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ORIGINAL ARTICLE

Beneficial Effect of Resveratrol on Conditioned Medium Human Adipose-derived Mesenchymal Stem Cell for Cutaneous Wound Healing Related Growth Factors

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ABSTRACT

Introduction: Cutaneous wound healing, a type of soft tissue injury, needs the interaction between multiple growth factors (epidermal growth factor [EGF], transforming growth factor [TGF], platelet-derived growth factor [PDGF], and vascular endothelial growth factor [VEGF]) in order to attain physiological healing. Nevertheless, in certain conditions, i.e., chronic wound, certain growth factors might be insufficient. VEGF is among the most significant pro-angiogenic mediators during wound healing to increase migration and invasion of endothelial cells. Conditioned medium adipose-derived mesenchymal stem cells (CM-AdMSCs) are a new hope to ameliorate impaired healing. Resveratrol (RV), a small molecule that can increase the effect of CM-AdMSCs, is needed to help stimulates growth factors from stem cells for culture. This study aims to evaluate growth factors in CM-AdMSCs with resveratrol. **Methods:** Isolated and characterized MSCs from CM-AdMSCs treated with RV supplemented Serum Deprived Medium (SDM) were used in this study. Growth factors level were measured using ELISA. **Results:** A decrease of mean were noted in EGF (290.19±53.19 VS 271.64±52.58) and VEGF (788.76±204.82 VS 117.92±49.22), while an increase of mean in TGF (633.14±11.38 VS 824.73±121.15) and PDGF (2999.00±203.54 VS 3961.40±378.68) between CM-AdMSCs without resveratrol and with resveratrol group, respectively. PDGF and VEGF were statistically significant ($p < 0.05$). **Conclusion:** In conclusion, RV promotes PDGF secretion and decreases VEGF in CM-AdMSCs.

Keywords: Wound healing; CM-AdMSCs; Resveratrol; VEGF; PDGF

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INTRODUCTION

Wound healing, a biophysiological process in the human body, is an intricate multi-stage process orchestrated reconstitution in the skin's dermal and epidermal layers (1,2). This multi-stage process is reached through four dynamic and integrated programmed phases: hemostasis, inflammation, proliferation, and remodeling/resolution where cells (i.e., thrombocyte, granulocytes, macrophages, fibroblast, and keratinocytes), cytokines, growth factors, and protease are involved (1,3). After a dermal injury, aggregation of platelet initiate the coagulation cascade and formation of clots. Subsequently, the wound bed will be infiltrated with leukocytes producing pro-

inflammatory cytokine (i.e., neutrophils and monocytes/macrophages). In later healing stages, fibroblasts will be recruited to the site of the wound to deposit extracellular matrix and provide the basis for regeneration of new tissue(4). Reported data suggest that essential wound-care products ought to have the composition that are similar to the skin; a mixture of distinct growth factors and extracellular matrix (ECM) proteins endogenous to the skin, viable epithelial cells, fibroblasts, and coupled with mesenchymal stem cells (MSCs) (5). Stem cells are distinguished by their multipotency and self-renewal capability, while MSCs are a group of stem cells with self-renewal ability, multiple differentiation potential, and strong immunoregulatory effects (6,7). Due to this nature, MSCs are desirable subjects for a number of cell therapies in previous literature (2,8,9).

The various MSCs' differentiation lineages induced by growth factors are as follows, 1) chondrocytes, 2) osteoblasts, 3) adipocytes, 4) hepatocytes, 5) cardiomyocytes, 6) neurons, 7) epithelium, 8) endothelial cells, 9) pancreatic β cells, and 10) epidermis (10). Adipose-derived mesenchymal stem cells (ADMSCs), stem cells derived from adipose tissue stroma, are characterized by its considerable self-renewal ability, ability to differentiate into numerous types of functional cells, and possible paracrine function of the cells (11,12). Studies have reported ADMSCs to enhance cutaneous wound healing, with significantly quicker reepithelization, greater granulation tissue formation (day 3 to day 7), and angiogenesis (6,13). This mechanism has shown its beneficial effect in wound healing, especially in chronic or non-healing wounds.

Resveratrol (RV), a naturally occurring polyphenol, is produced by various plants, such as grapes and peanuts. This compound has attracted research in cancer due to its ability to restrict growth, stimulate apoptosis in numerous malignancies, and increase tumor susceptibility to chemotherapeutic agents (14). To an additional extent, various studies published over the last few years have reported RV's advantage on the behavior of several stem cells. Nonetheless, only few literatures have reported RV's effect on stem cell behavior, especially in cell secretion products/secretomes. In this study, we examined the effects of resveratrol on CM-AdMSCs for cutaneous wound healing related growth factors *in vitro*.

MATERIALS AND METHODS

Mesenchymal stem cells isolation and expansion

MSCs are characterized by their capacity to attach to a plastic surface in standard culture conditions, their surface markers expression, their lack of hematopoietic markers expression, and their potential to differentiate along osteoblastic, adipocytic, and chondrocyte pathways *in vitro* (15).

Firstly, a 1 cm^3 fat tissue sample that is not contaminated with blood clots or connective tissue is prepared in alpha MEM transport medium inside a 50 ml conicle. Next, the sample is removed from the conicles and rinsed with PBS solution until it is clean and the erythrocytes are removed. Then, the fat tissue is chopped and mixed with collagenase to be incubated at 370 C hot plate for 30 minutes until it dissolves completely. Next, the solution is filtered to separate the remaining insoluble fatty tissue. The filtered products are then centrifuged at 3000 rpm for 5 minutes until pellets are formed. The pellets then re-suspended with 10 ml of alpha MEM medium to form a homogeneous solution that needs to be incubated until colonies are formed, and the cells achieve 80% confluence.

After the cells reach a confluence of 80%, various doses of resveratrol are added to the media of the cells (23). Propagation is done by collecting the conditioning medium from the petri dish and storing it in a 50 ml conicle, washing it with 5 ml of PBS solution, and adding triple express enzyme. If the monolayer is already released, a medium stopper is added and it will develop into a single cell. The single-cell solution is centrifuged at 3000 rpm for 5 minutes until pellets are formed and given Alpha MEM medium to be re-suspended and planted in 2 new Petri dishes afterward.

Before being characterized using CD 105, the mesenchymal stem cells must be effectively separated from fat tissue first. A fluorescent color on the membrane's surface indicates a positive test for CD 105.

To harvest the metabolites, 50 ml of conditioned medium is inserted into the dialysis tubing membrane that needs to be spun at 500 rpm on a hot plate magnetic stirrer. Let it sit overnight until the conditioning medium's color in the dialysis tubing is muted. After that, pour the contents from the dialysis tubing, filter the metabolite products with a size of 0.22 microns, and then pack in 50 ml conicles to be stored in a sealed sterile medipack at a -200°C temperature. It is ready to use when needed and as much as 1 ml is taken for ELISA examination purposes. This research was approved by the Ethical Committee in Health Research of Dr. Soetomo General Academic Hospital (reference number: 0052/LOE/301.4/VIII/2020.

Statistical analysis

Statistical analyses were carried out using the IBM Statistical Package for the Social Sciences (SPSS) Statistics 25 for Windows (International Business Machines Corporation, New York, United States). Data are expressed as mean ± standard deviation (SD). Groups were compared using independent T-test or one-way ANOVA. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Characterization of adipocyte-derived mesenchymal stem cells.

Comparison of growth factors in conditioned adipocyte-derived mesenchymal stem cells regarding resveratrol (RV)

Four growth factors were measured; namely, epidermal growth factor (EGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). A decrease of mean was noted in EGF (290.19±53.19 VS 271.64±52.58 [Figure 1a]) and VEGF (788.76±204.82 VS 117.92±49.22 [Figure 1b]) between CM-AdMSCs without RV and with RV group, respectively. On the contrary, an increase of mean in TGF (633.14±11.38 VS 824.73±121.15 [Figure 1c]) and PDGF (2999.00±203.54 VS 3961.40±378.68 [Figure 1d]) between CM-AdMSCs without RV and with RV group, respectively, were noted. To further clarify the mean difference of the growth factors investigated regarding RV, we analyzed the growth factors. We found that PDGF and VEGF were statistically significant (p-value of 0.018 and 0.005, respectively).

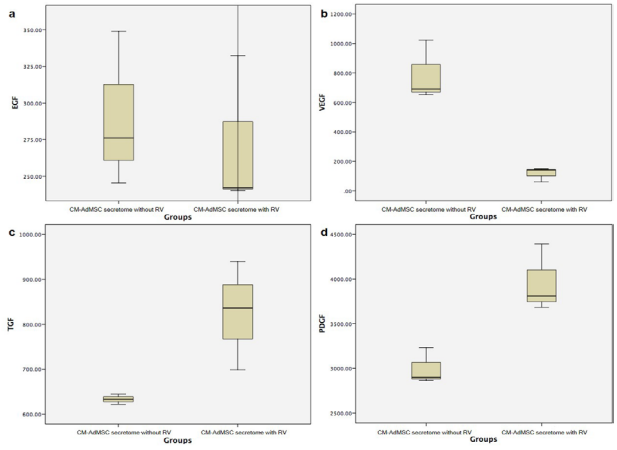

Figure 1:1a) Comparison of mean 1a) EGF levels, 1b) VEGF levels, 1c) TGF levels, 1d) PDGF levels in CM-AdMSCs without RV and with RV, respectively.

DISCUSSION

Adipose tissue stroma, an important secretory and endocrine organ, can be conveniently obtained through liposuction technique (16). This tissue can be harvested autologously and does not present the ethical, tumorigenic, or immunogenic issues presented by pluripotent stem cells with immunosuppressive characteristic (17,18). Adipose tissue volume is constituted almost 90% of adipocytes. It produces a diverse population of cell types (preadipocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, resident monocytes/macrophages, and lymphocytes) when broken down enzymatically (19). Once isolated, it is referred to as the stromal vascular fraction (SVF) (19). There are several ways of ADMSCs' mechanism of action in wound healing: 1) collagen synthesis and degradation, 2) site-specific differentiation and improved survival, 3) immunomodulation, and 4) neovascularization (20).

The alterations in the skin's cell composition and the various epithelial cells' ability to secrete specified growth factors (i.e., TGF-β, VEGF, matrix metalloproteinase [MMP]-1, MMP-2, MMP-9, and extracellular matrix [ECM]) offer the potential of determining an equilibrium between cell regeneration as well as rejuvenation to the ADMSCs' microenvironment (21). This milieu can be further enhanced through the addition of RV. Preconditioned RV promotes MSCs proliferation, sustains differentiation, and hinders MSCs senescence. Through this accepted approach of MSCs with RV, we hoped it would facilitate wound healing related growth factors secretion. Wound healing related growth factors are EGF, TGF, PDGF, VEGF, and fibroblast growth factor (FGF), to name a few (22). A Previous study has reported that 0.1 μM is the most potent RV dose to promote secretion of EGF, PDGF, TGF-β1, and hepatocyte growth factor (HGF) (23).

Resveratrol (3,4',5 trihydoxysilbene), a phytochemical, is a well-known biologically active compound synthesized by plants undergoing ionizing radiation or infection (24). RV was stated to display numerous therapeutic advantages, such as anti-inflammatory, antioxidant, immunomodulator, vasorelaxant, and neuroprotective effect, to name a few. In vitro, RV modulates angiogenesis through VEGF expression and the formation of vascular networks (25). Due to its properties, RV potential target is the adult stem cells that dwell in different tissues and organs through oral or intravenous injection (23).

The EGF family, also known as ErbB1 or Her1, consists of various members, four of which – EGF, heparin-binding EGF-like growth factor (HB-EGF), epiregulin, and TGF-α. The EGF family members are synthesized in membrane-associated forms and need MMPs or ADAMs (a disintegrin and metalloproteinase) activation (22). EGF, secreted by platelets, macrophages, fibroblasts, endothelial cells, keratinocytes, and bone marrow-derived MSCs, is a powerful inducer of epithelization, angiogenesis, fibroblast proliferation, granulation tissue formation, and survival (22). This role is not restricted to straightforward consequences on keratinocytes, fibroblasts, and endothelial cells; a considerable lot of these factors are powerful stimulator of inflammatory mediators and their receptors (22). For example, the increase of antimicrobial peptides and proinflammatory interleukin (IL)-8 production due to TGF-α induction of Toll-like receptors (TLR5 and TLR9) (22, 26).

The TGF-β superfamily, particularly the TGF-β1-3 (a bone morphogenetic proteins [BMPs]), is involved in wound healing. Various cell types, such as macrophages,

platelets, keratinocytes, and fibroblasts, produced this family of growth factors. TGF-β is activated by MMP-2, MMP-9, thrombospondin 1, and integrin αvβ6 along with membrane-type MMP (22). The influence of TGF-ß1 on cells is concentration-dependent; low TGF-β1 concentration promotes endothelial proliferation and migration, while high concentration increases matrix production (22). In a chronic wound, decreased level of TGF-β ligands has been documented, implying that an incorporation of exogenous TGF-βs may be advantageous for wound healing (22, 27).

Platelet-derived growth factor (PDGF) is multifunctional. It is also among the first growth factors produced in response to injury and stimulates cellular responses during the entirety of the repair processes (22). It is secreted by platelets, macrophages, keratinocytes, fibroblasts, and endothelial cells. Generally, activation of several pathways (i.e., phospholipase Cγ pathway, phosphatidylinositol-3-kinase (PI3K), and several mitogen-activated protein kinase (MAPK) pathways) results in the enhancement of cell migration and proliferation and the increase of VEGF and insulin-like growth factor production. IGF PDGF levels are of a low value in chronic wounds, possibly due to insufficient production and/or exceeding protease-mediated degradation. This underlying condition was advantageous for patients with chronic wounds (22, 28). The VEGF family includes six members. The VEGF is a heparin-binding glycoprotein, it needs to be bound to cell-surface tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3) to conduct their functions (22). Angiogenesis is predominantly mediated by VEGFR1 and VEGFR2, while VEGFR-3 mediates lymphangiogenesis. This family of growth factors plays a part during injury-induced hypoxia leading to their up-regulation. In wound healing, VEGF secreted by the platelets, macrophages, fibroblasts, and keratinocytes, acts in a paracrine approach on endothelial cells, stimulating and promoting wound angiogenesis (22). This growth factors also acts as an immunostimulator for the migration and activation of monocyte. It also assists in MMPs production by smooth myocytes, induces their migration and proliferation throughout hypoxia, and stimulates fibroblast proliferation, scars formation, and keratinocyte motility essential for wound re-epithelization. In chronic wound, a paradox occurred between increase VEGF mRNA and decrease VEGF protein levels due to proteolytic activity within wound bed (22). To our attention, RV suppressed the expression of VEGF as seen as shown in other studies. This is achieved through several proposed mechanism of 1) restrictive outcome in VEGF-induced phosphorylation of VEGFR2 without any effect on total VEGFR2 expression, 2) promotion of VEGF degradation, subsequently reducing the interaction with its receptor, and 3) glycolysis inhibition during latent endothelial cells activation (29, 30).

Our study showed that ADMSCs in conditioned RV medium could increase the secretion of PDGF form ADMSCs. This finding is supported through a proposed mechanism of RV to help preserve the human MSCs self-healing and multi-lineage differentiation abilities beyond passage 10 through a SIRT1-dependent pathway, especially adipogenic potential. SIRT1 (a NAD+-dependent lysine deacetylase) deacetylates SOX2 to prevent its degradation, subsequently preserving the MSCs stemness after a lengthy passaging (31). In addition, SIRT1 manages OCT4 and NANOG expression indirectly through p53 deacetylation in human embryonic and cancer stem cells (31). This is further enhanced through RV mechanism of reducing p53 level by stimulating its deacetylation in adult stem cells. Collectively, RV-activated signalling pathway is revealed as a straightforward relation of RV-SIRT1-SOX2 complex, and the activation of SIRT1 enables an approach for wound therapy acceleration (23, 31).

CONCLUSION

The present study indicated a favorable therapeutic potential for CM-AdMSCs in cutaneous wounds healing, especially in chronic wound. Increase production of PDGF in CM-AdMSCs plays a major role in chronic wounds where they are in a lower value. Lower VEGF should be put into consideration when considering utilizing this growth factor from a CM-AdMSCs. RV promotes PDGF secretion and decreases VEGF in CM-AdMSCs. Future research should be explored to the specific mechanism of CM-AdMSCs in cutaneous wound healing in clinical trials settings.

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