Review
https://doi.org/10.23934/2223-9022-2023-12-3-428-434

Immunological Aspects of the Pathogenesis of Cicatricial Tracheal Stenosis

E.S. Vladimirova ✉, ***V.P. Nikulina, M.A. Godkov, E.A. Kasholkina***

Laboratory of Clinical Immunology
N.V. Sklifosovsky Research Institute for Emergency Medicine
3, B. Sukharevskaya Sq., 129090, Moscow, Russian Federation

✉ **Contacts:** Valentina P. Nikulina, Candidate of Medical Sciences, Senior Researcher, Laboratory of Clinical Immunology N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: sa-to@yandex.ru

ABSTRACT Cicatricial tracheal stenosis is a fairly common complication that occurs after tracheal intubation or tracheostomy. However, critical tracheal stenosis is a rare case, sometimes not associated with trauma, and is probably due to the peculiarities of the patient's immune response during the development of stenosis. In this regard, the study of the immune mechanisms of the development of inflammation in the upper respiratory tract is a very relevant and promising direction. This review is devoted to the analysis of the immunological mechanisms of tracheal stricture formation, and presents modern data on the immunopathogenesis of the disease.

Clarification of some pathogenetic mechanisms of the immune response during the formation of tracheal strictures of various origins can help in identifying laboratory markers as risk factors for tracheal stricture and timely prevention of such complications.

Keywords: tracheal stricture, immune response, cytokines, fibroblasts, transforming growth factor (TGF-β), interleukin 17A
For citation Vladimirova ES, Nikulina VP, Godkov MA, Kasholkina EA. Immunological Aspects of the Pathogenesis of Cicatricial Tracheal Stenosis. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2023;12(3):428–434. https://doi.org/10.23934/2223-9022-2023-12-3-428-434 (in Russ.)
Conflict of interest Authors declare lack of the conflicts of interests
Acknowledgments, sponsorship The study has no sponsorship

Affiliations

Elizaveta S. Vladimirova	Doctor of Medical Sciences, Scientific Consultant, Thoracic Surgical Department N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/000-0002-7088-8645, prisma06@yandex.ru; 35%, idea and concept of the study, writing part of the manuscript
Valentina P. Nikulina	Candidate of Medical Sciences, Senior Researcher, Laboratory of Clinical Immunology N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-6811-6809, sa-to@yandex.ru; 30%, analysis of literary sources covering the problem
Mikhail A. Godkov	Doctor of Medical Sciences, Senior Researcher, Department of Laboratory Diagnostics N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-9612-6705, mgodkov@yandex.ru; 20%, article editing
Elena A. Kasholkina	Specialist in Clinical Laboratory Diagnostics N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-9395-7578, e.kasholkina@yandex.ru; 15%, article editing

bFGF – basic fibroblast growth factor
CTS – cicatricial tracheal stenosis
IL – interleukin
iSGS – idiopathic subglottic stenosis
SMAD proteins – intracellular signaling proteins
TGF-β1 – transforming growth factor β1
TNF – tumor necrosis factor
VEGF – vascular endothelial growth factor

INTRODUCTION

Cicatricial tracheal stenosis (CTS) is a pathological narrowing of the trachea, in most cases it is a post-intubation, post-tracheostomy complication. Some degree of tracheal stenosis is present in all patients after tracheostomy, but clinically significant stenosis is observed only in 3–12% of cases [1, 2]. The duration of exposure to an endotracheal or tracheostomy tube, the pressure exerted by the cuff or tip of the tracheostomy tube in the respiratory tract, can lead to ischemia and necrosis of the mucous membrane, infection with the development of inflammation and outcome in tubular stenosis [3–5].

The most common causes of CTS manifestations, in addition to tracheal intubation and tracheostomy, are inhalation trauma, complications of pulmonary tuberculosis, idiopathic stenosis, and a number of other reasons. In recent years, there has been an upward trend in the number of patients with CTS [6–10].

Thus, the mechanism of development of tracheal stricture most often includes: traumatic damage to the mucosa, ischemia and infection with the subsequent development of chronic inflammation. Based on these processes, granulation tissue is formed, leading to stricture formation. However, it remains unclear what additional factors influence the progressive development of CTS.

The **aim of this review** is to highlight some of the immunological mechanisms underlying the formation of tracheal stricture.

TYPES, STRUCTURE AND HOMEOSTASIS OF CARTILAGE

Cartilage is a strong but flexible type of connective tissue, consisting of cells and intercellular fibers located in an amorphous jelly-like substance. Cartilage tissue grows rapidly and consists predominantly of extracellular matrix proteins and a small amount (~ 5% of the total mass) of highly specific cells - chondrocytes [12]. Cartilage has a smooth and elastic surface and can withstand a lot of weight, second only to bone tissue in strength. Tracheal cartilage plays an important role in maintaining the mechanical stability of the trachea, as it performs a frame function and prevents the walls from drooping under negative pressure during the respiratory cycle. Cartilage provides rigidity, maintains the anatomical shape and function of the trachea, and is a site of muscle attachment. In case of CTS, destruction of the cartilaginous component of the tracheal wall with the loss of its frame function almost always occurs [6–8].

There are 3 types of cartilage: elastic, fibrous and hyaline, which provide the formation of the ears and nose, the framework of the trachea and the epiphyses of long bones during development and growth.

Elastic cartilage contains some elastin in the intercellular space. It forms the pinna which requires a certain degree of flexibility. Fibrous cartilage has an intermediate position between dense connective tissue and hyaline cartilage - it is found in the intervertebral discs, in the areas where tendons attach to bone (pubic bone). Hyaline cartilage is located on the articular surfaces, forms most of the cartilage of the respiratory tract, costal cartilages, attaching the ribs to the sternum and vertebrae [11]. The saturation of hyaline cartilage with water (2/3 of the total mass) allows it to be reversibly deformed and withstand large mechanical loads. Hyaline cartilage is made up of several types of collagen molecules. The heteropolymeric structure of type IX collagen molecules, covalently bound to the surface of collagen II and collagen XI, forms the internal thread-like pattern of the fibril [10, 13]. Other collagens found in articular cartilage include type III, type X, type XI, type XII and type XIV. When cartilage is damaged, both collagen II structures and a molecule like aggrecan (proteoglycan) are destroyed. Cartilage damage is the main cause of tracheal stricture. The ability of cartilage to regenerate is very limited, which leads to expansion of the damage zone and further degradation of the hyaline layer [11, 14, 16].

Cartilage cells - chondrocytes and fibroblasts - are located in the lacunae. The lacunae are surrounded by a jelly-like intercellular substance made of collagen fibers and ground substance. Cartilage tissue is devoid of blood vessels and nerves. About 65–80% of cartilage tissue is a gel-like fluid. This fluid ensures the diffusion of gases into the cartilage tissue, nutrition and removal of metabolic waste. When the intercellular space is saturated with calcium salts, the diffusion of gases stops and the cartilage dies.

Fibroblasts are connective tissue cells that synthesize and secrete fiber proteins and organic components of the ground substance. The cells take part in the formation of the intercellular substance of granulation tissue and connective tissue capsule. Fibroblasts produce collagen types I and II, proteoglycan, fibronectin, and basic fibroblast growth factor (bFGF) which stimulates the production of extracellular matrix components and new collagen fibers, elastin and fibronectin. Fibroblasts also produce components of the extracellular matrix: nidogen, laminin, tinascin, chondroitin-4-sulfate, proteoglycan. Under physiological conditions, this process occurs continuously and, thanks to it, the intercellular substance is constantly renewed. Activation, proliferation and survival of fibroblasts are carried out under the influence of fibroblast growth factors, cytokines, kinins and other immunocompetent cells. Fibrosis develops when tissue remodeling is inappropriate, and in the absence of proteolytic degradation of the extracellular matrix [17].

The process of inflammation represents a complex system of interaction between immunocompetent cells, the cytokines and growth factors they produce, as well as the activation of the receptor apparatus of each group of cells involved in the inflammatory process. At the site of primary damage, the inflammatory reaction is caused by phagocytes - neutrophils, macrophages, which are the main sources of cytokines - mediators of inflammation [18]. Experimental study on rabbits with traumatic injury to the trachea revealed that immunocompetent cells producing cytokines participate in the formation of stenosis at different stages of healing [19].

Cytokines are hormone-like proteins produced by various cells (lymphocytes, neutrophils, monocytes, macrophages, endotheliocytes, mastocytes, fibroblasts, etc.) and possessing a wide range of biological activities that carry out intercellular interactions during hematopoiesis, immune response, intersystem interactions [18, 20]. Cytokines are involved in the regulation of immune and inflammatory processes at the local level and provide paracrine and/or autocrine effects between cells of the immune system. They are synthesized by many organs and tissues, including the central nervous system, and form a single signaling network in the body [21, 22].

Enhanced synthesis of cytokines is formed in response to the penetration of microorganisms into the body or when tissue is damaged. These bioregulatory molecules determine the type and duration of the immune response. According to the figurative definition of a number of authors, "without cytokines, the immune system is dead" [23–25]. The main source of cytokines are cells of the monocyte-macrophage unit.

Cytokines are traditionally divided into interleukins (IL-1β, IL-6, IL-12, IL-18, IL-3, etc.), tumor necrosis factor (TNF α, β), migration inhibitory factor, interferons, chemotactic factors, growth factors (fibroblast growth factor, transforming growth factor, etc.) [20, 29].

Activation of the cytokine system, mainly the production of TNF α, is associated with high activity of the sympathetic-adrenal system. The synthesis of cytokines is influenced by the neurohumoral system. The process of inflammation is regulated by maintaining a balance between pro- and anti-inflammatory cytokines and apoptosis of phagocytes. For example, when apoptosis of neutrophils and macrophages is inhibited, the synthesis of pro-inflammatory cytokines increases, resulting in a greater risk of the development and proliferation of inflammation [26–29].

Traumatic injury to the trachea leads to the development of acute and chronic inflammatory reactions, promoting the production of a variety of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, TNF-α and pro-fibrotic cytokines, such as transforming growth factor β1 (TGF-β1), and vascular endothelial growth factor (VEGF) [33, 39]. These cytokines are involved in regenerative processes, activation of fibroblasts, proliferation of immunocompetent cells, inhibition of apoptosis, extracellular matrix deposition and imbalance of collagen synthesis. Excessive proliferation of granulation tissue can lead to tracheal stenosis [30–33, 40].

Transforming growth factor. One of the key cytokines is transforming growth factor (TGF-β). This is a multifunctional cytokine necessary for maintaining homeostasis, regulating cell proliferation and differentiation, cell apoptosis and migration to the site of infection [38]. TGF-β influences chondrogenesis, playing a major role in the proliferation of cartilage tissue. By interacting with ligands on the surface of the cell membrane, it triggers a cascade of molecular mechanisms with the participation of a Sox transcription factor [11]. TGF-β1, an isoform of TGF-β, is a potent inducer of the extracellular matrix, a chemotactic mediator of fibroblasts and polymorphonuclear cells, and a fibroblast mitogen that plays an important role in the regeneration of epithelial cells, the proliferation of fibroblasts, and the healing of tracheal wounds after mechanical damage. TGF-β1 enhances tissue repair and reconstruction by causing the release of VEGF (vascular endothelial growth factor). The expression of TGF-β1, VEGF and the number of fibroblasts are increased in tracheal granulation tissues obtained using interventional bronchoscopy after tracheostomy. Granulation tissue in tracheal stenosis is characterized by increased angiogenesis and extracellular matrix deposition. In addition, it was demonstrated that in the submucosal layer of granulation tissues there is a further increase in the expression of TGF-β1 and VEGF; and the number of fibroblasts, compared with the epithelial layer and small blood vessels in the submucosa of granulation tissues, increases markedly, which leads to fibrosis [19, 33–35, 55–58].

In total, more than 30 proteins are known, similar in structure and included in the so-called TGF-β superfamily [28, 29]. TGF-β limits the activation of immune cells, prevents the development of a hyperergic reaction and stimulates rapid healing. Proteins of the TGF-β superfamily have the most noticeable effect on cell differentiation in general and the synthesis of the extracellular matrix in particular [44, 43, 53]. TGF-β, being a

powerful inhibitory cytokine, suppresses the proliferation of endothelial cells and is involved as a "master switch" of cells towards fibrosis in many organs, including the lungs [49, 60]. In this case, there occurs breakdown of epithelial intercellular contacts, a violation of polarity, activation of the expression of mesenchymal genes, reorganization of the actin structure, migration of cells affecting the intercellular substance [50–52]. Epithelial cells change shape, approaching fibroblast-like one, proliferative activity decreases, and mesenchymal-epithelial transformation is observed [48]. Activation of the TGF-β receptor leads to an increase in the production of aggrecan, another important extracellular matrix protein [36, 37, 40, 41, 42, 48].

Besides, TGF-β is increased in lungs with idiopathic pulmonary fibrosis. In animal models, TGF-β expression induces a dramatic fibrotic response. Activation of TGF-β occurs through an initial step in which the inactive form of TGF-β is catalyzed to its active form [33, 39, 54, 55]. Activated TGF-β binds to the transmembrane receptor, which leads to the activation of intracellular signaling proteins known as SMAD proteins. SMAD proteins model the transcription of procollagen 1 and 3 [56]. In preclinical models of fibrosis, inhibition of TGF-β signaling has been shown to reduce collagen deposition and attenuate fibrosis [57].

Interleukin 17A. The main multitarget proinflammatory cytokine is interleukin 17A (IL-17A). The cytokine is synthesized during the immune response in case of chronic inflammation and is involved in the induction of fibroblast TGF-β with subsequent autocrine activation of ECM COL 1A2 genes [44]. IL-17A is synthesized by immune cells located outside the lymphoid tissue, where they are ready to immediately respond to injury or pathogenic influence [59]. For example, infection with Mycobacterium tuberculosis leads to proliferation and activation of γδ T lymphocytes, which in turn lead to increased production of IL-17A and recruitment of neutrophils to the site of inflammation [7, 9, 45–47, 60]. Morrison R.J. showed that IL-17A directly "controls" the proliferation of fibroblasts isolated from scar tissue of patients with idiopathic subglottic stenosis (iSGS) [58, 60]. In addition, IL-17A, being a TGF-β synergist, can stimulate increased collagen production in fibroblasts associated with scar tissue. The effects of TGF-β and IL-17A may be mediated by increased expression of the TGF-β receptor on fibroblasts [58, 60].

At the same time, scar fibroblasts in patients with iSGS form and enhance the local inflammatory response due to their own production of inflammatory chemokines and cytokines. According to Morrison R.J., resident fibroblasts play a dominant role in the pathogenesis of iSGS. This is also confirmed by data on alternative fibrotic diseases of the respiratory tract, when resident fibroblasts are responsible for the structural and functional remodeling of the epithelium of the respiratory tract. There is likely a common molecular program that drives the "reprogrammed" fibroblast phenotype in response to various external inflammatory signals in airway scar tissue [59, 60].

The data studied are consistent with pre-clinical setting demonstrating a cooperative and enhancing role of TGF-β1 and IL-17A in the development of airway fibrosis. Similar indicators were obtained when analyzing laboratory data from patients with bronchiolitis obliterans, which confirms the critical role of IL-17A in the pathogenesis of this disease [31, 60, 61].

CONCLUSION

Thus, the regulation of protective reactions and the preservation of homeostasis at the site of damage and/or infection is realized by attracting various immunocompetent cells that synthesize both pro- and anti-inflammatory cytokines. The process of inflammation is multifactorial in nature and represents a complex system of interaction between cells involved in the process of cytokines produced by them, as well as activation of the receptor response of each group of cells involved in the inflammatory process. The synthesis of cytokines is a response to the penetration of microorganisms into the body or tissue damage. Cytokines are involved in the regulation of immune and inflammatory processes not only at the local level, but also in intersystem interactions. An imbalance in the system of pro- and anti-inflammatory cytokines determines the degree of fibrosis and the transition of reversible destruction to irreversible one. Perhaps the chronicization of the process occurs as a result of an imbalance of cytokines, caused by a genetically determined response of the immune system of the macroorganism to damage.

Due to the high incidence of cicatricial tracheal stenosis and fibrosis as an outcome of diseases of traumatic and infectious origin, the study of the immune mechanisms of the development of inflammation in the upper respiratory tract is a very relevant and promising direction.

REFERENCES

1. Streitz JM Jr, Shapshay SM. Airway injury after tracheotomy and endotracheal intubation. *Surg Clin North Am*. 1991;71(6):1211–1230. https://doi.org/10.1016/s0039-6109(16)45586-6 PMID: 1948570
2. Fernandez-Bussy S, Mahajan B, Folch E, Caviedes I, Guerrero J, Majid A. Tracheostomy Tube Placement: Early and Late Complications. *J Bronchology Interv Pulmonol*. 2015;22(4):357–364. https://doi.org/10.1097/LBR.0000000000000177 PMID: 26348694
3. Norwood S, Vallina VL, Short K, Saigusa M, Fernandez LG, McLarty JW. Incidence of tracheal stenosis and other late complications after percutaneous tracheostomy. *Ann Surg*. 2000;232(2):233–241. https://doi.org/10.1097/00 000658-200008000-00014 PMID: 10903603
4. Kim SS, Khalpey Z, Hsu C, Little AG. Changes in tracheostomyand intubation-related tracheal stenosis: implications for surgery. *Ann Thorac Surg*. 2017;104(3):964–970. https://doi.org/10.1016/j.athoracsur.2017.03.063 PMID: 28619544
5. Parshin VD, Porkhanov VA. Khirurgiya trakhei s atlasom operativnoy khirurgii. Moscow: Al'di-Print Publ.; 2010. (In Russ.).
6. Parshin VD, Koroleva IM, Mishchenko MA, Parshin VV. Diagnosis and treatment of acquired tracheomalacia in patients with cicatrical tracheal stenosis. *Pirogov Russian Journal of Surgery*. 2016;(8):73–82. (In Russ.) https://doi.org/10.17116/hirurgia2016873-82
7. Mark EJ, Meng F, Kradin RL, Mathisen DJ, Matsubara O. Idiopathic tracheal stenosis: a clinicopathologic study of 63 cases and comparison of the pathology with chondromalacia. *Am J Surg Pathol*. 2008;32(8):1138–1143. https://doi.org/10.1097/PAS.0b013e3181648d4a PMID: 18545144
8. Maldonado F, Loiselle A, Depew ZS, Edell ES, Ekbom DC, Malinchoc M, et al. Idiopathic subglottic stenosis: an evolving therapeutic algorithm. Laryngoscope. 2014;124(2):498-503. https://doi.org/10.1002/lary.24287 PMID: 23818139
9. Nakagishi Y, Morimoto Y, Fujita M, Ozeki Y, Maehara T, Kikuchi M. Rabbit model of airway stenosis induced by scraping of the tracheal mucosa. *Laryngoscope*. 2005;115(6):1087–1092. https://doi.org/10.1097/01.MLG.0000163105.86513.6D PMID: 15933527
10. Eyre D. Collagen of articular cartilage. *Arthritis Res*. 2002;4(1):30–35. https://doi.org/10.1186/ar380 PMID: 11879535
11. Bozhokin MS, Bozhkova SA, Netylko GI. Possibilities of Current Cellular Technologies for Articular Cartilage Repair (Analytical Review). *Traumatology and Orthopedics of Russia*. 2016;22(3):122–134. https://doi.org/10.21823/2311-2905-2016-22-3-122-134
12. Bozhokin MS, Bozhkova SA, Netylko GI, Rumakin VP, Nakonechnyi DG, Chepurnenko MN. Morfo-funktsional characteristic of hondroregeneratorny process for articular cartilage injuries. *Mezhdunarodnyy zhurnal prikladnykh i fundamental'nykh issledovaniy*. 2017;(8–2):302–306. (In Russ.)
13. Eyre DR, Weis MA, Wu J-J. Articular cartilage collagen: an irreplaceable framework? *Eur Cells Mater*. 2006;12:57–63. PMID: 17083085 https://doi.org/10.22203/ecm.v012a07
14. Krishnan Y, Grodzinsky AJ. Cartilage diseases. *Matrix Biol*. 2018;71–72:51–69. https://doi.org/10.1016/j.matbio.2018.05.005 PMID: 29803938
15. Kurgansky IS, Makhutov VN, Lepekhova SA. The methods for the treatment and prevention of cicatricalstenoses of tracheal. *Vestnik Oto-Rino-Laringologii*. 2016;81(1):66–71. (In Russ.) https://doi.org/10.17116/otorino201681166-71
16. Nedz'ved' MK, Tatur AA, Leonovich SI, Nerovnya AM. Morfologicheskie izmeneniya v trakhee pri postintubatsionnom rubtsovom stenoze. *Medical Journal (BSMU)*. 2008;(1):43–46. (In Russ.).
17. Sime PJ, O'Reilly KM. Fibrosis of the lung and other tissues: new concepts in pathogenesis and treatment. *Clin Immunol*. 2001;99(3):308–319. https://doi.org/10.1006/clim.2001.5008 PMID: 11358425
18. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med*. 2020;383(23):2255–2273. https://doi.org/10.1056/NEJMra2026131 PMID: 33264547
19. Wei P, Huang Z, Gan L, Li Y, Qin C, Liu G. Nintedanib ameliorates tracheal stenosis by activating HDAC2 and suppressing IL-8 and VEGF in rabbit. *Am J Transl Res*. 2020;12(8):4739–4748. eCollection 2020. PMID: 32913546
20. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol*. 2017;39(5):517–528. https://doi.org/10.1007/s00281-017-0639-8 PMID: 28555385
21. Lin JX, Leonard WJ. Fine-Tuning Cytokine Signals. *Annu Rev Immunol*. 2019;37:295–324. https://doi.org/10.1146/annurev-immunol-042718-041447 PMID: 30649989
22. Oppenheim JJ. The Future of the Cytokine Discipline. *Cold Spring Harb Perspect Biol*. 2018;10(9):a028498. https://doi.org/10.1101/cshperspect.a028498 PMID: 28847901
23. Weledji EP. Citocynes and metabolic response to surgery. *J Clin Cell Immunol*. 2014;5(2). https://doi.org/10.4172/2155-9899.1000197 Available at: https://www.researchgate.net/publication/341265387_Cytokines_and_the_Metabolic_Response_to_Surgery [Accessed 04.10. 2021]
24. Il'ina AE, Stanislav ML, Denisov LN, Nasonov EL. Interleikin 1 kak mediator vospaleniya i terapevticheskaya mishen''. *Rheumatology Science and Practice*. 2011;49(5):62–71. (In Russ.) https://doi.org/10.14412/1995-4484-2011-1463.
25. Thielen NGM, van der Kraan PM, van Caam APM. TGFβ/BMP Signaling Pathway in Cartilage Homeostasis. *Cells*. 2019;8(9):969. https://doi.org/10.3390/cells8090969 PMID: 31450621
26. Blaney Davidson EN, Remst DF, Vitters EL, van Beuningen HM, Blom AB, Goumans MJ, et al. Increase in ALK1/ALK5 ratio as a cause for elevated MMP-13 expression in osteoarthritis in humans and mice. *J Immunol*. 2009;182(12):7937–7945. https://doi.org/10.4049/jimmunol.0803991 PMID: 19494318
27. Vitkovskiy YuA. Vliyanie interleykinov 4 i 10 na sistemu gemostaza in vitro. *Immunologiya*. 2004;(1):43–46. (In Russ.).
28. Li M, Jia J, Li S, Cui B, Huang J, Guo Z, et al. Exosomes derived from tendon stem cells promote cell proliferation and migration through the TGF β signal pathway. *Biochem Biophys Res Commun*. 2021;536:88–94. https://doi.org/10.1016/j.bbrc.2020.12.057 PMID: 33370718
29. Vander Ark A, Cao J, Li X. TGF-β receptors: In and beyond TGF-β signaling. *Cell Signal*. 2018;52:112–120. https://doi.org/10.1016/j.cellsig.2018.09.002 PMID: 30184463
30. Ge Y, Huang M, Yao YM. Autophagy and proinflammatory cytokines: Interactions and clinical implications. *Cytokine Growth Factor Rev*. 2018;43:38–46. https://doi.org/10.1016/j.cytogfr.2018.07.001 PMID: 30031632
31. Garcia-Rendueles AR, Rodrigues JS, Garcia-Rendueles ME, Suarez-Fariña M, Perez-Romero S, Barreiro F, et al. Rewiring of the apoptotic TGF-β–SMAD/NFκB pathway through an oncogenic function of p27 in human papillary thyroid cancer. *Oncogene*. 2017;36(5):652–666. https://doi.org/10.1038/onc.2016.233 PMID: 27452523
32. Simbirtsev AS, Totolyan AA. Tsitokiny v laboratornoy diagnostike. *Infectious Diseases: News, Views, Education*. 2015;2(11):82–98. (In Russ.).
33. Crecente-Campo J, Borrajo E, Vidal A, Garcia-Fuentes M. New scaffolds encapsulating TGF-β3/BMP-7 combinations driving strong chondrogenic differentiation. *Eur J Pharm Biopharm*. 2017;114:69–78. https://doi.org/10.1016/j.ejpb.2016.12.021 PMID: 28087378
34. Kronenberg HM. Developmental regulation of the growth plate. *Nature*. 2003;423(6937):332–336. https://doi.org/10.1038/nature01657 PMID: 12748651

35. Huang Z, Wei P, Gan L, Li W, Zeng T, Qin C, et al. Protective effects of different anti-inflammatory drugs on tracheal stenosis following injury and potential mechanisms. *Mol Med Rep*. 2021;23(5):314. https://doi.org/10.3892/mmr.2021.11953 PMID: 34240225
36. Greaves NS, Asheroft KJ, Baguneid M, Bayat A. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. *J Dermatal Sci*. 2013;72(3):206–217. https://doi.org/10.1016/j.jdermsci.2013.07.008 PMID: 23958517
37. Maher TM. Pirfenidone in idiopathic pulmonary fibrosis. *Drugs Today (Barc)*. 2010;46(7):473–482. https://doi.org/10.1358/dot.2010.46.7.1488336 PMID: 20683502
38. 38. Esakov IuS, Dubova EA, Zhestkov KG, Shchegolev AI. Morphologic changes by postintubation stenosis of trachea. *Pirogov Russian Journal of Surgery*. 2010;(2):60–63. (In Russ.).
39. Yanagawa Y, Hiraide S, Iizuka K. Isoform-specific regulation of transforming growth factor-β mRNA expression in macrophages in response to adrenoceptor stimulation. *Microbiol Immunol*. 2016;60(1):56–63. https://doi.org/10.1111/1348-0421.12344 PMID: 26612065
40. Li LH, Xu MP, Gan LM, Li Y, Liang YL, Li WT, et al. Effect of low dose erythromycin on the proliferation of granulation tissue after tracheal injury. *Zhonghua Yi Xue Za Zhi*. 2017;97(10):777–781. (In Chinese) https://doi.org/10.3760/cma.j.issn.0376-2491.2017.10.012 PMID: 28316160
41. Zhang J, Li Q, Bai C, Han Y, Huang Y. Inhalation of TGF-beta1 antibody: A new method to inhibit the airway stenosis induced by the endobronchial tuberculosis. *Med Hypotheses*. 2009;73(6):1065–1066. https://doi.org/10.1016/j.mehy.2009.04.037 PMID: 19819641
42. Lee YC, Hung MH, Liu LY, Chang KT, Chou TY, Wang YC, et al. The roles of transforming growth factor-beta (1) and vascular endothelial growth factor in the tracheal granulation formation. *Pulm Pharmacol Ther*. 2011;24(1):23–31. https://doi.org/10.1016/j.pupt.2010.10.016 PMID: 21056681
43. Morikawa M, Derynck R, Miyazono K. TGF-β and the TGF-β family: context-dependent roles in cell and tissue physiology. *Cold Spring Harb Perspect Biol*. 2016;8(5):a021873. https://doi.org/10.1101/cshperspect.a021873 PMID: 27141051
44. Derynck R, Budi E. Specificity, versatility, and control of TGF-β family signaling. *Sci Signal*. 2019;12(570):eaav5183. https://doi.org/10.1126/scisignal.aav5183 PMID: 30808818
45. Shao T, Song P, Hua H, Zhang H, Sun X, Kong Q, et al. Gamma synuclein is a novel Twist1 target that promotes TGF-β–induced cancer cell migration and invasion. *Cell Death Dis*. 2018;9(6):625. https://doi.org/10.1038/s41419-018-0657-z PMID: 29795373
46. Rockey DC, Bell PD, Hill JA. Fibrosis-a common pathway to organ injury and failure. *N Engl J Med*. 2015;372(12):1138–1149. PMID: 25785971 https://doi.org/10.1056/NEJMra1300575
47. Shiromizu CM, Jancic CC. Review. gammadelta T Lymphocytes: An Effector Cell in Autoimmunity and Infection. *Front Immunol*. 2018;9:2389. https://doi.org/10.3389/fimmu.2018.02389 eCollection 2018. PMID: 30386339
48. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol*. 2014;15(3):178–196. https://doi.org/10.1038/nrm3758 PMID: 24556840
49. Wynn TA. Cellular and molecular mechanisms of fibrosis. *J Pathol*. 2008;214(2):199–210. https://doi.org/10.1002/path.2277 PMID: 18161745
50. Yang J, Weinberg RA. Epitelial-Mesenchymal Transition: at the Crossroads of Development and Tumor Metastasis. *Dev Cell*. 2002;14(6):818–829. https://doi.org/10.1016/j.devcel.2008.05.009 PMID: 18539112
51. Xu J, Lamouille S, Derynck R. TGF –induced epithelial to mesenchymal Transition. *Cell Res*. 2009;19(2):156–172. https://doi.org/10.1038/cr.2009.5 PMID: 19153598
52. Datta A, Scotton CJ, Chambers RC. Novel therapeutic approaches for pulmonary fibrosis. *Br J Phamacol*. 2011;163(1):141–172. https://doi.org/10.1111/j.1476-5381.2011.01247 PMID: 21265830
53. Motz KM, Gelbard A. The role of inflammatory cytokines in the development of idiopathic subglottic stenosis. *Transl Cancer Res*. 2020;9(3):2102–2107. https://doi.org/10.21037/tcr.2019.12.37 PMID: 35117565
54. Griffits M, Ojeh N, Livingstone R, Price R, Navsaria H. Survival of Apligraf in acute human wounds. *Tissuee Engl*. 2004;10(7–8):1180–1195. https://doi.org/10.1089/ten.2004.10.1180 PMID: 15363174
55. Zhao J, Shi W, Wang YL, Chen H, Bringas P Jr, Datto MB, et al. Smad3 deficiency attenuates bleomycin-induced pulmonary fibrosis in mice. *Am J Physiol Lung Cell Mol Physiol*. 2002;282(3):L585–593. https://doi.org/10.1152/ajplung.00151.2001 PMID: 11839555
56. Roberts AB, Russo A, Felici A, Flanders KC. Smad3: a key player in pathogenetic mechanisms dependent on TGF-beta. *Ann N Y Acad Sci*. 2003;995:1–10. https://doi.org/10.1111/j.1749-6632.2003.tb03205.x PMID: 12814934
57. Elmallah RK, Cherian JJ, Jauregui JJ, Pierce TP, Beaver WB, Mont MA. Genetically modified chondrocytes expressing TGF-β1: a revolutionary treatment for articular cartilage damage? *Expert Opin Biol Ther*. 2015;15(3):455–464. https://doi.org/10.1517/14712598.2015.1009886 PMID: 25645308
58. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol*. 2014;14(9):585–600. https://doi.org/10.1038/nri3707 PMID: 25145755
59. Zhang Y, Alexander PB, Wang XF. TGF-β Family Signaling in the Control of Cell Proliferation and Survival. *Cold Spring Harb Perspect Biol*. 2017;9(4):a022145. https://doi.org/10.1101/cshperspect.a022145 PMID: 27920038
60. Morrison RJ, Katsantonis NG, Motz KM, Hillel AT, Garrett CG, Netterville JL, et al. Pathologic fibroblasts in idiopathic subglottic stenosis amplify local inflammatory signals. *Otolaryngol Head Neck Surg*. 2019;160(1):107–115. https://doi.org/10.1177/0194599818803584 PMID: 30322354
61. Hillel AT, Namba D, Ding D, Pandian V, Elisseeff JH, Horton MR. An in situ, in vivo murine model for the study of laryngotracheal stenosis. *JAMA Otolaryngol Head Neck Surg*. 2014;140(10):961–966. https://doi.org/10.1001/jamaoto.2014.1663 PMID: 25144860

Received on 15.06.2022
Review completed on 19.10.2022
Accepted on 27.06.2023