Liberski Sławomir, Marczak Daria, Migdalski Arkadiusz. **The influence of genetic factors on the pathogenesis of hypertrophic scars and keloids. Journal of Education, Health and Sport. 2018;8(8):313-321. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1310110**
http://ojs.ukw.edu.pl/index.php/johs/article/view/5645

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.06.2018. Revised: 28.06.2018. Accepted: 12.07.2018.

The influence of genetic factors on the pathogenesis of hypertrophic scars and keloids

Sławomir Liberski[1], liberski@o2.pl ORCID: https://orcid.org/0000-0002-6942-2506
Daria Marczak[1], dariamarczak1@wp.pl ORCID: https://orcid.org/0000-0003-2404-8001
Arkadiusz Migdalski[2], armigos@wp.pl ORCID: https://orcid.org/0000-0002-9835-5103
[1] Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, M. Curie 9, 85-090 Bydgoszcz, Poland
[2]Department of Vascular Surgery and Angiology, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, M. Curie 9, 85-090Bydgoszcz, Poland

Abstract:

Hypertrophic scars and keloids are forms of abnormal scarring, which may be the cause of somatic ailmants and, due to unfavorable aesthetic effect, also mental disorders and social problems. Given the unclear aetiology and the lack of effective treatment methods, they pose a serious challenge for modern science. The contribution of genetic factors is one of the proposed hypotheses regarding the formation of hypertrophic scars and keloids. Gene polymorphism and mutations occurring in them may interfere with the proper course of signaling pathways responsible for the subsequent stages of the wound healing process. An important role in the pathogenesis of abnormal scarring may be the TGF-B1/Smad pathway, MAPK kinase, pathway for IGF-I and its receptor, plasminogen activator inhibitor-1 and urokinase plasminogen activator, gene polymorphisms for the vitamin D receptor and the ADAM33 gene, as well as abnormal expression of suppressor genes. The effect on heat shock protein expression and type 2 hyaluronidase synthase was also shown. The explanation of the genetic basis of hypertrophic scar and keloid formation may lead to a full understanding of their pathogenesis and also have important implications in the form of therapeutic benefits resulting in the development of effective forms of treatment.

keywords: keloid, hypertrophic scar, wound healing, genes

1. Introduction

Hypertrophic scars and keloids represent a serious challenge for modern medicine due to the lack of effective treatments [1]. According to estimated data, the problem of developing hypertrophic and keloid scars occurs mainly in people aged 10-30 years [2]. Abnormal forms of scarring may cause somatic symptoms such as pain, pruritus and even limitation of joint mobility, however their

occurrence may also be associated with psychological problems - a sense of stress and psychological discomfort, which may lead to dysfunctions in society [1,3]. In recent years, many research results have been presented that combine the formation of hypertrophic and keloid scars with genetic factors that significantly contribute to the explanation of the pathogenesis of these disorders.

2. The physiological process of wound healing

In the process of wound healing, three stages can be specified: inflammation, proliferation and remodeling [4]. The inflammatory phase begins at the moment of wounding and lasts about 48 hours. During its course, the blood plaques that form the scab release cytokines and growth factors such as interleukins, tumor necrosis factor α (TNF-α) and transforming growth factor β (TGF-β). This results in concentration of the immune system cells at the site of tissue damage - neutrophils and activation of macrophages and keratinocytes [2,5]. The next stage is the proliferation phase, which starts 48-72 hours after the injury and can last from 21 to 42 days. It includes keratinocyte proliferation and fibroblast influx in place of wound and subsequent production of extracellular matrix (ECM). The aim of this process is the formation of granulation tissue consisting of a mixture of procollagen, proteoglycans, hyaluronic acid and elastin. The production of granulation tissue allows the initiation of angiogenesis [3]. The remodeling phase has a decisive impact on the final appearance of the scar. Fibroblast growth factor (FGF) plays a key role in its course, in particular FGF-2 and TGF-β forms [4]. It is believed that the final stage of scar remodeling can cover a period of more than 12 months, during which ECM changes are controlled by the degradation of matrix metalloproteinases (MMPs) dependent on zinc and inhibiting their tissue functions inhibitors of metalloproteinases (TIMP) [5].

The disturbance of physiological wound healing process resulting from improper activity of signaling pathways regulating this process in an indirect or direct way leads to abnormalities in the process of scarring, which may result in the formation of hypertrophic and keloid scars [3].

2. Differences between hypertrophic scar and keloid

The main differentiating factor between hypertrophic scar and keloid is the tendency to remain within, therefore, not growing and being limited to the initial wound boundary in the case of hypertrophic scars. Keloids, on the other hand, have the ability to cross the original wound [6]. Keloids and hypertrophic scars tend to have a specific location. Places with an increased likelihood of hypertrophic scarring are the skin of the cheeks, earlobes, as well as the regions of neck, shoulders and arms, for a change the chest skin is a frequent location of keloids [7]. A particular point in the development of hypertrophic scar is the regression stage that occurs after a rapid growth phase lasting about 6 months. This stage lasts for several years and allows the hypertrophic scar to turn into a flat scar. This process does not occur in the case of keloids, which determines the lack of their ability to spontaneously revert [8].

Currently, more and more attention is focused on the importance of keratinocytes, fibroblasts and Langerhans cells in the pathogenesis of abnormal scarring of the skin tissue. In the case of hypertrophic scars, overexpression of cyclooxygenase-1 (COX-1) in epidermal cells was observed, as well as increased concentration of Langerhans cells accompanied by an increased expression of interleukin 4 (IL-4), with simultaneously reduced Il-1α expression. In the case of keloids, epidermal cells show excessive expression of cyclooxygenase-2 (COX-2). It is worth emphasizing that the number of Langerhans cells within the epidermis usually does not exceed the norm, however, an increased concentration of T and B lymphocytes and M2 type macrophages is observed [9].

The histological features also show differences between the keloid and the hypertrophic scar.

Excess collagen fibers are characteristic for both hypertrophic and keloid scars [7]. The basic differentiating feature is the arrangement of collagen fibers. In normal skin tissue, collagen fibers run parallel to the epithelial plane, being grouped into bundles. In the case of hypertrophic scars, the type III collagen scars have a sigmoidal shape and their cross-section has flattening characteristics, whereas the parallel position in relation to the epithelial plane is preserved [3]. In this case, the collagen bundle may be characterized by a decrease in length and fragmentation [9]. A different structural organization is found in the case of keloids - type I and III collagen occurs in the form of thick bundles or in the form of less organized fibers that are loosely connected [3]. Collagen fibers exhibit hyalinization, length variation, and their spatial conformation may resemble spirals [9]. In this case, parallel arrangement of fibers in relation to the epithelial plane is not preserved [3,7]. Studies of the collagen I to collagen III ratio in abnormal forms of scarring showed its increase, which was expressed the most in the case of keloids (17.2), more than two times less in hypertrophic scars (7.73) being the same as the ratio measured in normal skin (6.28) [10].

3. Genetic mutations predisposing to the formation of hypertrophic and keloid scars

Many studies have been conducted, the results of which indicate a significant role of the genetic factor in the formation of keloids and hypertrophic scars. One of the evidence linking the development of these skin lesions to genetic changes is their increased incidence in genetic syndromes (Table 1). It has also been proven that patients with a dark skin phenotype are 15 times more likely to develop abnormal forms of scarring [3].

table 1.

3.1. The TGF-βI / Smad pathway and the effect of MAPK kinase

The TGF-β1 / Smad pathway significantly contributes to the process of abnormal skin healing and its inhibition may limit the formation of keloid [11]. TGF-β1 is a determinant of fibrotic processes by stimulating fibroblast proliferation in tissues, as well as the production of ECM components. It is believed that the cytokine TGF-β1 may play a major role in the pathogenesis of hypertrophic and keloid scars [12]. Song et al. in their studies among the Chinese population in the venous blood material indicated the polymorphism of the TGF-β1 gene by PCR method combined with DNA sequence analysis in patients with keloid, the control group in this study were patients with normal scarring. In the group of patients with keloid, a statistically significant correlation was found between the occurrence of TGF-β1 -509C / T polymorphism and elevated serum TGF-1β [13]. The influence of TGF-β1 gene polymorphism has also been studied in the Caucasian population. The study showed that the presence of the T allele at position -509 of the TGF-β1 gene is significantly associated with a reduced risk of keloids [14]. The importance of TGF-β1 in the increased migration of keratinocytes in patients with abnormal wound healing has also been demonstrated. Hahn et al. showed that inhibition of TGF-β1 signaling allows to reduce the migration of keratinocytes [15]. Studies conducted by Dong et al. showed that the chymase produced by mast cells present in keloid tissue may stimulate the production of TGF-β1, which results in increased fibroblast proliferation and a secondary increase in collagen synthesis [11]. Other studies have shown that TGF-β has the ability to stimulate the expression of fibroblast growth factor (FGF-2), which in turn is responsible for the positive regulation of MMP activity responsible for the regulation of the remodeling step in the wound healing process, hence it can be assumed that the disruption of gene expression FGF-2 coding may also be a factor favoring the formation of abnormal scars [16,17].

It has been demonstrated that the mitogen-activated kinase (MAPK) pathway can be activated by TGF-β transduction, which takes place independently of the Smad proteins. It is also postulated that the MAPK pathway through activation of extracellular signaled kinase (ERK) kinase may interfere with the Smad penetration into the nucleus through Smad-2 and Smad-3 phosphorylation. It was

also proved that inhibitors of JNK and p38 translated to the reduction of invasiveness of keloid fibroblasts secondary to inhibition of Smad protein complexes formation [12]. This was confirmed by studies carried out by Sood et al. who noticed that the mutation of sense change in the PTPN5 gene, whose product shows an inhibitory effect on MAPK, significantly correlates with a milder process of hypertrophic scar formation [18].

3.2. Insulin-like growth factor-1

The IGF-I / IGF-IR pathway plays an important role in the multiplication of cells as well as the inhibition of apoptosis. This confirms the association of this pathway with the occurrence of renal fibrosis associated with IgA nephropathy, as well as rat liver fibrosis. Activation of the IGF-I receptor (IGF-IR) can take place by binding IGF-I and IGF-II [19]. Increased concentration of insulin-like growth factor in keloid tissue has been demonstrated [12]. Research conducted by Daian et al. indicated a complex role of this factor in the pathogenesis of abnormal wound healing and the formation of hypertrophic and keloid scars. TGF-1β and IGF-1 have a synergistic ability to promote the synthesis of ECM proteins, such as fibronectin, type I collagen or plasminogen activator inhibitor (PAI-1). It is indicated that the essence of this process is the ability of IGF-1 to support TGF-1β in phosphorylation of p38 mitogen-activated kinase and stimulation of type 2 transcription factor [20]. In a study conducted by Hu et al., an increased level of expression for IGF-IR in fibroblast tissue originating from immature hypertrophic scars and kelodia was demonstrated. This suggests that the IGF-I / IGF-IR pathway plays an important role in the pathogenesis of abnormal scarring through negative effects on fibroblast apoptosis and a positive effect on collagen synthesis [19].

3.3. Plasminogen activator inhibitor (PAI-1) and urokinase-type plasminogen activator (uPA)

It is estimated that urokinase plasminogen activator plays an important role in the degradation of ECM, and thus may be one of the factors conditioning the ability of keloid to expand beyond the original wound. Research by Leake et al. [21] showed a strong expression (> 50%) of the uPA receptor (uPAR) in 40% of the keloid tissues tested. Importantly, the same study also showed a significant uPAR expression in the EMC for kelodia in 70% of cases and no increase in normal scar ECM. PAI-1 has a strong capacity to inhibit uPA, which determines its fibrogenic action [21]. Li et al. demonstrated reduced uPA expression in hypertrophic scars and an increase in PAI-1 expression compared to normal scars [22]. It is believed that the relationship between PAI-1 and the excessive accumulation of collagen in the tissue is an important causative factor in abnormal wound healing. In their studies, Wang et al. showed a positive correlation between the occurrence of keloid in patients and the occurrence of elevated serum PAI-1 levels. A statistically significant association of high concentrations of PAI-1 with the presence of the polymorphism -675 4G / 5G and the presence of the 4G / 4G genotype was observed. Importantly, no such association was proven, and thus there was no greater risk of occurrence of keloid in patients with polymorphism -844 A / G [23].

3.4. Vitamin D receptor (VDR)

Vitamin D has many functions in the body, one of them is participation in the regulation of cell differentiation and their proliferation and programmed death. Regulation of gene expression in the case of vitamin D takes place in two ways, the first mechanism is the formation of a complex of VDR receptors with retinoid receptors after being activated by calcitriol, while the second mechanism consists in direct binding of VDR to nuclear receptors [24]. Yu et al. have found a significant association between the TaqI C> T polymorphism of the VDR gene and the increased risk of keloid in the case of female sex. Patients with keloid were characterized by significantly lower levels of 1.25 (OH) in serum compared to patients in the control group. Also in the case of the TaqI C> T polymorphism, the level of 1.25 (OH) was significantly lower compared to the control

group [25]. The results of these studies show the relationship with the results obtained by Hahn together with Supp, which by means of immunohistochemical methods showed that in the keloid tissue there are significantly reduced amounts of VDR in comparison with normal scars. Also the presence of nuclear VDR was significantly lower in the case of material obtained from keloids, but importantly it was also noted that it is also lower in the case of dark-skinned donors. The results of this experiment may be a response to a noticeable relationship between dark skin tone and higher risk of keloid and hypertrophic scars [26].

3.5. ADAM33 - disintegrin gene and metalloproteinase

The ADAM33 gene belongs to the ADAM gene family, whose products are equivalent proteins. ADAM proteins are transmembrane proteins derived from the adamalysin protein family. It is postulated that they play an important role in the processes of cell signaling, cell growth, differentiation and proliferation. To date, 21 types of ADAM proteins have been detected in humans, of which only 13 are capable of proteolytic activity [27]. The ADAM33 protein is an endopeptidase whose function, like other ADAM proteins, is closely dependent on zinc ions [28]. Han et al. investigated the association between keloid occurrence and the presence of ADAM33 gene polymorphisms. The results of their experiments showed that GGAAGA haplotypes may predispose to the development of cheloids, whereas the GGGAGG haplotype may perform protective functions [29].

3.6. Suppressor genes

The PTEN suppressor gene found on the long arm of the chromosome 10 plays an important role in the life cycle of the cells. The PTEN protein can be found both in the cytoplasm and in the cell's nucleus. The cytoplasmic form has the ability to inhibit PI3K / AKT kinase activation, while the main function of the PTEN nuclear form is the regulation of the cell cycle, gene expression and the effect on genomic stability. NEDD4-1 can affect the stabilization and degradation of PTEN molecules, mediating PTVE in monofibiquitination and polyubiquitination [30], respectively. Sang et al. demonstrated statistically significant reduced concentrations of PTEN in deleted keloid tissues, in addition PTEN expression levels were inversely related to NEDD4-1 expression in keloid tissue [31]. Studies performed by Liu et al. also showed a reduced concentration of PTEN in keloid tissue compared to normal scars [32]. Studies carried out by Teofoli et al. show increased expression of mRNA and bcl-2 proteins, c-jun and c-fos, with simultaneously reduced expression of p53 in tissue fibroblasts taken from hypertrophic and keloid scars, which indicates the role of these factors in the pathogenesis of abnormal scarring [33].

Gao et al. demonstrated a relationship between the occurrence of the p53 gene variant with the presence of codon 72 CCC / CCC, and a greater risk of hypertrophic and keloid scar formation [34]. Another study showed reduced expression of p53 and increased expression of the DNp63 isoform compared to tissues obtained from hypertrophied and normal skin scars [35].

3.7. Heat shock proteins (Hsp)

Heat shock proteins are defined as a group of proteins responsible for the protection of cells against stressors. Their protective function manifests itself by stabilizing the synthesis, function and transport of proteins. Another function of Hsp is to modulate the cell apoptosis process, which has been noticed, e.g. observing the increase in Hsp expression in healing tissues [36]. Totana et al. demonstrated the essential role of heat shock proteins in the formation of keloid tissue. Their results revealed increased levels of hsp27, hsp47, hsp70 and no increase in hsp 60 and hsp 90 levels in keloid tissue compared to samples obtained from normal skin [36]. Another study conducted by Shin et al. investigated the effect of transfected siRNA on keloid fibroblasts on the effects of

inhibiting Hsp70 protein expression. It was observed that the decrease in Hsp70 positively correlated with lowering the level of collagen type I and III mRNA. This suggests that increased expression of heat shock proteins may play an important role in the formation of keloid by a positive effect on the production of collagen by fibroblasts [37].

3.8. Type 2 hyaluronidase (HAS2) synthase

Hyaluronic acid (HA) is a glycosaminoglycan commonly found in ECM. Three synthases of hyaluronic acid (HAS1, -2, -3) have been identified, which are enzymes associated with the cell membrane [38]. HA molecules have functions that regulate the transport of other molecules and cells through tissues, as well as regulate tissue renewal processes and inflammatory processes. HA is also the main factor responsible for proper hydration of the skin tissue [39]. The transmembrane glycoprotein CD44 is the main receptor for HA. CD44 is involved in signal transduction as well as plays an important role in cell-cell communication and between cell and ECM [40].

Supp et al. have demonstrated that the overexpression of HAS2 in keloid tissue is associated with the increased ability of keratinocytes to migrate keloid tissue, which may explain the tendency of keloid to spread beyond the original wound boundaries [41]. The results showing the protective and antiapoptotic effect of HAS2 expression on stressed fibroblasts under laboratory conditions were presented by Wang et al. [42].

Conclusions

Due to somatic complaints, as well as an important aesthetic defect associated with the occurrence of hypertrophic and keloid scars, which may lead to psychological and social problems, it is necessary to learn the mechanisms of these abnormal forms of scarring. Patients who may experience this process disorder should seek medical advice before body piercing and cosmetic procedures that may affect skin continuity.
Explanation of the genetic basis of the formation of hypertrophic and keloid scars can lead to a full understanding of their pathogenesis, as well as bring important implications in the form of therapeutic benefits, resulting in the development of effective forms of treatment.

References:

[1] Arno AI, Gauglitz GG, Barret JP, Jeschke MG. Up-to-date approach to manage keloids and hypertrophic scars: a useful guide. Burns. 2014; (40): 1255–66.

[2] Wysocka M, Żaba R. Patogeneza oraz wybrane metody leczenia blizn przerosłych i bliznowców. Przew Lek 2007; (5): 79-86.

[3] Wolfram D, Tzankov A, Pülzl P, Piza-Katzer H. Hypertrophic scars and keloids—a review of their pathophysiology, risk factors, and therapeutic management. Dermatologic Surgery. 2009; 171-81.

[4] Witmanowski H, Lewandowicz E, Zieliński T, Łuczkowska M, Kruk-Jeromin J. Hypertrophic scars and keloids. Part I. Pathogenesis and pathomechanism. Post. Dermatol. Alergol. 2009; (3): 107-15.

[5] Zielins E.R, Brett E.A, Luan A, Hu M.S, Walmsley G.G, Paik K, Senarath-Yapa K, Atashroo D.A, Wearda T, Lorenz H.P. Emerging drugs for the treatment of wound healing. Expert Opin. Emerg. Drugs. 2015; (20): 235–46.

[6] van den Broek LJ, Limandjaja GC, Niessen FB, Gibbs S. Human hypertrophic and keloid scar models: principles, limitations and future challenges from a tissue engineering perspective. Exp Dermatol. 2014; 23(6): 382-6.

[7] Hunasgi, S., Koneru, A., Vanishree, M., Shamala, R. Keloid: a case report and review of pathophysiology and differences between keloid and hypertrophic scars. J Oral Maxillofac Pathol. 2013; (17): 116–20.

[8] Gauglitz, G.G., Korting, H.C., Pavicic, T., Ruzicka, T., Jeschke, M.G. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med. 2011; (17): 113–25.

[9] Huang C, Murphy GF, Akaishi S. Keloids and hypertrophic scars: update and future directions. Plast Reconstr Surg Glob Open. 2013; 1:e25.

[10] Friedman DW, Boyd CD, Mackenzie JW. Regulation of collagen gene expression in keloids and hypertrophic scars. J Surg Res. 1993; (55): 214–22.

[11] Dong X, Zhang C, Ma S, Wen H. Mast cell chymase in keloid induces profibrotic response via transforming growth factor-beta1/Smad activation in keloid fibroblasts. Int J Clin Exp Pathol. 2014; (7): 3596–3607.

[12] Unahabhokha T, Sucontphunt A, Nimmannit U, Chanvorachote P, Yongsanguanchai N, Pongrakhananon V. Molecular signalings in keloid disease and current therapeutic approaches from natural based compounds. Pharm Biol. 2015; (53): 457–63.

[13] Song M, Liu Y. Analysis on polymorphism at -509 C/T site of TGF-β1 gene in patients with keloids. Zhonghua Shao Shang Za Zhi. 2014; (6): 482-6.

[14] Kulawczuk P, Czapla N, Bińczak-Kuleta A, Safranow K, Jaworska-Kulawczuk A, Gajewska D, Agata K, Brykczyński M, Bargiel P. Genetic basis of keloid formation in wounds after cardiac surgery. Kardiochir Torakochirurgia Pol. 2014; 11(3): 273-7.

[15] Hahn JM, McFarland KL, Combs KA, Supp DM. Partial epithelial-mesenchymal transition in keloid scars: regulation of keloid keratinocyte gene expression by transforming growth factor-β1. Burns Trauma. 2016; 23;4(1): 30.

[16] Eto H, Suga H, Aoi N, Kato H, Doi K, Kuno S, Tabata Y, Yoshimura K. Therapeutic potential of fibroblast growth factor-2 for hypertrophic scars: upregulation of MMP-1 and HGF expression. Lab Invest. 2012; 92(2): 214-23.

[17] Strand DW, Liang YY, Yang F, Barron DA, Ressler SJ, Schauer IG. TGF-beta induction of FGF-2 expression in stromal cells requires integrated smad3 and MAPK pathways. American journal of clinical and experimental urology. 2014; 2(3): 239–48.

[18] Sood RF, Arbabi S, Honari S, Gibran NS. Missense Variant in MAPK Inactivator PTPN5 Is Associated with Decreased Severity of Post-Burn Hypertrophic Scarring. PLoS One. 2016; 11(2): e0149206.

[19] Hu ZC, Tang B, Guo D, Zhang J, Liang YY, Ma D, Zhu JY. Expression of insulin-like growth factor-1 receptor in keloid and hypertrophic scar. Clin Exp Dermatol. 2014; 39(7): 822-8.

[20] Daian T, Ohtsuru A, Rogounovitch T, Ishihara H, Hirano A, Akiyama-Uchida Y, Saenko V, Fujii T, Yamashita S. Insulin-like growth factor-I enhances transforming growth factor-beta-induced extracellular matrix protein production through the P38/activating transcription factor-2 signaling pathway in keloid fibroblasts. J Invest Dermatol. 2003; 120: 956–62.

[21] Leake D, Doerr TD, Scott G. Expression of urokinase-type plasminogen activator and its receptor in keloids. Arch Otolaryngol Head Neck Surg. 2003; 129(12): 1334-8.

[22] Li C, Zhu HY, Bai WD, Su LL, Liu JQ, Cai WX, Zhao B, Gao JX, Han SC, Li J, Hu DH. MiR-10a and miR-181c regulate collagen type I generation in hypertrophic scars by targeting PAI-1 and uPA. FEBS Lett. 2015; 589(3): 380-9.

[23] Wang Y, Jianhong Long J, Wang X, Sun Y. Association of the Plasminogen Activator Inhibitor-1 (PAI-1) Gene -675 4G/5G and -844 A/G Promoter Polymorphism with Risk of Keloid in a Chinese Han Population. Med Sci Monit. 2014; (20): 2069–73.

[24] Gruber BL, Kew RR, Jelaska A. Human mast cells activate fibroblasts: tryptase is a fibrogenic factor stimulating collagen messenger ribonucleic acid synthesis and fibroblast chemotaxis. J Immunol. 1997; (158): 2310–7.

[25] Yu D, Shang Y, Luo S, et al. The TaqI gene polymorphisms of VDR and the circulating 1,25-dihydroxyvitamin D levels confer the risk for the keloid scarring in Chinese cohorts. Cell Physiol Biochem. 2013; (32): 39–45.

[26] Hahn JM, Supp DM. Abnormal expression of the vitamin D receptor in keloid scars. Burns. 2017; 43(7): 1506-15.

[27] Zhang P, Shen M, Fernandez-Patron C, Kassiri Z. ADAMs family and relatives in cardiovascular physiology and pathology. J Mol Cell Cardiol. 2016; (93): 186-99.

[28] Sampsonas F, Kaparianos A, Lykouras D, Karkoulias K, Spiropoulos K. DNA sequence variations of metalloproteinases: their role in asthma and COPD. Postgrad Med J. 2007; (83): 244–50.

[29] Han, J, Han, J, Yu, D. Association of ADAM33 gene polymorphisms with keloid scars in a northeastern Chinese population. Cell Physiol Biochem. 2014; 34(3): 981–7.

[30] Hong SW, Moon JH, Kim JS, Shin JS, Jung KA, Lee WK, Jeong SY, Hwang JJ, Lee SJ, Suh YA, et al. p34 is a novel regulator of the oncogenic behavior of NEDD4-1 and PTEN. Cell Death Differ. 2014; (21): 146–60.

[31] Sang PF, Wang H, Wang M, Hu C, Zhang JS, Li XJ, Zhu F. NEDD4-1 and PTEN expression in keloid scarring. Genet Mol Res. 2015; 28;14(4): 13467-75.

[32] Liu Y, Wang X, Yang D, Xiao Z, Chen X. MicroRNA-21 affects proliferation and apoptosis by regulating expression of PTEN in human keloid fibroblasts. Plast Reconstr Surg. 2014; (134): 561–73.

[33] Teofoli P, Barduagni S, Ribuffo M, Campanella A, De Pita O, Puddu P. Expression of Bcl-2, p53, c-jun and c-fos protooncogenes in keloids and hypertrophic scars. J Dermatol Sci 1999; 22(1): 31–7.

[34] Gao J, Chen Y, Liao N, Zhao W, Zeng W, Li Y, Wang S, Lu F. Relationship between p53 gene codon-72 polymorphisms and hypertrophic scar formation following caesarean section. Exp Ther Med 2014; (7): 1243-6.

[35] De Felice B, Ciarmiello L F, Mondola P, et al. Differential p63 and p53 expression in human keloid fibroblasts and hypertrophic scar fibroblasts. DNA Cell Biol. 2007; (26): 541–7.

[36] Totan S, Echo A, Yuksel E. Heat shock proteins modulate keloid formation. Eplasty. 2011; (11): 190–202.

[37] Shin J.U., Lee W.J., Tran T.N., Jung I., Lee J.H. Hsp70 knockdown by siRNA decreased collagen production in keloid fibroblasts. Yonsei Med. J. 2015; (56): 1619–26.

[38] Calve S, Isaac J, Gumucio JP, Mendias CL. Hyaluronic acid, HAS1, and HAS2 are significantly upregulated during muscle hypertrophy. American journal of physiology Cell physiology. 2012; 303(5): 577–88.

[39] Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: a key molecule in skin aging. Dermatoendocrinol. 2012; 4(3): 253–8.

[40] Hellström, M., Engström-Laurent, A., Mörner, S., Johansson, B. Hyaluronan and collagen in human hypertrophic cardiomyopathy: a morphological analysis. Cardiol. Res. Pract. 2012; 545219.

[41] Supp DM, Hahn JM, McFarland KL, Glaser K. Inhibition of hyaluronan synthase 2 reduces the abnormal migration rate of keloid keratinocytes. J Burn Care Res. 2014; 35(1): 84-92.

[42] Wang Y, Lauer ME, Anand S, Mack JA, Maytin EV. Hyaluronan synthase 2 protects skin fibroblasts against apoptosis induced by environmental stress. J Biol Chem. 2014; 289(46): 32253-65.