REPORTS OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
ISSN 2224-5227
Volume 2, Number 300 (2015), 156 – 163

УДК 577.152.54:57.042.2:616-035

Farnesyl transferase inhibitors. modern aspects of their application

Kozhanova S., Tarabayeva A., Nurmukhanbetova A., Bizhigitova B., Bitanova E., Shaikenova A.

S. Asfendiyarov Kazakh National Medical University

Key words: post-translational modification, farnesylation of proteins, farnesyl transferase, farnesyl transferase inhibitors

Abstract. This review presents an analysis of materials devoted to the study of the role of the farnesyl transferase inhibitors. There are more than two options for the posttranslational modification of proteins, the same protein may be subjected to various modifications. According to research by a number of authors, farnesylation of proteins is a form of post-translational modification, and is present in most eukaryotic cells. Farnesyl transferase inhibitors can specifically block the function of ras proteins and cause inhibition of tumor growth. Particular attention is paid to the action of microorganisms farnesyltransferase inhibitors, that is the latest trend in the treatment of fungal, parasitic and other diseases.

Ингибиторы фарнезилтрансферазы. Современные аспекты их применения

Кожанова С., Тарабаева А., Нурмуханбетова А., Бижигитова Б., Битанова Е., Шайкенова А.
Казахский Национальный медицинский университет им.С.Д. Асфендиярова

Ключевые слова: посттрансляционная модификация, фарнезилирование белков, фарнезилтрансфераза, ингибиторы фарнезилтрансферазы.

Аннотация. Этот обзор представляет собой анализ материалов, посвященных изучению роли ингибиторов фарнезилтрансферазы. Есть более двух вариантов посттрансляционной модификации белков, тот же белок может быть подвергнут различным модификациям. Согласно исследованиям ряда авторов, фарнезилирования белков является форма пост-трансляционной модификации и присутствует в большинстве эукариотических клеток. Ингибиторы фарнезилтрансферазы могут, в частности, блокировать функцию ras белков и вызвать ингибирование роста опухоли. Особое внимание уделено действию микроорганизмов ингибитор jd фарнезилтрансферазы, то есть последним тенденциям в лечении грибковых, паразитарных и других заболеваний.

The role of farnesylation of proteins in post-translational modification.

Post-translational modification is the final step in the biosynthesis of many proteins, and is part of the process of gene expression [1, 2].

To date, there are more than two options for post-translational modification of proteins. Moreover, the same protein may be subjected to several different modifications. Post-translational modifications have different effects on proteins [3]. They regulate the enzymatic activity [4], the duration of their existence in the cell, as well as interaction with other proteins. In some cases, they are an essential step in the maturation of the protein, otherwise protein becomes functionally inactive. For example, glycosylation is one of the most common modifications [5,6]. It is believed that about half the human proteins are glycosylated, and 1-2% of human genes encode proteins related to glycosylation. Furthermore, the value of post-translational modifications for normal functioning of the body is confirmed by the fact, that there

are diseases which are based on a violation of the posttranslational modification of proteins (Alzheimer's desease, different types of cancer, ect) [7]. Ras mutations associated with 20-25% of human cancers and in 90% of pancreatic carcinomas [8].

Farnesylation of proteins is one of the forms of post-translational modification that is present in most eukaryotic cells [9]. Farnesyl transferase is an enzyme that causes the accession of 15 farnesyl groups with SOOH-ends of the protein [10]. In the case of gene ras mutation, production of mutated ras protein occurs. This protein transmits signals from the receptors to the cell nucleus and causes their proliferation. Normal protein rax connects to guanine diphosphate and becomes inactive [11,12]. The mutated protein rax loses this ability and it is constantly active and stimulats proliferation. To perform this function, protein ras must obtain the appropriate spatial structure and attachs to the inner surface of the cell membrane. This occurs with participation of the enzyme farnesyl transferase [10,13]. Protein ras without farnesylation is incapable to phosphorylate and transmit signals from the receptor cell to the nucleus.

We will describe in detail the mechanism. Protein R21ras is product of ras gene and it is a transmembrane regulatory protein binding guanine nucleotides. As the other G proteins r21ras is active in GTP-bound state and inactive in GDP-bound form. G proteins are involved in the transmission of extracellular signals of regulatory hormones, growth factors, neurotransmitters to intracellular second messenger system [14,15]. Direct target of the action of p21ras is intracellular serine-threonine protein kinase raf (protein r74c-raf). Raf-kinase activates a cascade of intracellular kinases. As a result of this activation protooncogene c-jun phosphorylation occurs, which is a transcription factor. Then, transcription of oncogenes-fos, c-myc and other genes is induced that initiate mitosis. Raf-kinases can also phosphorylate and activate directly located in the cytoplasm inactive c-myc. As a result, it returns to the nucleus and binds to specific sections of the chromatin, initiating the expression of a-fos, c-jun and c-ras. EGFR regulatory signal transmission from the cell membrane to the nucleus in this way occurs.

A further effect on ras is carried out through complex interactions of adapter and effector proteins. On the one hand, the molecule rasGAP comprises the amino acid sequence SH2On the other hand, researchers deciphered chain molecules that transmit the activating signal to the nucleotide exchange factors. Such a protein is called SOS ("son of sevenless"). Direct carrier signal from the phosphorylated receptor to SOS is a protein GRB2, which is composed of a single SH2 domain and two domains SH3. These domains are able to recognize in some parts of the protein molecules are filled with proline [15].

According to recent reports, the way GRB2 - SOS is more important for the activation of ras, than direct interaction EGFR with GRB2. It is also shown that the whole process ras activation occurs at the cell membrane. As a result of this regulatory protein SOS is close to an effector protein r21ras.

In this regard, the reaction farnesylation of r21ras plays an important role in the transmission of mitogenic signals EGF through the ras [10, 16].

Thus, farnesyl transferase inhibitors can specifically block the function of rax proteins and cause inhibition of tumor growth.

Hsuan proposed a model of the formation on the cell membrane of the molecular complex that facilitates transfer of regulatory signals and interactions between different intracellular signaling systems [17].

Blocking any transmission of the mitogenic signal phase growth factors leads to the deregulation of the proliferation of tumor cells and to inhibit tumor growth. Scientists have studied drugs that affect the above processes [18].

One such drug is a domestic product, which is prepared from wormwood - "Arglabin." The drug inhibits adherence farnesyl group to cellular proteins and disrupts the farnesylation of the ras oncogene product [19, 20].

Prospects for the use of farnesyl transferase inhibitors.

Prenylation of proteins exists in a wide range of pathogenic Protozoa, including T.brucei, T.cruzi, leishmania species, giardia lamblia, entamoeba histolitica, toxoplasma gondii [21, 22,23,24].Currently, researchers are exploring the use of farnesyl transferase inhibitor (FTI) for the treatment of diseases which are caused by the pathogenic eukaryotes. FTI demonstrated their effectiveness in the treatment of eukaryotic pathogens, including Trypanosoma brucei and Plasmodium falcipatum [25, 26].The study of enzymes involved in the prenylation of proteins is important. Prenyl transferases are present in most fungi and protozoa. Thus, a dysplasia protozoon is more pronounced due to the inhibition of protein

farnesylation.

Isoprenoid synthesis of mevalonic acid is required for eukaryotes to synthesize sterol, ubiquinone and other isoprene derivatives [27]. It is known that sterols are components of cell membranes of eukaryotes and they are necessary for their function and interaction with other cells and active substances. Twenty steps involving numerous specific enzymes are necessary for the biosynthesis of sterols at least. There are specific enzymes differing between microorganisms and mammalian cells which are involved in certain stages of sterol biosynthesis [15, 28]. A number of these enzymes has been studied intensively for the creation of new drugs that affect the growth of parasites without the formation of severe side effects on the host cell. For example, different sterol biosynthesis inhibitors were tested in vivo in murine models of disease Chaga, leishmaniasis and malaria [22, 29]. These components are present in virtually all eukaryotic cells, in one form or another. For example, in humans, they exist in the form of cholesterol in fungi and protozoa in the form of a special class of sterols, including ergosterol[30]. Cholesterol and ergosterol differ from each other by several features. Some features of ergosterol are not typical for molecules of cholesterol. Fig 1

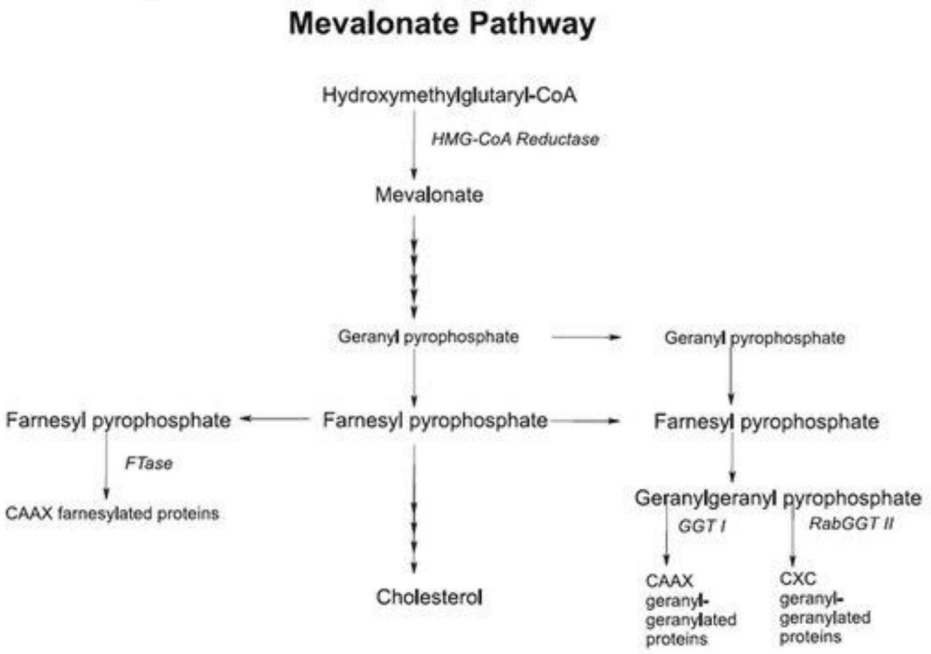

Fig. 1 Relationship of posttranslational protein isoprenylation pathways to the mevalonate pathway of cholesterol biosynthesis

If we know the mechanism of the synthesis of sterols, we can influence the growth and activity of pathogenic protozoa and fungi. Interaction between statin and HMG-CoA reductase prevents the conversion HMG-CoA to mevalonate I. It inhibits the biosynthesis of cholesterol, and numerous isoprenoid metabolites such as GGPP and FPP.

GGPP and FPP are lipid "clips". They provide attachment of certain proteins to membranes and are key mediators for the post-translational modification of activation of various cell signaling proteins. Ras, Rac, Rho are such proteins [31]. Attaching these lipids are fundamental for the activation of these proteins and their intracellular transport. These processes act as molecular switches and control multiple metabolic pathways and cellular functions. Cell functionы are: preservation of cell shape, motility, secretion factors, differentiation and proliferation.

For the synthesis of sterols at least 20 steps are necessary.

The main ones are:

1. The condensation of two acetyl-CoA units and the formation of acetoacetyl-CoA.
2. Formation of HMG-CoA
3. Recovery and synthesis of mevalonic acid. Mevalonic path ends here.
4. The conversion of mevalonate to IPP

5. Transformation into DMAPP.

6. Condensation of IPP with DMAPP and GDF. Creating FPP and FPPS. Isoprenoid pathway ends here. Sterol synthesis is identical in all investigated organisms to this stage [32].

FPP is a substrate for different enzymes, which are necessary for the further synthesis of sterols and a donor for prenylation. Prenylation of proteins is a lipid posttranslational modification of proteins with cysteine residues. This is required for association with a lipophilic membrane protein, as well as for interactions between proteins. The basis for protein prenylation are H-, N-, K-Ras, Rac, Rho, Rab, involved in vesicle transport, signal transduction and cell activity [33].

To date, three enzymes that provide prenylation are known. Это FPT, GGPT-I, и GGPT-II.

During the work FT and GGT-I prenylated protein-specific protease cleaves terminal tripeptide from the prenylated protein. This leads to a terminal carboxylic acid methylation in using prenyl-protein-specific methyltransferase. Because of the strong similarity of these enzymes their cross-effect has been proved. This means that in the absence of the enzyme, the second one completely takes all the work itself (Fig 2).

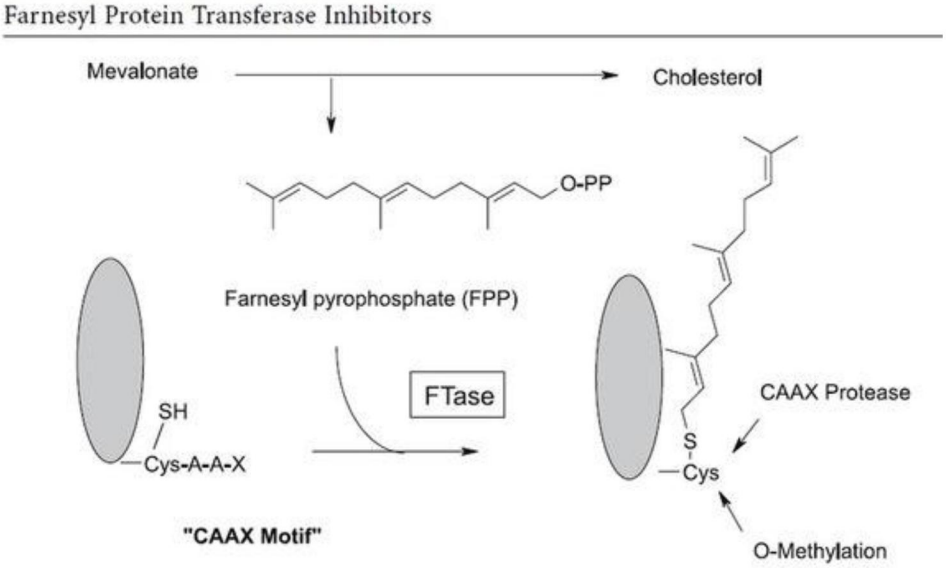

Fig. 2 Schematic representation of the farnesyl protein transferase (FTase) reaction

GGPT-II stimulates the addition of two G-G groups to the terminal residues of proteins, which belong to kRab protein.

The reason of more effective inhibition of cancer and parasitic farnesyl compared to normal mammalian cells is still not clear. It is assumed that this selectivity is based on the biological differences between these cells. In addition, the effect of FTI on protozoa and fungi may be based on the presence of only FT and absence a workaround in the form of GT.

Prenyl transferases are available in many fungal and protozoal pathogens that infect humans[34]. Candida albicans, which causes systemic fungal infections in immuno-compromised individuals is one of the pathogens for which prenylation of proteins is necessary for survival. Fungal diseases are usually caused by dermatophytes and Candida [35]. In recent years the number of fungal diseases has been grown. Because of the underestimating of their danger, fungal infections are more common in organ transplants, cancer chemotherapy, AIDS. Fungal infection also occurs in the application of broad-spectrum antibiotics, invasive techniques. One of the problems that arise when creating products with antimicrobial activity is the presence of toxic side effects and high cost of these drugs. One of the problems that arise when creating products with antimicrobial activity is the presence of toxic side effects and high cost of these drugs. In this regard, scientists turned their eyes to the FTI.

As noted previously, FT and GT are in many fungal and protozoan pathogens, and they need to survive. What is more, it was shown that growth of parasites more significantly disturbed due to the inhibition protein prenylation in comparison with mammalian cells [31,35].

Impact on microorganisms.

Effect on Trypanosoma cruzi.

FTI has demonstrated high activity in Chagas disease and leishmaniasis [22, 29,36]. Thus FT was investigated as a target for the treatment tripanosomatoza as inhibitors of this enzyme is highly toxic to the parasite. Chagas disease is a protozoan vector-borne infectious disease that is caused by Trypanosoma cruzi. It carries by bedbugs and affects parenchymal organs. Reservoir of infection is the man, and also some mammals. That is why the objects of study became insects and mammals. Expression of messenger RNA for the alpha and beta subunits of farnesyltransferase to different stages of the life cycle of the parasite was investigated.

Scientists [37] have proved the presence in Trypanosoma cruzi as GGT-1, as FT. It has been proven that most proteins containing Caax (x is leucine) are suitable as object for GGT-I. Proteins in which X is methionine are subject to both enzymes. At the same time, the proteins containing Caax in which x is a phenylalanine are poor targets for GGT-1, and therefore more are acceptable for FT. In the genome of Trypanosoma cruzi set of proteins with Caax pattern was found. For example, ras - like protein C-terminal with sequence CVLL is selective for the 1-GGT. But other peptides with CTQQ-, CAVM-, CHFM-, GOLF-terminal sequences are specific substrates for FT.

As a result, at different stages of the life cycle of Trypanosoma cruzi (both insects and mammals in) activity level GGT-1 was 100 times lower than FT.

Effect on Trypanosoma brucei.

African trypanosomiasis is a parasitic disease of humans and animals, which is caused by Trypanosoma brucei and is carried by the tsetse fly. It is a common disease that annually kills about 10,000 lives in Africa. For FTI use against the parasite we need to know the differences between FT of T.brucei and FT of mammals. The authors [38,39]identified FT of T.brucei and cleared it by affinity chromatography. As well as mammal's FT, T.brucei's FT is a heterodimer. However, it has a large size, due to the numerous segments of peptide inserts. These inserts were detected by molecular modeling using known structures of mammal's FT. These inserts form loops on the protein surface and are at a distance from the active center of the enzyme. Currently, their function is not known. Substrate specificity is also different from the FT mammals (here x is a methionine or glycine). The authors [40,41] also demonstrated a positive impact of the FTI on FT T.brucei in vitro.

Effect on Plasmoidum falciparum.

Pathogen Plasmoidum falciparum is a protozoan that causes malaria in humans. It is transmitted female mosquitoes that are from the genus Anapheles. Malaria, which is caused by this pathogen, is called lightning fast or tropical and it is the most dangerous form of the disease. Some authors [42, 43] have characterized FT, obtained from P.falciparum. It is shown that the Caax specificity is similar to in T.brucei, (x is methionine or glycine). Radiometric method showed that P.falciparum FT is composed of proteins with a molecular weight 50kDa and several proteins of lower molecular weight. Proteins with a molecular weight 50 kDa were modified via FT. Thus, proteins with lower molecular weight when were subjected by GG prenylation provisional conversion of farnesol in FPF, as well as GPF. Subsequently, researchers demonstrated a positive effect FTI on the proteins with a molecular weight of 50kDa, and no effect on the proteins of lower molecular weight, i.e., those who have been subjected by GG prenylation [31,35].

Other effects of FTI.

Currently in the literature a large number of structurally diverse FTI is represented [25, 26]. It should be noted that FTI are capable to inhibit FT both mammals and parasites. It is shown that they are more active against parasitic FT. This is due to the fact that due to the lack of GGPT-I some protozoan parasites are more sensitive to inhibition of FT, than human cells.

Except antiproliferative effect FTI have other biological effects. Some authors [20] have shown immune stimulating effect of "Arglabin" on the maturation all groups of T lymphocytes. Other scientists have proved its stimulatory effect on macrophages, IL-1,2, TNF [21]. An interesting fact is that the immune stimulatory effect Arglabin provides in a much lower concentration (1.25 mkg / ml and 0.125 mkg / ml).

According to recent data, in the pathogenesis of the Hutchinson-Gilford disease FT plays a key role. FT inhibition reduces the severity of the disease. Lamin protein that has a value in the pathogenesis of Hutchinson-Gilford disease to penetrate the nucleus of the cell needs to farnesylation. But, later in the

nucleus by the action of protein LMNA defarnesylation occurs, which contributes to the activation of the genome and, consequently, cell growth and development[44].

At present, the social significance and economic interest in the known inhibitors prenyl transferases that should be investigated in relation to infectious pathogens is increasing for several reasons:

1) lack of safe, low-cost products with less dangerous side effects;

2) increasing resistance to conventional preparations;

3) growing list of pathogens;

4) delay of the development of new medicines.

This approach will not only increase the interest of researchers to study the mechanisms of action of inhibitors of prenyl transferases against parasitic and fungal infections, but also due to the use of such drugs will avoid the costs associated with drug development[42].

To date, FTI drugs are effective against fungi and protozoa [20,38]. The only difficulty is ensuring the delivery of the inhibitor to a pathogens cell. If such a modification IPT, which will help deliver the inhibitor to a substrate, is ensured we can get a complete elimination of the pathogen.

Perhaps Arglabin, which is capable of inhibiting FT, will also have a relatively selective action GGT-I, since it has structural similarities to FT[19,20]. Accordingly, it may be useful in the treatment of pathologies that are associated with intracellular signaling in using Ras-proteins or other proteins of the family of ras.

In turn, this will create the preconditions for studying the possibility of using drugs that are based on wormwood, growing mainly in Kazakhstan. All this will allow come out of these drugs on the international pharmaceutical market as new antifungal agents and drugs against Giardia.

ЛИТЕРАТУРА

[1] *Eastman R.T., Buckner F.S., Yokoyama K., Gelb M.H., Van Voorhis W.C.* Thematic review series: lipid posttranslational modifications. Fighting parasitic disease by blocking protein farnesylation. J. Lipid Res. - 2006. - V. 47 (2). - P.233–240.

[2] *Burg J.S., Espenshade P.J.* Prog. Lipid Res. -2011. -V. 50.- P. 403–410.

[3] *Душкин М.И., Кудинова Е.Н., Шварц Я.Ш.* Интеграция сигнальных путей регуляции липидного обмена и воспалительного ответа // Цитокины и воспаление. - 2007. - Т. 6. - № 2. - С.18-25.

[4] *Sinensky, M.* Recent advances in the study of prenylated proteins // Biochim. Biophys. Acta. - 2000. - V.1484. - P.93–106.

[5] *Casey P.J., Seabra M.C.* Protein prenyltransferases// J. Biol. Chem. 1996. -V.271.- P.5289-5292.

[6] *Berg J.M., Tymoczko J.L., Stryer L.* //Biochemistry – 2002. - New York. - 1100 p.

[7] *Hindler K., Cleeland C.S., Rivera E., Collard C.D.* // Oncologist. - 2006. -V. 11. - P. 306–315.

[8] *Garcia-Ruiz C., Morales A., Fernandez-Checa J.C.* // Anticancer Agents Med. Chem. - 2012. - V. 12. - P. 303–315.

[9] *Sebti S.M., A.A. Adjei.* Farnezyltransferase inhibitors// Semin.Oncol.- 2004. -V.31.- p.28-39.

[10] *TamanoiF., Kato-StankieviczJ., JiangC., MachagoI., ThaparN.* Farnezylated proteins and cell cycle progression //J.Cell.Biochem.Suppl.- 2001. V.37. -p.64-70.

[11] *Laezza C., Fiorentino L., Pisanti S., Gazzerro P., Caraglia M., Portella G. et al.* Lovastatin induces apoptosis of k-ras-transformed thyroid cells via inhibition of rasfarnesylation and by modulating redox state// J.Mol.Med.- 2008.-V.86- p.1341–1351.

[12] *Burg J.S., Espenshade P.J.* // Prog. Lipid Res. - 2011. - V. 50. - P. 403–410.

[13] *Clinkenbeard K.D., Reed W.D., Mooney R.A., Lane M.D.* // J. Biol. Chem.- 1975. - V. 250. - P. 3108– 3116.

[14] *Barbacid M.* Ras genes//Annu. Rev. Biochem. -1987. - V.56. - P.779-827.

[15] *Mo H., Elson C.E.* // Exp. Biol. Med. 2004. V. 229. P. 567–585

[16] *Thurnher M., Nussbaumer O., Gruenbacher G.* // Clin. Cancer Res. 2012. V. 18. P. 3524–3531.

[17] *Zhu K., A.D.Hamilton, S.M.Sebti.* Farnezyltransferase inhibitors as anticancer agents: current status// Curr.Opin.Investig.Drugs. - 2003. - V.4.- P.1428-1435.

[18] *Garcia-Ruiz C., Morales A., Fernandez-Checa J.C.*// Anticancer Agents Med. Chem. - 2012. - V.12. - P.303–315.

[19] Способ получения гидрохлорида 1(10)β-эпокси-13-диметиламино-5,7α,6,11β(н)-гвай-3(4)-ен-6,12-олида, лиофилизированного противоопухолевого средства "Арглабин". 2011. Описание изобретения к евразийскому патенту №015557 (B1).

[20] *Shaikenov T.E, Adekenov S.M, Williams R.M, Prashad N, Baker F.L, Madden T.L, Newman R.* Arglabin-DMA, a plant derived sesquiterpene, inhibits farnesyltransferase// Biochem. J. - 2001.- V.348, P.318–326.

[21] *Hasne, M. P., Lawrence F.* Characterization of prenylated protein methyltransferase in Leishmania // Biochem. J. -1999. - V.342.- P.513–518.

[22] *S.H. Szajnman, G.E. Garsia, Z.-H. Li* Syntetic and biological evaluation of 2-alkilaminoethil-1,1-bisphosponic acids against Tripanosoma cruzi and Toxoplasma gondii targeting farnesyl diphosphate synthase // Bioorganic and medicinal chemistry - 2008.-V.16.- P.3283–3290.

[23] *L.R. Garzoni, A. Caldera, et al.* Selective in vitro effects of the farnesyl pirophosphate synthase ingibitor risedronate on Tripanosoma cruzi // Int.J. of Antimicr.Agents.-2004.- V.23. P.303–315.

[24] *V. Yardley, A. Khan, M.B.Martin, et al.* `In vivo activites of farnesyl pyrophosphate synthase inhibitors against Leishmania donovani and Toxoplasma gondii //Antimicrobial Agents and Chemotherapy. – 2002. -V.46. - P.929-931
[25] *M.B.Martin, J.S.Grimley, J.C.Lewis, et al.*`Bisphosphonates inhibit the growth of Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondii, and Plasmodium falciparum: a potential route to chemotherapy//Journal of Medicinal Ghemistry. – 2001. – V.44. - P.909-916
[26] *Gauthaman K., Fong C.Y., Bongso A.* Statins, stem cells, and cancer// J. Cell Biochem. - 2009. -V.106. - P.975-983.
[27] *Taoufiq Z., Pino P., N'dilimabaka N., Arrouss I., Assi S., Soubrier F., Rebollo A., Mazier D.* // Malar. J. 2011. -V. 10. - P. 1–9.
[28] Zhou Q., Liao J.K. // Curr. Pharm. Des. 2009. - V. 15. - P. 3108–3115.
[29] *L.R.Garzoni, M.C.Waghabi, M.M.Baptista, et al.* Antiparasitic acyivity of risedronate in a murine model of acute Chagas'disease // International Journal of Antimicrobial Agents. – 2004 - vol.23. - P. -286-290.
[30] *Y.Ling, Z-H. Li, K.Miranda, E.Oldfield, ahd S.N.J.Moreno* The farnesyl-diphosphate synthase of Toxoplasma gondii is a bifunctoinal enzyme and a molecular target of bisphosphonates // The Journal of Biological Chemistry. – 2007. – V.282. - P.3804-3816
[31] *Gauthaman K., Fong C.Y., Bongso A.* // J. Cell Biochem. - 2009. -V. 106. - P. 975–983.
[32] *Mo H., Elson C.E.* // Exp. Biol. Med. - 2004. - V. 229. - P. 567–585
[33] *Chugh A., Ray A., Gupta J.B.* // Prog. Lipid. Res. - 2003. - V. 42.- P. 37–50.
[34] *Hast M.A., Beese L.S* .Structure of protein geranylgeranyltransferase-1 from the human pathogen Candida albicans complexed with a lipid substrate// J.Biol.Chem. - 2008. - 283 (46). - P.3193-31940.
[35] *K.Barret-Bee,L.Newboult,and P.Pinder.* Biochemical changes associated with the antifungal action of the triazole ICI 153,066 on Candida albicans and Trichophyton quinckeanum// FEMS Microbiology Letters.-1991.-V.79. - P.127-131.
[36] *N.Rodriguez, B.N.Bailey, M.B.Martin, E.Oldfield, J.A.Urbina,and R.Docampo.* Radical cure of experimental cutaneous leismaniasis by the bisphosphonate pamidronate //Journal of Infectious Diseases.-2002. -V.186. - P.138-140.
[37] *M.Sealey-Cardona, S.Cammerer, S.Jones, et al* Kinetic characterization of squalene synthase from Trypanosoma cruzi: selective inhibition by quinuclidine derivatives//Antimicfobial Agents and Chemotherapy.-2007. -V.51.- P.2123-2129.
[38] *S.O.Lorente, R.Gomez, C.Jimenez, et al* . Biphenylquinuclidines as inhibitors of squalene synthase and growth of parasitic protozoa// Bio org. Med. Chem. Lett.- 2005. – V. 13. – P. 3519-3529
[39] *Hatori H., Shibata T., Tsurumi Y., Nakanishi T., Katsuoka M., Ohtsu Y., Sakamoto K., Takase S., Ueda H., Hino M., Fujii T.* // J. Antibiot., Tokyo. 2004. - V. 57. - P. 253–259.
[40] *A. Urbina.* Lipid biosynthesis pathways as chemotherapeutic targets in kinetoplastid parasites// Parasitology. - 1997. - V.114. - P. 91-99
[41] *C. W.Roberts, R. McLeod.* Fatty acid and sterol metabolism tripanosomatid parasitic protozoa // Mol.Biochem.Parasitology. - 2003. - V. - 126. -P.129-142
[42] *Ohcanda J., J.W. Lockman, K.Yokoyama, M.H. Gelb, S.L.Groft, H.Kendrick.,M.I.Harrel, J.E. Feagin, M.A.Braskovich, S.M.Sebti. et.al.* Peptidomimetic inhibitors of protein farnezyltransferase show potent antimalarial activity// Bio org. Med. Chem. Lett. - 2001. - V.11. - P.761-764.
[43] *Laezza C., Fiorentino L., Pisanti S., Gazzerro P., Caraglia M., Portella G., Vitale M., Bifulco M.* // J. Mol. Med., Berl. - 2008. - V. 86. - P. 1341–1351.
[44] *Belter A., Skupinska M., Giel-Pietraszuk M., Grabarkiewicz T., Rychlewski L., Barciszewski J.* // Biol. Chem. - 2011. - V. 392. - P. 1053–1075.

REFERENCES

[1] *Eastman R.T., Buckner F.S., Yokoyama K., Gelb M.H., Van Voorhis W.C.* Thematic review series: lipid posttranslational modifications. Fighting parasitic disease by blocking protein farnesylation. J. Lipid Res. - 2006. - V. 47 (2). - P.233–240.
[2] *Burg J.S., Espenshade P.J.* Prog. Lipid Res. -2011. -V. 50.- P. 403–410.
[3] *Dushkin M.I., Kudinova E.N., Schwartz Ya.Sh.* The integration of signaling pathways regulate lipid metabolism and inflammatory response. Cytokines and inflammation. - 2007. - V. 6. - № 2. - p.18-25. (in Russ.).
[4] *Sinensky M.* Recent advances in the study of prenylated proteins. Biochim. Biophys. Acta. - 2000. - V.1484. - P.93–106.
[5] *Casey P.J., Seabra M.C.* Protein prenyltransferases. J. Biol. Chem. 1996. -V.271.- P.5289-5292.
[6] *Berg J.M., Tymoczko J.L., Stryer L.* Biochemistry – 2002. - New York. - 1100 p.
[7] *Hindler K., Cleeland C.S., Rivera E., Collard C.D.* Oncologist. - 2006. -V. 11. - P. 306–315.
[8] *Garcia-Ruiz C., Morales A., Fernandez-Checa J.C.* Anticancer Agents Med. Chem. - 2012. - V. 12. - P. 303–315.
[9] *Sebti S.M., A.A. Adjei.* Farnezyltransferase inhibitors. Semin.Oncol.- 2004. -V.31.- p.28-39.
[10] *TamanoiF., Kato-StankieviczJ., JiangC., MachagoI., ThaparN.* Farnezylated proteins and cell cycle progression. J.Cell.Biochem.Suppl.- 2001. V.37. -p.64-70.
[11] *Laezza C., Fiorentino L., Pisanti S., Gazzerro P., Caraglia M., Portella G. et al.* Lovastatin induces apoptosis of k-ras-transformed thyroid cells via inhibition of rasfarnesylation and by modulating redox state. J.Mol.Med.- 2008.-V.86- p.1341–1351.
[12] *Burg J.S., Espenshade P.J.* Prog. Lipid Res. - 2011. - V. 50. - P. 403–410.
[13] *Clinkenbeard K.D., Reed W.D., Mooney R.A., Lane M.D.* J. Biol. Chem.- 1975. - V. 250. - P. 3108– 3116.
[14] *Barbacid M.* Ras genes. Annu. Rev. Biochem. -1987. - V.56. - P.779-827.
[15] *Mo H., Elson C.E.* Exp. Biol. Med. 2004. V. 229. P. 567–585
[16] *Thurnher M., Nussbaumer O., Gruenbacher G.* Clin. Cancer Res. 2012. V. 18. P. 3524–3531.
[17] *Zhu K., A.D.Hamilton, S.M.Sebti.* Farnezyltransferase inhibitors as anticancer agents: current status// Curr.Opin.Investig.Drugs. - 2003. - V.4.- P.1428-1435.
[18] *Garcia-Ruiz C., Morales A., Fernandez-Checa J.C.* Anticancer Agents Med. Chem. - 2012. - V.12. - P.303–315.

[19] A method for obtaining hydrochloride1(10)β-epoxy-13-dimethylamino-5,7α,6,11β(н)-guai-3(4)-ene-6,12-olide, lyophilized antineoplastic agent "Arglabin." 2011. Description of a Eurasian patent №015557 (B1). (in Russ.).
[20] *Shaikenov T.E, Adekenov S.M, Williams R.M, Prashad N, Baker F.L, Madden T.L, Newman R.* Arglabin-DMA, a plant derived sesquiterpene, inhibits farnesyltransferase. Biochem. J. - 2001.- V.348, P.318–326.
[21] *Hasne, M. P., Lawrence F.* Characterization of prenylated protein methyltransferase in Leishmania. Biochem. J. -1999. - V.342.- P.513–518.
[22] *S.H. Szajnman, G.E. Garsia, Z.-H. Li* Syntetic and biological evaluation of 2-alkilaminoethil-1,1-bisphosponic acids against Tripanosoma cruzi and Toxoplasma gondii targeting farnesyl diphosphate synthase. Bioorganic and medicinal chemistry - 2008.-V.16.- P.3283–3290.
[23] *L.R. Garzoni, A. Caldera, et al.* Selective in vitro effects of the farnesyl pirophosphate synthase ingibitor risedronate on Tripanosoma cruzi. Int.J. of Antimicr.Agents.-2004.- V.23. P.303–315.
[24] *V. Yardley, A. Khan, M.B.Martin, et al.* `In vivo activites of farnesyl pyrophosphate synthase inhibitors against Leishmania donovani and Toxoplasma gondii. Antimicrobial Agents and Chemotherapy. – 2002. -V.46. - P.929-931
[25] *M.B.Martin, J.S.Grimley, J.C.Lewis, et al.*`Bisphosphonates inhibit the growth of Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondii, and Plasmodium falciparum: a potential route to chemotherapy. Journal of Medicinal Chemistry. – 2001. – V.44. - P.909-916
[26] *Gauthaman K., Fong C.Y., Bongso A.* Statins, stem cells, and cancer. J. Cell Biochem. - 2009. -V.106. - P.975-983.
[27] *Taoufiq Z., Pino P., N'dilimabaka N., Arrouss I., Assi S., Soubrier F., Rebollo A., Mazier D.* Malar. J. 2011. -V. 10. - P. 1–9.
[28] Zhou Q., Liao J.K. Curr. Pharm. Des. 2009. - V. 15. - P. 3108–3115.
[29] *L.R.Garzoni, M.C.Waghabi, M.M.Baptista, et al.* Antiparasitic acyivity of risedronate in a murine model of acute Chagas'disease. International Journal of Antimicrobial Agents. – 2004 - vol.23. - P. -286-290.
[30] *Y.Ling, Z-H. Li, K.Miranda, E.Oldfield, ahd S.N.J.Moreno* The farnesyl-diphosphate synthase of Toxoplasma gondii is a bifunctoinal enzyme and a molecular target of bisphosphonates. The Journal of Biological Chemistry. – 2007. – V.282. - P.3804-3816
[31] *Gauthaman K., Fong C.Y., Bongso A.* J. Cell Biochem. - 2009. -V. 106. - P. 975–983.
[32] *Mo H., Elson C.E.* Exp. Biol. Med. - 2004. - V. 229. - P. 567–585
[33] *Chugh A., Ray A., Gupta J.B.* Prog. Lipid. Res. - 2003. - V. 42.- P. 37–50.
[34] *Hast M.A., Beese L.S* .Structure of protein geranylgeranyltransferase-1 from the human pathogen Candida albicans complexed with a lipid substrate// J.Biol.Chem. - 2008. - 283 (46). - P.3193-31940.
[35] *K. Barret-Bee, L. Newboult, P. Pinder.* Biochemical changes associated with the antifungal action of the triazole ICI 153,066 on Candida albicans and Trichophyton quinckeanum. FEMS Microbiology Letters.-1991.-V.79. - P.127-131.
[36] *N. Rodriguez, B.N. Bailey, M.B. Martin, E. Oldfield, J.A. Urbina, R. Docampo.* Radical cure of experimental cutaneous leismaniasis by the bisphosphonate pamidronate. Journal of Infectious Diseases.-2002. -V.186. - P.138-140.
[37] *M.Sealey-Cardona, S.Cammerer, S.Jones, et al.* Kinetic characterization of squalene synthase from Trypanosoma cruzi: selective inhibition by quinuclidine derivatives. Antimicfobial Agents and Chemotherapy.-2007. -V.51.- P.2123-2129.
[38] *S.O. Lorente, R. Gomez, C. Jimenez, et al.* Biphenylquinuclidines as inhibitors of squalene synthase and growth of parasitic protozoa. Bio org. Med. Chem. Lett.- 2005. – V. 13. – P. 3519-3529
[39] *Hatori H., Shibata T., Tsurumi Y., Nakanishi T., Katsuoka M., Ohtsu Y., Sakamoto K., Takase S., Ueda H., Hino M., Fujii T.* J. Antibiot., Tokyo. 2004. - V. 57. - P. 253–259.
[40] *A. Urbina.* Lipid biosynthesis pathways as chemotherapeutic targets in kinetoplastid parasites. Parasitology. - 1997. - V.114. - P. 91-99
[41] *C. W. Roberts, R. McLeod.* Fatty acid and sterol metabolism tripanosomatid parasitic protozoa. Mol.Biochem.Parasitology. - 2003. - V. - 126. -P.129-142
[42] *Ohcanda J., J.W. Lockman, K.Yokoyama, M.H. Gelb, S.L. Groft, H. Kendrick.,M.I. Harrel, J.E. Feagin, M.A.Braskovich, S.M.Sebti. et.al.* Peptidomimetic inhibitors of protein farnezyltransferase show potent antimalarial activity. Bio org. Med. Chem. Lett. - 2001. - V.11. - P.761-764.
[43] *Laezza C., Fiorentino L., Pisanti S., Gazzerro P., Caraglia M., Portella G., Vitale M., Bifulco M.* J. Mol. Med., Berl. - 2008. - V. 86. - P. 1341–1351.
[44] *Belter A., Skupinska M., Giel-Pietraszuk M., Grabarkiewicz T., Rychlewski L., Barciszewski J.* Biol. Chem. - 2011. - V. 392. - P. 1053–1075.

Фарнезилтрансфераза ингибиторлары. оларды заманауи қолдану аспектілері

С. Қожанова, А. Тарабаева, А. Нұрмұханбетова, Б. Бижігітова,
Е. Битанова, А. Шайкенова

Кілт сөздер: трансляциядан кейінгі модификация, ақуыздардың фарнезилденуі, фарнезилтрансфераза, фарнезилтрансфераза ингибиторлары.

Аннотация. Бұл мақала трансфераза ингибиторларының рөлін зерттеуге арналған. Ақуыздың посттрансляциялық өзгерісінің екіден астам түрі бар. Бірқатар авторлардың зерттеулеріне сүйенсек, ақуызды фарнезилдеу посттрансляциялық модификацияның жемісі және ол эукариотты жасушаның көбінде кездеседі. Фарнезилтрансфераза ингибиторлары ras ақуызы қызметін тежеп, қатерлі ісіктің өсу ингибиторын нығайтады. jd фарнезидтрансфераза ингибиторына көңіл бөлініп, яғни саңырауқұлақтық, паразиттік және басқа да ауруларға қарсы ем ретінде пайдалану үрдістеріне баса назар аударылған.

Поступила 15.01.2015 г.