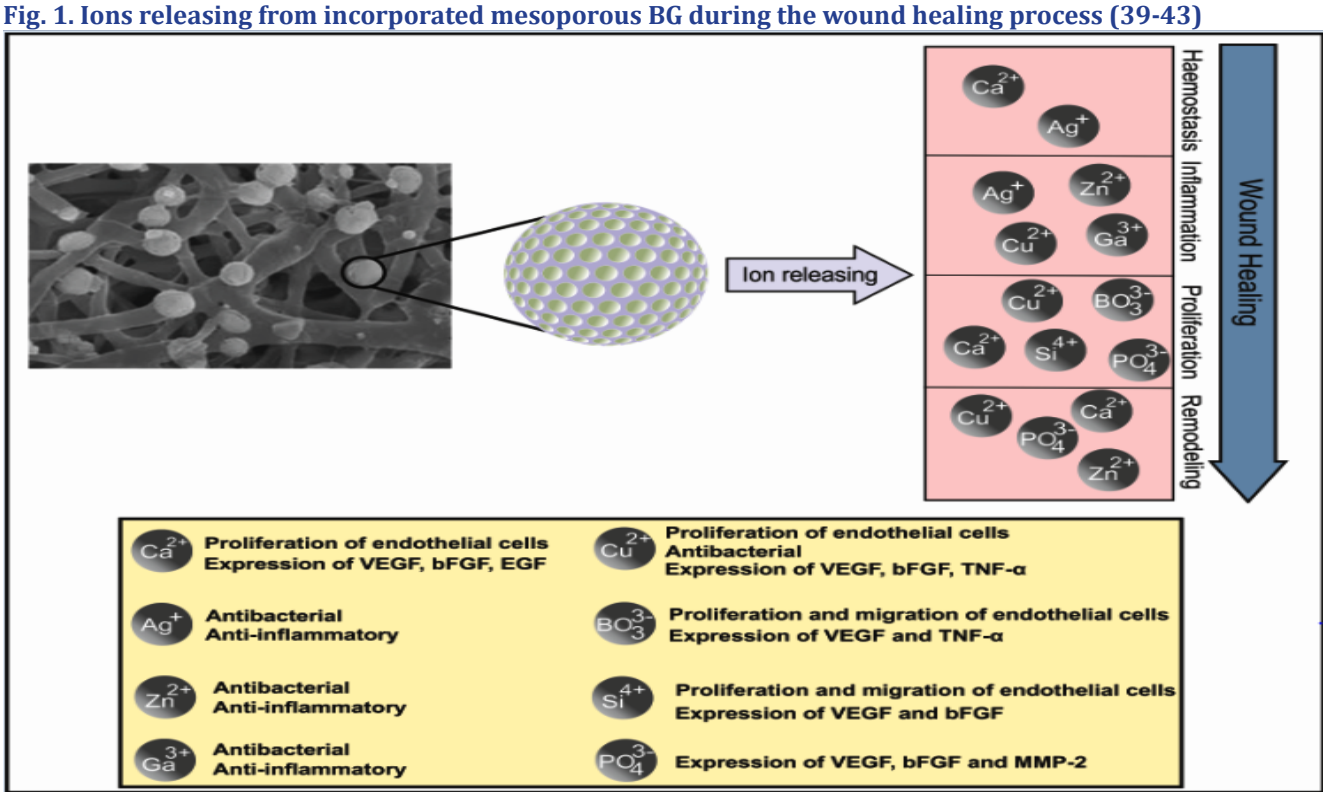
Fig. 1. Ions releasing from incorporated mesoporous BG during the wound healing process (39-43)



Among these ions, Co2+ and Cu2+ have been known as strong angiogenesis enhancers. Cu2+ regulates many factors involving in angiogenesis process including angiogenin, VEGF, prostaglandin E-1, fibronectin, caeruloplasmin, collagenase, and bFGF which play critical roles in initiation, maturation and regulation of blood vessel formation (44, 45). Bührer et al. revealed that copper-doped 45S5 BG promotes angiogenesis in the rat arteriovenous loop model compared to 45S5 BG (46). In this regard, Zhao et al. showed that copper-doped borate-based BG can induce the migration of human umbilical vein endothelial cells (HUVECs), VEGF secretion, and angiogenic genes expression (47). It has been shown that Co2+-containing BG increase angiogenesis by activating HIF-1a regulatory pathway. Activation of the HIF-1a pathway leads to overexpression of proteins involved in angiogenesis, such as VEGF (48). Kargozar et al. demonstrated that adding Co2+ ions to BGs is an effective way to enhance angiogenesis in vitro and in vivo (49).

In addition to the ions discussed above, it has been shown that the incorporation of Eu3+, Mg2+ and Nb5+ and into BG-NPs can also improve angiogenesis (39). Table 1 summarizes some of the BGs that can induce angiogenesis.

Table 1. Angiogenic BGs in biomedical applications (42, 50-54)

Angiogenic Element	*BG Type*	*In vitro (cell type)*	*In vivo (animal model)*	*Results*	*Ref*
Boron	45S5 BG	-	CAM of quail embryos	Increased expression of integrin $\alpha_v\beta_3$, Increased number of blood vessels	(50)
Copper	Borate BG	hBMSCs	In vivo (rat with calvarial defects)	Proliferation of hBMSCs, Blood vessels formation (confirmed by IHC staining for CD31)	(42)
Magnesium	Silicate BG	HAECs	Rabbit bone defect	Proliferation of HAECs, HAECs alignment and exhibition of branch nodes that confirms the primary stage of angiogenesis, Enhanced angiogenesis in the defect area	(51)
Europium	BG 45S5	HUVECs	Mice with full- thickness wound	Upregulated angiogenesis-related genes (MMP9, VEGFR1/2, CD31 and PDGFR α/β) ofHUVECs, Formation of blood vessels, Deposition of collagen and re-epithelialization at wounded site	(52)
Niobium	45S5 BG	ST-2 bone marrow stromal cells	-	Proliferation of bone marrow stromal cells, Significant increase in VEGF release	(53)
Strontium	Borate BG	hBMSCs	Critical-sized rabbit femoral condyle defect model	Proliferation of hBMSCs, Upregulated expression of genes associated with angiogenesis andosteogenesis, such as VEGF, RUNX2, BMP-2, and osteopontin	(54)

CAM: chorioallantoic membrane; hBMSCs: human bone marrow mesenchymal stem cells; HAECs: human amniotic epithelial cells; HUVECs: human umblical vein endothelial cells; stem cells

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Electrospun nanofibrous silk fibroin membrane as a scaffold

By electrospinning technique, more than 200 polymers could produce nano- or microfibers with a high surface-to-volume ratio (55). Biocompatibility is the most important feature that determines the suitability of a material for tissue engineering applications. After identifying the biocompatibility of a polymer, other features that make a polymeric construct appropriate for the regeneration of a target tissue should be considered. Appropriate mechanical, physicochemical and biological properties are important for the regeneration of wounded tissues (56, 57).

Natural biopolymers such as silk fibroin have attracted much attention and widely utilized in scaffold fabrication due to some significant features such as better imitation of extracellular matrix and promotion of cell adhesion, differentiation and migration. In addition, the degradation products of these biopolymers have no cell toxicity. Silk fibroin, a FDA approved natural polymer (1993), shows suitable mechanical properties and cell compatibility (58). Silk fibroin could be used single or blended to produce nanofibrous membranes for various biomedical applications. Different studies have also demonstrated that BG-NPs could be incorporated into silk fibroin nanofibers (59).

We can conclude that BG-incorporated silk fibroin nanofibers could provide a suitable surface for cell attachment as well as an appropriate microstructure for the proliferation and differentiation of ADSCs.

Consequences of the hypothesis and discussion

We hypothesized that the local delivery of doped mesoporous BG-NPs and ADSCs via electrospun nanofibrous silk fibroin membrane could accelerate chronic wound healing by enhancing angiogenesis. Based on the data mentioned above, we discussed the capacity of ADSCs to differentiate into epithelial and endothelial cells under appropriate conditions (19-23). Based on other evidence, angiogenic factors that could be responsible for the role of ADSCs in promoting angiogenesis could be released by ADSCs engrafted in ischemic injury animal models (34, 35, 60).

In addition, it is suggested that ADSCs could improve angiogenesis through both differentiation into endothelial cells and secretion of angiogenic factors.

Doped mesoporous BG-NPs have been widely used in biomedical applications as their ion dissolution products have been recognized to enhance angiogenesis, bactericidal effects and anti- inflammatory properties which are important for chronic wound healing (39) (Fig. 1). The basic composition of BG-NPs has been modified using additives or dopants in order to improve their angiogenic properties. The presence of Cu2+, Co2+, Zn2+, Eu3+, Nb5+, Mg2+, and Sr2+ ions in the BG structure has been shown to induce the secretion of angiogenic growth factors in vitro and in vivo (49-53). It is therefore reasonable to assume that the presence of doped BG-NPs could induce ADSCs, differentiated endothelial cells and native fibroblasts to secrete angiogenic growth factors leading to accelerated chronic wound healing.

List of Abbreviations

Extracellular matrix (ECM); adipose-derived stem cells (ADSCs); doped bioactive glass nanoparticles (BG-NPs); vascular endothelial growth factor (VEGF); basic fibroblast growth factor-2 (bFGF); hepatocyte growth factor (HGF) ; chick embryo chorioallantoic membranes (CAM); human umbilical vein endothelial cells (HUVECs); human bone marrow mesenchymal stem cells (hBMSCs); human amniotic epithelial cells (HAECs)

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

No fund was used for this manuscript.

Authors' contributions

HN, as the corresponding author, conducted the research idea. AN and RA wrote the main draft. MK, MB, KA and ZA reviewed the paper and were major contributors in writing the manuscript.

Cite this article: Delivery of doped mesoporous bioactive glass nanoparticles and adipose-derived stem cells via electrospun nanofibrous silk fibroin membrane to accelerate chronic wound healing by enhancing angiogenesis. Sci J Mat Sci & Eng.2020; 2(2); 01-08.

All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Cite this article: Delivery of doped mesoporous bioactive glass nanoparticles and adipose-derived stem cells via electrospun nanofibrous silk fibroin membrane to accelerate chronic wound healing by enhancing angiogenesis. Sci J Mat Sci & Eng.2020; 2(2); 01-08.