Рус. Eng.

UDC: 615.2

DOI: 10.18413/2500-235X -2016-2-3-101-106

Martynov M.A.[1]
Martynova O.V. [2]
Shkileva I.Yu.[3]
Tokarev I.A.[4]
Dovgan A.N.[5]

THYMOSIN β4 AS BASIS FOR CREATION OF A REPARATION PREPARATION OF NEW GENERATION

1) Surgeon, Belgorod Regional Clinical Hospital Saint Joasaph str. Gagarina 2, Belgorod, 308007 Russia e-mail: *ma.martynov@rambler.ru*
2) Graduate student of Department of pharmacology, clinical pharmacology of Medical Institute Belgorod State National Research University, 85, Pobedy St., Belgorod, 308015, Russia, e-mail: *m.olga91@mail.ru*
3) Student of Medical Institute Belgorod State National Research University, 85, Pobedy St., Belgorod, 308015, Russia e-mail: *iceirinka1395@yandex.ru*
4) Oncologist Belgorod regional oncological clinic, 1, Kuibyshev St., Belgorod, 308010, Russia, e-mail: *best209@rambler.ru*
5) Graduate student of Department of pharmacology, clinical pharmacology of Medical Institute Belgorod State National Research University, 85, Pobedy St., Belgorod, 308015, Russia, e-mail: *dr.dovgun@gmail.com*

Abstract. In article is narrated about Thymosin β4. Its structure, a number of strategically important properties and opportunities is described. The list of researches and achievements over the past few years of researches is provided. On the basis of its multipurpose activities during regeneration of fabrics in various experiments on animals, Thymosin β4 has the potential for new researches, in kidneys and a liver, and also recovery of a spinal cord, bones and injury of ligaments. Besides, it can be useful in case of treatment of a wide range of other diseases, including concerning consequences of old bacterial damages and viral infections.
Keywords: Thymosin β4, reparation, traumatism.

Today injury rate level constantly grows. Thanks to access to extreme sports, fixed haste, to emergencies people often are traumatized, both household, and production: whether it is small defect of integuments or extensive combined injury. Violation of healing of wounds is a problem for the immobilized patients sick with diabetes, and also elderly people. According to RosStat for 2015-2016 the registered surplus, both a production, and household injury rate on 1000 people – 92.2 persons, i.e. nearly 10% is observed. The surgery, orthopedics, traumatology is engaged in their diagnostics and treatment. For treatment and rehabilitation of patients a number of medicines such as is used: analgetic preparations, antihistaminic preparations, antibiotics, hormonal preparations, calcium preparations, vascular preparations, spazmolitik, locally – ointments. In case of inefficiency of conservative treatment resort to surgical. Now creation of the reparation preparation possessing a high reparative capability is very actual task for modern medicine and pharmacology as there is a great demand which becomes covered only for 40%.

Proceeding from statistical data of the authoritative medical Pubmed portal (Figure) it is visible that every year scientists show the increasing interest concerning a Thymosin β4 (Tβ4).

In spite of the fact that interest in studying of properties and structure of a Tβ4 has arisen 30 years ago – only the small part of properties of this peptide is studied. It proves a number of several experiments which are already made diversely and systems (Table 1).

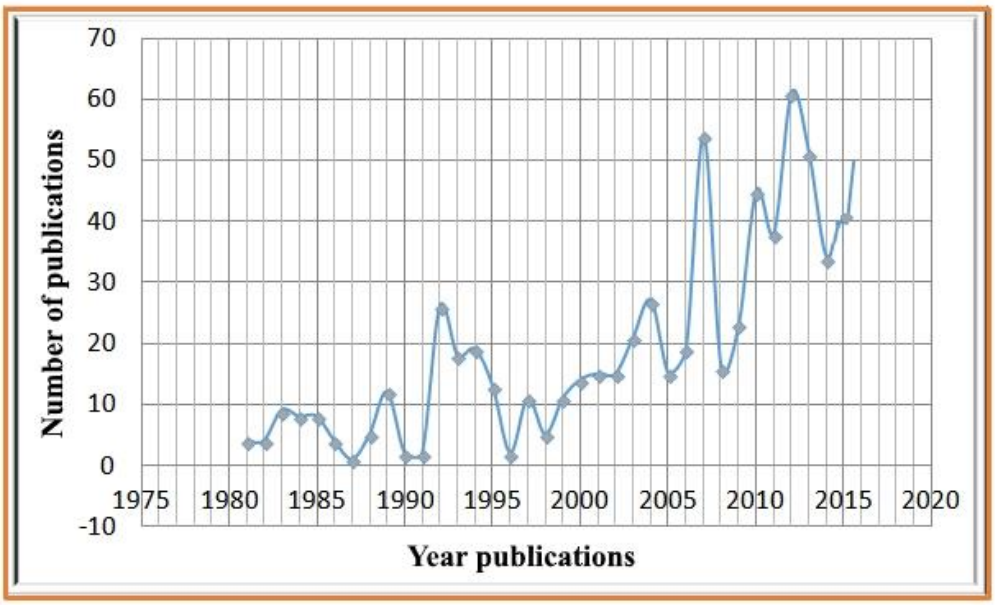

Figure. Chronology of the publication on the subject Tβ4

Table 1

Some researches of properties of peptide of Tβ4

Tβ4		
AUTHORS	**SUBJECT**	**RESULT**
Gabriel Sosne, George W Ousler	Tβ4 ophthalmologic solution for a dry eye. (randomized, placebo – controlled, the phase II of clinical trials, is carried out with use of controlled medium) (CAE ™).	This research confirms efficiency of 0,1% of Tβ4 as topical treatment for simpli-fication of signs and symptoms of a dry eye. The therapeutic window of safety is defined.
Tian-JiaoXu , Qi Wang Xiao-Wen Ma, Zhen ZhangWei Zhang, Xiao-Chang Xue, Cun Zhang, QiangHao, Wei-Na Li, Ying-Qi Zhang Meng Li	Tβ4 represents a peptide from 43 amino acids. Has crucial importan-ce for restoration and reconstruction of tissues of a skin, eyes, heart and a nervous system after a trauma. Fully to use the efficiency as an agent for treatment of the disease caused by a trauma it is recommended to spread out it to dimeasures.	Dimeasures of Tβ4 render a superactivity on an adhesion of wounds, than native Tβ4. Process of cleaning is simple and very effective with the smallest expenses.
Ildiko Bock-Marquette, Ankur Saxena, Michael D. White	Tβ4 activates the integrin-sewed kinases and activates migration of stem cells in heart, thereby increases survival of cardiomyocy-tes and restoration of normal work of heart.	Participation of Tβ4 in migration of cells and survival of cardiomyocytes at distur-bance of a circulation in heart, them redistribution is mini-mized by losses of cardio-myocytes later myocar-dialinfarction.
Yue Zhou, Eliana Martinez, Li-Ping Su, Kok-Onn Lee1, Lei Ye	Tβ4 stimulates an angiogenesis and enlarges a pool of cells precursors of muscles at ischemic option of sceletal muscles in model of an ischemia of back extremities of a mouse	Now research proved that Tβ4 makes direct impact on neovascularization and neo-genesis of sceletal muscles in model of an ischemia of a back extremity of a mouse. Tβ4 considerably enlarged density of capillaries. It is bound to its biological function on endothelial cells: migrations of endothelial cells and their proliferation.
Deborah Philp, MahnazBadamchian, Brooke Scheremeta, Mychi Nguyen, Allan L. Goldstein, Hynda K. Kleinman	Tβ4 – the synthetic peptide containingits actin – the binding domain promote a fast adhesion of dermal defect.	It is proved on experimental model at mice with a diabetes mellitus and old mice.

In this article we will consider Thymosin derivatives β4 which can be a basis for creation of modern and innovative reparation drug and a vasoprotective.

Adhesion of wounds includes several stages: 1) inflammation (hemostases / vasoconstrictions), 2) proliferation (angiogenesis or vasifaction) and 3) migration of keratinotsit and remodeling (collagen adjournment).

Tβ4 represent family of highly conservative polar peptides with a molecular weight of 5kd. One of representatives of this family Tβ4. It consists of 43 amino acids and the 4964th dalton has molecular weight [1, 2]. With the N-trailer acetylated rest of a serine. Tβ4 is a larger water-soluble peptide which was for the first time allocated in 1966 by scientists Goldstein and Whyte from a bull tissue of a thymus. Researches in the field of hormones of a thymus led to a conclusion that Thymosin beta contain practically in all tissues and various cells of a human body except for erythrocytes. High concentration were noted in a lien, a thymus, mild and peritoneal macrophages, and also in thrombocytes, a blood plasma, a wound exsudate. After a skin trauma, the high Tβ4 levels naturally are present (13 mkg/ml) at wound liquid [3, 4]. He also acts as the main molecule of a complexing actin in all eukaryotic cells and is the potent regulator of an aktinapolimerization at mammals [5].

Thymosin β4 is bound to a G-actin, blocks an actin polymerization with a factor of XIIIa of thrombocytes, exerting a great influence on process of an adhesion of wounds [6, 7]. Two proteins supporting a G-actin pool (a monomeric actin) are Tβ4 and a pro-eagle owl. In turn, the G-actin, is the water-soluble globular protein (weight 42 000 dalton) consisting of 376 amino-acid remains. One molecule ATP is bound to each molecule of a G-actin. Tβ4 as well as pro-eagle owls – low-molecular proteins with a molecular mass of a 12-15kd. They accelerate ADF exchange mechanism for ATP, as well as Tβ4. Acting as the buffer, it binds a monomeric actin from where follows that it prevents polymerization the aktin of microfilaments for maintenance of the general pool the monomers of aktin for needs of a cell. Changes in Thymosin expression β4 are bound to a differentiation of cells, that is it is possible to assume what Tβ4 suppresses energy release, at the same time keeping a cytoskeleton, cellular structure and cellular mobility from destruction. Release of Thymosin from a complex with an actin and emergence it in a blood plasma, possessing a hypotoxicity and presence at rather high concentration at many types of cells of mammals, both at a cytoplasma, and at an extracellular environment. Tβ4 plays an important role in differentiation of stem cells in developments, and also activation of cells of precursors, induction of their migration, differentiation and integration in processes of an angenesis, in particular induction of a neoangiogenesis. Tβ4 can be the signal starting immune system, induction of a chemotaxis, inhibition of a proliferation of stem cells of marrow, inhibition of an inflammation, an important property of induction of a neoangiogenesis with the subsequent reparative neogenesis of organs and tissues. A series of the active centers in Tβ4 amino acids define the action on physiological processes [8, 9].

Fragments in amino acid 1-4 have antiinflammatory properties, 1-15 antiapoptozny and cytoprotective effect and 17-23 an angiogenesis and growth of hair is active for migration of cells, binding by an actin, a dermal adhesion of wounds. Tβ4 participates in a series of cellular reactions, such as an angiogenesis, an adhesion of wounds, body height of hair, an apoptosis and an inflammation [3, 10, 11, 12, 13, 14]. It inhibits an inflammation, microbial body height, formation of the cicatrix (due to depression of level of miofibroblast) and an apoptosis, protects cells from cytotoxic damage, including glutamatneyronalny toxicity [1, 15, 16, 17, 18, 19].

Tβ4 represents multipurpose protein which stimulates migration and a differentiation of stem cells, synthesis of a protease, and also an expression of various regulatory genes, such as laminin-332, a fibronectin, matrix metalproteases, factors of body height of hepatocytes and antioxidatic enzymes [11, 18, 20, 21, 22, 23, 24, 25]. Migration of cells represents difficult process. Tβ4 promotes activity of matrix proteinases which is necessary for migration of epithelial cells [9, 26, 27, 28].

Inhibitors of these enzymes reduce migration of various types of cells. Such enzymes also degrade and let out matrix molecules which can be hemotaktilny factors of migration, thereby Tβ4 promotes chemotactic migration of cells to the place of the damaged site [6, 16, 26, 30, 31,32, 33]. Such type of epithelial migration has crucial importance for adhesion process. Migrations of Tβ4 it is carried out in several ways. Direct migration assumes ability of Tβ4 to bind an actin. Proteases promote and improve migration, way the chemotoxicity factors of a matrix and inhibition of receptors of adhesion. Tβ4 induces synthesis of laminin-332 which is important factors of adhesion and migration of cells. Other mechanism includes stabilization of a factor of a transcription of HIF1 which is bound to the laminin-332 pro-motor, its chains. Proteases also reduce production of laminin-332, generate smaller chemotoxicity activity. Laminin-332 also stabilizes a complex: a cell and a cell matrix, their interaction which are important for migration of cells to the damaged site of tissues. Tβ4 possesses antiapoptichesky activity by conservation integral structure an epithelium for migration of a leaf.

Cosecreted thrombocyte Tβ4 in the field of the injured derma, can accelerate an adhesion of dermal wounds, promoting migration of cells, accelerating collagen adjournment, inhibiting both an inflammation and an apoptosis [34, 35]. Tβ4 reduces an inflammation in tissues after different types of injuries by depression of migration of inflammatory factors; now are defined at the molecular level [1, 16, 30, 38, 39]. This decrease of an inflammation in fabric defect promotes Tβ4-mediated of a reparation and is important for this process, and also solves concrete actions for migration, Tβ4-mediated of cells for exercise of restoration of tissues. For example, Tβ4 reduces inflammatory factors, cytokines and chemokines in many tissues, also reduces inflammatory infiltration, activates anti-oxidizing enzymes, and reduces formation of active forms of oxygen. Tβ4 inhibits TNF-α- inducibility of a nuclear factor an activation kappa In and blocks the Rela / translocation of p65 and the sensitizing effects of the intracellular binding partners pinch-1 and integrin-sewed kinazy.

Tβ4 selektivno bridges tissue XIIIa factor transglutaminases for various molecules, including an actin, collagen, fibrin and a fibrinogen [39, 41]. Other molecules, such as a plasmin, alcohol dehydrogenase, a hexokinase, a pyruvatekinase, and a lactate dehydrogenase, can't be sewed Tβ4. Tβ4 it was identified as an angiogenic factor in the screen of the early genes induced during a differentiation of endothelial cells of invitro [42].

Tβ4 the best conservation of cardiomyocytes is promoted after an ischemia, by effect which is mediated by rising of an expression of a factor of body height of an endothelium of vessels (VEGF) and activation integrina-sewed kinases (ILK) [29]. It is surprising that it is little-known about potential receptors. Considering purinoceptor alarm ways of the active centers it would be possible to expect several receptors [8]. A lot of things are also unknown of Tβ4 role in a core. After an incubation with cells, it quickly (in 30 minutes), is transported in a core where functions as a factor of a transcription [1, 43]. The arising data demonstrate to what recent researches showed, чтоTβ4 is superfluous expresses in malignant tumors, and was suggested that it is bound to metastatic ability and an angiogenesis [10, 31, 44, 45, 46]. The induced expression of Tβ4 strengthens body height of a tumor and an innidiation in cellular lines of a melanoma and fibrosarcoma of a mouse [47]. Besides, Tβ4 hyper expression in cancer cells of a large intestine of the person cause the strengthened body height and an invasion at transplantation these cancer cells of mice [46, 48]. It is proved what an excess expression of Tβ4 promoted penetration of cells and their migration through ILK/AKT/β katenina-of an alarm way, causing transition epithelial to mesenchymal cancer in colorectal a blast. Tβ4 also works as the hypoxia regulator which controls migration of cancer cells to places of an angiogenesis and innidiation of a tumor [49]. These various cellular answers are regulated by Tβ4-опосредованной of an expression of several genes, such as specific proteases, laminin-5, and several inflammatory cytokines and chemokines. Tβ4 the beta (TGF beta) in the cultivated cornea cells strengthens an expression of laminin-5 and the transforming body height factor that in turn increases the activity of laminin-5 and TGF-β- induced of migration of cells and synthesis of a collagen, respectively [14].

Tβ4 influences alarm ways of Want by an activation regulation a glycogen – synthase – kinases-3 (GSK-3) in migration of cells of a carcinoma of the stomach [50].

The factor of body height of hepatocytes (HGF) promotes rising a regulation of Tβ4 which influences a wound repair in endothelial cells of an umbilical vein of the person [51].

Tβ4 promotes a full normal adhesion of all surface of a dermal wound at steroid treatment at animals with a diabetes mellitus [1, 41, 43]. Tβ4 also activly restores and regenerates tissues of an eye, heart, a brain, a peripheric nervous system and a spinal cord and stimulates an angiogenesis in some tissues at systemic use, but not at local use on a wounded surface of an eye.

Two independent randomized double blind people clinical tests proved that experimental gel in structure with Tβ4 accelerates a dermal adhesion. Uses of Tβ4 in treatment of other diseases caused by a trauma such as a myocardial infarction or reperfusion damage trauma corneas, and an ischemia of a brain induces migration of cells to the place of damage [1, 6, 15, 16, 18, 41,]. It was revealed that Tβ4 in any phosphatic and buffer saline solution or hydrogel activly accelerates dermal an adhesion of wounds at healthy rats. At the mice sick with Diabetum where the slowed-down adhesion, was revealed that adjournment of a collagen were much lower, than at the mice receiving Tβ4 as well as in any phosphatic and saline buffered solution or hydrogel. No differences were observed in migration of keratinotsit, at all animals with Diabetum, showing almost full wound repair for the 8th day. These researches show that Tβ4 is active for an adhesion of wounds in models of disturbance of an adhesion and can be effective the relation of chronic diseases at the person.

Tβ4 participate in activation the multipotent of cells precursors, integration of new cells at the place of a lesion and formation of their microvascular niche, increases neogenesis. Neogenesis of any tissue it isn't possible without a full-fledged neoangiogenesis. For this reason development and creation of the drugs activating a neoangiogenesis and possessing endotelioprotektivny properties is one of the main tasks of modern pharmacology and medicine in general. Several additional biological activities were identified,

but not localized in a molecule, including its antimicrobic activity, induction of different genes (including laminin-5, MMP, TGF a beta, a terminal dezoksinukleotidiltransferaza and the proteins connected to angiogenesis), and ability to activate ILK/Pinch/Akt and other signal molecules important in ways of apoptosis and inflammatory ways. Biological activity of Tβ4, is defined by the active centers in short peptide sequences.

Thus, as Tβ4 renders a wide range of functions, interacting with different molecules, it is important to research as Tβ4 is regulated to understand the mechanism of action Tβ4.

On the basis of its multifunction activities during regeneration of fabrics in different experiments on animals, Tβ4 has the potential for new researches, in kidneys and a liver, and also restoration of a spinal cord, bones and injury of ligaments. Besides, it can be useful in case of treatment of a wide range of other diseases, including concerning consequences of old bacterial damages and viral infections.

References

1. Lee J.W., Bae S.H., Jeong J.W., Kim S.H. & Kim K.W. Hypoxia-inducible factor (HIF-1)alpha: its protein stability and biological functions. *Experimental & Molecular Medicine.* №36 (2004): 1-12. [PubMed]
2. Bock-Marquette I., Saxena A., White M.D., Dimaio J.M. & Srivastava D. Thymosin beta4 activates integrin-linked kinase and promotes cardiac cell migration, survival and cardiac repair. *Nature.* №432 (2004): 466-472. [PubMed] [Full text]
3. Larsson L.I., Holck S. Occurrence of thymosin β4 in human breast cancer cells and in other cell types of the tumor microenvironment. *Human Pathology.* №38 (2007): 114–119. [PubMed]
4. Huang H., Hu C., Tang M., Wang W., Chen P., Su Y. Thymosin β4 triggers an epithelial-mesenchymal transition in colorectal carcinoma by upregulating integrin-linked kinase. *Oncogene.* №26 (2007): 2781-2790. [PubMed] [Full text]
5. Schaper J., Konig R., Franz D. & Schaper W. The endothelial surface of growing coronary collateral arteries. Intimal margination and diapedesis of monocytes. A combined SEM and TEM study. *Virchows Arch A Pathol Anat Histol.* №370 (1976): 193-205. [PubMed]
6. Hoefer I.E., et al. Arteriogenesis proceeds via ICAM-1/Mac-1- mediated mechanisms. *Circulation Research.* №94 (2004): 1179-1185. [PubMed] [Full text]
7. Murakami M., et al. The FGF system has a key role in regulating vascular integrity. *Journal of Clinical Investigation.* №118 (2008): 3355-3366. [PubMed] [Full text]
8. Malinda K.M., Sidhu G.S., Mani H., Banaudha K., Maheshwari R.K., Goldstein A.L., Kleinman H.K. Thymosin β4 acceleratеswoundhealing. *J. Investig. Dermatol.* №113 (1999): 364-368.
9. Regensteiner J.G., et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. *Vascular Medicine.* №13 (2008): 15-24. [PubMed]
10. Chappell D.C., Varner S.E., Nerem R.M., Medford R.M. & Alexander R.W. Oscillatory shear stress stimulates adhesion molecule expression in cultured human endothelium. *Circulation Research.* №82 (1998): 532-539. [PubMed] [Full text]
11. Hannappel E. & van Kampen M. Determination of thymosin beta 4 in human blood cells and serum. *J Chromatogr.* №397 (1987): 279-285. [PubMed]
12. Pollard T.D. & Cooper J.A. Actin, a central player in cell shape and movement. *Science.* №326 (2009): 1208-1212. [PubMed]
13. Puri K.D., et al. The role of endothelial PI3Kgamma activity in neutrophil trafficking. *Blood.* №106 (2005): 150-157. [PubMed] [Full text]
14. Sosne G., Xu L., Prach L., Mrock L.K., Kleinman H.K., Letterio J.J., Hazlett L.D., Kurpakus-Wheater M. Thymosin beta 4 stimulates laminin-5 production independent of TGF-beta. Exp. *Cell Res.* №293 (2004): 175-183. [PubMed]
15. Dimmeler S., Fleming I., Fisslthaler B., et al. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature.* №399 (1999): 601-605. [Full text]
16. Hooper J.A., et al. Purification and properties of bovine thymosin. *Annals of The New York Academy of Sciences.* №249 (1975): 125-144.
17. Kosaki K., Ando J., Korenaga R., Kurokawa T. & Kamiya A. Fluid shear stress increases the production of granulocyte-macrophage colony-stimulating factor by endothelial cells via mRNA stabilization. *Circ Res.* №82 (1998): 794-802. [PubMed]
18. Schirmer S.H., van Nooijen F.C., Piek J.J. & van Royen N. Stimulation of collateral artery growth: travelling further down the road to clinical application. *Heart.* №95 (2009): 191-197. [PubMed] [Full text]
19. Shaw P.E., Schroter H. & Nordheim A. The ability of a ternary complex to form over the serum response element correlates with serum inducibility of the human c-fos promoter. *Cell.* №56 (1989): 563-572. [PubMed]
20. Gao T., Furnari F. & Newton A.C. PHLPP: a phosphatase that directly dephosphorylates Akt, promotes apoptosis, and suppresses tumor growth. *Molecular Cell.* №18 (2005). [PubMed]
21. Low T., Hu S.-K., Goldstein A.L. Complete amino acid sequence of bovine thymosin beta 4: A thymic hormone that induces terminal deoxynucleotidyltransferase activity in thymocyte populations. *Proceeding of the National Academy of Sciences of the United States of America.* №78 (1981): 1162-1166. [PubMed]
22. Moon E.-Y., Im Y.-S., Ryu Y.-K., Kang J.-H. Actin-sequestering protein, thymosin beta-4, is a novel hypoxia responsive regulator. *Clinical & Experimental Metastasis.* №27 (2010): 601-609. [PubMed] [Full text]
23. Murakami M. Signaling required for blood vessel maintenance: molecular basis and pathological manifestations. *International Journal Vascular Medicine.* №2 (2012): 10-15. [PubMed]
24. Risau W. Mechanisms of angiogenesis. *Nature.* №386 (1997): 671-674. [PubMed]
25. Ryu Y.K., Lee Y.S., Lee G.H., Song K.S., Kim Y.S., Moon E.Y. Regulation of glycogen synthase kinase-3 by thymosin beta-4 is associated with gastric cancer cell

migration. *International Journal of Cancer*. №131 (2012): 2067-2077. [PubMed] [Full text]

26. Goldstein A.L. Thymosin β4: a new molecular target for antitumor strategies. *Journal of the National Cancer Institute*. №95 (2003): 1646-1647. [Full text] 9

27. Stossel T.P., Fenteany G. & Hartwig J.H. Cell surface actin remodeling. *J Cell Sci.* №119 (2006): 3261-3264.

28. Vanhaesebroeck B., et al. Synthesis and function of 3-phosphorylated inositol lipids. *Annual Reviews Biochemistry*. №70 (2001): 535-602. [PubMed]

29. Cha H.-J., Jeong M.-J., Kleinman H.K. Role of thymosin β4 in tumor metastasis and angiogenesis. *Journal of the National Cancer Institute*. №95 (2003): 1674-1680. [PubMed] [Full text]

30. Goldstein A.L., Low T.L., et al. Thymosin alpha 1: isolation and sequence analysis of an immunologically active thymic polypeptide. *Proceeding of the National Academy of Sciences of the USA*. №74 (1977): 725-729. [PubMed] [Full text]

31. Goldstein A.L., Slater F.D. & White A. Preparation, assay, and partial purification of a thymiclymphocytopoietic factor (thymosin). *Proceeding of the National Academy of Sciences of the USA*. №56 (1966): 1010-1017. [Full text]

32. Heil M. & Schaper W. Insights into pathways of arteriogenesis. *Curr Pharm Biotechnol*. №8 (2007): 35-42. [PubMed]

33. Muhlhauser J., et al. VEGF165 expressed by a replication-deficient recombinant adenovirus vector induces angiogenesis in vivo. *Circ Res.* №77 (1995): 1077-1086. [PubMed]

34. McDermott M.M., et al. Depressive symptoms and lower extremity functioning in men and women with peripheral arterial disease. *J Gen Intern Med*. №18 (2003): 461-467. [PubMed] [PMC]

35. Wang W.-S., Chen P.-M., Hsiao H.-L., Wang H.-S., Liang W.-Y., Su Y. Overexpression of the thymosin β-4 gene is associated with increased invasion of sw480 colon carcinoma cells and the distant metastasis of human colorectal carcinoma. *Oncogene*. №23 (2004): 6666–6671. [PubMed] [Full text]

36. Alessi D.R., James S.R., Downes C.P., Holmes A.B., Gaffney P.R., Reese C.B., Cohen P. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Balpha. *Current Biology*. №7 (1997): 261-269. [PubMed] [Full text]

37. Drake C.J. Embryonic and adult vasculogenesis. *Birth Defects Research Part C Embryo Today*. №69 (2003): 73-82. [PubMed]

38. Gerber H.P., McMurtrey A., Kowalski J., Yan M., et al. Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. Requirement for Flk-1/KDR activation. *Journal Biological Chemistry*. №273 (1998): 30336-30343. [PubMed] [Full text]

39. Shioi T., et al. The conserved phosphoinositide 3-kinase pathway determines heart size in mice. *EMBO Journal*. №19 (2000): 2537-2548. [PubMed] [Full text]

40. Graupera M., Guillermet-Guibert J., Foukas L.C., et al. Angiogenesis selectively requires the p110alpha isoform of PI3K to control endothelial cell migration. *Nature*. №453 (2008): 662-666. [PubMed] [Full text]

41. Oh I.S., So S.S., Jahng K.Y., Kim H.G. Hepatocyte growth factor up regulates thymosin β4 in human umbilical vein endothelial cells. *Biochem Biophys Res Commun*. №296 (2002): 401-405. [PubMed]

42. Yuan T.L., et al. Class 1A PI3K regulates vessel integrity during development and tumorigenesis. *Proceeding of the National Academy of Sciences of the USA*. №105 (2008): 9739-9744. [PubMed] [Full text]

43. Sosne G., Szliter E.A., Barrett R., Kernacki K.A., Kleinman H., Hazlett L.D. Thymosin beta 4 promotes corneal wound healing and decreases inflammation in vivo following alkali injury. *Experimental Eye Research*. №74 (2002): 293-299. [PubMed]

44. Kobayashi T., Okada F., Fujii N., Tomita N., Ito S., Tazawa H., Aoyama T., Choi S.K., Shibata T., Fujita H. Thymosin-β4 regulates motility and metastasis of malignant mouse fibrosarcoma cells. *American Journal of Pathology*. №160 (2002): 869-882. [PubMed] [Full text]

45. Philp D., St-surin S., Cha H.J., Moon H.S., Kleinman H.K., Elkin M. Thymosin beta 4 induces hair growth via stem cell migration and differentiation. *Annals of The New York Academy of Sciences*. №1112 (2007): 95-103. [PubMed]

46. Williams J.K. Endothelial FGF receptor signaling: angiogenic versus atherogenic effects. *Am J Physiol Heart CircPhysiol*. №300 (2011): 27-28.

47. Kok K., Geering B. & Vanhaesebroeck B. Regulation of phosphoinositide 3-kinase expression in health and disease. *Trends in Biochemical Sciences*. №34 (2009): 115-127. [PubMed] [Full text]

48. Ji Y.-I., Lee B.-Y., Kang Y.-J., Jo J.-O., Lee S.H., Kim H.Y., Kim Y.-O., Lee C., Koh S.B., Kim A. Expression patterns of thymosin β4 and cancer stem cell marker cd133 in ovarian cancers. *Pathology & Oncology Research*. №19 (2013): 237-245. [PubMed] [Full text]

49. Morbidelli L., Donnini S. & Ziche M. Role of nitric oxide in the modulation of angiogenesis. *Curr Pharm Des*. №9 (2003): 521-530. [PubMed]

50. Sanders M.C., Goldstein A.L., Wang Y.-L. Thymosin beta 4 (Fx peptide) is a potent regulator of actin polymerizationin living cells. *Proceeding of the National Academy of Sciences of the USA*. №89 (1992): 4678-4682. [PubMed]

51. Patrucco E., et al. PI3Kgamma modulates the cardiac response to chronic pressure overload by distinct kinase-dependent and -independent effects. *Cell*. № 118 (2004): 375-387. [PubMed]

52. Grunewald M., et al. VEGF-induced adult neovascularization: recruitment, retention, and role of accessory cells. *Cell*. №124 (2006): 175-189. [PubMed] [Full text]