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IMMUNOLOGICAL MECHANISMS OF THE REGENERATIVE EFFECT OF PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) is an autologous blood derivative that contains a supraphysiological concentration of platelets. The theoretical benefit of using PRP to stimulate tissue regeneration, due to the presence of a large number of growth factors and other cytokines, has been described in many studies.
The aim of this review is to analyze immunological mechanism of the regenerating effect of PRP. Comprehensive search through Medline, Cochrane Collaboration database, EBSCO.
The positive effect of PRP on the migration of cells, proliferation, neoangiogenesis was proved in many studies. Growth factors such as TGF-β1, β2, PDGF-αα, ββ, αβ, VEGF-A, -C, IGF-1, EGF etc. stimulate local angiogenesis, cell migration, proliferation and differentiation of collagen-protein cells that play a key role in restoring of normal structure and function. The mechanisms of PRP growth factors action are not fully understood.
Keywords: *platelet rich plasma, growth factors, regeneration.*

Introduction.
PRP-therapy is a procedure that results in the treatment with own blood plasma enriched with platelets. Platelet rich plasma is a plasma, the concentration of platelets in which exceeds normal. Normally, the concentration of platelets in the blood varies between 150,000/μL and 350,000/μL. It was proved that the stimulating effect of PRP is manifested if the platelet concentration in it is 1.000.000/μl. At a lower concentration the stimulatory effect does not appear, while it has not yet been shownthat an increase in platelet counts above 1,000,000 / μL leads to a further acceleration of regeneration [1].
The regenerative action of PRP is based on the immunological mechanisms of the growth factors contained in the granules of platelets [3].
Purpose of the review: to analyze immunological mechanism of the regenerating effect of PRP.
Sources and methods:
Search in databases: Medline, Cochrane Collaboration database, EBSCO.
Key words - Platelet Rich Plasma, Growth factors, Regeneration
Inclusion criteria:
- original articles;
- full text articlein English language;
- articles published after 2000;
- articles presenting studies of regenerative mechanisms of platelets rich plasma application in wound healing process.

Exclusion criteria:
- abstracts, repeating articles;
- articles published before 2000;
- non-English articles;
- case reports;
- review articles;

Results:
The search started by using keywords – "Platelet Rich Plasma, Growth factors, Regeneration". The total number of relevant titles was 844. Among the selected articles in English from the period after 2000year only 130 works were chosen according to inclusion criteria. Among them 22 were presenting research of growth factors actions on different wound healing.
Platelet rich plasma contains the following growth factors:TGF-b1, b2; PDGF-αα, -ββ, -αβ; PDEGF; VEGF - A, -B,-C, -D; IGF-1, 2; EGF; VEGF etc. Growth factors are proteins with a certain set of amino acids. Theactive growth factors bind to transmembrane receptors of target cells, such as mesenchymalstem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells.Platelet-derived factors directly influence cellular growth, morphogenesis, and differentiation [2].

1. Insulin-like growth factor (IGF).
IGF exists as IGF-1 and IGF-2. IGF promotes differentiation of stem cells, enhances the metabolism of bone tissue and the synthesis of collagen [3]. Receptors for IGF are presented in mesenchymal cells, osteoblasts, chondrocytes. [4].IGF-1 is a chemotactic agent for osteoblasts, vascular smooth muscle, and endothelial cells [5], through which it can promote neoangiogenesis. IGF-1 has a mitogenic effect on fibroblasts. Also IGF-1 can enhance epidermal and dermal growth [6] and it's effectiveness showed in studies of chronic wound healing. IGF-1 plays essential role in bone formation [7]. Schmidmaier G. et al. in 2001, Raschke M. et al. in 2002and Fowlkes J. et al. in 2006 in animal models showed that local application of IGF-1 accelerate fracture healing.

2. Platelet-derived growth factor (PDGF).
PDGF is a protein, that consists of two subunits (α and β). PDGF can exist in three forms – PDGF-αα, PDGF-ββ, PDGF-αβ PDGF is producing by platelets and macrophages [3]. It is a chemotactic factor and mitogen for many cells, such as neutrophils, fibroblasts, mesenchymal stem cells, osteoblasts, endothelial cells [8], which are responsible for tissue healing and angiogenesis. PDGF helps collagen breakdown during the remodeling phase of wound healing through up-regulating matrix metalloproteinases. PDGF also plays a role in reepithelialization after wounding [9]. PDGF increases inflammatory phase of wound healing and accelerate normal wound repair processes and early matrix deposition. Platelet-released PDGF promoting the chemotaxis of monocytes, neutrophils, and smooth muscle cells into wounds, enhances the expression of alpha-smooth muscleactin protein and the differentiation of dermal fibroblasts into myofibroblasts, which promotes wound contraction [10].

Kovacevic D. et al. in 2015 affirmed that rhPDGF-BB promotes early healing in a rat rotator cuff repair model. Scientists showed rhPDGF-BB delivery on a collagen scaffold enhanced cellular proliferation and angiogenesis during the early phase of healing [11].

3. Epidermal growth factor (EGF).

EGF is a polypeptide, which stimulates proliferation of fibroblasts and osteoblasts. EGF is a chemotactic factor and mitogen for epithelial, endothelial cells [12], it stimulate angiogenesis, increase epithelization. Mechanism of action is a adherence of EGF to specific extracellular receptors and activation of tyrosinekinase, which gives signal to cell proliferation. Dai C. et al. in 2000 studied effects of epidermal growth factor on wound healing of penetrating keratoplasty in rabbits and come to conclusion that the intensity of EGF group on 8 days, 14 days and 21 days after penetrating keratoplasty was significantly higher than that of the control group. Kwon Y. et al. in 2006 proved that recombinant human epidermal growth factor (rhEGF) stimulates the proliferation and migration of epithelial cells in human cell culture systems and animal models of partial-thickness skin wounds [13]. Later Kim T. et al. in 2008 showed also that recombinant human epidermal growth factor enhances wound healing of pyoderma gangrenosum in a patient with ulcerative colitis [14].

4. Fibroblast growth factor (FGF).

FGF is producing by endothelial cells, macrophages, osteoblasts, platelets. It promotes angiogenesis, ossification and induces production of TGF in osteoblasts. Matsumoto S. et al. in 2013 suggested that control-released bFGF using gelatin sheet is effective for promoting wound healing [15]. Nakamizo S. et al. in the same year proved that topical treatment with basic fibroblast growth factor promotes wound healing which were induced by skin abrasion [16].

5. Transforming growth factor-β (TGF-β).

Producing by platelets and osteoblasts has five isomers. TGF-β play role in all stages of wound healing. TGF-β stimulates other cells like monocytes to secrete growth factors. TGF-β stimulates fibroblast chemotaxis and proliferation and influences on the organization of extracellular matrix and scar remodeling [3, 17].

TGF-β receptors presenting in bone and cartilage. In view of this fact TGF-β promotes bone synthesis and show effectiveness in tendons injuries healing. Farhat Y.M. et al. in 2015 supported the hypothesis that TGF-β1 induces plasminogen activator inhibitor-1, which suppresses plasmin and plasmin-mediated matrix metalloproteinases activity, and provided evidence that it could be a novel therapeutic target for preventing adhesions and promoting a scarless, regenerative repair of flexor tendon injuries [18].

6. Vascular endothelial growth factor (VEGF).

Has four types VEGF-A, B, C and D. Take part in angiogenesis inducing the proliferation of endothelial cells of vessels.

In cases involving ischemic diabetic limbs, several animal studies involving the administration of VEGF-A have shown a restoration of impaired angiogenesis. Additionally, in vivo studies have reported an improvement in reepithelialization of diabetic wounds secondary to enhanced vessel formation with administration of VEGF-A [19].

Niyaz M. et al.in 2015 studied effects of VEGF and mesenchymal stem cells on vascular regeneration in a trauma model in rats, scientists mixture VEGF and mesenchymal stem cells (MSCs) and applied it on the dorsum of a rat, which was traumatized. Only combination of VEGF and MSCs showed good results [20].

Conclusion: The positive effect of PRP on the migration of cells, proliferation, neoangiogenesis was proved in many studies. Growth factors such as TGF-β1, β2, PDGF-αα, ββ, αβ, VEGF-A, -C, IGF-1, EGF etc. stimulate local angiogenesis, cell migration, proliferation and differentiation of collagen-protein cells that play a key role in restoring of normal structure and function. The mechanisms of PRP growth factors action are not fully understood.

REFERENCES

1 Robert E. Marx. PRP: what is PRP and what is not PRP? // Implant dentistry. – 2001. - Vol.10. - No.4. – P. 45-48.
2 Simon E. Smith, Thomas S. Roukis. Bone andWoundHealing Augmentation with Platelet-RichPlasmaClinPodiatr // Med Surg. – 2009. - №26. – P. 559–588.
3 AhmerovR.Regenerative medicine based on autologous plasma // Technology Plasmolifting™. - 2014. – №1. – P. 160-167.
4 Okazaki K, Jingushi S, Ikenoue T, et al. Expression of parathyroid hormonerelated peptide and insulin-like growth factor I during rat fracture healing // J Orthop Res. – 2003. - №21(3). – P. 511–520.
5 Clemmons DR, Maile LA, Ling Y, et al. Role of the integrin alphaVbeta3 in mediatingincreased smooth muscle cell responsiveness to IGF-I in response to hyperglycemic stress // Growth Horm IGF Res. – 2007. - №17(4). – P. 265–270.
6 Guvakova MA. Insulin-like growth factors control cell migration in health and disease // Int J Biochem Cell Biol. – 2007. - №39(5). – P. 890–909.
7 Niu T, Rosen CJ. The insulin-like growth factor-I gene and osteoporosis: a criticalappraisal // Gene. – 2005. - №361. – P. 38–56.
8 Lin H, Chen B, Sun W, et al. The effect of collagen-targeting platelet-derived growth factor on cellularization and vascularization of collagen scaffolds // Biomaterials. – 2006. - №27(33). – P. 5708–5714.
9 Jinnin M, Ihn H, Mimura Y, et al. Regulation of fibrogenic/fibrolytic genes by platelet-derived growth factor C, a novel growth factor, in human dermal fibroblasts // J Cell Biol. – 2005. - №202(2). – P. 510–517.
10 Notodihardjo FZ, Kakudo N, Kushida S, Suzuki K, Kusumoto K. Boneregeneration with BMP-2 and hydroxyapatite in critical-size calvarial defects in rats // J CraniomaxillofacSurg. – 2012. - №40. – P. 287–291.
11 Kovacevic D. et al. rhPDGF-BB promotes early healing in a rat rotator cuff repair model // Clinical Orthopaedics And Related Research. . – 2015. - №5. – P. 1644-1654.
12 Tokumaru S, Higashiyama S, Endo T, et al. Ectodomain shedding of epidermalgrowth factor receptor ligands is required for keratinocyte migration in cutaneous wound healing // J Cell Biol. – 2000. - №151(2). – P. 209–220.
13 Kwon Y, Kim H, Lee J, et al. Topical application of epidermal growth factor accelerates wound healing by myofibroblast proliferation and collagen synthesis in rat // Journal Of Veterinary Science. – 2006. - №7(2). – P. 105-109.
14 Kim T.Y. et al. Recombinant human epidermal growth factor enhances wound healing of pyoderma gangrenosum in a patient with ulcerative colitis // Inflammatory Bowel Diseases. – 2008. - №14(5). – P. 725-727.
15 Matsumoto S et al. The Effect of Control-released Basic Fibroblast Growth Factor in Wound Healing: Histological Analyses and Clinical Application // Plastic And Reconstructive Surgery. – 2013. - №1(6). – P. 44-48.

16 Nakamizo S; et al. Topical treatment with basic fibroblast growth factor promotes wound healing and barrier recovery induced by skin abrasion // Skin Pharmacology And Physiology. – 2013. - №26(1). – P. 22-29.
17 Lieberman JR, Daluiski A, Einhorn TA. The role of growth factors in the repair of bone: biology and clinical applications // J Bone Joint Surg Am. – 2002. - №84. – P. 1032–1044.
18 Farhat Y.M. et al. TGF-β1 Suppresses Plasmin and MMP Activity in Flexor Tendon Cells via PAI-1: Implications for Scarless Flexor Tendon Repair // Journal Of Cellular Physiology. – 2015. - №2. – P. 318-326.
19 Galiano RD, Tepper OM, Pelo CR, et al. Topical vascular endothelial growth factor accelerates diabetic wound healing through increased angiogenesis and by mobilizing and recruiting bone marrow-derived cells // Am J Pathol. -2004. - №164(6). – P. 1935–1947.
20 Niyaz M; et al. Effects of VEGF and MSCs on vascular regeneration in a trauma model in rats. Wound Repair And Regeneration: Official Publication Of The Wound Healing Society [And] // The European Tissue Repair Society. – 2015. - №23. – P. 262-267.

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ТРОМБОЦИТТЕРГЕ БАЙ САРЫ СУДЫҢ ҚАЛПЫНА КЕЛТІРУ ПАЙДАСЫНЫҢ ИММУНОЛОГИЯЛЫҚ МЕХАНИЗМІ

Түйін: Тромбоцитке бай сарысу (PRP) – супрафизиологиялық тромбоциттер жинақталған қанның аутологиялық туындысы. Ұлпалардың қалпына келуін жақсарудағы PRP-ді қолданудың теориялық пайдасы өсу факторларының көп төмиерде болуымен және тағы да басқа цитокіндердің көптеген байланысты жәнебірнеше зерттеулерде сипатталған.
Бақылаудың мақсаты PRP-дің қалпына келтіру пайдасының иммунологиялық механизмін талдау.
Іздеу PubMed, Cochrane Collaborationdatabase, EBSCO базасының негіздеріне сүеніп жүргізілді.
PRP-ді қолдану жасушаның қозғалысына, пролиферацияға, неоангиогенезге оңтайлы әсер етеді. TGF-β1, β2, PDGF-αα, ββ, αβ, VEGF-A, -C, IGF-1, EGF сияқты өсу факторлары және тағы басқалары жергілікті ангиогенезге жасушаның қозғаласына пролиферацияны және жасушаның жеке ажырап протеин-коллагеннің бөлініп шығуыны итермелеп, ұлпаның қалпына келдіне негіз болады. Жергілікті қолданылуына қарамастан PRP терапиясының клиникалық тиімділігі, оның әсер ету механизмі соңына дейін зерттелмеген.
Түйінді сөздер: тромбоциттерге бай сары су, дыму факторлар қалпына келу.

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ИММУНОЛОГИЧЕСКИЕ МЕХАНИЗМЫ РЕГЕНЕРИРУЮЩЕГО ЭФФЕКТА БОГАТОЙ ТРОМБОЦИТАМИ ПЛАЗМЫ

Резюме: Богатая тромбоцитами плазма (PRP) – аутологичный дериват крови, который содержит супрафизиологичную концентрацию тромбоцитов. Теоретическая польза применения PRP для стимулирования регенерации тканей, обусловленная наличием большого количества факторов роста и других цитокинов, была описана во многих исследованиях.
Целью данного обзора явился анализ иммунологических механизмов регенерирующего эффекта PRP. Поискпроводился в базах данных PubMed, Cochrane Collaborationdatabase, EBSCO.
Применение PRP положительно влияет на миграцию клеток, пролиферацию, неоангеогенез. Такие факторы роста как TGF-β1, β2, PDGF-αα, ββ, αβ, VEGF-A, -C, IGF-1, EGF и др. стимулируют локальный ангиогенез, миграцию клеток, пролиферацию и дифференцировку клеток с отложением протеинов – коллагена, которые играют ключевую роль в восстановлении нормальной структуры и функции тканей. Несмотря на повсеместное использование, клиническую эффективность PRP терапии, механизмы ее действия до конца не изучены.
Ключевые слова: богатая тромбоцитами плазма, факторы роста, регенерация.