POSSIBILITIES OF REGENERATION OF THE MUSCLES OF THE SOFT PALATE DURING ITS NONUNION DEPENDING ON THE MYOGENIC POTENTIAL OF STEM CELLS. Review

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Relevance. Today there are more than 150 methods for eliminating congenital defects of the hard and soft palate. However, these techniques do not always lead to high functional results, which leads to repeated surgical interventions and long-term speech therapy rehabilitation. Therefore, there is a problem of prognosis of such treatment. The search for a marker for assessing the prognosis of surgical intervention is relevant. One of these markers may be the state of the myogenic potential of stem cells.

Objective: to analyze the possibility of preliminary assessment of muscle regeneration, depending on the myogenic potential of stem cells, in order to increase the effectiveness of treatment of children with non-union of the soft palate.

Method. An analytical review of the literature on keywords from the scientometric databases PubMed, Scopus, Web of Science.

Results. Satellite cells represent an adequate system model for studying the biology of adult stem cells. Satellite cells can be considered candidates for cell therapy in muscle regeneration. First, they are one of the most abundant and most accessible cells in our body. Secondly, there is a panel of specific markers that can be used to isolate satellite cells. Third, satellite cells are localized within clear boundaries of the anatomical niche, and signaling mechanisms are currently being studied. Fourth, there is the possibility of recreating muscle injuries in which satellite cells can be studied. Future research aimed at increasing the purification of satellite cells so as to maintain their low differentiation, increase the engraftment potential, as well as new approaches aimed at obtaining satellite cells from iPS cells, will help accelerate the progress and development of drugs for cell therapy in the treatment of muscle degenerative diseases.

Conclusions. The data on the myogenic potential of stem cells, in muscle regeneration, obtained on satellite cell models, can be used to increase the effectiveness of the treatment of children with nonunion of the soft palate.

Key words: nonunion of the upper lip and palate, muscle injury, satellite stem cells, engraftment, myofibrils, marker

Relevance. Nonunion of the upper lip and palate is the most common congenital malformation of the maxillofacial region. There is a tendency to an increase in the birth rate of children with this pathology. The incidence of lip and palate unions is approximately 1: 500-1: 1000 live births.

The anatomy of deformation disorders of the maxillofacial region with non-union of the upper lip and palate reflects not only the different length and size of the defect that arose during embryonic development, but also the long-term consequences of a violation of the growth model of development in the absence of intact labial muscles and structural support by the bone arch, the presence of a message between the mouth and nose [9].

There are more than 150 methods for eliminating congenital defects of the hard and soft palate. Surgical treatment of congenital nonunions of the palate is carried out by moving the mucoperiosteal flaps. Over the years, the authors have proposed using various surgical techniques to optimize the ratio of the length of the soft palate and the width of the mesopharynx.

However, these techniques do not always lead to high functional results, which leads to repeated surgical interventions and long-term speech therapy rehabilitation.

There is a problem of choosing the most adequate technique for each specific case. Therefore, the actual issue is the search for a marker when choosing a

technique. One of these markers may be the state of the myogenic potential of stem cells.

Objective: to analyze the possibility of preliminary assessment of muscle regeneration, depending on the myogenic potential of stem cells, in order to increase the effectiveness of treatment of children with non-union of the soft palate.

METHOD

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RESULTS AND DISCUSSION

The effectiveness of primary uranostaphyloplasty is diverse. Thus, cicatricial of the tissues of the soft palate and its shortening were observed in 19-68% of patients operated on according to known methods. The main indicator of the functional efficiency of the performed uranostaphyloplasty is good pharyngeal closure. It is it that largely determines the «purity» of speech [23].

The muscles of the soft palate (5 pairs) form an aponeurosis in the center of the soft palate. The lack of connection to the skeleton at one end contributes to the development of static contractions and high tension. The main function of the soft palate in humans is to control

the flow of air through the mouth or nasopharynx during a conversation and to protect against the ingress of food and liquid into the nasal cavity during swallowing. It also plays an important role in middle ear breathing and ventilation. For the normal functioning of the palatopharyngeal ring, the muscles of the soft palate contract as synergists, and if they do not join, this is not, since they have a pathological attachment, namely: the muscles are attached to the posterior surface of the hard palate. Accordingly, the muscles do not work, and we can talk about dystrophy of muscle fibers and a decrease in myogenic potential. Surgical treatment aimed at eliminating anatomical and functional defect, which should subsequently improve speech quality and feeding. However, problems often persist after surgery. After surgery, scar tissue is formed, which subsequently causes problems with the function of the muscles of the soft palate, namely: it disrupts the organization and construction of new muscle fibers, and the connections between them [8].

By histochemical reaction to myofibrillar ATPase (mATPase), two main types of muscle fibers are distinguished - type I and II. Type II fibers are classified into type IIA, IIB, IIC depending on the dye density after acidic preincubation. The additional type of IM fibers is usually present in the muscles that close the jaw of a person. mATPase is located on the myosin heavy chain (MyHC), a molecule that is the main contractile protein in muscles [22]. The main MUNS isoforms that are expressed in human limb muscles are slow MyHC, fast A MyHC and fast X MyHC. Slow MyHC is present in type I fibers and co-expressed with fast MyHC in type IIC fibers. Fast A MyHC is mainly present in type IIA fibers, and fast X MyHC, but not B MyHC, in type IID fibers. Additional MyHC isoforms such as fetal, embryonic, α -cardiac, and slow tonic are usually not expressed in muscle fibers of adult limbs, but are present in cranial muscles and intrafusal fibers of muscle spindles [23].

It has been established that each muscle of the soft palate has characteristic differences and that they are more similar to the muscles of the face than the limbs. The palatopharyngeal (palatopharyngeus) and lingual (uvula) muscles contain the highest proportion of type II fibers among human muscles (only the facial m. Zygomaticus minor is comparable), which are characterized by fast contractility with a large high threshold of motor units. In contrast, the levator and tensor veli palatini muscles contain predominantly type I fibers.

Fetal-myosin MyHC is present in a small number of fibers in all muscles of the palate. In the limbs, fetal-myosin is only expressed during early fetal muscle development. The muscles of the palate are characterized by the presence of small fibers of less polygonal shape and a higher content of connective tissue. The same morphology is characteristic of the human facial muscles. Their fiber diameter is smaller and exhibits significant variability. All muscles have a high capillary density and

an unusually high activity of mitochondrial enzymes in type II fibers. This indicates a high potential for aerobic metabolism and therefore resistance to fatigue. The absence of conventional muscle spindles indicates a special system of proprioceptive control, which is usually mediated by muscle spindle receptors. The absence of muscle spindles is important for regulating the tension and rate of contraction in the limb muscles. In the masticatory muscles, numerous muscle fibers are observed, while in the facial muscles they are completely absent [19].

A number of pathological conditions, including congenital myopathies, dystrophies, are associated with progressive loss of muscle mass and strength, and may also be accompanied by a decrease in the number and proliferative potential of satellite cell muscles. The main mechanisms responsible for these changes in the affected muscles have not yet been elucidated, but may be associated with internal changes, namely: the inclusion of proliferative stress associated with the need for repeated muscle regeneration in response to chronic degenerative conditions. However, in addition to internal deficits, environmental changes can occur that can affect the pools and suppress the myogenic activity of these cells.

Children with various types of congenital defects, which include congenital nonunion of the palate, in which the functional state of the muscles is of paramount importance, are also a problem. However, at the moment there is no idea about the primary state of the muscles of the soft palate in such patients. Therefore, the reasons for the unsatisfactory results of surgical treatment can be both congenital myopathy of the muscles of the soft palate or a decrease in the myogenic potential before surgery, due to atrophy caused by pathological attachment, and improper functioning of these muscles.

Regeneration of skeletal muscles is of great clinical importance in muscular dystrophies and various injuries; it depends on the cambial reserve formed by myosatellite cells [4].

Satellite cells – mononuclear myogenic stem cells located between the basal lamina and the cell membrane (sarcolemma) of skeletal muscle fiber, are the main participants in postnatal muscle growth. Satellite cells were first described in 1961 by Mauro A. This discovery made it possible to solve a long-term problem: why is the number of nuclei and the size of myofibrils growing without visible nuclear divisions? As a result of subsequent electron microscopic studies, resting cells lying on the surface of the muscle fiber under its basement membrane were called satellite. They make up 2-5% of the subluminal nuclei and are mitotically inert under normal conditions, but they are activated to proliferate during postnatal growth and muscle regeneration in response to injury or exercise and begin to divide, passing through self-renewal and differentiation into a mature muscle cell. With age, the ability of skeletal muscles to regenerate decreases [18].

Typically, stem (progenitor) cells are characterized by molecular markers typical for each stage of their development. Satellite cells resting in normal adult muscle can be activated, divide, forming myoblasts, which then undergo the stages of proliferation, committing (preparation) for differentiation, and fusion into immature myocytes, which form myofibrils after maturation [14]. The activation of satellite cells is accompanied by a transition to the expression of the marker MyoD, and the expression of myogenin corresponds to commitment to differentiation. As the transcription factor Pax7 decreases and the myo-specific transcription factors MyoD and myogenin grow, myoblasts enter the phase of differentiation [14]. The manifestation of cells expressing Pax7, but not MyoD, indicates a self-renewing population of satellite cells [5]. Expression of MLC3F-tg is typical of many structural muscle genes, such as skeletal muscle actin and MyHC myosin, which characterize sarcomeres in the late stages of differentiation.

Since satellite cells move from their immediate position under the basal lamina during muscle regeneration, this formally contradicts their status as stem cells. Direct evidence of the functioning of satellite cells as myogenic progenitors was first obtained using labeled thymidine in growing or regenerating muscles and then on isolated myofibrils, which led to the general acceptance of the ability of satellite cells to give rise to myoblasts differentiating into multinucleated myofibrils [15].

One of the most important characteristics of stem cells is the ability to self-renew in vivo – long-term proliferation without concomitant differentiation. Therefore, in order to reasonably define one of the subpopulations of myosatellitocytes as myogenic stem cells, most researchers are trying to establish their ability to multiple division [3].

Self-renewal of satellite cells can occur during the initial asymmetric division of the satellite cell and/or upon the return to a dormant state of the myoblasts formed by these cells.

A small number of muscle nuclei can also be formed at the expense of non-satellite cells (interstitial or circulatory), but the possibility of them creating proliferating myogenic progenitors has not yet been established.

The recent transplantation of such single myofibrils into muscle was a good confirmation of the fact that satellite cells are indeed myogenic stem cells that form new myofibrils, as well as new satellite cells [17].

Until recently, satellite cells were considered as unipotent myogenic precursors, because their myogenic potential was manifested on isolated myofibrils. However, it turned out that satellite cells can leave the myogenic pathway (exhibit plasticity) when treated, for example, with adipogenic factors. In addition, the expression of osteogenic and adipogenic markers was found in the culture of satellite cells from a single myofibril [6].

When satellite cells isolated from mouse myofibrils were cultured, both myogenic and non-myogenic clones were obtained in blood serum, and only myogenic clones expressed myogenic transcription factors with further myofibril formation. A model of mesenchymal plasticity of skeletal muscle satellite cells is proposed. According to this model, satellite cells located in the corresponding myogenic environment enter myogenic differentiation, forming myoblasts, which turn into myofibrils. Another subpopulation of satellite cells undergoing de-homing, i.e. losing the myogenic environment, they follow a different path – mesenchymal alternative differentiation (MAD), giving non-myogenic cells like adipocytes and osteoblasts [21]. Thus, the multipotency of satellite cells is fully proven.

Adult muscle tissue can repair itself in response to direct injury, neurological dysfunction, and genetic defects. The regeneration process begins with the activation of satellite cells. Once activated, satellite cells divide, differentiate into specific types of muscle tissue, and ultimately fuse with the tissue being repaired [1].

Skeletal muscle can be damaged by injury, illness, and certain types of exercise. The lesions go through the following phases: necrosis/degeneration, inflammation, repair and scarring (fibrosis). Necrosis/degeneration is accompanied by the destruction of the plasma and basement membranes, the entry of extracellular calcium and the subsequent destruction of the myofibril. First, the surface is filled with inflammatory cells (monocytes, macrophages and T-lymphocytes). Subsequent secretion of growth factors and cytokines causes blood flow to the site of injury and intensifies the inflammatory response. Muscle regeneration begins after phagocytes clear it of necrotic tissue, therefore blocking inflammatory cells (for example, non-steroidal anti-inflammatory drugs) slows down the regeneration process, since factors secreted by macrophages may play a role in the proliferation and differentiation of myoblasts. Active muscle regeneration usually lasts 2-3 weeks after injury.

It is known that stem cells do not exist in the body by themselves, they are located in a microenvironment, which is usually denoted by the term «niche». At present, this term is usually understood as a combination of factors that ensure the viability and self-reproduction of stem cells, and the differentiation of transient daughter cells. For satellite cells, these factors include the presence of the basement membrane, extracellular matrix molecules, and the presence of neighboring cells that produce growth factors and various regulatory molecules.

Niches are part of the structural and functional units that make up tissues, and stem cells are firmly anchored in the niche with the help of adhesion molecules, for this purpose, in particular, a class of adhesion molecules called integrins is used.

An important component of the satellite cell stem niche is the basal lamina, which consists of matrix proteins – laminin, collagen and proteoglycans, interacting with

membrane proteins of the satellite cell, and is a reservoir for some growth factors. In addition, the activity of satellite cells is influenced by other types of cells from the local environment (for example, fibroblasts secreting paracrine factors, nerves acting through the myofibril, endothelial cells secreting growth factors, immune cells that promote muscle regeneration through phagocytic activity and cytokine secretion).

This anatomical position of the satellite cell niche determines the combination of signals from the myofibril, blood circulation, and extracellular matrix, which control dormancy, activation, and proliferation of the satellite cell.

Various strategies have now been tried in order to optimize and improve muscle regeneration. Injections of growth factors and transplantation of satellite cells (myosatellites) have been used with different results [8]. These approaches can be combined to optimize the treatment of muscle injuries. However, treatment still faces challenges.

Satellite cells must be isolated from cultured prior to transplantation, resulting in a loss of myogenic potential. In addition, satellite cells have low survival rates and limited migration after transplantation [16].

A number of studies and clinical trials have tested the efficacy of cell therapy for muscle regeneration and have met with rather disappointing results, namely low engraftment rates and minor improvements in muscle function [11].

Improved clinical outcomes can be achieved by using more primitive satellite cells freshly isolated from donor tissue. Nevertheless, this approach introduces its limitations due to the scarcity of satellite cells in normal skeletal muscles, relatively laborious currently methods of access to extract them from tissues, and the impossibility of increasing these cells in vivo without a strong decrease in their ability to self-renewal [7].

Thus, the effective use of the regenerative potential of satellite cells during transplantation still requires the development of new strategies that support the increase in the number of these cells while maintaining their functional engraftment potential. These factors prevent the use of stem cell therapy for muscular dystrophy.

The age characteristics of satellite cells and their regeneration capabilities should also be noted.

Several studies have shown that the decrease in muscle regeneration, the number of satellite cells and the decrease in function is directly related to age [2]. In newborn mice, satellite cell nuclei make up about 30% of myofibrils, but their number decreases with maturity, and only about 5% of the nuclei in satellite cells in the muscles of adult mice [19].

The number of cells associated with muscle fibers decreases with age [10], accompanied by a relative increase in the frequency of muscle resident FAP cells, which usually form adipose and scar tissue, as well as the time of myogenesis [20].

It was shown that the regeneration of muscle fibrils ceases to be dependent on Pax7 progenitor cells after 21 days of postnatal development. It is at this period of development that the formation of the structure of the muscle fiber is completed, the nuclei are distributed and the resting myosatellite cells are isolated. It was found that the Pax7 protein functionally not only coordinates the survival and proliferation of myosatellite cells, but also prevents their differentiation and fusion into muscle fiber, preserving the potential for regeneration in myosatellite cells. The critical period of dependence on Pax7 was also determined during the transition from myosatellitocytes to the state of stem cells, which provide skeletal muscles with the ability to regenerate. This period in mice ends on day 21 after birth. The integral role of Pax3 and Pax7 for embryonic muscle progenitors is shown, and the role of only one Pax7 for perinatal. It has also been shown that adult satellite cells do not require either Pax3 or Pax7 for muscle regeneration. This finding contradicts the generally accepted concept that «regeneration repeats development.» Changes in the genetic program of muscle stem cells during the transition from the embryonic stage to the juvenile stage and further to the adult stage prompts caution in applying the knowledge gained from embryonic research to the biology of adult stem cells. Age-dependent changes in the properties of stem cells suggest the need for a thorough analysis of the age of the cell material used in transplantation in regenerative medicine [12].

A strategy for obtaining a rapidly dividing population of human skeletal myogenic progenitor cells derived from induced pluripotent stem (iPS) cells is described. iPS cells have all the potential of embryonic stem (ES) cells, but are produced by reprogramming skin cells (fibroblasts). They can be patient-specific, which reduces the likelihood of immune rejection, and does not heighten the ethical concerns surrounding the killing of human embryos. To achieve these results, the scientists genetically modified two well-studied human iPS cell lines and a human embryonic stem cell line with the PAX7 gene. This allowed them to regulate the levels of the Pax7 protein, which is necessary for the regeneration of skeletal muscle tissue after injury. The researchers found that this regulation stimulates the differentiation of naive ES and iPS cells into muscle-forming cells. Thus, the PAX7 gene - introduced at exactly the right time – helped shape the fate of human ES and iPS cells, pushing them to differentiate into muscle progenitor cells.

Once the researchers were able to pinpoint the optimal timing of differentiation, the cells became fully functional for the resumption of muscle growth needed to treat conditions such as muscular dystrophy. Moreover, Pax7-induced progenitor cells have been shown to be much more effective in improving muscle function than human myoblasts, which have been shown in clinical trials to persist after transplantation.

The first model for soft palate regeneration after surgical injury is presented. Studies show that the anatomy and histology of the muscles of the soft palate of rats are in many ways comparable to humans. The widespread use of rodents in biomedical research provides specific immune antibodies for staining. The combination of ease of handling and low cost makes rats the most suitable animal models. The model includes an isolated non-union of the soft palate. Pax7-, Muod- and MyoG-positive cells were found at the wound edges, the presence of activated SatCs and myofibril differentiation was demonstrated.

The results of the research carried out are relevant and important for solving the problems of modern maxillofacial surgery. This is especially true of congenital pathology of the maxillofacial region, since a congenital anomaly of development leads to deformation of the middle third of the face, disharmony in the development of the facial skeleton, grossly disrupts the functions of various vital organs and systems, of the facial aesthetics and negatively affects the formation of the psycho-emotional status of the child.

CONCLUSIONS

Satellite cells represent an adequate system model for studying the biology of adult stem cells, as well as potential candidates for cell therapy in muscle regeneration. First, they are one of the most abundant and most readily available cells in our body. Second, there is a panel of specific markers that can be used to isolate satellite cells. Third, satellite cells are localized within distinct anatomical niches, and signaling mechanisms are currently being studied. Fourth, there is the possibility of reconstructing muscle injuries in which satellite cells can be studied. Future research aimed at increasing the purification of satellite cells so as to maintain their low differentiation, increase the engraftment potential, as well as new approaches aimed at obtaining satellite cells from iPS cells, will help accelerate the progress and development of drugs for cell therapy in the treatment of muscle degenerative diseases.

REFERENCES

1. Boldrin L., Neal A., Zammit P.S., Muntoni F., Morgan J.E. Donor satellite cell engraftment is significantly augmented when the host niche is preserved and endogenous satellite cells are incapacitated. *Stem Cells*. 2012 Sep; 30(9): 1971-84. DOI: 10.1002/stem.1158.
2. Conboy IM1, Rando TA. Aging, stem cells and tissue regeneration: lessons from muscle. *Cell Cycle*. 2005 Mar; 4(3): 407-10. DOI: <https://doi.org/10.4161/cc.4.3.1518>
3. Daubas P., Buckingham M.E. Direct molecular regulation of the myogenic determination gene Myf5 by Pax3, with modulation by Six1/4 factors, is exemplified by the -111 kb-Myf5 enhancer. *Dev Biol*. 2013 Apr 15; 376(2): 236-44. DOI: 10.1016/j.ydbio.2013.01.028.
4. Davidson E.H. Emerging properties of animal gene regulatory networks. *Nature*. 2010 Dec 16; 468(7326): 911-20. DOI: 10.1038/nature09645.
5. de la Garza-Rodea AS, van der Velde-van Dijke I, Boersma H, Gonçalves MA, van Bekkum DW, de Vries AA, Knaän-Shanzer S. Myogenic properties of human mesenchymal stem cells derived from three different sources. *Cell Transplant*. 2012; 21(1):153-73. DOI:10.3727/096368911X580554.
6. Dmitriev P, Barat A, Polesskaya A, O'Connell MJ, Robert T, Dessen P, Walsh TA, Lazar V, Turki A, Carnac G, Laoudj-Chenivess D, Lipinski M, Vassetzky YS. Simultaneous miRNA and mRNA transcriptome profiling of human myoblasts reveals a novel set of myogenic differentiation-associated miRNAs and their target genes. *BMC Genomics*. 2013 Apr 18; 14:265. DOI: 10.1186/1471-2164-14-265.
7. Gilbert PM, Havenstrite KL, Magnusson KE, Sacco A, Leonardi NA, Kraft P, Nguyen NK, Thrun S, Lutolf MP, Blau HM. Substrate elasticity regulates skeletal muscle stem cell self-renewal in culture. *Science*. 2010 Aug 27; 329(5995): 1078-81. DOI: 10.1126/science.1191035.
8. Grefte S, Kuijpers-Jagtman AM, Torensma R, Von den Hoff JW. Skeletal muscle development and regeneration. *Stem Cells Dev*. 2007 Oct; 16(5): 857-68. DOI: <https://doi.org/10.1089/scd.2007.0058>
9. Damstra J, Mistry D, Cruz C, Ren Y. Antero-posterior and transverse changes in the positions of palatal rugae after rapid maxillary expansion. *Eur J Orthod*. 2009 Jun 31; 31(3): 327-32. DOI: <https://doi.org/10.1093/ejo/cjn113>
10. Kleinstein RN, Sinnott LT, Jones-Jordan LA, Sims J, Zadnik K. New cases of myopia in children. Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error Study Group. *Arch Ophthalmol*. 2012 Oct; 130(10): 1274-9. DOI: <https://doi.org/10.1001/archophthalmol.2012.1449>
11. Kroehne V, Heschel I, Schuegner F, Lasrich D, Bartsch JW, Jockusch H. Use of a novel collagen matrix with oriented pore structure for muscle cell differentiation in cell culture and in grafts: *Journal of cellular and molecular medicine*. 2008; 12(5a): 1640-8. DOI: <https://doi.org/10.1111/j.1582-4934.2008.00238.x>
12. Lepper CI, Conway SJ, Fan CM. Adult satellite cells and embryonic muscle progenitors have distinct genetic requirements. *Nature*. 2009 Jul 30; 460(7255): 627-31. DOI: 10.1038/nature08209.
13. Liao YF1, Prasad NK, Chiu YT, Yun C, Chen PK. Cleft size at the time of palate repair in complete unilateral cleft lip and palate as an indicator of maxillary growth. *Int J Oral Maxillofac Surg*. 2010 Oct; 39(10): 956-61. DOI: 10.1016/j.ijom.2010.01.024.
14. MacQuarrie KL, Yao Z, Fong AP, Diede SJ, Rudzinski ER, Hawkins DS, Tapscott SJ. Comparison of genome-wide binding of MyoD in normal human myogenic cells and rhabdomyosarcomas identifies regional and local suppression of promyogenic transcription factors. *Mol Cell Biol*. 2013 Feb; 33(4):773-84. DOI: 10.1128/MCB.00916-12

15. Meligy FYI, Shigemura K, Behnsawy HM, Fujisawa M, Kawabata M, Shirakawa T. The efficiency of in vitro isolation and myogenic differentiation of MSCs derived from adipose connective tissue, bone marrow, and skeletal muscle tissue. *In Vitro Cell & Dev Biol Anim.* 2012 Apr; 48(4):203-15. DOI: 10.1007/s11626-012-9488-x
16. Montarras DI, Morgan J, Collins C, Relaix F, Zaffran S, Cumano A, Partridge T, Buckingham M. Direct isolation of satellite cells for skeletal muscle regeneration. *Science.* 2005 Sep 23; 309(5743):2064-7. DOI: <https://doi.org/10.1126/science.1114758>
17. Sacco A, Doyonnas R, Kraft P, Vitorovic S, Blau HM. Self-renewal and expansion of single transplanted muscle stem cells. *Nature.* 2008 Nov 27; 456(7221):502-6. DOI:10.1038/nature07384.
18. Soleimani VD, Punch VG, Kawabe Y, Jones AE, Palidwor GA, Porter CJ, Cross JW, Carvajal JJ, Kockx CE, van IJcken WF, Perkins TJ, Rigby PW, Grosveld F, Rudnicki MA. Transcriptional dominance of Pax7 in adult myogenesis is due to high-affinity recognition of homeodomain motifs. *Dev Cell.* 2012 Jun 12; 22(6):1208-20. DOI: 10.1016/j.devcel.2012.03.014.
19. Tran S, Wang L, Le J, Guan J, Wu L, Zou J, Wang Z, Wang J, Wang F, Chen X, Cai L, Lu X, Zhao H, Guo J, Bao Y, Zheng X, Zhang T. Altered methylation of the DNA repair gene MGMT is associated with neural tube defects. *J Mol Neurosci.* 2012 May; 47(1):42-51. DOI: 10.1007/s12031-011-9676-2.
20. Uezumi A1, Fukada S, Yamamoto N, Takeda S, Tsuchida K. Mesenchymal progenitors distinct from satellite cells contribute to ectopic fat cell formation in skeletal muscle. *Nat Cell Biol.* 2010 Feb; 12(2): 143-52. DOI: 10.1038/ncb2014.
21. Qureshi IA1, Mehler MF. Emerging roles of non-coding RNAs in brain evolution, development, plasticity and disease. *Nat Rev Neurosci.* 2012 Jul 20; 13(8):528-41. DOI: 10.1038/nrn3234.
22. Valastyan S, Benaich N, Chang A, Reinhardt F, Weinberg RA. Concomitant suppression of three target genes can explain the impact of a microRNA on metastasis. *Genes Dev.* 2009 Nov 15; 23(22):2592-7. DOI: 10.1101/gad.1832709.
23. Eichhorn W, Blessmann M, Vorwig O, Gehrke G, Schmelzle R, Heiland M. Influence of lip closure on alveolar cleft width in patients with cleft lip and palate. *Head & Face Medicine.* 2011; 7:3. DOI:10.1186/1746-160X-7-3

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МОЖЛИВОСТІ РЕГЕНЕРАЦІЇ М'ЯЗІВ М'ЯКОГО НЕБА ПРИ ЙОГО НЕЗРОЩЕННІ ЗАЛЕЖНО ВІД МІОГЕННОГО ПОТЕНЦІАЛУ СТОВБУРОВИХ КЛІТИН. Огляд

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Резюме. Вагініт є загальною проблемою для жінок у всьому світі, з багатьма побічними ефектами. Вагініт – одна з найбільш актуальних. Сьогодні існують більш 150 методик усунення вроджених дефектів твердого та м'якого піднебіння. Однак ці прийоми не завжди приводять до високих функціональних результатів, що призводить до повторних оперативних втручань і тривалої логопедичної реабілітації. Тому існує проблема прогнозу такого лікування. Актуальним є пошук маркера для оцінки прогнозу хірургічного втручання. Одним з таких маркерів може бути стан міогенного потенціалу стовбурових клітин.

Мета. Проаналізувати можливість попередньої оцінки (на дохірургічному етапі) регенерації м'язів, в залежності від міогенного потенціалу стовбурових клітин, з метою підвищення ефективності лікування дітей з незрошенням м'якого піднебіння.

Метод. Аналітичний огляд літератури за ключовими словами з наукометричних баз PubMed, Scopus, Web of Science.

Результати. Сателітні клітини можуть розглядатися, як кандидати для клітинної терапії в м'язовій регенерації. По-перше, вони одні з найпоширеніших і найбільш доступних клітин в нашому організмі. По-друге, є панель конкретних маркерів, які можуть бути використані для виділення клітин-сателітів. По-третє, сателітні клітини локалізовані в чітких межах анатомічної ніші, і сигнальні механізми в даний час вивчені. По-четверте, є можливість відтворення м'язових травм, при яких сателітні клітини можуть бути вивчені. Майбутні дослідження, спрямовані на підвищення очищення сателітних клітин таким чином, щоб зберігалася їхня низька диференціювання, підвищувався потенціал приживлення, а також нові підходи, спрямовані на отримання сателітних клітин від іPS-клітин, допоможуть прискорити прогрес і розробку ліків для клітинної терапії при лікуванні м'язових дегенеративних захворювань.

Висновок. Сателітні клітини є адекватною моделлю системи для вивчення біології дорослих стовбурових клітин.

Ключові слова: незрошення верхньої губи та піднебіння, м'язова травма, сателітні стовбурові клітини, приживлення, міофібрили, маркер.

ВОЗМОЖНОСТИ РЕГЕНЕРАЦИИ МЫШЦ МЯГКОГО НЕБА ПРИ ЕГО НЕСРАЩЕНИИ В ЗАВИСИМОСТИ ОТ МИОГЕННОГО ПОТЕНЦИАЛА СТВОЛОВЫХ КЛЕТОК. Обзор

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Актуальность. Сегодня существуют более 150 методик устранения врожденных дефектов твердого и мягкого неба. Однако эти приемы не всегда приводят к высоким функциональным результатам, что приводит к повторным оперативным вмешательствам и продолжительной логопедической реабилитации. Поэтому существует проблема прогноза такого лечения. Актуальным является поиск маркера для оценки прогноза хирургического вмешательства. Одним из таких маркеров может быть состояние миогенного потенциала стволовых клеток.

Цель. Проанализировать возможность предварительной оценки (на дохирургическом этапе) регенерации мышц, в зависимости от миогенного потенциала стволовых клеток, с целью повышения эффективности лечения детей с несращением мягкого неба.

Метод. Аналитический обзор литературы по ключевым словам из наукометрических баз PubMed, Scopus, Web of Science.

Результаты. Сателлитные клетки могут рассматриваться, как кандидаты для клеточной терапии в мышечной регенерации. Во-первых, они одни из самых распространенных и наиболее доступных клеток в нашем организме. Во-вторых, есть панель конкретных маркеров, которые могут быть использованы для выделения клеток-сателлитов. В-третьих, сателлитные клетки локализованы в четких пределах анатомической ниши, и сигнальные механизмы в настоящее время изучены. В-четвертых, есть возможность воссоздания мышечных травм, при которых сателлитные клетки могут быть изучены. Будущие исследования, направленные на повышение очистки сателлитных клеток таким образом, чтобы сохранялась их низкая дифференцировка, повышался потенциал приживления, а также новые подходы, направленные на получение сателлитных клеток от iPS-клеток, помогут ускорить прогресс и разработку лекарств для клеточной терапии при лечении мышечных дегенеративных заболеваний.

Вывод. Сателлитные клетки представляют собой адекватную модель системы для изучения биологии взрослых стволовых клеток.

Ключевые слова: несращение верхней губы и неба, мышечная травма, сателлитные стволовые клетки, приживление, миофибриллы, маркер