MCT

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Exosome secretion kinetics are controlled by temperature

Anarkali Mahmood,[1] Zdeněk Otruba,[1] Alan W. Weisgerber,[1] Max D. Palay,[1] Melodie T. Nguyen,[2] Broderick L. Bills,[2] and Michelle K. Knowles[1,2,*]
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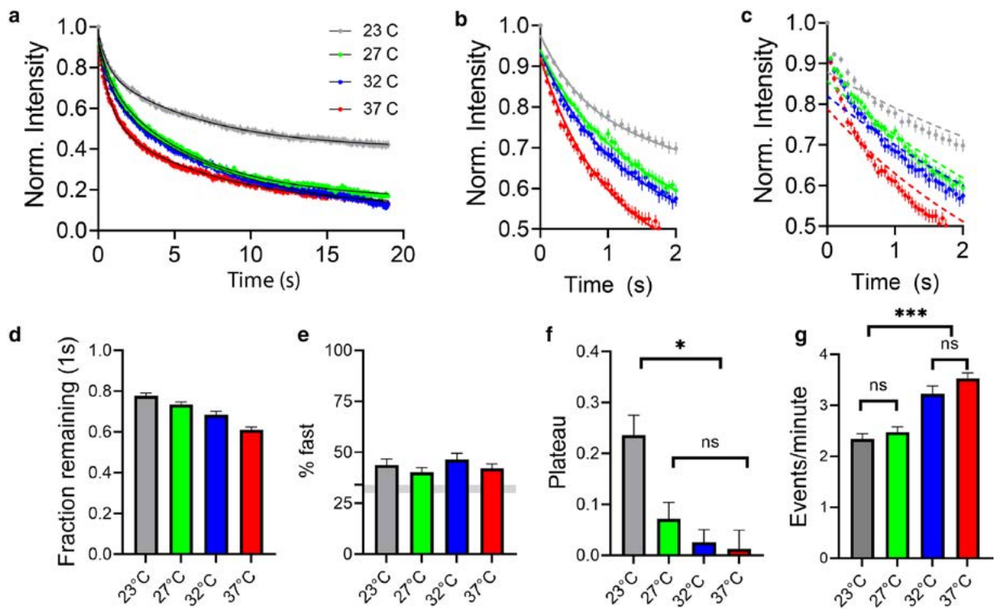
ABSTRACT When multivesicular endosomes (MVEs) fuse with the plasma membrane, exosomes are released into the extracellular space where they can affect other cells. The ability of exosomes to regulate cells nearby or further away depends on whether they remain attached to the secreting cell membrane. The regulation and kinetics of exosome secretion are not well characterized, but probes for directly imaging single MVE fusion events have allowed for visualization of the fusion and release process. In particular, the design of an exosome marker with a pH-sensitive dye in the middle of the tetraspanin protein CD63 has facilitated studies of individual MVE fusion events. Using TIRF microscopy, single fusion events were measured in A549 cells held at 23–37°C and events were identified using an automated detection algorithm. Stable docking precedes fusion almost always and a decrease in temperature was accompanied by decrease in the rate of content loss and in the frequency of fusion events. The loss of CD63-pHluorin fluorescence was measured at fusion sites and fit with a single or double exponential decay, with most events requiring two components and a plateau because the loss of fluorescence was typically incomplete. To interpret the kinetics, fusion events were simulated as a localized release of tethered/untethered exosomes coupled with the membrane diffusion of CD63. The experimentally observed decay required three components in the simulation: 1) free exosomes, 2) CD63 membrane diffusion from the endosomal membrane into the plasma membrane, and 3) tethered exosomes. Modeling with slow diffusion of the tethered exosomes (0.0015–0.004 $\mu m^2/s$) accurately fits the experimental data for all temperatures. However, simulating with immobile tethers or the absence of tethers fails to replicate the data. Our model suggests that exosome release from the fusion site is incomplete due to postfusion, membrane attachment.

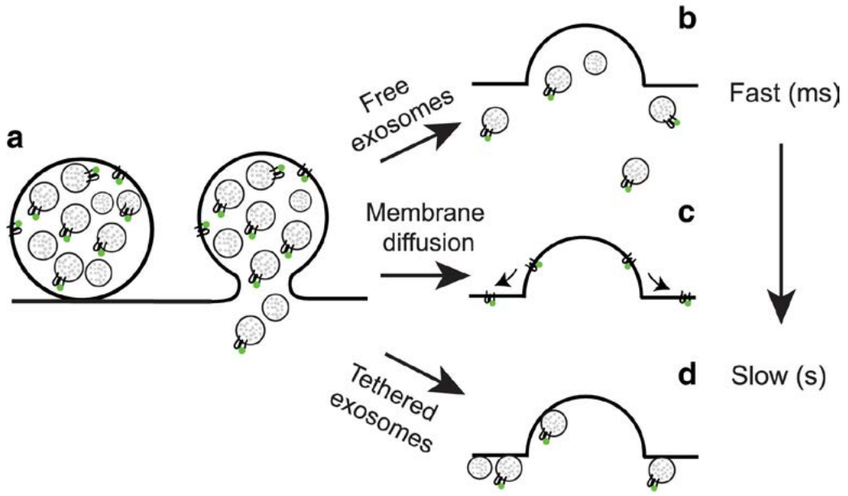
SIGNIFICANCE Exosomes are nanoscale vesicles secreted from a wide variety of cells and they are involved with a number of disease states, from cancer to Alzheimer's disease. For cells to secrete exosomes, multivesicular endosomes (MVEs) fuse with the plasma membrane in a constitutive fashion. Postfusion, exosomes circulate to affect cells both near and far. In this work, the fusion of MVEs was characterized by fluorescence microscopy and the rate of release was measured then simulated to develop a model for the fate of exosomes postfusion. Exosomes are secreted from MVEs more frequently at higher temperatures and modeling suggests that some exosomes remain attached to the cell surface for a period of time.

Kinetics of MVE fusion events depend on temperature



(a) Average intensity traces in time of single MVE fusion events at 23°C (*n = 86*), 27°C (*n = 83*), 32°C (*n = 77*), and 37°C (*n = 110*). For fitting, the time alignment was done with respect to the maximum intensity (0 s) and individual traces were normalized by the maximum. Black lines are fits with a biexponential function. **(b)** Zoom of the biphasic fit and the **(c)** single exponential fit at short times. Error bars are mean ± SE. **(d)** The percent loss in intensity 1 s after the maximum. All are significantly different in t-tests ($p<0.05$) from the nearest temperature (mean ± SE). **(e)** The portion of the decay that is fast for each temperature is not significantly different. The light gray bar indicates the amount of CD63 expected to be present on the MVE limiting membrane (mean ± SE). **(f)** The plateau from the biexponential fit relates the long time, remaining intensity (median ± 95%CI, only 23°C is significantly different from others in a t-test, $p<0.05$). **(g)** Fusion events observed per minute of data acquisition at different temperatures (mean ± SE). Extracted from Mahmood, A. et al. (2023). Exosome secretion kinetics are controlled by temperature. *Biophysical Journal*.

Model of MVE fusion and how CD63 leaves the fusion site



(a) MVEs first dock then fuse. Postfusion, three outcomes can occur simultaneously in single fusion events: **(b)** exosomes quickly leave the fusion site (24%, <0.5 s), **(c)** CD63-pHluorin on the endosomal membrane diffuses into the plasma membrane (36%, 1–2 s), or **(d)** tethered exosomes remain attached to the membrane and slowly leave the fusion site (40%, 5–10 s). The percent of each component and approximate time to leave the fusion site were determined from a simulation of the average fusion decay measured at 37°C. Extracted from Mahmood, A. et al. (2023). Exosome secretion kinetics are controlled by temperature. *Biophysical Journal.*

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Research paper

Sustained release of growth factors from photoactivated platelet rich plasma (PRP)

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ARTICLE INFO

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Growth factor
Photobiomodulation (photostimulation)
Tissue engineering

ABSTRACT

The goal of this study is to specify the ability of polychromatic light source (PAC), providing effective wavelengths in the range of 600–1200 nm (near-infrared region, NIR), to activate human platelets in platelet-rich plasma (PRP) and to achieve sustained and controlled release of growth factors from photoactivated platelets. PRP was isolated from human blood and treated with PAC in different time intervals during 1, 5 and 10 min from 10 cm distance to the platelets. ATP secretion and then, calcium release from platelets significantly increased after light application. Photostimulation of platelets triggered lamellipodia extension, numerous filopodia formation, and platelet agglomeration as activation indicators. P-selectin expression was significantly increased after the application of PAC. In conclusion, PRP was successfully activated with PAC for 10 min and realized activation-dependent sustained growth factor release during 28 days. We proved that PAC which has a great potential of activation of PRP enables sustained growth factor release from PRP with a periodic use for therapeutic applications of PRP.

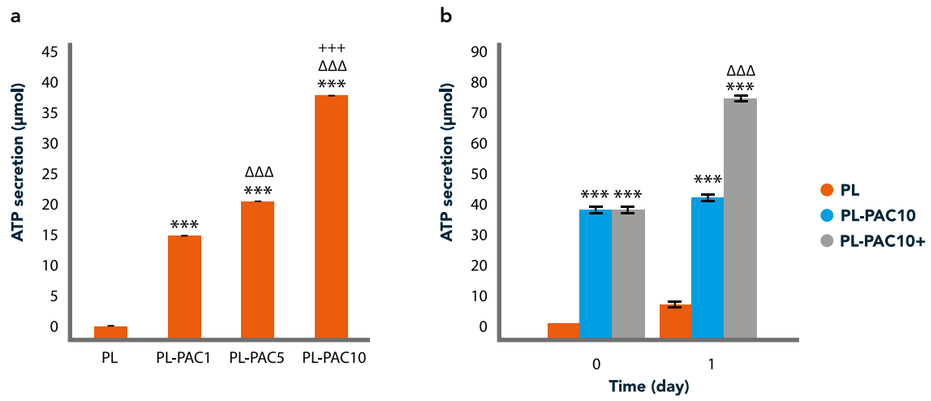
1. Introduction

Platelet-rich plasma (PRP) that is the concentrated platelets in a small volume of blood plasma, is currently used in clinic and tissue engineering studies. The basic foundation behind the mechanism of action of PRP is that by increasing the concentration of growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor ß (TGF-ß), vascular endothelial growth factor (VEGF), interleukins, hormones and several hundred other proteins that are released by platelets, healing accelerated [1,2].

In blood circulation, platelets exist in a resting, discoid state unless thrombin and collagen can stimulate an allergic response in patients [6]. Calcium sources which are synthetic ingredients have also side effects and toxicity. Besides, all of these chemical agents can activate the PRP only once. Therefore, in this study we decided to investigate the potential use of photostimulation for PRP activation in order to achieve sustained and controlled release of growth factors from PRP for tissue engineering and clinic usage.

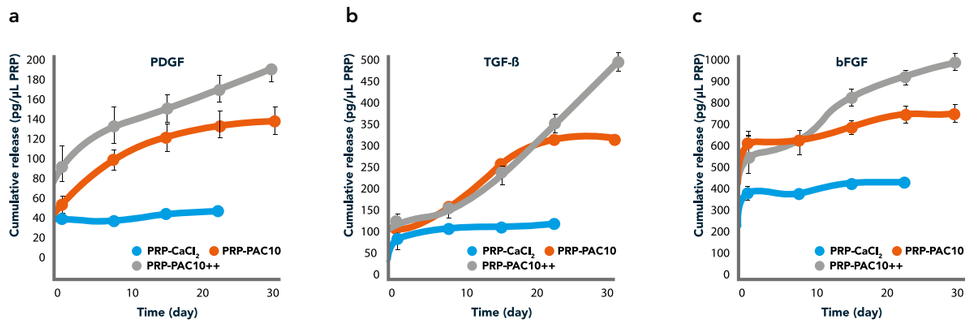
Photostimulation based on low-level laser (or light) therapy (LLLT) has been used for a variety of medical therapies such as wound healing and pain control as well as basic scientific research [7]. *In-vitro* data demonstrate that LLLT can stimulate cell proliferation [8,9] collagen synthesis [8] and cell differentiation [8,10,11].

Comparison of ATP secretion from unstimulated and photostimulated platelets



(a) Adenosine triphosphate (ATP) secretion from platelet mitochondria was induced by photostimulation during 1 (PL-PAC1), 5 (PL-PAC5), and 10 (PL-PAC10) minutes. Bioluminescence ATP assay showed that ATP secretion increased with increasing light application time. While ATP amount was normal level in resting platelets, it significantly increased (p<0.001) in all groups after photostimulation, and reached a high level (38.32 µmol) after stimulation with polychromatic light source (PAC) for 10 minutes. **(b)** Evaluation of secreted ATP amount of resting platelets and photoactivated platelets after 24 hours incubation period. While ATP secretion augmented after 24 hours in all groups, it significantly increased in PAC-treated platelets and was statistically higher than in the other groups (p<0.001). Data are expressed as mean value of triplicates, and error bars as the standard deviation. Statistically significant differences are stated by symbols: ***p<0.001 when the control group is PL; ΔΔΔp<0.001, when the control group is PL-PAC1; +++p<0.001 when the control group is PL-PAC5. Adapted and extracted from Irmak, G. et al. (2019). Sustained Release of Growth Factors from Photoactivated Platelet Rich Plasma (PRP). *European Journal of Pharmaceutics and Biopharmaceutics.*

In vitro cumulative growth factor release from activated PRP



(a-c) PDGF, TGF-ß, and b-FGF were chosen as representative growth factors in this study. Results showed that photoactivated PRP via polychromatic light (PAC) released significantly more prolonged and higher amount of PDGF **(a)**, TGF-ß **(b)**, and bFGF **(c)** than PRP activated with $CaCl_2$. In vitro release of PRP was performed for 28 days, and cumulative release profiles of growth factors measured. PRP activated by $CaCl_2$ released 50% of the growth factors at the end of the first day with the burst effect (PRP-$CaCl_2$, blue line). Release amount of growth factors from the photoactivated platelets increased over time within the 28 days incubation period, a burst release was observed in the first 24 hours, then growth factor release reached a maximum value at day 21. Photoactivated PRP was exposed to polychromatic lights for 10 minutes (PRP-PAC10, orange line) or every other day for 10 minutes (PRP-PAC10++, grey line) and cumulative release profiles were determined. Again, burst release was observed in the first 24 hours. In the following days, the released amount of growth factors increased in a controlled manner. Data are expressed as mean value of triplicates and error bars as the standard deviation. Adapted and extracted from Irmak, G. et al. (2019). Sustained Release of Growth Factors from Photoactivated Platelet Rich Plasma (PRP). *European Journal of Pharmaceutics and Biopharmaceutics.*

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An optimised protocol for platelet-rich plasma preparation to improve its angiogenic and regenerative properties

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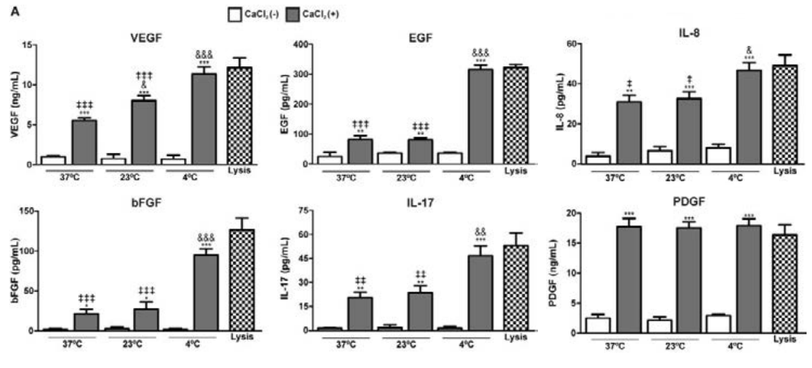
Julia Etulain[1], Hebe A. Mena[1], Roberto P. Meiss[2], Gustavo Frechtel[3], Susana Gutt[4], Soledad Negrotto[1] & Mirta Schattner[1]

Although platelet-rich plasma (PRP) is used as a source of growth factors in regenerative medicine, its effectiveness remains controversial, partially due to the absence of PRP preparation protocols based on the regenerative role of platelets. Here, we aimed to optimise the protocol by analysing PRP angiogenic and regenerative properties. Three optimising strategies were evaluated: dilution, 4 °C pre-incubation, and plasma cryoprecipitate supplementation. Following coagulation, PRP releasates (PRPr) were used to induce angiogenesis *in vitro* (HMEC-1 proliferation, migration, and tubule formation) and *in vivo* (chorioallantoic membrane), as well as regeneration of excisional wounds on mouse skin. Washed platelet releasates induced greater angiogenesis than PRPr due to the anti-angiogenic effect of plasma, which was decreased by diluting PRPr with saline. Angiogenesis was also improved by both PRP pre-incubation at 4 °C and cryoprecipitate supplementation. A combination of optimising variables exerted an additive effect, thereby increasing the angiogenic activity of PRPr from healthy donors and diabetic patients. Optimised PRPr induced faster and more efficient mouse skin wound repair compared to that induced by non-optimised PRPr. Acetylsalicylic acid inhibited angiogenesis and tissue regeneration mediated by PRPr; this inhibition was reversed following optimisation. Our findings indicate that PRP pre-incubation at 4 °C, PRPr dilution, and cryoprecipitate supplementation improve the angiogenic and regenerative properties of PRP compared to the obtained by current methods.

Wound repair is a dynamic and physiological process for regenerating damaged tissues[1]. Physiological wound healing may be disrupted by local factors (foreign bodies at the wound site, tissue maceration, ischaemia, or infection) or intrinsic individual factors (age, inflammatory diseases, drugs, or malnutrition) resulting in several clinical complications, including abnormal scarring, pain, pruritus, malignant transformation (Marjolin's ulcer), haemorrhage, ulcer, infection, and amputation. These complications affect morbidity and mortality rates; hence, the healing of wounds is a current medical challenge[2]. Currently there are several techniques to promote wound repair, including biological tissue replacement, gene therapy, recombinant growth factors, and cell-based treatments[3,4]. Additionally, there are local methods for improving blood circulation in patients with chronic wounds associated with neuropathies and vascular diseases. These techniques include mechanical/physical methods (negative pressure therapy and intermittent pneumatic compression injuries) and ionic methods (hyperbaric treatment with ozone)[4].

Cold preconditioning promotes the release of growth factors and cytokines from platelets



PRP was incubated at 37°C, 23°C, or 4°C for 30 minutes, and the levels of VEGF, EGF, bFGF, IL-17, IL-8, and PDGF in releasates of PRP before clotting ($CaCl^{2-}$) or after clotting ($CaCl^{2+}$) were determined by ELISA. The secretion of VEGF, EGF, bFGF, IL-17, and IL-8, but not PDGF, was induced in a temperature-dependent manner. While VEGF, EGF, bFGF, IL-17, and IL-8 were partially released when PRP was incubated at 37°C or 23°C (20%–60% of the total intra-platelet amount), total secretion of these molecules was only achieved when PRP was incubated at 4°C, indicating that cold preconditioning maximises the release of platelet-derived pro-angiogenic molecules. Total intraplatelet levels were measured in platelet lysates. (n=4–5, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ vs. unstimulated; $^{\&}p<0.05$, $^{\&\&}p<0.01$, $^{\&\&\&}p<0.001$ vs. 37°C; $^{\ddagger}p<0.05$, $^{\ddagger\ddagger}p<0.01$, $^{\ddagger\ddagger\ddagger}p<0.001$ vs. lysis). VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor; IL, interleukin. Adapted and extracted from Etulain, J. et al. (2018). An optimised protocol for platelet rich plasma preparation to improve its angiogenic and regenerative properties. *Scientific Reports.*

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Yang et al. Stem Cell Research & Therapy (2019) 10:358
https://doi.org/10.1186/s13287-019-1472-x

Stem Cell Research & Therapy

RESEARCH Open Access

Exposure to blue light stimulates the proangiogenic capability of exosomes derived from human umbilical cord mesenchymal stem cells

Kun Yang[1], Dong Li[2,3], Meitian Wang[1], Zhiliang Xu[1], Xiao Chen[1], Qiao Liu[1], Wenjie Sun[1], Jiangxia Li[1], Yaoqin Gong[1], Duo Liu[4], Changshun Shao[5], Qiji Liu[1] and Xi Li[1,6*]

Abstract

Background: The therapeutic potential of mesenchymal stem cells (MSCs) may be attributed partly to the secreted paracrine factors, which comprise exosomes. Exosomes are small, saucer-shaped vesicles containing miRNAs, mRNAs, and proteins. Exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs) have been reported to promote angiogenesis. However, the efficacy of exosome-based therapies is still limited both in vitro and in vivo. The present study aimed to develop a new optical manipulation approach to stimulate the proangiogenic potential of exosomes and characterize its mechanism underlying tissue regeneration.

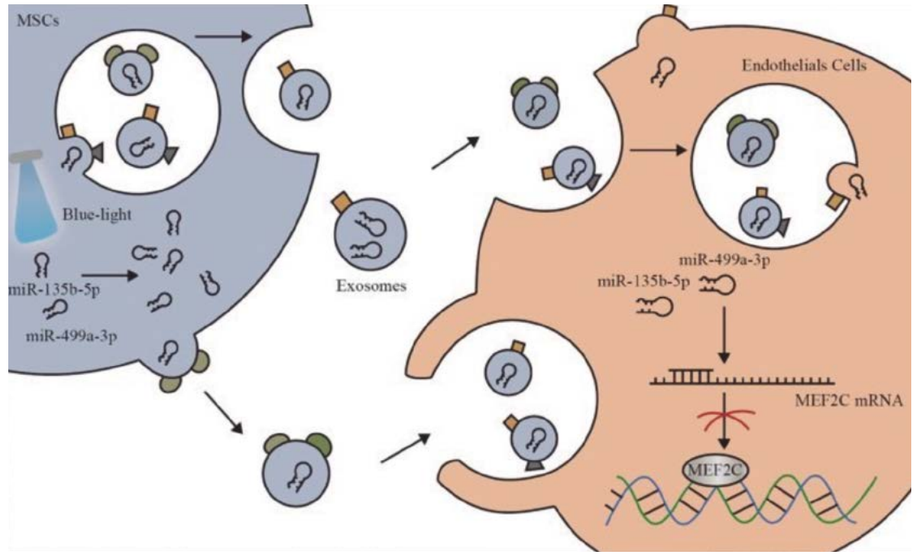
Methods: We used blue (455 nm) and red (638 nm) monochromatic light exposure to investigate the processing of stimuli. Exosomes were prepared by QIAGEN exoEasy Maxi kit and confirmed to be present by transmission electron microscopy and immunoblotting analyses. The proangiogenic activity of blue light-treated human umbilical vein endothelial cells (HUVECs), when co-cultured with hUC-MSCs, was assessed by EdU (5-ethynyl-2′-deoxyuridine) incorporation, wound closure, and endothelial tube formation assays. The in vivo angiogenic activity of blue light-treated MSC-derived exosomes (MSC-Exs) was evaluated using both murine matrigel plug and skin wound models.

Results: We found that 455-nm blue light is effective for promoting proliferation, migration, and tube formation of HUVECs co-cultured with MSCs. Furthermore, MSC-Exs stimulated in vivo angiogenesis and their proangiogenic potential were enhanced significantly upon blue light illumination. Finally, activation of the endothelial cells in response to stimulation by blue light-treated exosomes was demonstrated by upregulation of two miRNAs, miR-135b-5p, and miR-499a-3p.

Conclusions: Blue (455 nm) light illumination improved the therapeutic effects of hUC-MSC exosomes by enhancing their proangiogenic ability in vitro and in vivo with the upregulation of the following two miRNAs: miR-135b-5p and miR-499a-3p.

Keywords: Mesenchymal stem cells, Exosomes, Angiogenesis, Light exposure, microRNAs

Putative mechanism by which blue light increases the two miRNAs to activate the endothelial cells



Human umbilical cord mesenchymal stem cells (hUC-MSCs) inherently express blue (455 nm) and red (638 nm) light-sensitive opsins, photoreceptors present in the mammalian retina and skin. Upon exposure to blue light, hUC-MSCs exhibited enhanced proangiogenic capabilities, both in vitro and in vivo, by triggering the release of exosomes. Notably, the microRNAs miR-135b-5p and miR-499a-3p, identified within these exosomes, showed a significant upregulation following blue light stimulation. These two microRNAs collaboratively facilitated the proliferation and migration of endothelial cells (ECs) by modulating the expression of their target gene *MEF2C* (myocyte enhancer factor 2C). This discovery unraveled a mechanistic connection between monochromatic blue light exposure and the proangiogenic potential of exosomes derived from hUC-MSCs. Adapted and extracted from Yang, K. et al. (2019). Exposure to blue light stimulates the proangiogenic capability of exosomes derived from human umbilical cord mesenchymal stem cells. *Stem Cell Research & Therapy.*

BASIC RESEARCH ARTICLES PUBLICATION

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Original Article

Photoactivation of Autologous Materials with a New Reliable, Safe and Effective Set-Up

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Abstract

Background: The possibility of improving conditions and pathologies using biological materials prepared with the patient's own tissues has always been an attractive idea. There is a great disparity between the huge amount of preclinical data and the limited research conducted on photomodulation or photoactivation. This is because, for an effective and controlled management of light energy, several obstacles must be overcome.
Aim: The aim of this study is to evaluate the physical obstacles encountered by light in its path from the source to the biological tissue lodged in a receptacle specifically built for this purpose.
Methods: Total reflectance (specular + diffuse for an incidence angle of 8o) and total transmittance (regular + diffuse) of a rectangular area of 2 cm2 corresponding to a 5-cm long, 4-cm wide, 1-mm thick Terlux 2812HD plastic polymer sheet were evaluated.
Results: Showed that, with this set-up, over 90% of emitted light energy reaches the targeted tissue, with less than 10% loss in the process.
Conclusion: Data obtained in this study enable us to establish the suitability of this system as an effective tool to take advantage of the clinical benefit of photoactivation of biological materials.

Keywords

Autografting, cell transplantation, light, photoactivation, photomodulation

Abbreviations: LEDs, light-emitting diodes; CSIC, Consejo Superior de Investigaciones Científicas (Spanish National Research Council)

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The effect of short-term refrigeration on platelet responsiveness

Anna Kobsar[1,2], Karina Koehnlechner[1,2], Philipp Klingler[1], Marius Niklaus[1], Julia Zeller-Hahn[1], Angela Koessler[1], Katja Weber[1], Markus Boeck[1] & Juergen Koessler[1]✉

Storage of platelet concentrates (PC) at cold temperature (CT) is discussed as an alternative to the current standard of storage at room temperature (RT). Recently, we could show that cold-induced attenuation of inhibitory signaling is an important mechanism promoting platelet reactivity. For developing strategies in blood banking, it is required to elucidate the time-dependent onset of facilitated platelet activation. Thus, freshly prepared platelet-rich-plasma (PRP) was stored for 1 and 2 h at CT (2–6 °C) or at RT (20–24 °C), followed by subsequent comparative analysis. Compared to RT, basal and induced vasodilator-stimulated phosphoprotein (VASP) phosphorylation levels were decreased under CT within 1 h by approximately 20%, determined by Western blot analysis and flow cytometry. Concomitantly, ADP- and collagen-induced threshold aggregation values were enhanced by up to 30–40%. Furthermore, platelet-covered areas on collagen-coated slides and aggregate formation under flow conditions were increased after storage at CT, in addition to induced activation markers. In conclusion, a time period of 1–2 h for refrigeration is sufficient to induce an attenuation of inhibitory signaling, accompanied with an enhancement of platelet responsiveness. Short-term refrigeration may be considered as a rational approach to obtain PC with higher functional reactivity for the treatment of hemorrhage.

In transfusion medicine, platelet concentrates (PC) are frequently manufactured blood components, particularly used for prophylaxis or treatment of hemorrhage due to thrombocytopenia or for patients with reduced platelet function[1]. Currently, PC are regularly stored at room temperature (RT, 20–24 °C), accompanied by two major disadvantages: the risk of bacterial growth and the development of functional restrictions called storage lesions[2,3]. Therefore, according to manufacturing conditions and legal regulations, the shelf life of PC is commonly restricted to 4–7 days in many countries. Platelet storage at cold temperature (CT, 2–6 °C), which was performed until the 1980s, offers an alternative to reduce the risk of bacterial growth and to prolong the storage period[4–6]. RT has become the standard for platelet storage, since refrigeration induces clustering of glycoprotein Ib (GPIb) on the platelet surface and desialylation resulting in rapid clearance of re-transfused platelets in vivo[7,8], although cold-stored platelets are considered to be superior in acute hemorrhage due to increased responsiveness[2].

Recently, we could demonstrate that higher platelet reactivity upon cold storage is mediated by attenuation of inhibitory signaling, contributing to enhanced ADP-induced aggregation responses[9]. Vasodilator-stimulated phosphoprotein (VASP) phosphorylation, as a representative marker of platelet inhibition[10], developed continu-

02

CLINICAL STUDIES

- Adult-Onset Linear Morphea (en coupe de sabre) of the Face Successfully Treated with Photoactivated Low-Temperature Platelet-Rich Plasma: A Valid Therapeutic Option. Mercuri, S. R. et al. (2023). *Medicina.*

- Efficacy of photo-thermal-bioactivated platelet-rich plasma for skin biostimulation in patients not eligible for other medical-aesthetic treatment: A pilot study. Hernández Sanz, C. & Pinto, H. (2023). *Skin Research and Technology.*

- Efficacy and safety of photothermal-bioactivated platelet-rich plasma for facial rejuvenation. Beltrán, B. et al. (2022). *Journal of Cosmetic Dermatology.*

- Thermal conditioning: improving prp growth factor content. Pinto, H. & Melamed, G. (2020). *Prime Journal.*

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Case Report

Adult-Onset Linear Morphea (*en coupe de sabre*) of the Face Successfully Treated with Photoactivated Low-Temperature Platelet-Rich Plasma: A Valid Therapeutic Option

Santo Raffaele Mercuri [1,2], Matteo Riccardo Di Nicola [1,*], Vittoria Giulia Bianchi [1] and Giovanni Paolino [1,2]

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Abstract: Localized scleroderma (also known as morphea) is a chronic autoimmune disorder characterized by depressed, fibrotic, and dyschromic cutaneous lesions. It has a significant impact on the patient's daily life due to the unaesthetic evolution of the cutaneous lesions. Morphea is clinically divided into linear, circumscribed (plaque), generalized, pansclerotic, and mixed forms. Linear morphea *en coupe de sabre* (LM) usually arises in childhood. However, in about 32% of cases, it may arise in adulthood, showing a more aggressive course with also an increased risk of systemic involvement. Methotrexate is the first-line treatment for LM, although systemic steroids, topical agents (corticosteroids and calcineurin inhibitors), hyaluronic acid injections, and hydroxychloroquine or mycophenolate mofetil are valid therapeutic options. In any case, these treatments are not always effective and sometimes can be associated with important side effects and/or not tolerated by the patients. In this spectrum, platelet-rich plasma (PRP) injection can be considered a valid and safe alternative since PRP injections in the skin induce the release of anti-inflammatory cytokines and growth factors, thus reducing inflammation and increasing collagen remodeling. Herein, we describe a successful treatment of an adult-onset LM *en coupe de sabre* with photoactivated low-temperature PRP (Meta Cell Technology Plasma) sessions, showing an important local improvement of the lesion and patient satisfaction.

Keywords: morphea; linear; *en coupe de sabre*; MCT Plasma; scleroderma; platelet rich plasma; PRP; therapy; treatment

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Citation: Mercuri, S.R.; Di Nicola, M.R.; Bianchi, V.G.; Paolino, G. Adult-Onset Linear Morphea (*en coupe de sabre*) of the Face Successfully Treated with Photoactivated Low-Temperature Platelet-Rich Plasma: A Valid Therapeutic Option. *Medicina* **2023**, *59*, 1114. https://doi.org/10.3390/medicina59061114

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1. Introduction

Localized scleroderma (also known as morphea) is a cutaneous chronic and autoimmune disorder characterized by fibrosis of the skin with a higher incidence in female patients, causing cutaneous morpho-structural alterations with considerable aesthetic impact in the daily life of patients. Morphea can show different clinical presentations. Indeed, it is usually divided into linear, circumscribed (plaque), generalized, pansclerotic, and mixed forms [1–3]. Linear morphea (LM) mainly involves the head/neck region and usu-

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ORIGINAL ARTICLE

WILEY

Efficacy of photo-thermal-bioactivated platelet-rich plasma for skin biostimulation in patients not eligible for other medical-aesthetic treatment: A pilot study

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Abstract

Purpose: To evaluate the efficacy and safety of photothermal bioactivated platelet-rich plasma for reducing laxity in facial rejuvenation in patients not eligible for other aesthetic treatments due to several comorbidities.

Methods: A prospective, nonrandomized study was conducted. Efficacy was assessed through a satisfaction scale and the Facial Laxity Rating Scale. Safety assessments were based on the data of all adverse events and the visual analog pain scale.

Results: Seven patients with a mean age of 51 (standard deviation [SD] 7.46, range 42–63) were included. In six patients (85.7%), the treatment was applied to the face and neck, and in one patient (14.3%), only to the lower half of the face and neck. The physician's perception of laxity decreased, and the procedure was not complex. Patients' and physician satisfaction increased as the study progressed. Adverse effects were not serious and resolved without sequelae. The patients' pain perceived during the treatment was mild in most cases.

Conclusion: The photothermal bioactivated platelet-rich plasma injections were a safe and effective treatment for facial laxity in patients not eligible for other procedures, providing good satisfaction.

KEYWORDS
aging, growth factors, laxity, photothermal bioactivated platelet-rich plasma, rejuvenation

CLINICAL STUDIES PUBLICATION

WILEY

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LETTERS TO THE EDITOR

JCD Journal of Cosmetic Dermatology WILEY

Efficacy and safety of photothermal-bioactivated platelet-rich plasma for facial rejuvenation

Dear Editor,

It is well known that skin aging results from an intrinsic process involving genetic background and an extrinsic process influenced by environmental factors.[1] Many anti-aging cosmetic products are used to prevent and treat it,[2] while others, which are minimally invasive, safe, and effective, have not been so widespread, perhaps due to their characteristics and application method. One example is the intradermal injections with platelet-rich plasma (PRP),[3] whose results are significant, with high patient satisfaction, and without serious adverse effects.[4] A novelty related to these products is the use of light and temperature to activate PRP (see Appendix S1) and produce photothermal-bioactivated platelet-rich plasma (PTBA-PRP), whose promising preliminary results we want to present in this letter.[5,6]

The study's objective was to evaluate the safety and efficacy of PTBA-PRP for facial rejuvenation compared to previous treatments with PRP without this type of activation, using subjective perception scales.

We conducted a prospective, multicenter, open-label, non-randomized pilot study in healthy volunteers with Fitzpatrick skin type I~III and previous facial treatments for skin rejuvenation with PRP. Exclusion criteria included: pregnancy or breastfeeding, malignancy, viral infection, systemic autoimmune or blood diseases, and predisposition to hypertrophic/keloid scarring. The study was conducted following the principles outlined in the revised version of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and in compliance with all applicable laws and regulatory requirements.

Blood samples (10–20 ml) were collected in tubes with sodium citrate 3.8% anticoagulant solution and gel and centrifuged at 3500 rpm for 5 min. After centrifugation, platelets and white blood cells were pelleted on the separating gel and resuspended with plasma. PTBA was made through the MCT Unit® (Metacell Technology®, Sant Cugat, Spain). Samples were included in the MCT Kit® (Metacell Technology®, Sant Cugat, Spain), a sterile, single-use container for a 10 ml sample, and subjected to 620 nm and 5.6 J for 10 min and 4°C for 15 min, simultaneously. Doctors applied the product through superficial microinjections (0.05 ml with a 30G½" needle, 2.0 mm depth, and approximately 8 ml by face) and following the "point-to-point" mesotherapy technique (spacing of approximately 1 cm).

Patients and doctors assessed treatment satisfaction through subjective scales with four categories of results: very dissatisfied (0—implying no improvement), somewhat dissatisfied (1 to 3—implying a slight improvement), satisfied (4 to 6—implying a good, noticeable improvement), and very satisfied (7 to 10—implying an extraordinary improvement). Furthermore, patients were asked

AESTHETIC FEATURE | PLATELET-RICH PLASMA | PRIME

THERMAL CONDITIONING: IMPROVING PRP GROWTH FACTOR CONTENT

Hernán Pinto and **Graciela Melamed** share the results of their study examining the change to PRP growth factor content when exposed to thermal conditioning for ten minutes

ABSTRACT

There is currently great interest in the procedures and handling of patient blood preparations. In recent years, PRP application has been made accessible to all, though the technique has undergone moderate advances, while the end product has not really improved much. To achieve the latter, autologous materials are being subjected to conditioning protocols. In this context, conditioning stands for the controlled exposure of an autologous material to a certain physical and/or chemical stimulus, relying on the fact that the exposure itself will determine changes in the material that will ultimately lead to an enhancement of its clinical capabilities and curative potential. Today, new conditioning protocols are changing the game and there is currently an important corpus of evidence about the positive effects of tissue conditioning. It is a known fact that light and temperature affect organisms in multiple ways and are able to alter all kinds of biological processes. In this exploratory study, we have evaluated the effects of a thermal conditioning protocol in PRP, using an innovative, pioneering set-up. Our results were consistent with those previously reported, achieving statistically significant increments of growth factor concentration in PRP thermo-conditioned samples.

03

REVIEWS

- The biology, function, and biomedical applications of exosomes. Kalluri, R. & LeBleu, V. S. (2020). *Science.*
- The novel mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics. Xiong, M. et al. (2021). *Pharmacological Research.*
- Platelet-rich plasma-derived extracellular vesicles: A superior alternative in regenerative medicine? Wu, J. et al. (2021). *Cell Proliferation.*
- Effect of Photobiomodulation on Platelet-Rich Plasma: Review Series on New Tools in Regenerative Medicine. Pinto, H. et al. (2021). *Aesthetic Medicine.*
- The Effect of Photobiomodulation on Human Mesenchymal Cells: A Literature Review. Pinto, H. et al. (2020). *Aesthetic Plastic Surgery.*
- Role of opsins and light or heat activated transient receptor potential ion channels in the mechanisms of photobiomodulation and infrared therapy. Sharma, S. K. et al. (2023). *Journal of Photochemistry and Photobiology.*

Science

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RESEARCH

REVIEW SUMMARY

MEDICINE

The biology, function, and biomedical applications of exosomes

Raghu Kalluri* and Valerie S. LeBleu

BACKGROUND: All cells, prokaryotes and eukaryotes, release extracellular vesicles (EVs) as part of their normal physiology and during acquired abnormalities. EVs can be broadly divided into two categories, ectosomes and exosomes. Ectosomes are vesicles that pinch off the surface of the plasma membrane via outward budding, and include microvesicles, microparticles, and large vesicles in the size range of ~50 nm to 1 μm in diameter. Exosomes are EVs with a size range of ~40 to 160 nm (average ~100 nm) in diameter with an endosomal origin. Sequential invagination of the plasma membrane ultimately results in the formation of multivesicular bodies, which can intersect with other intracellular vesicles and organelles, contributing to diversity in the constituents of exosomes. Depending on the cell of origin, EVs, including exosomes, can contain many constituents of a cell, including DNA, RNA, lipids, metabolites, and cytosolic and cell-surface proteins. The physiological purpose of generating exosomes remains largely unknown and needs investigation. One speculated role is that exosomes likely remove excess and/or unnecessary constituents from cells to maintain cellular homeostasis. Recent studies reviewed here also indicate a functional, targeted, mechanism-driven accumulation of specific cellular components in exosomes, suggesting that they have a role in regulating intercellular communication.

ADVANCES: Exosomes are associated with immune responses, viral pathogenicity, pregnancy, cardiovascular diseases, central nervous system–related diseases, and cancer progression. Proteins, metabolites, and nucleic acids delivered by exosomes into recipient cells effectively alter their biological response. Such exosome-mediated responses can be disease promoting or restraining. The intrinsic properties of exosomes in regulating complex intracellular pathways has advanced their potential utility in the therapeutic control of many diseases, including neurodegenerative conditions and cancer. Exosomes can be engineered to deliver diverse therapeutic payloads, including short interfering RNAs, antisense oligonucleotides, chemotherapeutic agents, and immune modulators, with an ability to direct their delivery to a desired target. The lipid and protein composition of exosomes can affect their pharmacokinetic properties, and their natural constituents may play a role in enhanced bioavailability and in minimizing adverse reactions. In addition to their therapeutic potential, exosomes also have the potential to aid in disease diagnosis. They have been reported in all biological fluids, and the composition of the complex cargo of exosomes is readily accessible via sampling of biological fluids (liquid biopsies). Exosome-based liquid biopsy highlights their potential utility in diagnosis and determining the prognosis of patients with cancer and other diseases. Disease progression and response to therapy may also be ascertained by a multicomponent analysis of exosomes.

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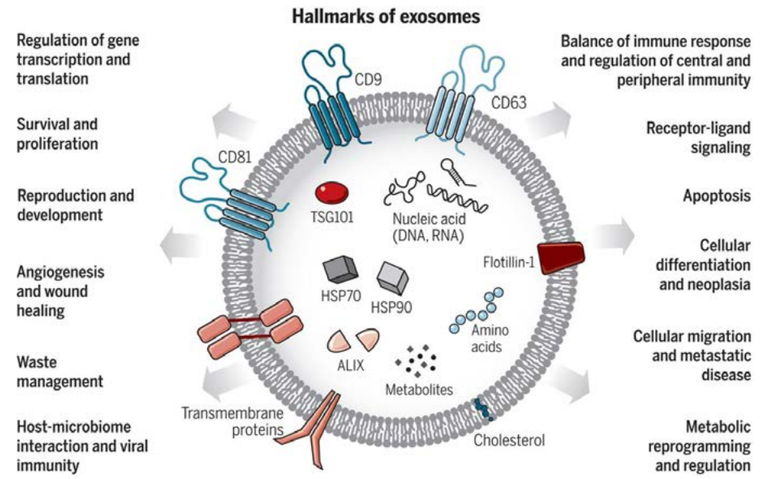
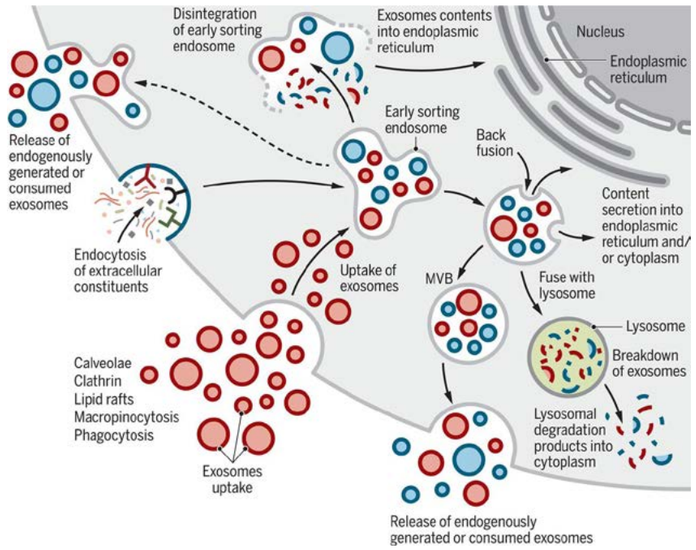
OUTLOOK: The study of exosomes is an active area of research. Ongoing technological and experimental advances are likely to yield valuable information regarding their heterogeneity and biological function(s), as well as enhance our ability to harness their therapeutic and diagnostic potential. As we develop more standardized purification and analytical procedures for the study of exosomes, this will likely reveal their functional heterogeneity. Nonetheless, functional readouts using EVs enriched for exosomes have already provided new insights into their contribution to various diseases. New genetic mouse models with the ability for de novo or induced generation of cell-specific exosomes in health and disease will likely show the causal role of exosomes in cell-to-cell communication locally and between organs. Whether exosome generation and content change with age needs investigation, and such information

Exosomes: A cell-to-cell transit system in the human body with pleiotropic functions



Exosomes are extracellular vesicles that play pivotal roles as mediators in both near and long-distance intercellular communication, impacting diverse aspects of cellular biology in health and disease. The composition of exosomes, including their biological markers, is influenced by the microenvironment and the inherent biology of the originating cells. Notably, exosomes encompass a rich repertoire of components, including membrane proteins (e.g., tetraspanins CD81, CD63, and CD9; antigen-presenting molecules; adhesion molecules; glycoproteins; signaling receptors; and membrane transport and fusion proteins, like Flotillin-1), cytosolic and nuclear proteins (heat shock proteins 70 and 90, cytoskeletal proteins, and components of the ESCRT machinery, such as ALIX and TSG101), growth factors, cytokines, extracellular matrix proteins, as well as metabolites and various nucleic acids (mRNA, miRNA, noncoding RNA species, and DNA). Moreover, exosomes boast a diverse lipid profile, encompassing cholesterol, ceramides, and sphingomyelin. Adapted and extracted from Kalluri, R. & LeBleu, V. S. (2020). The biology, function, and biomedical applications of exosomes. *Science.*

Cellular journey of internalized exosomes and endogenously produced exosomes



Exosomes may directly enter cells by different mechanisms (red). Exosomes are generated de novo by cells through the endocytosis process (blue). Exosomes are continuously being generated by and taken up by cells. It is likely that they can be secreted as a mixture of the de novo–generated and consumed exosomes (red and blue). It is unknown if the release of endogenously generated or consumed exosomes occurs together or separately. Exosomes that are taken up can get degraded by lysosomes. Exosomes that enter cells may enter or fuse with preexisting early-sorting endosomes (ESEs) and subsequently disintegrate and release their contents into the cytoplasm. Alternatively, endosomes could fuse back with the plasma membrane and release exosomes outside the cells. Extracted from Kalluri, R. & LeBleu, V. S. (2020). The biology, function, and biomedical applications of exosomes. *Science.*

Contents lists available at ScienceDirect

Pharmacological Research

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Review

The novel mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics

Mingchen Xiong [1], Qi Zhang [1], Weijie Hu [1], Chongru Zhao, Wenchang Lv, Yi Yi, Yichen Wang, Hongbo Tang *, Min Wu *, Yiping Wu *

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Exosomes
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Chemical compounds studied in this article:
Gelatin (PubChem CID: 441411)
Methacryloyl (PubChem CID: 53627882)
Alginate (PubChem CID: 91666318)
Pluronic F127 (PubChem CID: 24751)
Polyethylenimine (PubChem CID: 9033)
Pullulan (PubChem CID: 3085039)
Polyurethane (PubChem CID: 12254)
Hyaluronic Acid (PubChem CID: 24847767)
UK5099 (PubChem CID: 6438504)

ABSTRACT

Exposure to the external environment may lead to instability and dysfunction of the skin, resulting in refractory wound, skin aging, pigmented dermatosis, hair loss, some immune-mediated dermatoses, and connective tissue diseases. Nowadays, many skin treatments have not achieved a commendable balance between medical recovery and cosmetic needs. Exosomes are cell-derived nanoscale vesicles carrying various biomolecules, including proteins, nucleic acids, and lipids, with the capability to communicate with adjacent or distant cells. Recent studies have demonstrated that endogenic multiple kinds of exosomes are crucial orchestrators in shaping physiological and pathological development of the skin. Besides, exogenous exosomes, such as stem cell exosomes, can serve as novel treatment options to repair, regenerate, and rejuvenate skin tissue. Herein, we review new insights into the role of endogenic and exogenous exosomes in the skin microenvironment and recent advances in applications of exosomes related to dermatology and cutaneous medical aesthetics. The deep understanding of the mechanisms by which exosomes perform biological functions in skin is of great potential to establish attractive therapeutic methods for the skin.

1. Introduction

Skin is the largest physical, chemical, and immunological barrier organism of the body, which is composed of the epidermis, dermis, and subcutaneous tissue [1]. The external outermost layer is the 10–20 μm thick stratum corneum containing 10–15 layers of interdigitated dead cells. The second layer is called the viable epidermis in 100–150 μm thick, mostly composed of keratinocytes at various stages of

Abbreviations: MSCs, Mesenchymal Stem Cells; CM, Conditioned Medium; HDFs, Human Dermal Fibroblasts; HaCaTs, Human Keratinocytes; HUVECs, Human Umbilical Vein Endothelial Cells; BMSCs, Bone Marrow MSCs; uMSCs, Umbilical Cord-derived MSCs; ADSCs, adipose-derived MSCs; iPSC-MSCs, Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells; HFSCs, Hair Follicle Stem Cells; DPCs, Dermal Papilla Cells; HF, Hair Follicle; ORSCs, Outer Root Sheath Cells; ECM, Extracellular Matrix; ROS, Reactive Oxygen Species; MMP, Matrix Metalloproteinase; IFN-γ, Interferon Gamma; IFN-α, Interferon Alpha; TNF-α, Tumor Necrosis Factor Alpha; TGF-β, Transforming Growth Factor Beta; IL, Interleukin; VEGF, Vascular Endothelial Growth Factor; FGF, Fibroblast Growth Factor; Shh, Sonic Hedgehog; SA-β-gal, Senescence-Associated β-galactosidase; UV, Ultraviolet; 3D, Three-Dimensional; H2O2, Hydrogen Peroxide; I/R, Ischemia-Reperfusion; MAPKs, Mitogen-Activated Protein Kinases; AMPK, Adenosine Monophosphate Activated Protein Kinase; NF-κB, Nuclear Factor Kappa B; PI3K, Phosphatidylinositol-4,5-

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Cell Proliferation WILEY

REVIEW

Platelet-rich plasma-derived extracellular vesicles: A superior alternative in regenerative medicine?

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Abstract

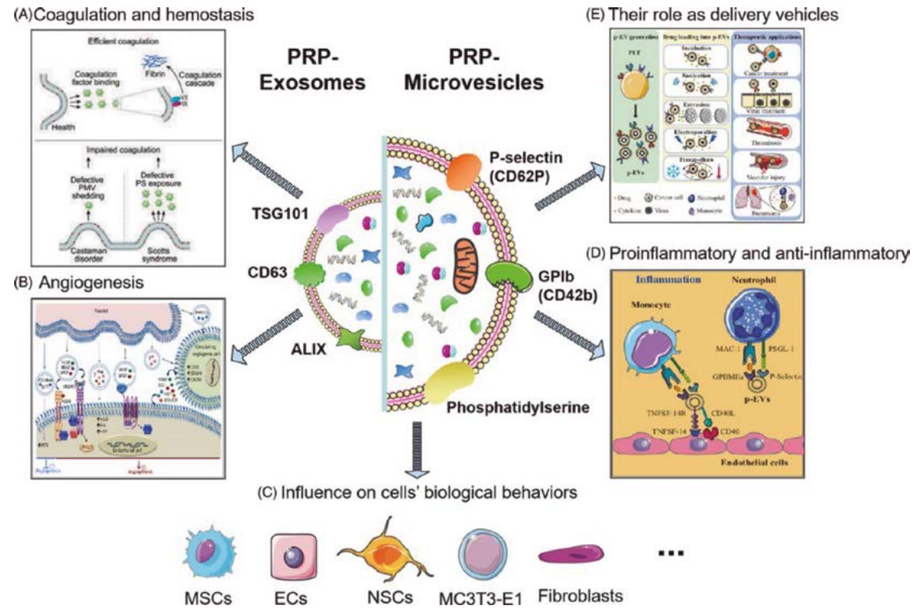
Platelet-rich plasma (PRP), due to its promising therapeutic properties, has been used in regenerative medicine for more than 30 years and numerous encouraging outcomes have been obtained. Currently, by benefiting from new insights into PRP mechanisms and the excellent performance of extracellular vesicles (EVs) in the field of tissue repair and regeneration, studies have found that a large number of EVs released from activated platelets also participate in the regulation of tissue repair. A growing number of preclinical studies are exploring the functions of PRP-derived EVs (PRP-EVs), especially in tissue regeneration. Here, we summarize the latest progress in PRP-EVs as a superior alternative cell-free therapeutic strategy in regenerative medicine, clarify their underlying molecular mechanisms, and discuss the advantages and limitations of the upcoming clinical applications. This review highlights the potential of PRP-EVs to replace the application of PRP or even become a superior alternative in regenerative medicine.

1 | INTRODUCTION

As the human population continues to age and the incidence of degenerative and traumatic diseases continues to increase, developing therapeutic strategies to repair and regenerate damaged tissues and restore their normal functions is the most important goal of regenerative medicine.[1] To date, the strategies of regenerative medicine have focused on using materials science and engineering techniques to develop novel biomaterials that can regulate cellular functions and activate their innate regenerative potential.[2–4] However, in recent decades, the potential of platelet-rich plasma (PRP) therapies promising, but there remain some disadvantages and limitations that need to be considered.

In the past couple of decades, the discovery of extracellular vesicles (EVs) has been one of the most revolutionary contributions to cell biology.[17] The ability of EVs to transport proteins, nucleic acids and lipids to target specific tissues and maintain the stability of therapeutic cargo makes EVs interesting as part of new strategies for the treatment of various diseases.[18] Similarly, EV-based subcellular therapies are expected to pave the way for the clinical application of regenerative medicine by overcoming the challenges of cell-based therapies. However, most recent preclinical studies in regenerative

Platelet-derived EVs: Unique characteristics and regenerative potential



Features between two different subtypes of platelet-derived EVs, PRP-Exosomes and PRP-Microvesicles. PRP-Microvesicles are characterized by a high expression of P-selectin (CD62P), GPIb (CD42b), and phosphatidylserine (PS). Similarly, PRP-Exosomes are characterized by a high expression of marker proteins of exosomes, such as CD9, CD63, TSG101 and ALIX. PRP-EVs have been found to participate in five main underlining mechanisms concerning regenerative medicine: procoagulant activity and hemostasis (A), angiogenesis (B), the influence on cells' biological behaviors (C), pro-inflammatory and anti-inflammatory properties (D), and delivery vehicles (E). Adapted and extracted from Wu, J. et al. (2021). Platelet-rich plasma-derived extracellular vesicles: A superior alternative in regenerative medicine? *Cell Proliferation.*

REVIEWS PUBLICATION

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Effect of Photobiomodulation on Platelet-Rich Plasma: Review Series on New Tools in Regenerative Medicine

Review

Effect of Photobiomodulation on Platelet-Rich Plasma: Review Series on New Tools in Regenerative Medicine

Hernán Pinto[1], Elena Sánchez-Vizcaíno Mengual[1]

[1]Instituto de Investigaciones Biomédicas i2e3, Santa Coloma de Gramenet, Spain

Short title: Photobiomodulation and Platelet-Rich Plasma

Abstract

Objective: platelet-rich plasma is one of the blood-derived autologous biological products, that has now become a therapeutic tool. Though its properties have not been fully elucidated yet, the ease of its sample obtention, product processing, and patient application, along with the good results obtained, has extended its application to many medical specialties such as orthopedics, sports, and aesthetic medicine, or gynecology. Lately, photobiomodulation has been presented as an effective PRP activator, resembling what occurs on mesenchymal cells that have been widely studied. This article aims to give a modern view on PRP and its activation through photobiomodulation.
Methods: A review series was carried out in PubMed, Cochrane, and Scopus to find articles about studies done on humans on PRP and photobiomodulation.
Results: a total of five studies with small samples were found. In all of them, the activation with photobiomodulation had positive results.
Conclusion: photobiomodulation showed great potential for PRP activation. However, more studies must be carried out to establish the appropriate protocols with which all potential clinical benefits can be obtained.

Keywords

Photobiomodulation, photoactivation, platelet-rich plasma, platelet, infrared, near-infrared

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REVIEW

BASIC SCIENCE/EXPERIMENTAL

The Effect of Photobiomodulation on Human Mesenchymal Cells: A Literature Review

Hernán Pinto[1] · Paloma Goñi Oliver[1] · Elena Sánchez-Vizcaíno Mengual[1]

Received: 11 October 2020 / Accepted: 3 February 2021

Abstract

Background Mesenchymal stem cell-based therapy is known to have the potential to induce angiogenesis. However, there are still some limitations regarding their clinical application. Photomodulation/photobiomodulation is non-invasive and non-toxic phototherapy able to stimulate cell viability, proliferation, differentiation, and migration, when the right irradiation parameters are applied. A review of the published articles on human conditioned-by-photobiomodulation mesenchymal cells in an in vitro set up was carried out. Our aim was to describe the studies' results and identify any possible tendency that might highlight the most suitable procedures.

Methods A search in English of the PubMed database was carried out with the search criteria: photobiomodulation or photoactivation or photomodulation, and mesenchymal cells. All irradiations applied in vitro, on human mesenchymal cells, with wavelengths ranged from 600 to 1000 nm.

Results The search yielded 42 original articles and five reviews. Finally, 37 articles were selected with a total of 43 procedures. Three procedures (7.0%) from 620 to 625 nm; 26 procedures (60.5%) from 625 to 740 nm; 13 procedures (30.2%) from 740 to 1000 nm; and one procedure (2.3%) with combinations of wavelengths. Of the 43 procedures, 14 assessed cell viability (n = 14/43, 32.6%); 34 cell proliferation (n = 34/43, 79.1%); 19 cell differentiation (n = 19/43, 44.2%); and three cell migration (n = 3/43, 7.0%).

Conclusions Photobiomodulation is a promising technology that can impact on cell viability, differentiation, proliferation, or migration, leading to enhance its regenerative capacity.

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Keywords Photobiomodulation · Mesenchymal cells · Low-level laser · Cell conditioning · Irradiation · Cell regeneration

Introduction

Mesenchymal stem cell-based therapy is known to have the potential to induce angiogenesis, primarily through the

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Role of opsins and light or heat activated transient receptor potential ion channels in the mechanisms of photobiomodulation and infrared therapy

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[c] Laser Research Centre, Faculty of Health Science University of Johannesburg, Doornfontein 2028, South Africa
[d] Radiation Biology Research Center, Iran University of Medical Sciences, Tehran, Iran

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Infrared therapy
IR emitting fabrics
Mitochondrial chromophores
Transient receptor potential ion channels
Opsins
Nanostructured water

ABSTRACT

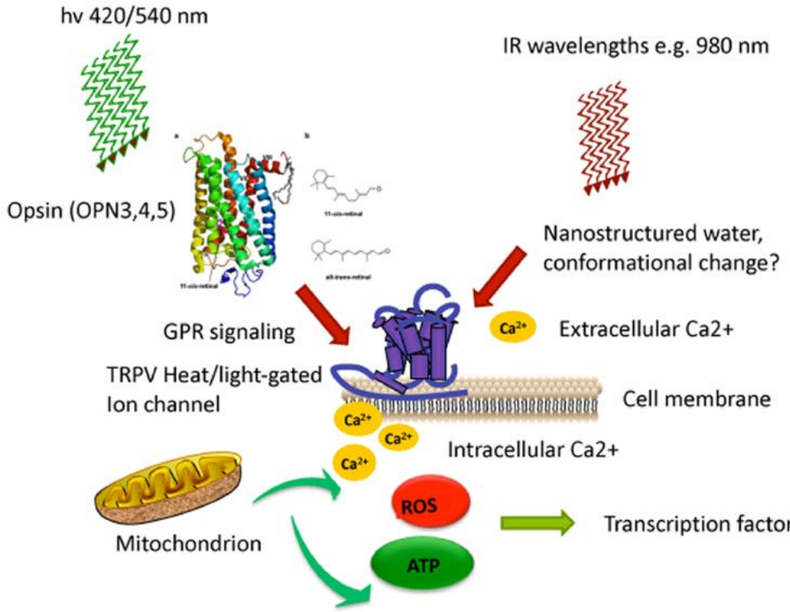
Photobiomodulation (otherwise known as low level light therapy) is an emerging approach for treating many diseases and conditions such as pain, inflammation, wound healing, brain disorders, hair regrowth etc. The light used in this therapy generally lies in the red and near-infrared spectral regions. Despite many positive studies for treating different conditions, this therapy still faces some skepticism, which has prevented its widespread adoption in clinics. The main reasons behind this skepticism are the lack of comprehensive information about the molecular, cellular, and tissular mechanisms of action, which underpin the positive effects of photobiomodulation. Moreover, there is also another therapeutic application using longer wavelength infrared radiation, involving either infrared saunas or heat lamps which are powered by electricity, as well as infrared emitting textiles and garments which are solely powered by the wearer's own body heat. In recent years, much knowledge has been gained about the mechanism of action underlying these treatments, which will be summarized in this review. There are three broad classes of primary chromophores, which have so far been identified. One is mitochondrial cytochromes (including cytochrome c oxidase), another is opsins and light or heat-sensitive calcium ion channels, and a third is nanostructured water clusters. Light sensitive ion channels are activated by the absorption of light by the chromophore proteins, opsin-3 and opsin-4, while mitochondrial chromophores are activated by red or near-infra red (NIR) light up to about 850 nm. However NIR light at 980 nm or longer wavelengths can activate transient receptor potential (TRP) ion channels, probably after being absorbed by nanostructured water clusters. Heat-activated TRP channels undergo a conformational change triggered by only small temperature changes. Here we will discuss the role of opsins and light or heat activated TRP channels in the mechanism of photobiomodulation and infrared therapy.

1. Introduction

Photobiomodulation (PBM) or low-level light therapy employs a light source of an appropriate wavelength and intensity to treat different diseases or conditions. In the past few decades, several studies have reported the efficacy of PBM as a treatment for various diseases and injuries, such as diabetes, brain injury, spinal cord damage, dermato- have been used for centuries in certain cultures for their health-giving benefits [2]. However, recently the use of IR saunas and IR heat lamps has become popular [3]. Another application uses IR emitting ceramic minerals, which are incorporated into fabrics or garments, and are solely powered by the wearers own body heat [4].

There is still uncertainty about the molecular, cellular, and tissular mechanisms of action of PBM and IR therapy, and whether there is any

Illustration of the possible involvement of heat/light-gated TRPV ion channels in PBM and IR therapy



Blue or green wavelengths could be absorbed by opsins based on photoisomerization of a retinal cofactor leading to GPR signaling which opens TRPV ion channels. Infrared (IR) wavelengths could be absorbed by nanostructured water leading to a conformational change in the protein, which also opens TRPV ion channels. The influx of calcium affects mitochondria in the cells producing increased ATP and a brief burst of ROS. Eventually transcription factors are activated leading to long-lasting changes in the tissue. Extracted from Sharma, S. K. et al. (2023). Role of opsins and light or heat activated transient receptor potential ion channels in the mechanisms of photobiomodulation and infrared therapy. *Journal of Photochemistry and Photobiology.*

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