Aesth Plast Surg (2019) 43:457–469
https://doi.org/10.1007/s00266-018-1256-1

ORIGINAL ARTICLE NON-SURGICAL AESTHETIC

Problems and Solutions for Platelet-Rich Plasma in Facial Rejuvenation: A Systematic Review

Xiaoxuan Lei[1,2] · Pengcheng Xu[2] · Biao Cheng[1,2]

Received: 24 August 2018 / Accepted: 2 October 2018 / Published online: 16 October 2018

Abstract

Background In recent years, platelet-rich plasma (PRP) has been widely applied in orthopedics, maxillofacial surgery, burns, and plastic surgery, especially in facial rejuvenation. Research is ongoing into new indications and mechanisms of PRP to promote its wider, safer, and more effective use in the clinic. This article reviews the possible mechanisms of PRP in facial rejuvenation and related research. It is expected that the application of PRP in this field will increase.

Methods The use of PRP in facial rejuvenation was screened using inclusion and exclusion criteria. The relevant articles were searched through Pubmed digest database, SCI full-text database, ScienceDirect full-text database, and the CNKI full-text database. The different effects and limitations of PRP were extracted.

Results A total of 108 articles were obtained, including 18 articles researching PRP in cells, 10 articles on animal research using PRP, 16 articles on the clinical study of PRP, 24 articles involving signs of skin aging, and four articles on the limitations of PRP. The remaining articles were related to the preparation of PRP, the introduction of PRP, and other aspects.

Conclusion Based on in vitro and in vivo research, PRP may play a role in promoting tissue regeneration, oxidative stress and revascularization, which form the theoretical basis for the use of PRP in the clinical treatment of facial rejuvenation.

Level of Evidence III This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords PRP · Facial rejuvenation · Skin aging · Wrinkles

Introduction

With increasing material wealth and spiritual life, people are paying increased attention to body aging problems, especially facial aging. The main clinical signs of facial aging include changes to the skin and soft tissue (such as fat tissue), ligament, muscles, bone and other structural changes that leads to facial wrinkles; abnormal secretion of sebum leading to large pores; pigmentation caused by abnormal pigment metabolism; gravity, lost capacity, muscle atrophy, support ligament relaxation, and bone resorption leading to skin laxity and collapse; and aging and hormonal disorders leading to hair loss.

Subcutaneous injection of various fillers and muscle control invasive surgery are common clinical treatments [1–3]. In recent years, platelet-rich plasma (PRP) has been widely used in patients for facial rejuvenation, with good clinical effects. PRP is a platelet concentrate obtained after centrifugation of autologous whole blood, the main components of which are platelets and fibrin, with or without leukocytes [4]. After platelet activation, the platelets degranulate and secrete a variety of growth factors, cytokines, microRNAs (miRNA) and other active

✉ Biao Cheng
chengbiaocheng@163.com

[1] The Graduate School of Southern Medical University, Guangzhou 510515, China

[2] Center of Wound Treatment, Guangzhou General Hospital of Guangzhou Military Command, Guangzhou 510010, China

molecules to promote tissue repair and regeneration. Studies have shown that over 800 proteins are present in this matrix [5], such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor 1 (IGF-1). These proteins act on the target cells through paracrine, autocrine, endocrine, and other means, affecting various cell types, including osteoblasts [6], fibroblasts [7], endothelial cells [8], and different sources of mesenchymal stem cells [9]. Various types of growth factors bind to cell surface receptors, activating cell signaling pathways, which results in the expression of genes and the synthesis of various proteins required for tissue repair and regeneration [10]. PRP has been widely used in plastic surgery, orthopedics, oral and maxillofacial surgery, dermatology, and other departments. The concentration of purified PRP varies because of its different preparation methods, resulting in significant differences in its clinical effect [11–14]. In this paper, we searched the PubMed digest database, the SCI full-text database, the ScienceDirect full-text database, and the CNKI full-text database to identify papers related to the application of PRP in facial rejuvenation and then performed a systematic review.

Materials and Methods

Search Strategy

Articles were searched for using the PubMed digest database, the SCI full-text database, the ScienceDirect full-text database, and the CNKI full-text database. The search terms used were "platelet rich plasma[Title/Theme]". In addition, references of selected articles were searched to analyze whether the references met our requirements.

Inclusion and Exclusion Criteria

Articles related to the application of PRP in facial rejuvenation, including cell research, animal research, clinical research, and the signs of skin aging were included. Articles related to the preparation of PRP and the limitations of PRP were also included, while articles involving orthopedics and the application of PRP in other diseases were excluded. Non-science Citation Indexed articles and comments were also excluded.

Article Selection

We analyzed all the retrieved articles using the inclusion and exclusion criteria. The appropriate references were cited based on the following standards: Study type, publication year, SCI factor, citation frequency, the preparation method of PRP, the application of PRP, the effect of PRP and so forth.

Results

After removing duplicates, the database search retrieved 2210 articles. Using the inclusion and exclusion criteria, 108 articles were included. There were 18 studies on cell research with PRP, 10 articles were related to animal research using PRP, 16 articles were related to clinical research using PRP, 24 articles dealt with the signs of skin aging, and four articles dealt with PRP's limitations. The remaining articles were related to the preparation of PRP, the introduction of PRP, and so on (Fig. 1).

The Clinical Signs of Facial Aging

The main clinical signs of facial aging are wrinkles, large pores, pigmentation, skin laxity, and hair loss. With age, the functions of the sebaceous glands and sweat glands decline, and epidermal thickness decreases [15]. Reduction and degradation of extracellular matrix components (such as collagen, elastin, proteoglycan, and polysaccharides) cause dermal atrophy [16]. Decreased skin proliferation potential, the loss of response to growth factors, reduced production of type I and type III collagen, and overexpression of extracellular matrix-degrading proteases [17], the loss of fat capacity [18], and gravity gradually produce wrinkles. Ultraviolet radiation, smoking, and drinking can also lead to wrinkles [19, 20].

Pores are enlarged because old keratin in skin is poorly metabolized and blocks the pores. The old keratin mixes with the accumulated sebum in the pores to form a solid keratotic plug, which blocks the pores. Furthermore, with age, collagen and elastin become thin and fragile, and cannot effectively support the skin, leading to skin laxity around the pores, which also results in enlarged pores [21, 22].

Pigmentation is caused by a variety of factors, including age, endocrine disorders (estrogen deficiency), genetic factors, UV exposure, drugs, diet, light sensitivity, specific physiology, and mood [23, 24]. Pigmentation is divided into immediate pigment darkening (IPD) and delayed tanning (DT). IPD is mainly caused by the redistribution of melanosomes. DT is mainly caused by melanocyte proliferation, the increase in dendrites and melanosomes, increased melanin synthesis, and the transport of melanosomes to keratinocytes [25–27]. Tagashira et al. [28] demonstrated that ultraviolet light stimulates the endothelin B receptor, which is a paracrine factor of melanocytes and keratinocytes, further activating melanogenesis associated

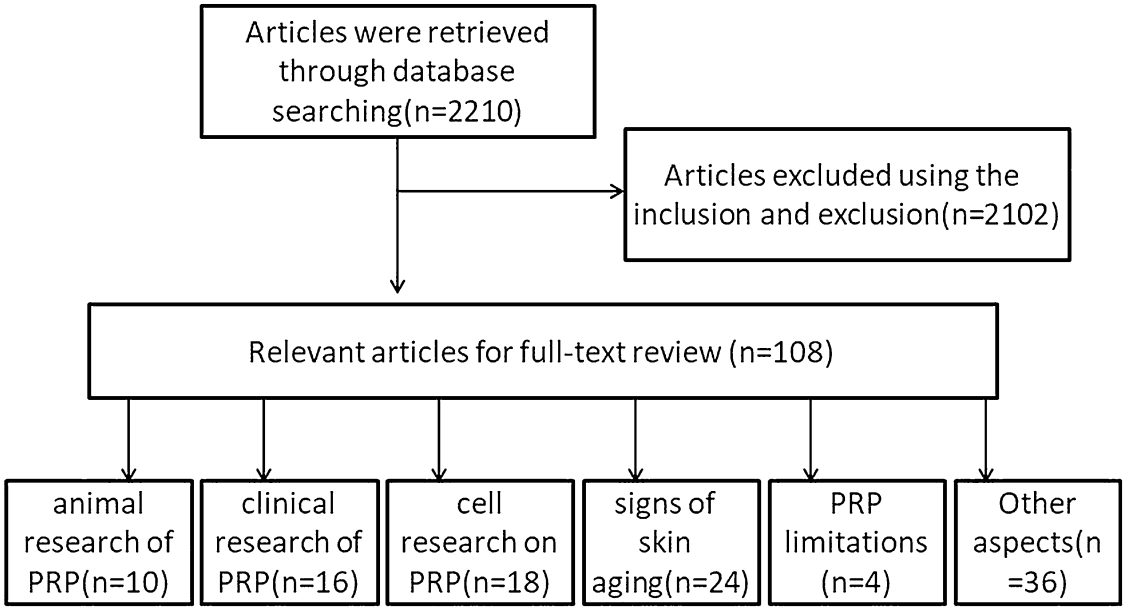

Fig. 1 A flow diagram of article retrieval method

transcription factor (MITF) to promote melanogenesis. Marin-Castaño et al. [29] found that estrogen deficiency could lead to disordered extracellular matrix synthesis and degradation, leading to the accumulation of collagen, and causing pigmentation.

Sagging skin is caused by age, genetics, disease, gravity and other factors. With aging, the cell structure of skin has corresponding changes. Decreased numbers of fibroblasts, reduced collagen production, decreased barrier of the stratum corneum, lower fat capacity, relaxation of the ligaments of the facial soft tissue, bone resorption, and the effects of gravity finally lead to facial skin sagging [30–35].

The growth cycle of hair follicles includes a growth phase, degenerative phase, quiescent phase, and shedding phase. If the growth phase is terminated prematurely, it leads to alopecia [36]. Alopecia is caused by a variety of factors, such as aging, medication (e.g., chemotherapy, high-dose vitamin A, and antidepressants), neuroendocrine factors. Elevated levels of dihydroxy testosterone (DHT, a testosterone metabolite) shorten the hair cycle and gradually reduce the number of hair follicles [37]. Excess sebum elevates 5-alpha reductase levels and clog pores, which causes hair root malnutrition. Harmful substances in tobacco can damage vascular endothelial cells and reduce the production of nitric oxide, leading to hair loss. In addition, genetic factors (androgenic alopecia), mental and emotional stress, unbalanced diet, malnutrition, and severe illness can also lead to hair loss [38].

The Cell Research of PRP

When PRP acts on damaged or aged skin tissue, platelets degranulate to release a large number of growth factors. These growth factors attract inflammatory cells and fibroblasts, stimulate collagen synthesis and endothelial sprouting, causing a series of intracellular skin reactions, including triggering gene expression [10, 39]. Platelet-derived growth factor (PDGF) stimulates cell mitosis during injury repair, and recruits neutrophils, macrophages, and fibroblasts [40]. In addition, PDGF stimulates macrophages to produce and secrete growth factors, such as TGF-β [41]. TGF-β is involved in the production of collagen, especially type I and type III, and can effectively inhibit the matrix metalloproteinases MMP-1, MMP-3, and MMP-9, which further inhibits collagen breakdown [42, 43]. Collagen formation can improve skin elasticity and wrinkles. PDGF can upregulate the synthesis of IGF-1 and thromboxane-1 in epidermal regeneration. IGF-1 can increase the vitality of keratinocytes and promote their formation [44]. IGF-1 can also enhance skin barrier function and resist external stimulation. The dimeric PDGF, PDGF-BB, is involved in tissue repair and promotes the synthesis of extracellular matrix, collagen, and neovascularization by promoting the proliferation of fibroblasts [45, 46]. Vascular Endothelial Growth Factor (VEGF) promotes the formation of three-dimensional blood vessels in vitro and induces the infiltration of microvascular endothelial cells into collagen gels to form capillary-like structures [47]. In vitro, VEGF inhibits endothelial cell apoptosis through the phosphatidylinositol 3-kinase (PI3 K)-mediated PI3K/Akt

pathway [48], promotes endothelial cell proliferation and blood vessel formation, and increases vascular permeability y [49]. The epidermal growth factor receptor (EGFR) is mainly secreted by platelets, macrophages, and monocytes [50]. EGF is involved in regulating cell proliferation, migration, adhesion, and inflammation after binding to its receptor [51].

Bertrand-Duchesne et al. [52] cultured venous endothelial cells by removing EGF from PRP using antibody-coated beads, and found that the proliferation of venous endothelial cells was significantly decreased. Supplementation with recombinant human EGF increased the proliferation of human venous endothelial cells in a dose-dependent manner. Kim et al. [53] cultured human epidermal fibroblasts in vitro and found that the expression of type I collagen, and the MMP-1 protein and mRNA was significantly increased by the application of 5% PRP. Accumulation of newly synthesized collagen can improve the integrity of the extracellular matrix of the skin and stimulate fibroblasts to produce more collagen, thereby increasing facial elasticity. Li et al. [54] cultured human adipose stem cells in vitro. One group was supplemented with 10% PRP and neuroinductive medium and the other received neuroinductive medium only. Two weeks later, the neural induction of adipose stem cells was detected. The results showed that the levels of neuron-specific enolase, annexin growth-associated protein (GAP-43), neuronal cell adhesion molecule (NCAM), and synaptophysin 1 were significantly higher in the PRP/neuroinductive medium group than in the neuroinductive medium alone group. These results showed that PRP could promote cell proliferation and neural differentiation of adipose stem cells in vitro. Kakudo et al. [55] cultured human adipose-derived stem cells and epidermal fibroblasts with activated PRP at concentrations of 1, 5, 10, and 20%. At 5% PRP, cell proliferation was significantly increased; however, 20% PRP did not significantly promote cell proliferation. Sadoghi et al. [56] cultured human rotator cuff fibroblasts in vitro with 1, 5, and 10% PRP. After 21 days of culture, the fibroblasts were maximally stimulated at 5% PRP, which suggested that 5% PRP could maximally stimulate cell proliferation. Xian et al. [57] co-culture human keratinocytes and fibroblasts in vitro with 10 and 20% PRP and found that the growth rate of keratinocytes was higher in 10% PRP, and hepatocyte growth factor and monocyte chemokine-1, neutrophil activator protein 78, and vascular endothelial growth factor had higher expression levels. At 20% PRP, the expression of type I and III collagen and secreted granulocyte–macrophage colony-stimulating factor were increased.

Leukocytes in PRP are also involved in facial rejuvenation. Sclafani [39] believed that leukocytes in PRP mainly release matrix MMPs and collagenase from neutrophils and monocytes, and promote the degradation of the extracellular matrix. However, macrophages can remove tissue debris and initiate tissue repair. Matrix metalloproteinases can induce new collagen regeneration by removing harmful collagen fragments and skin connective tissue. Thus skin rejuvenation may be explained by the promoting of tissue regeneration.

Cytologically, PRP can regulate the secretion of biological factors and the proliferation and differentiation of many kinds of cells. PRP promotes collagen regeneration and angiogenesis, reduces pigment secretion, and further promotes facial rejuvenation (Table 1).

PRP Research in Animals

Cho et al. [71] produced photo-aging models from 30 nude mice exposed to ultraviolet radiation for 8 weeks and then divided them into three groups. One group received no treatment, one group received saline injection, and the other was injected with PRP. Subsequently, the formation of wrinkles in the three groups was observed and tissues were taken for analysis. There were significantly fewer wrinkles in the nude mice injected with PRP than in the other two groups. Dermal thickness, fibroblast proliferation, and collagen synthesis were significantly higher in the PRP group than in the other two groups.

Bhang et al. [72] constructed skin wound models in 6-week-old female athymic nude mice and divided them into four groups. One group was not treated, one group was treated with PRP, one group was treated with human adipose-derived mesenchymal stem cells, and the last group was treated with PRP and human mesenchymal stem cells. The results showed that the skin regeneration in the nude mice injected with PRP with human mesenchymal stem cells was good, and the proliferation of wound neovascularization was significant. PRP could promote secretion of growth factors by human mesenchymal stem cells and their proliferation, and enhanced tissue repair. Liu et al. [73] injected PRP into the bone marrow of OVX–SAMP8 rats once a month and found that PRP could restore cell aging, promote cell proliferation, increase osteogenesis, reduce fat formation, and resist cell aging, thus achieving anti-aging effects. Aging delay was mainly reflected in the survival time and aging phenotype.

Miao et al. [74] transplanted isolated epidermal cells, hair papilla cells, and activated PRP mixture on the back skin of 7–9-week-old male nude mice and monitored the formation of hair follicles for 4 weeks. The number of new hair follicles in the PRP group was higher in the transplanted area than that in the control group, and PRP shortened hair cycle in the long-term. Houdek et al. [75] created a full-thickness skin wound on SD rats and implanted a PRP hydrogel formed by PRP and type I

Table 1 The effects of PRP on various types of cells in vitro

Cell type	PRP preparation (activation method)	PRP concentration	The effect of PRP	First author [Ref. no]
Keratinocyte	No data (thrombin)	5% PRP	Promoted keratinocyte proliferation and epithelial differentiation	Xiao et al. [58]
Pigment cells	3000 rpm/5 min, then 3000 rpm/5 min	No data	Reduced melanin production and pigmentation	Shin et al. [59]
	1600–1800 g/6 min, then 2000 g/5 min	No data		Mehryan et al. [60]
Fibroblasts	3000 rpm/7 min, then 4000 rpm/5 min (calcium chloride/thrombin mixture)	5% PRP	Promoted cell proliferation, increased the expression of type I and type III collagen	Kim et al. [53]
	1700 rpm/7 min, then 3200 rpm/5 min (calcium chloride/thrombin mixture)	5% PRP		Kakudo et al. [55]
	No data	Fivefold PRP concentration		Sadoghi et al. [56]
	100 g/15 min, then 600 g/5 min	20% PRP		Xian eeet al. [57]
Endothelial cells	3000 rpm/7 min, then 4000 rpm/5 min (calcium chloride/thrombin mixture)	No data	Promoted the proliferation of endothelial cells and the formation of capillaries in vitro, induced the expression of bone growth factor in endothelial cells	Mooren et al. [61]
	1700 rpm/7 min, then 3200 rpm/5 min (calcium chloride/thrombin mixture)	0.8 ml of 1% FCS medium and 0.2 ml PRP		Cenni et al. [62]
	No data	10% PRP		Li et al. [63]
	100 g/15 min, then 600 g/5 min	5% PRP		Kakudo et al. [64]
Macrophages	No data	No data	Promoted the proliferation of macrophages and dendritic cells and increased cell viability	Woodall et al. [65]
Dendritic Cells	300 g/20 min	No data		Czakai et al. [66]
Hair follicle stem cells	1100 g/10 min	No data	Promoted the increase in epidermis and hair follicle bulge cells, and increased of small blood vessels	Cervelli et al. [67]
Adipose stem cells	1500 rpm/10 min, then 3000 rpm/10 min	10% PRP	Promoted proliferation and multiple differentiation	Li et al. [54]
	215 dg/10 d min, then 863 g/10 min	5% PRP		Castro et al. [68]
Mesenchymal stem cells	2400 rpm/10 min, then 3600 rpm/15 min	No data	Promoted the differentiation and proliferation	Drengk et al. [69]
	200–300 g/15 min, then 1600 g/10 min	1% PRP		Murphy et al. [70]

collagen into the wound surface. The PRP hydrogel promoted the recruitment and differentiation of dermal-derived stem cells, thereby promoting the growth of hair and sebaceous glands. Kawazoe and Kim [76] compared the effect of PRP and leukocyte-rich platelet plasma on tissue hyperplasia using animal experiments and found that leukocyte-rich platelet plasma promotes tissue healing by promoting the formation of myofibroblasts to promote wound healing.

In animal research, PRP can promote collagen regeneration, fat transplantation survival, shorten the hair growth cycle, and promote hair growth (Table 2).

Clinical Research on PRP

In the clinic, botulinum toxins (Botox) are used to remove wrinkles. Botox interferes with the release of acetylcholine from the motor nerve endings, resulting in non-contraction of muscle fibers. However, there are many side effects of Botox, such as ptosis, local edema, ecchymosis, and facial stiffness [81]. For large pores, the most common treatment is a CO_2 laser. This results in three areas of thermal peeling, thermal coagulation, and thermal effects in the skin layer, which in turn cause a series of skin biochemical reactions and stimulate the skin to repair itself [82]. Intense pulsed light (IPL) technology can improve skin pigmentation. Through selective photothermolysis, it conducts heat to the blood vessel wall and causes damage to it. Finally, the thrombosis is absorbed. IPL can penetrate the

Table 2 The effect of PRP in various animal models

Animal type [Ref. no]	PRP preparation (activation method)	PRP dose	Age	Animal model	The effect of PRP	First author [Ref. no]
Female nude mice [71]	No data	1 ml	6-week-old	Photo-aging model	Promoted dermal thickness, fibroblast proliferation, and collagen synthesis	Cho et al. [71]
Female nude mice [72]	1500 rpm/10 min, then 3000 rpm/ 10 min	100 μl	6-week-old	Skin wound model	Promoted the secretion and proliferation of human mesenchymal stem cells and the recruitment and differentiation of dermal stem cells	Bhang et al. [72]
SD rats [75]	5500 g/3 h	No data	No data			[Houdek et al. 75]
ovx-samp8 rats [73]	3000 rpm/6 min	1 0 μl	1-month-old and 10-month-old	Ovarian aging model	Recovered the potential of cell aging, promoted cell proliferation, increased osteogenesis, reduced fat formation, resisted cell aging	Liu et al. [73]
Male nude mice [58]	No data	5%	No data	Hair follicle transplantation model	Promoted new hair follicle formation, shortened the hair growth cycle, promoted hair growth	Xiao et al. [58]
C57BL/6J female mice and nude male mice [74]	328 g/10 min, then 4975 g/10 min (calcium chloride)	10%	1–3 days old/ 5–6 weeks/ 7–9 week-old			Miao et al. [74]
FemaleC57BL/ 6 mice [77]	660 g/7 min, then 2350 g/5 min (calcium chloride/ thrombin minture)	100 μl	7-week-old			Li et al. [77]
Male nude mice [78] Inbred male	160 g/10 min, then 400 g/10 min (calcium chloride/ thrombin mixture)	0.21 ml	7-week-old	Fat transplantation model	Promoted fat survival, reduced fat liquefaction, necrosis, and promoted blood vessel growth	Oh et al. [78]
Fisher rats [79]	No data	1 ml	No data			Nakamura et al. [79]
New Zealand male rabbits [80]	1450 rpm/10 min, then 2100 rpm/ 10 min	1 ml	6-month-old			Pires et al. [80]

skin and be absorbed by melanocytes. This thermal effect also stimulates fibroblasts to secrete collagen [83]. In the clinic, autologous fat transplantation is commonly used to fill the cheeks, nasolabial folds, and sacral areas to improve facial skin relaxation [84]. However, the low graft survival rate represents a challenge. For hair loss, autologous hair transplantation is commonly used in clinical practice. The principle of hair implantation is to use microsurgical techniques to remove healthy hair follicles from donors and plant them in sparsely populated areas. However, the survival rate of hair transplantation is low, which limits its therapeutic effect [85].

PRP has multiple functions. Clinically, PRP can be used alone or in combination with lasers, biopolymer materials, and water light needles to achieve good results in facial rejuvenation treatment, especially in improving facial wrinkles, reducing pigmentation around the eyes, improving the elasticity of the skin's color texture, and treating hair loss.

The Use of PRP

Mehryan et al. [60] injected PRP into the infrapatellar area and periocular crow's feet of 10 patients to observe the recovery of wrinkles and underarm dark circles. After 3 months, the underarm dark circles of participants were significantly reduced, wrinkles were significantly improved, and they were satisfied with the results. Yuksel et al. [86] injected PRP into the forehead, ankle, jaw, and crow's feet of 10 subjects twice a week for a total of three injections. PRP significantly reduced wrinkles, improved sagging skin, promoted skin firmness and induced facial rejuvenation. Sclafani [87] injected platelet-rich fibrin intradermally, subcutaneously, or into the periosteum in 50 patients for a mean follow-up of 9.9 months. The treatment

range included deep nasolabial folds, atrophy of the middle facial area, superficial wrinkles, and acne scars. The patients received an average of 1.6 treatments. None of the patients experienced swelling that lasted for more than 5 days. Most of the patients were satisfied with the results of the treatment. Only one patient considered the improvement to be limited.

Gentile et al. [88] treated the alopecia patients with PRP. Half of the 23 patients had autologous PRP injected into their scalp and half of them were injected with saline. After 3 treatment cycles, the average number and density of hairs were increased in the PRP group. Under the microscope, the epidermal thickness, the number of hair follicles, and the density of small blood vessels were increased compared with those of the control group. Studies have shown that as the age of the patient increases, the ability for tissue regeneration gradually declines, the expression of growth factor receptors decreases, and the ability of fibroblasts to produce collagen is reduced [89]. Vavken et al. [90] confirmed that young fibroblasts respond well to PRP treatment. Furthermore, as age increases, the tissue regeneration ability is poor and the expression of the cell growth factor receptor is reduced, resulting in poor PRP action [91]. At present, there are few reports of age-related changes in the response to PRP in facial rejuvenation. However, young fibroblasts respond well to PRP treatment, which may imply that the regenerative ability of PRP will decline with age [90] (Table 3).

The Use of PRP with Other Technology

Shin et al. [59] used a CO_2 lattice laser to treat 22 Korean women, of which 11 cases were treated with the laser combined with PRP. The results showed that women treated with the plus PRP laser were more satisfied with the treatment effect, their skin elasticity was better, and the skin erythema index was lower than that of the women treated with the laser alone. PRP increased the length of the junction between the epidermis and the dermis, the content of collagen, and the number of fibroblasts. Nita et al. [96] used low-intensity carbon dioxide lasers combined with PRP for neck rejuvenation. They found that PRP could improve the survival rate of fat grafts and increase collagen synthesis. Gentile et al. [97] used PRP combined with fat transplantation to treat 50 women with breast soft tissue defects and found that PRP could improve the survival rate of fat transplantation and improve breast volume.

Garg performed hair transplants on 40 patients. One group was treated with PRP and one group was treated without PRP. PRP was observed to promote hair follicle proliferation, increase hair density, and reduce the loss of transplanted hair [98] (Table 4). Ulusal applied PRP with hyaluronic acid to treat 94 patients with different degrees of facial aging and found that the combination could improve skin texture, pigmentation, and facial relaxation, with high patient satisfaction [99] (Fig. 2).

Limitations

There are few reports of the side effects of PRP; however, PRP treatment may have serious complications. Kalyam et al. [104] reported one patient who was injected with PRP to treat eyebrow wrinkles who eventually suffered irreversible blindness of the right eye and infarctions of the optic nerve. This was the most serious complication of PRP reported in the paper; however, it may have been caused by operational errors and not PRP.

In this review, most of the articles we found only focused on the effects of PRP and few commented on its mechanism of action. The role of growth factors in facial aging is unclear. This review mainly analyzed the application of PRP in facial rejuvenation, but did not investigate other applications of PRP. In the retrieved studies, there was some confusion about the definition of leukocyte PRP, platelet-rich fibrin (PRF), platelet growth factors (PGF), and concentrate growth factors (CGF). In addition, some papers reported that PRP has a significant effect, whereas other papers reported no significant effect. This may be related to the different preparation process and treatment methods. There are many factors that could influence the efficacy of PRP, for example, the centrifugal force, centrifugation time, number of centrifugations, the activation method, donor age, gender, disease status, the number of platelets, and whether or not the PRP contains white blood cells [105–107]. The number of injections and the interval between them are also main factors affecting the efficacy of PRP. Thus, the lack of PRP standardization is the main problem with assessing its efficacy between studies.

Conclusion

This article reviewed the signs of skin aging and the multiple roles of PRP in promoting facial rejuvenation from cellular, animal, and clinical research aspects. The main clinical signs of facial aging include facial wrinkles, large pores, pigmentation, skin laxity, hair loss. Decreased skin proliferation potential, reduced production of collagen, the loss of fat capacity produced wrinkles. Abnormal pigment metabolism and sebum secretion caused pigmentation and large pores. Ligament relaxation and bone resorption lead to skin laxity. The numerous growth factors in PRP may present observed effects in facial rejuvenation. PDGF recruits macrophages and fibroblasts and stimulates macrophages to secrete growth factors, such as TGF-β,

Table 3 The use of PRP in facial rejuvenation

PRP treatment range	Sample size	Experimental design	PRP preparation (activation method)	PRP concentration ratio	PRP injection dose	Observation time	PRP effect	First author [Ref. no]
Infraorbital dark circle	10	Self-control study	1600–1800 g/6 min, then 2000 g/5 min	No data	1 ml	3 months	8 (+), 2 (−)	Mehryan et al. [60]
Wrinkles	10	Self-control study	3200 rpm/8 min	8 ml:1.5 m	No data	3 months	+	Yukse et al. [86]
	20		388 g/7 min, then 1376 g/5 min	18 ml:5–6 ml	No data	2/4/8 weeks	85% (+)	Elnehrawy et al. [92]
	134		1800 rpm/10 min, then 3200 rpm/10 min	9 ml:1 ml	0.4–0.6 ml	180 days	98.4 (+)	Kamakura et al. [93]
Deep nasolabial fold	50	Self-control study	1100 rpm/6 min	No data	No data	3–30 months	Most patients (+), 1 (−)	Sclafani [87]
	1461		1800 rpm/10 min, then 3200 rpm/10 min	9 ml:1 ml	2.0–2.5 ml	180 days	98.4% (+)	Kamakura et al. [93]
Alopecia	23	Randomized controlled study [88]	1100 g/10 min(Ca^{2+})	60 ml:9 ml	0.1 ml/cm^2	12 months	16 (+), 4 (−)	Gentile et al. [88]
	64	Self-control study [95]	No data	60 ml:6–8 ml	0.2–0.3 ml/each injection 8–12 ml	6 months	62 (+), 2 (−)	Schiavone et al. [94]
	10	[96]	1500 rpm/6 min, then 2500 rpm/15 min (calcium chloride)	20 ml:4 ml		3 months	10 (+)	Singhal et al. [95]

+ represents a significant effect; − represents no significant effect

Table 4 The use of PRP with other technologies in facial rejuvenation

Combination	Sample size	experimental design	PRP preparation (activation method)	PRP concentration ratio	Observation time	PRP effect	First author [Ref. no]
PRP versus laser	22	Randomized controlled study	3000 rpm/5 min (calcium chloride)	12 ml:3 ml	1 month	Improved facial	Shin et al. [59]
	13	Randomized, double-blind controlled study	1200 rpm/min, then 3500 rpm/5 min (calcium gluconate)	30 ml:15 ml	3 months	wrinkles, skin elasticity and texture	Hui et al. [100]
PRP versus hair transplantation	40	Randomized controlled study	3200 rpm/4 min	20 ml:3 ml	2/4/8 weeks, 3/6 months	Promoted hair regrowth and increased hair density	Garg [98]
	41	A retrospective study	1500 g/5 min	16 ml:3 ml	6 months		Rossano et al. [101]
PRP versus hyaluronic acid	94	Self-control study	1800 rpm/20–50 min	No data	3/6 months	Improved skin firmness-sagging, skin texture and minimized the skin pores	Ulusal [99]
	31	A prospective study	No data	No data	6 months		Hersant et al. [102]
PRP versus fat transplantation	82	Randomized controlled study	3000 rpm/15 min (calcium chloride)	27 ml:3 ml	3 months	Improved the aesthetic outcome	Willemsen et al. [103]

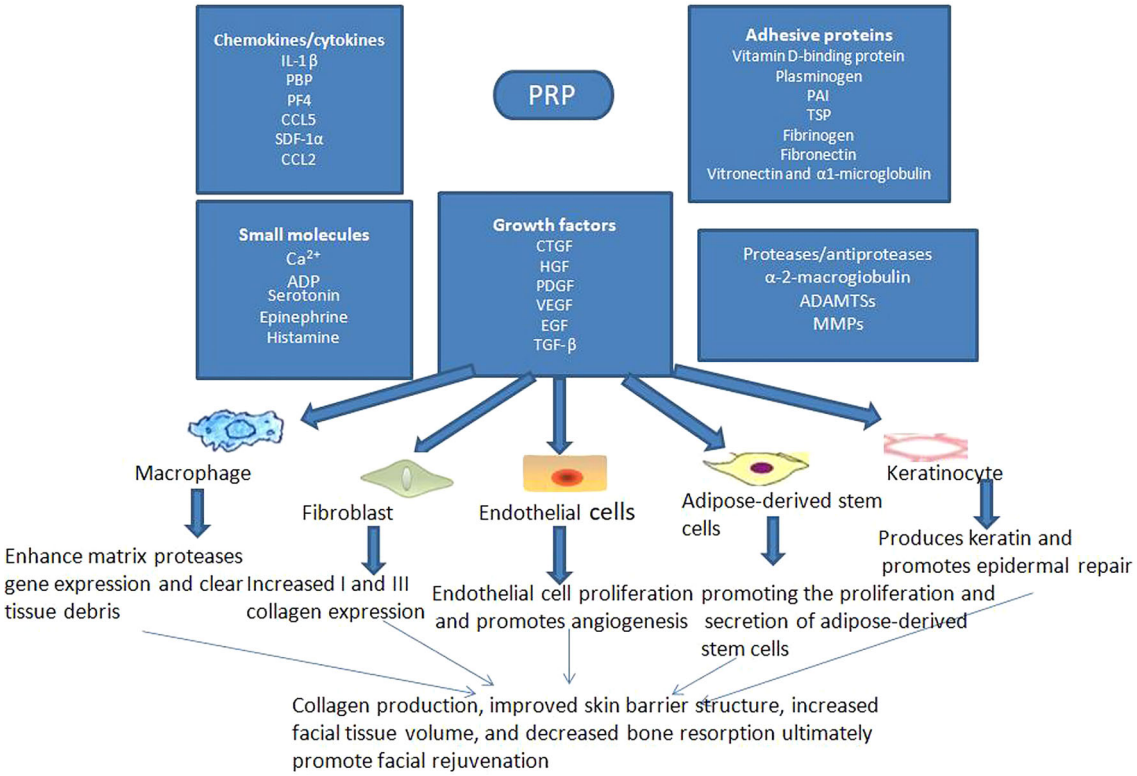

Fig. 2 The multiple effects of PRP in facial rejuvenation

then produce collagen [42, 43]. Collagen formation can improve skin elasticity and wrinkles. IGF-1 can also enhance skin barrier function and resist external stimulation. VEGF promotes endothelial cell proliferation and blood vessel formation. EGF promotes cell differentiation and re-epithelialization [61, 64]. PRP can promote the proliferation and multiple differentiation of adipose-derived stem cells, then improve the loss of fat volume [54, 68]. PRP can also promote new hair follicle formation and shorten the hair growth cycle, then promoted hair growth [58, 74]. However, the mechanism of action for these observed effects is still unknown. Many studies are merely superficial observations.

In this article, cellular research showed that PRP could promote the proliferation of fibroblasts, endothelial cells, and hair follicle stem cells, thereby promoting angiogenesis and collagen formation, increasing the number of hair follicles, and reducing pigmentation. In animal studies, PRP was demonstrated to increase the proliferation and differentiation of stem cells in animal models, increase the proliferation of collagen fibers, and promote fat transplantation and hair follicle transplantation survival. In the clinic, PRP, alone or in combination, can improve wrinkles, reduce pigmentation, improve pore size, improve skin relaxation, and promote hair growth. Facial aging is not only manifested in the generation of dynamic wrinkles, loose skin, and the formation of age spots, but also in the relaxation of ligaments, atrophy of the fat compartment, and decreased muscle elasticity and bone absorption. Whether PRP has a therapeutic effect on ligaments, muscle elasticity, and bone resorption requires further study.

PRP contains a large number of growth factors and active substances. The ratio of growth factors is similar to that in vivo. PRP is convenient to prepare, easy to source, low cost, and simple to administer. PRP has also been clinically proven to be safe and effective. The good efficacy of PRP may be related to paracrine effects, stem cell regulation, and oxidation–reduction balance. However, the biggest problem with biological therapy or cell therapy is stability. This is the basis for the importance of quality control. How to control PRP standardization is the main problem. The description of the concept of PRP-related platelet concentrates in the selected studies varied and the classification was also inconsistent. This can easily lead to confusion and inconvenience to those engaged in related scientific research. Therefore, it is necessary to regulate the preparation and purification methods of PRP, and classify the concept of PRP. There are few reports and relevant literature on the mechanism of PRP in promoting facial rejuvenation. In addition, PRP may play a role in oxidative stress, anti-aging and other aspects which provides a new

theoretical basis and therapeutic targets for facial rejuvenation.

Acknowledgements This study was supported by the National Natural Science Foundation of China (No. 81171812, No. 81671924, and No. 81272105), the National Key Research and Development Plan of China (No. 2017YFC1103301), the National Basic Science and Development Program (No. 2012CB518105), Health and Medical Treatment Collaborative Innovation Major Special Projects of Guangzhou (No. 201508020253), the Science and Technology Program of Guangzhou (201508020115), and Science and Technology Project of Guangdong province (No. 2014B020212010, No. 508113150092, No. 2015A010101313, and No. 2017A050506011).

Compliance with Ethical Standards

Conflict of interest The authors declared that they have no conflicts of interest in this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

References

1. Innocenti M, Ramoni S, Doria C, Antropoli C, Garbagna N, Grossi E, Veraldi S (2010) Treatment of periocular wrinkles with topical nifedipine. J Dermatolog Treat 21:282–285
2. Gold MH, Biron JA, Sensing W (2016) Facial skin rejuvenation by combination treatment of IPL followed by continuous and fractional radiofrequency. J Cosmet Laser Ther 18:2–6
3. Beeson W, Woods E, Agha R (2011) Tissue engineering, regenerative medicine, and rejuvenation in 2010: the role of adipose-derived stem cells. Facial Plast Surg 27:378–387
4. Harrison P, Cramer EM (1993) Platelet alpha-granules. Blood Rev 7:52–62
5. Garcia BA, Smalley DM, Cho H, Shabanowitz J, Ley K, Hunt DF (2005) The platelet microparticle proteome. J Proteome Res 4:1516–1521
6. Mazzocca AD, McCarthy MB, Chowaniec DM, Dugdale EM, Hansen D, Cote MP, Bradley JP, Romeo AA, Arciero RA, Beitzel K (2012) The positive effects of different platelet-rich plasma methods on human muscle, bone, and tendon cells. Am J Sports Med 40:1742–1749
7. Browning SR, Weiser AM, Woolf N, Golish SR, San Giovanni TP, Scuderi GJ, Carballo C, Hanna LS (2012) Platelet-rich plasma increases matrix metalloproteinases in cultures of human synovial fibroblasts. J Bone Joint Surg Am 94:e1721–e1727
8. Freire V, Andollo N, Etxebarria J, Duran JA, Morales MC (2012) In vitro effects of three blood derivatives on human corneal epithelial cells. Invest Ophthalmol Vis Sci 53:5571–5578
9. Cho HS, Song IH, Park SY, Sung MC, Ahn MW, Song KE (2011) Individual variation in growth factor concentrations in platelet-rich plasma and its influence on human mesenchymal stem cells. Korean J Lab Med 31:212–218
10. Alsousou J, Thompson M, Hulley P, Noble A, Willett K (2009) The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. J Bone Joint Surg Br 91:987–996
11. Edelblute CM, Donate AL, Hargrave BY, Heller LC (2015) Human platelet gel supernatant inactivates opportunistic wound pathogens on skin. Platelets 26:13–16
12. Dhillon RS, Schwarz EM, Maloney MD (2012) Platelet-rich plasma therapy—future or trend? Arthritis Res Ther 14:219
13. Nicoli F, Balzani A, Lazzeri D, Gentile P, Chilgar RM, Di Pasquali C, Nicoli M, Bocchini I, Agovino A, Cervelli V (2015) Severe hidradenitis suppurativa treatment using platelet-rich plasma gel and Hyalomatrix. Int Wound J 12:338–343
14. Hou X, Yuan J, Aisaiti A, Liu Y, Zhao J (2016) The effect of platelet–rich plasma on clinical outcomes of the surgical treatment of periodontal intrabony defects: a systematic review and meta–analysis. Bmc Oral Health 16:71
15. Lavker RM, Zheng PS, Dong G (1987) Aged skin: a study by light, transmission electron, and scanning electron microscopy. J Invest Dermatol 88:44s–51s
16. Montagna W, Carlisle K (1979) Structural changes in aging human skin. J Invest Dermatol 73:47–53
17. West MD, Pereira-Smith OM, Smith JR (1989) Replicative senescence of human skin fibroblasts correlates with a loss of regulation and overexpression of collagenase activity. Exp Cell Res 184:138–147
18. Wan D, Amirlak B, Giessler P, Rasko Y, Rohrich RJ, Yuan C, Lysikowski J, Delgado I, Davis K (2014) The differing adipocyte morphologies of deep versus superficial midfacial fat compartments: a cadaveric study. Plast Reconstr Surg 133:615e–622e
19. Fujimura T, Hotta M (2012) The preliminary study of the relationship between facial movements and wrinkle formation. Skin Res Technol 18:219–224
20. Lee S, Lim JM, Jin MH, Park HK, Lee EJ, Kang S, Kim YS, Cho WG (2006) Partially purified paeoniflorin exerts protective effects on UV-induced DNA damage and reduces facial wrinkles in human skin. J Cosmet Sci 57:57–64
21. Chung H, Goo B, Lee H, Roh M, Chung K (2011) Enlarged pores treated with a combination of Q-switched and micropulsed 1064 nm Nd: YAG laser with and without topical carbon suspension: a simultaneous split-face trial. Laser Ther 20:181–188
22. Cho SB, Lee JH, Choi MJ, Lee KY, Oh SH (2009) Efficacy of the fractional photothermolysis system with dynamic operating mode on acne scars and enlarged facial pores. Dermatol Surg 35:108–114
23. Hirobe T, Kiuchi M, Wakamatsu K, Ito S (2010) Estrogen increases hair pigmentation in female recessive yellow mice. Zoolog Sci 27:470–476
24. Kim NH, Cheong KA, Lee TR, Lee AY (2012) PDZK1 upregulation in estrogen-related hyperpigmentation in melasma. J Invest Dermatol 132:2622–2631
25. Kosmadaki MG, Naif A, Hee-Young P (2010) Recent progresses in understanding pigmentation. G Ital Dermatol Venereol 145:47–55
26. Wolber R, Schlenz K, Wakamatsu K, Smuda C, Nakanishi Y, Hearing VJ, Ito S (2008) Pigmentation effects of solar-simulated radiation as compared with UVA and UVB radiation. Pigment Cell Melanoma Res 21:487–491
27. Sklar LR, Almutawa F, Lim HW, Hamzavi I (2013) Effects of ultraviolet radiation, visible light, and infrared radiation on erythema and pigmentation: a review. Photochem Photobiol Sci 12:54–64
28. Tagashira H, Miyamoto A, Kitamura S, Tsubata M, Yamaguchi K, Takagaki K, Imokawa G (2015) UVB stimulates the expression of endothelin B receptor in human melanocytes via a sequential activation of the p38/MSK1/CREB/MITF pathway which can be interrupted by a French maritime pine bark extract through a direct inactivation of MSK1. PLoS ONE 10:e0128678
29. Marin-Castano ME, Elliot SJ, Potier M, Karl M, Striker LJ, Striker GE, Csaky KG, Cousins SW (2003) Regulation of estrogen receptors and MMP-2 expression by estrogens in human retinal pigment epithelium. Invest Ophthalmol Vis Sci 44:50–59

30. Mendelson BC, Jacobson SR (2008) Surgical anatomy of the midcheek: facial layers, spaces, and the midcheek segments. Clin Plast Surg 35:395–404 **(discussion 393)**
31. Rubinsztein DC, Marino G, Kroemer G (2011) Autophagy and aging. Cell 146:682–695
32. Le Louarn C (2009) Muscular aging and its involvement in facial aging: the face recurve concept. Ann Dermatol Venereol 136(Suppl 4):S67–S72
33. Mendelson B, Wong CH (2012) Changes in the facial skeleton with aging: implications and clinical applications in facial rejuvenation. Aesthetic Plast Surg 36:753–760
34. Furnas DW (1989) The retaining ligaments of the cheek. Plast Reconstr Surg 83:11–16
35. Gierloff M, Stohring C, Buder T, Wiltfang J (2012) The subcutaneous fat compartments in relation to aesthetically important facial folds and rhytides. J Plast Reconstr Aesthet Surg 65:1292–1297
36. Paus R, Cotsarelis G (1999) The biology of hair follicles. N Engl J Med 341:491–497
37. Leiros GJ, Ceruti JM, Castellanos ML, Kusinsky AG, Balana ME (2017) Androgens modify Wnt agonists/antagonists expression balance in dermal papilla cells preventing hair follicle stem cell differentiation in androgenetic alopecia. Mol Cell Endocrinol 439:26–34
38. Semalty M, Semalty A, Joshi GP, Rawat MS (2011) Hair growth and rejuvenation: an overview. J Dermatolog Treat 22:123–132
39. Sclafani AP (2009) Applications of platelet-rich fibrin matrix in facial plastic surgery. Facial Plast Surg 25:270–276
40. Heldin CH, Westermark B (1999) Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev 79:1283–1316
41. Uutela M, Wirzenius M, Paavonen K, Rajantie I, He Y, Karpanen T, Lohela M, Wiig H, Salven P, Pajusola K et al (2004) PDGF-D induces macrophage recruitment, increased interstitial pressure, and blood vessel maturation during angiogenesis. Blood 104:3198–3204
42. Papakonstantinou E, Aletras AJ, Roth M, Tamm M, Karakiulakis G (2003) Hypoxia modulates the effects of transforming growth factor-beta isoforms on matrix-formation by primary human lung fibroblasts. Cytokine 24:25–35
43. White LA, Mitchell TI, Brinckerhoff CE (2000) Transforming growth factor beta inhibitory element in the rabbit matrix metalloproteinase-1 (collagenase-1) gene functions as a repressor of constitutive transcription. Biochim Biophys Acta 1490:259–268
44. Rabhi-Sabile S, Pidard D, Lawler J, Renesto P, Chignard M, Legrand C (1996) Proteolysis of thrombospondin during cathepsin-G-induced platelet aggregation: functional role of the 165-kDa carboxy-terminal fragment. FEBS Lett 386:82–86
45. Pierce GF, Tarpley JE, Tseng J, Bready J, Chang D, Kenney WC, Rudolph R, Robson MC, Vande BJ, Reid P et al (1995) Detection of platelet-derived growth factor (PDGF)-AA in actively healing human wounds treated with recombinant PDGF-BB and absence of PDGF in chronic nonhealing wounds. J Clin Invest 96:1336–1350
46. Lin H, Chen B, Sun W, Zhao W, Zhao Y, Dai J (2006) The effect of collagen-targeting platelet-derived growth factor on cellularization and vascularization of collagen scaffolds. Biomaterials 27:5708–5714
47. Nicosia RF, Nicosia SV, Smith M (1994) Vascular endothelial growth factor, platelet-derived growth factor, and insulin-like growth factor-1 promote rat aortic angiogenesis in vitro. Am J Pathol 145:1023–1029
48. Gerber HP, McMurtrey A, Kowalski J, Yan M, Keyt BA, Dixit V, Ferrara N (1998) Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3′-kinase/Akt signal transduction pathway. Requirement for Flk-1/KDR activation. J Biol Chem 273:30336–30343
49. Ferrara N (2004) Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 25:581–611
50. Bennett SP, Griffiths GD, Schor AM, Leese GP, Schor SL (2003) Growth factors in the treatment of diabetic foot ulcers. Br J Surg 90:133–146
51. Pastore S, Mascia F, Mariani V, Girolomoni G (2008) The epidermal growth factor receptor system in skin repair and inflammation. J Invest Dermatol 128:1365–1374
52. Bertrand-Duchesne MP, Grenier D, Gagnon G (2010) Epidermal growth factor released from platelet-rich plasma promotes endothelial cell proliferation in vitro. J Periodontal Res 45:87–93
53. Kim DH, Je YJ, Kim CD, Lee YH, Seo YJ, Lee JH, Lee Y (2011) Can platelet-rich plasma be used for skin rejuvenation? Evaluation of effects of platelet-rich plasma on human dermal fibroblast. Ann Dermatol 23:424–431
54. Li H, Han Z, Liu D, Zhao P, Liang S, Xu K (2013) Autologous platelet-rich plasma promotes neurogenic differentiation of human adipose-derived stem cells in vitro. Int J Neurosci 123:184–190
55. Kakudo N, Minakata T, Mitsui T, Kushida S, Notodihardjo FZ, Kusumoto K (2008) Proliferation-promoting effect of platelet-rich plasma on human adipose-derived stem cells and human dermal fibroblasts. Plast Reconstr Surg 122:1352–1360
56. Sadoghi P, Lohberger B, Aigner B, Kaltenegger H, Friesenbichler J, Wolf M, Sununu T, Leithner A, Vavken P (2013) Effect of platelet-rich plasma on the biologic activity of the human rotator-cuff fibroblasts: a controlled in vitro study. J Orthop Res 31:1249–1253
57. Xian LJ, Chowdhury SR, Bin SA, Idrus RB (2015) Concentration-dependent effect of platelet-rich plasma on keratinocyte and fibroblast wound healing. Cytotherapy 17:293–300
58. Xiao SE, Miao Y, Wang J, Jiang W, Fan ZX, Liu XM, Hu ZQ (2017) As a carrier-transporter for hair follicle reconstitution, platelet-rich plasma promotes proliferation and induction of mouse dermal papilla cells. Sci Rep 7:1125
59. Shin MK, Lee JH, Lee SJ, Kim NI (2012) Platelet-rich plasma combined with fractional laser therapy for skin rejuvenation. Dermatol Surg 38:623–630
60. Mehryan P, Zartab H, Rajabi A, Pazhoohi N, Firooz A (2014) Assessment of efficacy of platelet-rich plasma (PRP) on infraorbital dark circles and crow's feet wrinkles. J Cosmet Dermatol 13:72–78
61. Mooren RE, Hendriks EJ, van den Beucken JJ, Merkx MA, Meijer GJ, Jansen JA, Stoelinga PJ (2010) The effect of platelet-rich plasma in vitro on primary cells: rat osteoblast-like cells and human endothelial cells. Tissue Eng Part A 16:3159–3172
62. Cenni E, Ciapetti G, Granchi D, Fotia C, Perut F, Giunti A, Baldini N (2009) Endothelial cells incubated with platelet-rich plasma express PDGF-B and ICAM-1 and induce bone marrow stromal cell migration. J Orthop Res 27:1493–1498
63. Li X, Hou J, Wu B, Chen T, Luo A (2014) Effects of platelet-rich plasma and cell coculture on angiogenesis in human dental pulp stem cells and endothelial progenitor cells. J Endod 40:1810–1814
64. Kakudo N, Morimoto N, Kushida S, Ogawa T, Kusumoto K (2014) Platelet-rich plasma releasate promotes angiogenesis in vitro and in vivo. Med Mol Morphol 47:83–89
65. Woodall JJ, Tucci M, Mishra A, Benghuzzi H (2007) Cellular effects of platelet rich plasma: a study on HL-60 macrophage-like cells. Biomed Sci Instrum 43:266–271
66. Czakai K, Dittrich M, Kaltdorf M, Muller T, Krappmann S, Schedler A, Bonin M, Duhring S, Schuster S, Speth C et al (2017) Influence of platelet-rich plasma on the immune response

of human monocyte-derived dendritic cells and macrophages stimulated with *Aspergillus fumigatus*. Int J Med Microbiol 307:95–107
67. Cervelli V, Garcovich S, Bielli A, Cervelli G, Curcio BC, Scioli MG, Orlandi A, Gentile P (2014) The effect of autologous activated platelet rich plasma (AA-PRP) injection on pattern hair loss: clinical and histomorphometric evaluation. Biomed Res Int 2014:760709
68. Castro FO, Torres A, Cabezas J, Rodriguez-Alvarez L (2014) Combined use of platelet rich plasma and vitamin C positively affects differentiation in vitro to mesodermal lineage of adult adipose equine mesenchymal stem cells. Res Vet Sci 96:95–101
69. Drengk A, Zapf A, Sturmer EK, Sturmer KM, Frosch KH (2009) Influence of platelet-rich plasma on chondrogenic differentiation and proliferation of chondrocytes and mesenchymal stem cells. Cells Tissues Organs 189:317–326
70. Murphy MB, Blashki D, Buchanan RM, Yazdi IK, Ferrari M, Simmons PJ, Tasciotti E (2012) Adult and umbilical cord blood-derived platelet-rich plasma for mesenchymal stem cell proliferation, chemotaxis, and cryo-preservation. Biomaterials 33:5308–5316
71. Cho JM, Lee YH, Baek RM, Lee SW (2011) Effect of platelet-rich plasma on ultraviolet b-induced skin wrinkles in nude mice. J Plast Reconstr Aesthet Surg 64:e31–e39
72. Bhang SH, Park J, Yang HS, Shin J, Kim BS (2013) Platelet-rich plasma enhances the dermal regeneration efficacy of human adipose-derived stromal cells administered to skin wounds. Cell Transplant 22:437–445
73. Liu HY, Huang CF, Lin TC, Tsai CY, Tina CS, Liu A, Chen WH, Wei HJ, Wang MF, Williams DF et al (2014) Delayed animal aging through the recovery of stem cell senescence by platelet rich plasma. Biomaterials 35:9767–9776
74. Miao Y, Sun YB, Sun XJ, Du BJ, Jiang JD, Hu ZQ (2013) Promotional effect of platelet-rich plasma on hair follicle reconstitution in vivo. Dermatol Surg 39:1868–1876
75. Houdek MT, Wyles CC, Stalboerger PG, Terzic A, Behfar A, Moran SL (2016) Collagen and fractionated platelet-rich plasma scaffold for dermal regeneration. Plast Reconstr Surg 137:1498–1506
76. Kawazoe T, Kim HH (2012) Tissue augmentation by white blood cell-containing platelet-rich plasma. Cell Transplant 21:601–607
77. Li ZJ, Choi HI, Choi DK, Sohn KC, Im M, Seo YJ, Lee YH, Lee JH, Lee Y (2012) Autologous platelet-rich plasma: a potential therapeutic tool for promoting hair growth. Dermatol Surg 38:1040–1046
78. Oh DS, Cheon YW, Jeon YR, Lew DH (2011) Activated platelet-rich plasma improves fat graft survival in nude mice: a pilot study. Dermatol Surg 37:619–625
79. Nakamura S, Ishihara M, Takikawa M, Murakami K, Kishimoto S, Nakamura S, Yanagibayashi S, Kubo S, Yamamoto N, Kiyosawa T (2010) Platelet-rich plasma (PRP) promotes survival of fat-grafts in rats. Ann Plast Surg 65:101–106
80. Pires FM, Nishio RT, Ishikawa RS, Perin LF, Helene AJ, Malheiros CA (2010) Increased survival of free fat grafts with platelet-rich plasma in rabbits. J Plast Reconstr Aesthet Surg 63:e818–e822
81. Karsai S, Adrian R, Hammes S, Thimm J, Raulin C (2007) A randomized double-blind study of the effect of Botox and Dysport/Reloxin on forehead wrinkles and electromyographic activity. Arch Dermatol 143:1447–1449
82. Campolmi P, Bonan P, Cannarozzo G, Bruscino N, Moretti S (2013) Efficacy and safety evaluation of an innovative CO_2 laser/radiofrequency device in dermatology. J Eur Acad Dermatol Venereol 27:1481–1490
83. Babilas P, Schreml S, Szeimies RM, Landthaler M (2010) Intense pulsed light (IPL): a review. Lasers Surg Med 42:93–104
84. Guyuron B, Majzoub RK (2007) Facial augmentation with core fat graft: a preliminary report. Plast Reconstr Surg 120:295–302
85. Rassman WR, Bernstein RM (1998) rapid fire hair implanter carousel. A new surgical instrument for the automation of hair transplantation. Dermatol Surg 24:623–627
86. Yuksel EP, Sahin G, Aydin F, Senturk N, Turanli AY (2014) Evaluation of effects of platelet-rich plasma on human facial skin. J Cosmet Laser Ther 16:206–208
87. Sclafani AP (2011) Safety, efficacy, and utility of platelet-rich fibrin matrix in facial plastic surgery. Arch Facial Plast Surg 13:247–251
88. Gentile P, Garcovich S, Bielli A, Scioli MG, Orlandi A, Cervelli V (2015) The effect of platelet-rich plasma in hair regrowth: a randomized placebo-controlled trial. Stem Cells Transl Med 4:1317–1323
89. Goldstein S, Harley CB (1979) In vitro studies of age-associated diseases. Fed Proc 38:1862–1867
90. Vavken P, Saad FA, Murray MM (2010) Age dependence of expression of growth factor receptors in porcine ACL fibroblasts. J Orthop Res 28:1107–1112
91. Mori Y, Hatamochi A, Arakawa M, Ueki H (1998) Reduced expression of mRNA for transforming growth factor beta (TGF beta) and TGF beta receptors I and II and decreased TGF beta binding to the receptors in in vitro-aged fibroblasts. Arch Dermatol Res 290:158–162
92. Elnehrawy NY, Ibrahim ZA, Eltoukhy AM, Nagy HM (2017) Assessment of the efficacy and safety of single platelet-rich plasma injection on different types and grades of facial wrinkles. J Cosmet Dermatol 16:103–111
93. Kamakura T, Kataoka J, Maeda K, Teramachi H, Mihara H, Miyata K, Ooi K, Sasaki N, Kobayashi M, Ito K (2015) Platelet-rich plasma with basic fibroblast growth factor for treatment of wrinkles and depressed areas of the skin. Plast Reconstr Surg 136:931–939
94. Schiavone G, Raskovic D, Greco J, Abeni D (2014) Platelet-rich plasma for androgenetic alopecia: a pilot study. Dermatol Surg 40:1010–1019
95. Singhal P, Agarwal S, Dhot PS, Sayal SK (2015) Efficacy of platelet-rich plasma in treatment of androgenic alopecia. Asian J Transfus Sci 9:159–162
96. Nita AC, Jianu DM, Florescu IP, Filipescu M, Cobani O, Jianu SA, Chirita DA, Bold A (2013) The synergy between lasers and adipose tissues surgery in cervicofacial rejuvenation: histopathological aspects. Rom J Morphol Embryol 54:1039–1043
97. Gentile P, Di Pasquali C, Bocchini I, Floris M, Eleonora T, Fiaschetti V, Floris R, Cervelli V (2013) Breast reconstruction with autologous fat graft mixed with platelet-rich plasma. Surg Innov 20:370–376
98. Garg S (2016) Outcome of intra-operative injected platelet-rich plasma therapy during follicular unit extraction hair transplant: a prospective randomised study in forty patients. J Cutan Aesthet Surg 9:157–164
99. Ulusal BG (2017) Platelet-rich plasma and hyaluronic acid—an efficient biostimulation method for face rejuvenation. J Cosmet Dermatol 16:112–119
100. Hui Q, Chang P, Guo B, Zhang Y, Tao K (2017) The clinical efficacy of autologous platelet-rich plasma combined with ultra-pulsed fractional CO_2 laser therapy for facial rejuvenation. Rejuvenation Res 20:25–31
101. Rossano F, Di Martino S, Iodice L, Di Paolo M, Misso S, Tomeo R, Marini AM, Brugnone R, Marlino S, Santorelli A et al (2017) Correlation between individual inflammation genetic profile and

platelet rich plasma efficacy in hair follicle regeneration: a pilot study reveals prognostic value of IL-1a polymorphism. Eur Rev Med Pharmacol Sci 21:5247–5257
102. Hersant B, SidAhmed-Mezi M, Niddam J, La Padula S, Noel W, Ezzedine K, Rodriguez AM, Meningaud JP (2017) Efficacy of autologous platelet-rich plasma combined with hyaluronic acid on skin facial rejuvenation: a prospective study. J Am Acad Dermatol 77:584–586
103. Willemsen JC, van der Lei B, Vermeulen KM, Stevens HP (2014) The effects of platelet-rich plasma on recovery time and aesthetic outcome in facial rejuvenation: preliminary retrospective observations. Aesthetic Plast Surg 38:1057–1063
104. Kalyam K, Kavoussi SC, Ehrlich M, Teng CC, Chadha N, Khodadadeh S, Liu J (2016) Irreversible blindness following periocular autologous platelet-rich plasma skin rejuvenation treatment. Ophthal Plast Reconstr Surg 33:S12–S16
105. Jo CH, Roh YH, Kim JE, Shin S, Yoon KS (2013) Optimizing platelet-rich plasma gel formation by varying time and gravitational forces during centrifugation. J Oral Implantol 39:525–532
106. Amable PR, Carias RB, Teixeira MV, Da CPI, Correa DAR, Granjeiro JM, Borojevic R (2013) Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther 4:67
107. Sonker A, Dubey A (2015) Determining the effect of preparation and storage: an effort to streamline platelet components as a source of growth factors for clinical application. Transfus Med Hemother 42:174–180