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RATIONAL COMBINATION OF ONCOLYTIC VIRUSES AND RAPAMYCIN ANALOGUES IN CANCER THERAPY (LITERATURE REVIEW)

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Abstract. Malignant neoplasms are currently one of the main causes of death in most countries of the world, and therefore the issue of developing new drugs for the treatment of cancer is extremely acute. Among the possible promising ways to combat it, the use of drugs containing oncolytic viruses and drugs based on rapamycin attracts attention. Oncolytic viruses (viruses that mainly affect cancer cells) have a direct cytolytic effect, destroying a malignant tumor, and also stimulate the antitumor immunity of the body. Rapamycin is a potent inhibitor of the mTOR -mechanical (formerly mammalian) target of rapamycin signaling pathway. It has been proven that rapamycin and its analogues can be effectively used for the treatment and prevention of cancer, as well as affect the aging process. While each group of drugs individually has certain disadvantages, there is a possibility of leveling them when used together, which in a number of studies has shown a good therapeutic result. The synergistic effect of oncolytic viruses and rapamycin is primarily due to the ability of the latter to stimulate the replication of the virus in the affected cells, showing its own cytostatic effect in the unaffected ones. Replication stimulation can occur through Akt activation or through suppression of mTORC1-dependent interferon type I production. Also, the catalytic inhibitors mTORC1 and mTORC2 enhance the replication of the herpes simplex virus in cancer cells along the eIF4E/4EBP axis. The mechanisms of action of oncolytic viruses, rapamycin and their combinations on malignant cells are considered in this literature review.

Keywords: mTOR, rapamycin, rapalogs, oncolytic viruses, carcinogenesis, cancer, aging, antitumor immunity, T-VEC, myxoma virus

РАЦИОНАЛЬНОЕ СОЧЕТАНИЕ ОНКОЛИТИЧЕСКИХ ВИРУСОВ И АНАЛОГОВ РАПАМИЦИНА В ТЕРАПИИ РАКА (ЛИТЕРАТУРНЫЙ ОБЗОР)

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Резюме. Злокачественные новообразования являются в настоящее время одной из главных причин смертности в большинстве стран мира, в связи с чем крайне остро стоит вопрос разработки новых лекарственных

средств для лечения рака. Среди возможных перспективных направлений борьбы с ним обращает на себя внимание использование препаратов, содержащих онколитические вирусы, и препаратов на основе рапамицина. Онколитические вирусы, преимущественно поражающие раковые клетки, оказывают прямой цитолитический эффект, разрушая злокачественную опухоль, а также стимулируют противоопухолевый иммунитет организма. Рапамицин представляет собой мощный ингибитор сигнального пути mTOR — mechanistic (ранее mammalian) target of rapamycin. Доказано, что рапамицин и его аналоги могут эффективно применяться для лечения и профилактики рака, а также влиять на процессы старения. В то время как каждая группа препаратов в отдельности имеет определенные недостатки, существует возможность их нивелирования при совместном применении, которое в ряде исследований показало хороший терапевтический результат. Синергидное действие онколитических вирусов и рапамицина связано, прежде всего, со способностью последнего стимулировать репликацию вируса в пораженных им клетках, проявляя в непораженных свой собственный цитостатический эффект. Стимулирование репликации может происходить через активацию Akt или через подавление mTORC1-зависимой продукции интерферона I типа. Также каталитические ингибиторы mTORC1 и mTORC2 усиливают репликацию вируса простого герпеса в раковых клетках по оси eIF4E/4EBP. Механизмы действия онколитических вирусов, рапамицина и их комбинации на злокачественные клетки рассмотрены в данном литературном обзоре.

Ключевые слова: mTOR, рапамицин, рапалоги, онколитические вирусы, канцерогенез, рак, старение, противоопухолевый иммунитет, T-VEC, вирус миксомы

BACKGROUND

In recent years, scientific and technological progress, including in the medical area, has gone a long way forward. It has significantly improved the quality of life of people in most countries, as well as life expectancy. However, these achievements turned out to be dialectically connected with new difficulties. In particular, humanity has faced the aging of the population, and, accordingly, the so-called diseases of civilization. The most formidable pathology among them is undoubtedly malignant neoplasms, which are second only to cardiovascular diseases in terms of mortality. According to academician of the USSR Academy of Medical Sciences I.V. Davydovsky, “everyone will die of cancer, but not everyone will live to see it”, which implies, in fact, the inevitability of oncology development with a significant increase in life expectancy in the absence of other diseases. There is no doubt that the number of cancer patients will steadily increase in the coming years, and, therefore, the search for new ways of their treatment now is more relevant than ever.

Surgery, radiation and chemotherapy have proven themselves and have become the “gold standard” for the treatment of cancerous neoplasms. At the same time, even combined therapy is not always successful, especially in the late stages of oncology. In addition, there are a number of contraindications for it, often found in the elderly, and the consequences of such treatment are very severe and can lead to death. To the promising alternative directions of therapy of malignant neoplasms at the present time can be attributed virotherapy with the use of oncolytic viruses, as well as therapy using rapamycin and its analogs. Mechanisms of effect of oncolytic viruses, rapamycin and their combination on malignant cells and analysis of the possibility of their use both separately and in combination are analyzed in this literature review.

RAPAMYCIN

Rapamycin is a product of *Streptomyces hygroscopicus*, which were discovered in 1964 on Easter Island (Rapa Nui) by a Canadian expedition led by Suren Segal [1, 37].

Another common name for rapamycin is Sirolimus. It is a macrolipid in structure, which is currently produced using biosynthesis technology. In the course of trials, it became clear that rapamycin has unique immunosuppressive, antifungal, and antitumor properties that quickly found wide application in clinical practice, but further studies showed that the cause of these effects is much more fundamental than it seemed at the first glance [1, 37].

mTOR AND ITS FUNCTIONS

In 1994, a protein that is a direct target of rapamycin action was discovered — Mechanistic (formerly mammalian) target of rapamycin (abbreviated as mTOR). The mTOR protein is a serine/threonine protein kinase of the PI3K-kinase family, which forms the catalytic subunit of two different protein complexes: mTORC1 and mTORC2. These enzymes phosphorylate other proteins, thus forming an intracellular mTOR signaling network [1, 34].

It has been established that mTORC1 has a central role in controlling the balance between anabolism and catabolism in response to environmental conditions. Thus, it is activated when the cell receives sufficient energy, amino acids, oxygen, and growth factors (including steroid hormones). In contrast, stress and DNA damage inhibit mTORC1 activity [1, 37, 42]. In turn, mTORC1 itself stimulates mRNA translation, promotes lipid and nucleotide synthesis, shifts glucose metabolism from oxidative phosphorylation to glycolysis, and suppresses proteosome assembly, lysosome biogenesis, and autophagy. Thus, mTORC1 regulates the relationship between nutrition and cell growth [1, 37, 42].

mTORC2, in turn, is also activated by growth factors (including insulin) and stimulates cytoskeleton reorganization, cell migration, ion transport, regulates glucose metabolism and suppresses apoptosis. Thus, it is responsible for cell survival and tissue proliferation [1, 37, 42].

mTOR PATHWAY HYPERACTIVATION, AGING AND CANCEROGENESIS

Thus, it is obvious that mTOR regulates the processes of life activity of the cell and the whole organism at the deepest level. It is noteworthy that this signaling pathway is peculiar to almost all eukaryotes. In the course of experiments it was found that inhibition of the mTOR pathway by rapamycin leads to a marked increase in the life span of all model organisms and human cell cultures. A similar effect is also produced by limiting the amount of food without malnutrition, which led researchers to the idea that these phenomena are interrelated [4, 7, 37]. It is believed that in the wild, where animals face the constant need to search for food and periods of starvation, mTOR activity has a wave-like character. Modern humans and laboratory animals are deprived of this stress, resulting in stable mTOR hyperactivation in their organisms [6, 7, 42]. It was shown, for example, that short-term hyperactivation of mTORC1 leads to muscle hypertrophy due to cell growth, but further hyperfunction of this metabolic regulator leads to muscle atrophy and rapid death, presumably due to suppression of autophagy and, consequently, disruption of muscle tissue remodeling processes. This is one of the possible explanations for the influence of mTOR hyperfunction on the aging process [7, 42].

Another theory is “quasi-programmed aging”. It states that aging is a growth program that has not been turned off in time. Thus, mTOR, as it was said above, is responsible for cell growth, but having completed its program, it continues its action, which leads to the so-called cellular hyperfunction. Such enhanced work, as a rule, is destructive for cells, and at the organismal level it is manifested as aging [1, 11].

It has been shown that hyperactivated mTOR through a number of intermediates leads to such phenomena as excessive stimulation of protein biosynthesis in the cell, suppression of autophagy and proteosome assembly, which can lead to oxidative and proteotoxic stress, and, as a consequence, to cellular aging. This in turn leads to Alzheimer’s disease, muscle atrophy, ulcers and gastritis, anemia, joint disease and hair loss, senile hyperpigmentation of the skin. The role of mTOR hyperactivation in the pathogenesis of type 2 diabetes mellitus, obesity, atherosclerosis, etc. is great. [1, 3, 7, 38, 42].

It is obvious that if mTOR hyperfunction leads to such a large number of diseases associated with aging, it leads to aging itself. In addition, it has been found that mTOR activity in elderly people is indeed higher than in young people, which confirms the hypothesis [1, 7].

Among other things, mTOR hyperactivation can stimulate cancerogenesis, which should be discussed in more detail.

It has been found that mTORC1 activates the enzyme S6K (ribosomal protein kinase), which in turn phosphorylates and activates several substrates that promote mRNA translation, including eIF4B (a positive regulator of 5’cap complex binding). Also, S6K enhances the translation efficiency of spliced mRNA (EJK) through its interaction with SKAR (a component of exon-junction complexes) [27]. In addition, S6K suppresses the action of programmed cell death protein (PDCD4 — eIF4B inhibitor) [14]. On top of that, mTORC1 itself inhibits the action of the 4EBP complex (eukaryotic translation initiation factor eIF4E binding protein) [19]. All of the above induces protein synthesis in the cell. In addition, it was found that besides increasing the overall level of translation, mTORC1 particularly stimulates the translation of mRNAs rich in pyrimidine nitrogenous bases, which encode translational and ribosomal proteins, as well as metabolic genes [41].

Excessive accumulation of protein in the cell leads to deterioration of its stacking and also increases the risk of various pathological modifications (carbonylation, glycation and glycoxidation, cross-linking of proteins with fats, with DNA and among themselves). All this leads to the so-called proteotoxic stress and disruption of normal cell function [1, 7].

In addition, enhanced translation requires additional energy expenditure. In an effort to compensate for its deficiency, mitochondria quickly fail and release free radicals (reactive oxygen and nitrogen species) into the cell cytoplasm. Free radicals increase the toxicity of iron and copper ions, and oxidative stress occurs, leading to damage to DNA, proteins, and membranes [1, 7].

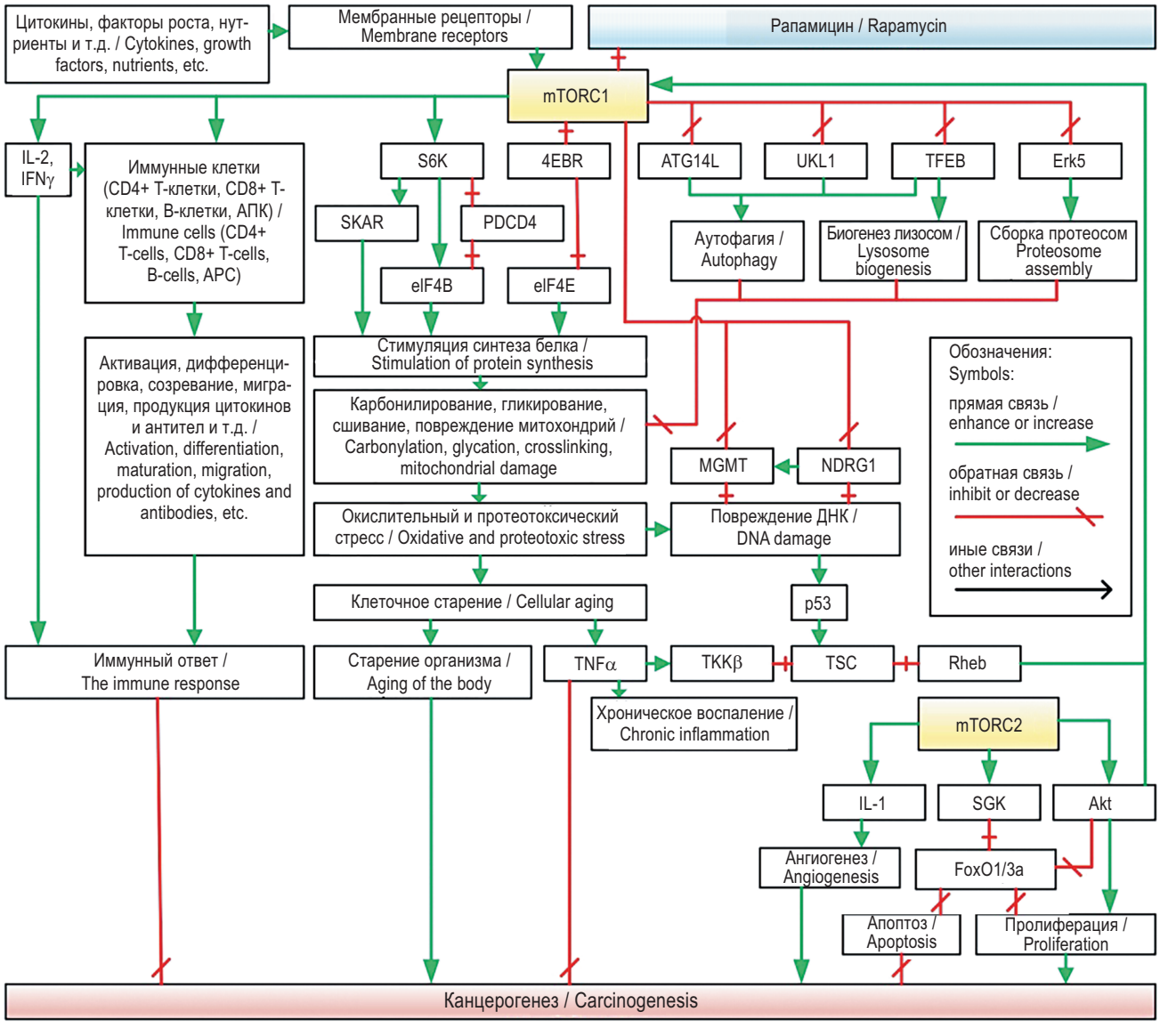

Fig. 1. **The connection of the mTOR signaling pathway with the process of carcinogenesis (compiled by Baranov I.A.). IL-2 — interleukin-2; IFNγ — interferon gamma; APK — antigen-presenting cells; S6K — ribosomal S6 Kinase; 4EBP — eukaryotic Translation Initiation Factor 4E Binding Protein; SKAR — a component of exon-junction complexes; PDCD4 — programmed cell death protein 4; eIF4B — eukaryotic translation initiation factor 4B; eIF4E — eukaryotic translation initiation factor 4E; ATG14L — autophagy related 14; ULK1 — unc-51 like autophagy activating kinase 1; TFEB — Transcription factor EB; ERK5 — extracellular signal-regulated kinase 5; MGMT — O6-alkylguanine DNA alkyltransferase; NDRG1 — N-myc downstream regulated 1; p53 — transformation-related protein 53; TNFα — tumor necrosis factor alpha; TSC — tuberous sclerosis complex; Rheb — Ras homolog enriched in brain; IL-1 — interleukin-1; SGK — serum/glucocorticoid regulated kinase; Akt — RAC-alpha serine/threonine-protein kinase; FoxO1/3a — forkhead box protein O1/3a**

Рис. 1. **Связь сигнального пути mTOR с процессом канцерогенеза (составлено Барановым И.А.). IL-2 — интерлейкин-2; IFNγ — интерферон гамма; АПК — антигенпредставляющие клетки; S6K — рибосомальная S6-киназа; 4EBP — белок, связывающий фактор инициации трансляции эукариот 4E; SKAR — компонент экзон-переходных комплексов; PDCD4 — белок программируемой клеточной гибели 4; eIF4B — фактор инициации трансляции эукариот 4B; eIF4E — фактор инициации трансляции эукариот 4E; ATG14L — связанный с аутофагией комплекс 14; ULK1 — unc-51-подобная киназа, активирующая аутофагию 1; TFEB — фактор транскрипции EB; ERK5 — киназа, регулируемая внеклеточным сигналом 5; MGMT — O6-алкилгуаниновая ДНК-алкилтрансфераза; NDRG1 — N-myc, регулируемый ниже по течению 1; p53 — связанный с трансформацией белок 53; TNFα — фактор некроза опухоли альфа; TSC — комплекс туберозного склероза; Rheb — гомолог Ras, обогащенный в мозге; IL-1 — интерлейкин-1; SGK — киназа, регулируемая сывороткой/глюкокортикоидами; Akt — RAC-альфа серин/треонин-протеинкиназа; FoxO1/3a — раздвоенный блок O1/3a**

Normally, damaged molecules and organoids should be destroyed by proteosomes and autophagy. However, mTORC1 blocks these processes. It suppresses the action of such important activators of autophagy as ULK1 (kinase) and ATG14L complex [24], inhibits the action of the transcription factor of lysosomal hydrolases and membrane proteins (TFEB) [29], and also reduces the activity of Erk5 complex, which leads to a decrease in the number of chaperone proteins providing protein folding and disrupts proteosome assembly [35]. This only aggravates proteotoxic and oxidative stresses, which in turn lead to damage of DNA molecules and, consequently, to malignant cell degeneration. Suppression of MGMT methyltransferase and NDRG1 regulatory protein also contributes to the accumulation of genomic mistakes [13].

In addition, hyperactivated mTORC2 complex contributes to carcinogenesis. It activates SGK (kinase), an inhibitor of FoxO1/3a substrate, which prevents cell apoptosis [16]. Along with this, mTORC2 activates Akt (a key effector of insulin signaling), which further inhibits FoxO1/3a substrate and also stimulates proliferation [36]. In addition, mTORC2 promotes the secretion of interleukin-1 (IL-1), which activates angiogenesis in growing tumor [25].

TNFα (tumor necrosis factor α) can cause rapid hemorrhagic necrosis of a number of tumors. However, it can also be released in large quantities by aging cells and activate mTORC1 through inhibition of TSC (tuberous sclerosis complex — the main inhibitor of mTORC1), forming a vicious circle. This leads to chronic inflammation in the elderly, which itself can cause some diseases [1, 5, 37].

Interestingly, mutations associated with TSC deficiency lead to the development of a polysystemic tumor disease, tuberous sclerosis [2]. It is also necessary to mention the role of the now widely known p53 protein, which activates TSC and thereby suppresses tumor growth [21].

In addition, mTOR is now believed to be a central regulator of immune responses. In particular, mTOR appears to function as a central node in the signaling cascade that directs the integration of various environmental factors into the immune microenvironment [33, 37].

Thus, antigen recognition by T-cell receptor, cytokines, growth factors, nutrients and costimulation lead to mTOR activation in CD4+ T-cells via membrane receptors, which, in turn, leads to their activation, differentiation, proliferation, and acquisition of periferic tolerance. Similar processes in CD8+ T cells also lead to their activation, differentiation, migration, and memory formation [33, 37].

Some other factors of extracellular signaling also mediated by mTOR cause activation, maturation, proliferation of antigen-presenting cells, their production of cytokines and costimulatory molecules [33, 37].

In B-lymphocytes, it leads to their activation, maturation, differentiation, antibody production and survival [33, 37].

In addition, mTORC1 stimulates T-cell synthesis of interleukin-2 (IL-2) and tumor necrosis factor-γ (TNFγ), which also plays an important role in the regulation of the immune response [28].

Table 1

mTOR inhibitors approved by the Food and Drug Administration (FDA) for the treatment of human cancer (USA) [32]

Таблица 1

Ингибиторы mTOR, одобренные Управлением по контролю за продуктами питания и лекарствами (FDA) для лечения рака человека (США) [32]

Препарат (торговое название) / Drug (trade name)	Показания / Indications	Дата утверждения / Approval date
Сиролимус (Рапамун) / Sirolimus (Rapamune)	Лимфангиолейомиоматоз / Lymphangioleiomyomatosis	Август 2000 г. / August 2000
Темсиролимус (Торизел) / Temsirolimus (Torisel)	Почечно-клеточный рак / Renal cell carcinoma	Май 2007 г. / May 2007
Эверолимус (Афинитор)/ / Everolimus (Afinitor)	• Почечно-клеточный рак / Renal cell carcinoma. • Прогрессирующий рак молочной железы HR+ / Advanced HR+ breast cancer. • Прогрессирующие нейроэндокринные опухоли поджелудочной железы, желудочно-кишечного тракта или легких / Progressive neuroendocrine tumors of pancreatic origin, of gastrointestinal or lung origin. • Ангиомиолипома почки / Angiomyolipoma of the kidney. • Субэпендимальная гигантоклеточная астроцитома, ассоциированная с комплексом туберозного склероза (TSC) / Subependymal giant cell astrocytoma associated with tuberous sclerosis complex (TSC)	Март 2009 г., август 2012 г., февраль 2016 г. / March 2009 August 2012, February 2016

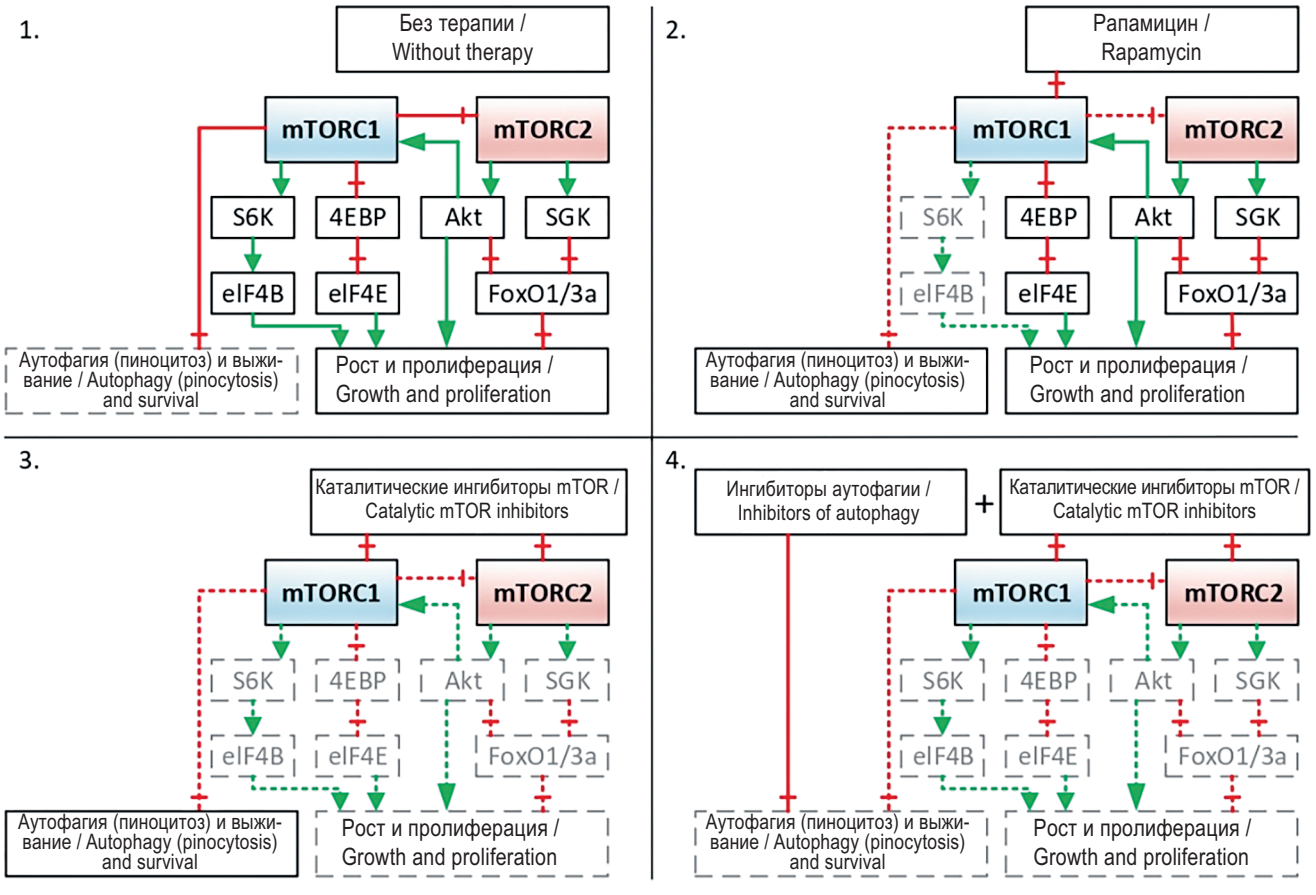

Fig. 2. Different effects of rapamycin, mTOR catalytic inhibitors and their combination with autophagy inhibitors on cancer cells. S6K — Ribosomal S6 Kinase; 4EBP — Eukaryotic Translation Initiation Factor 4E Binding Protein; eIF4B — eukaryotic translation initiation factor 4B; eIF4E — eukaryotic translation initiation factor 4E; Akt — RAC-alpha serine/threonine-protein kinase; SGK – serum/glucocorticoid regulated kinase; FoxO1/3a — forkhead box O1/3a

Рис. 2. Различное влияние на раковые клетки рапамицина, каталитических ингибиторов mTOR и их сочетания с ингибиторами аутофагии. S6K — рибосомальная S6-киназа; 4EBP — белок, связывающий фактор инициации трансляции эукариот 4E; eIF4B — фактор инициации трансляции эукариот 4B; eIF4E — фактор инициации трансляции эукариот 4E; Akt — RAC-альфа серин/треонин-протеинкиназа; SGK — киназа, регулируемая сывороткой/глюкокортикоидами; FoxO1/3a — раздвоенный блок O1/3a

This is what allowed rapamycin to be used as an immunosuppressor. All the above-mentioned interrelationships are clearly presented in the form of a summarizing scheme (Fig. 1).

mTOR INHIBITORS IN ANTI-TUMOR THERAPY

Thus, it is obvious that mTOR has a dual effect on the process of carcinogenesis, activating it on the one hand and inhibiting it on the other hand. This is what caused difficulties in the development of rapamycin-based antitumor therapy. First of all, it concerns the selection of adequate doses of the drug. As mentioned above, mTOR is one of the most important regulators of the immune response. Rapamycin, used as an immunosuppressant in organ transplantation, also suppresses antitumor immunity and may stimulate carcinogenesis [31, 33]. Interestingly, an imbalance of the human microbiota can also suppress antitumor immunity [8].

However, this does not prevent the use of rapamycin and its analogs in the therapy of malignant neoplasms due to careful selection of effective doses based on the ratio of harm to benefit for the patient in each specific case, which, in turn, becomes possible due to the dose-dependent effect of rapamycin. First, different doses of rapamycin are required to inhibit mTOR in different cell lines; second, different doses of rapamycin inhibit phosphorylation of different mTOR substrates; and third, there is different sensitivity of two complexes (mTORC1 and mTORC2) to rapamycin [31]. Interestingly, the enigmatic dosage properties of rapamycin may be explained largely by the competition between rapamycin and phosphatidic acid for mTOR. Rapamycin and phosphatidic acid have opposite effects on mTOR, with

rapamycin destabilizing and phosphatidic acid stabilizing both mTOR complexes [31].

Rapamycin-based drugs have undergone a significant evolution during the development of antitumor therapy [32]. Rapamycin and its analogs (rapalogs) are first-generation mTOR inhibitors that selectively inhibit mTORC1 activity by binding to FKBP-12 and forming a ternary complex with mTOR. Rapamycin is an allosteric inhibitor of mTOR, and it suppresses some functions of mTORC1, such as phosphorylation of protein kinase S6K1. The clinical use of rapamycin is limited due to its poor water solubility and insufficient stability; to overcome this drawback, pharmaceutical companies have developed rapamycin analogs with improved pharmacokinetic properties [32, 37].

Rapalogs differ in their chemical properties in terms of solubility and metabolism. For example, temsirolimus, a prodrug of rapamycin, and ridaforolimus are water soluble and can be administered intravenously, whereas rapamycin and everolimus have low solubility and are therefore only suitable for oral administration. Rapalogs have undergone clinical trials in various malignancies and have already been approved by the FDA for the treatment of certain types of cancer [32, 37].

However, in a number of cases, first-generation mTOR inhibitors showed insufficient efficacy and exhibited more cytostatic than cytotoxic effects [32, 37]. There are a number of explanations for that fact. Firstly, rapalogs block mTORC1 to a greater extent and hardly block mTORC2. Secondly, although rapamycin inhibits S6K, it does not completely inhibit 4EBP phosphorylation, making it ineffective in blocking cap-dependent translation in most cell types. In addition, suppression of mTORC1 activates autophagy but also activates both lysosome biogenesis and micropinocytosis, which may promote cancer cell survival in poorly vascularized, nutrient-poor tumor tissue (e.g., pancreatic tumor), as depicted in Figure 2 (2) [32, 37].

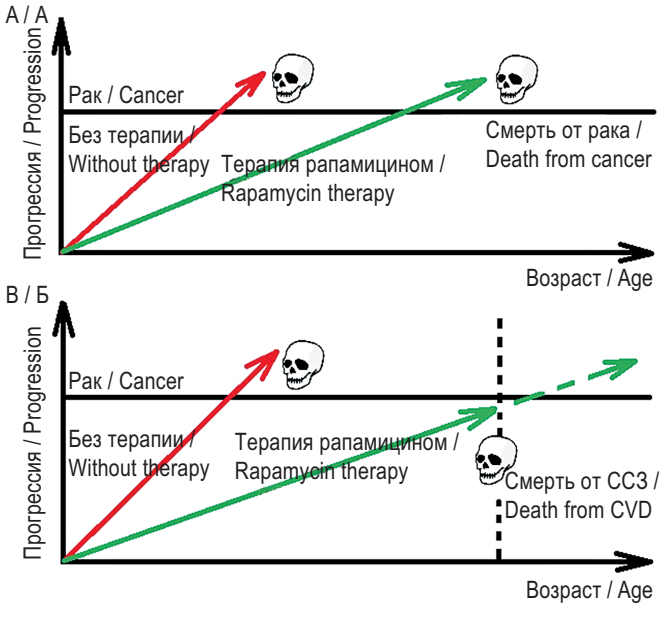

Fig. 3. Hypothetical scheme of preventive therapy with rapamycin. CVD — cardiovascular diseases

Рис. 3. Гипотетическая схема профилактической терапии рапамицином. ССЗ — сердечно-сосудистые заболевания)

The second generation of mTOR inhibitors is a series of ATP-competitive inhibitors (TORKIs), which are low-molecular-weight ATP analogs that compete with ATP to occupy the active site of mTOR kinase and block both mTORC1 and mTORC2. They are also called catalytic inhibitors. They have not yet been tested on a large scale and are not approved for cancer treatment. In addition, the problem of excessive activation of autophagy and pinocytosis (3) remains. In this situation, the combined use of mTOR catalytic inhibitors and autophagy inhibitors (4) seems promising (Fig. 2) [32, 37]. In addition, third-generation mTOR inhibitors, which are conjugated rapamycin and mTOR catalytic inhibitors, have been developed. The new compounds are called Rapalink. They exhibit greater efficacy and stability due to two points of application and are also under trial [32].

In addition, it should be noted that mTOR inhibitors are particularly effective in tumors characterized by mutations in the *mTOR gene (OMIM 601231*) accompanied by its increased expression. Detection of these mutations requires genetic research [17].

Another promising direction is cancer prevention with the help of rapalogs. As mentioned above, cancer is an age-related disease, and, figuratively speaking, by slowing down aging, rapamycin can delay the development of cancer as well. Thus, death may also occur from other causes, such as cardiovascular disease (Fig. 3). It is noted that in this case rapamycin is more effective at early stages of the disease development (at the precancer stage) [10]. Prophylactic treatment with rapamycin has been proposed for ex-smokers [18]. Many patients around the world are already taking off-label rapalogs, but rapamycin will never become an “old age pill”, because it is impossible to predict all the side effects of switching off such an important link in the regulation of metabolism as mTOR [1, 10, 11].

ONCOLYTIC VIRUSES

Another, no less promising area in the fight against cancer is oncolytic viruses, which predominantly affect malignant tumor cells but relatively neglect normal cells [23].

The idea of using viruses to fight cancer was first born at the beginning of the last century, but active research began only in the 1960s and continues to date [23].

The antitumor effect of viruses is believed to be realized through two main mechanisms [30]:

1) direct cytotoxic action of the virus;
2) stimulation of antitumor immunity of the organism.

Currently, a large number of different viruses are proposed and used as oncolytic [23], including:

- DNA viruses: adenovirus, cowpox virus, herpes virus, parvovirus H1;
- RNA viruses: reovirus, coxsackie virus, senecavirus (Seneca Valley virus), poliovirus, measles virus, Newcastle disease virus, vesicular stomatitis virus, etc.

Some of them are more or less promising for clinical application. In general, a number of requirements for oncolytic viruses can be put forward [22, 30]:

1) pronounced oncotropism of viruses;
2) a wide spectrum of target cells;
3) rapid spread of the virus in tumors;
4) efficient reaching of metastatic foci by the virus;
5) stability of the genome;
6) sufficient genome volume for trans-gene insertion;
7) high immunogenicity;
8) availability of antiviral drugs in case of unfavorable course, etc.

Why do a number of viruses exhibit increased tropism to tumor cells? There are also a number of explanations for this.

1) The antiviral defense system may be disrupted in tumor cells. For example, protein kinase R (PKR) is a critical factor that helps in eliminating intracellular viral infections. PKR may be absent in some cancer cells, which promotes increased viral replication in them [40].

2) Viruses can exploit the immune evasion ability of cancer cells. For example, key signaling pathways can be suppressed in cancer cells, which impairs recognition of viral particles by toll-like receptors (TLRs). Proapoptotic mechanisms are also suppressed in tumor cells [23].

3) In addition, tumor cells may express an excessive number of receptors on their surface through which viruses can enter. For example, herpes simplex virus 1 (HPV-1) utilizes herpes virus entry mediator (HVEM) and some nectins to enter cells. These surface receptors are overexpressed on some cancer cells, including melanoma cells [44].

Three generations of oncolytic viruses are distinguished [15]:

1) native (genetically unmodified) viruses;
2) modified viruses with increased “oncotropism”;

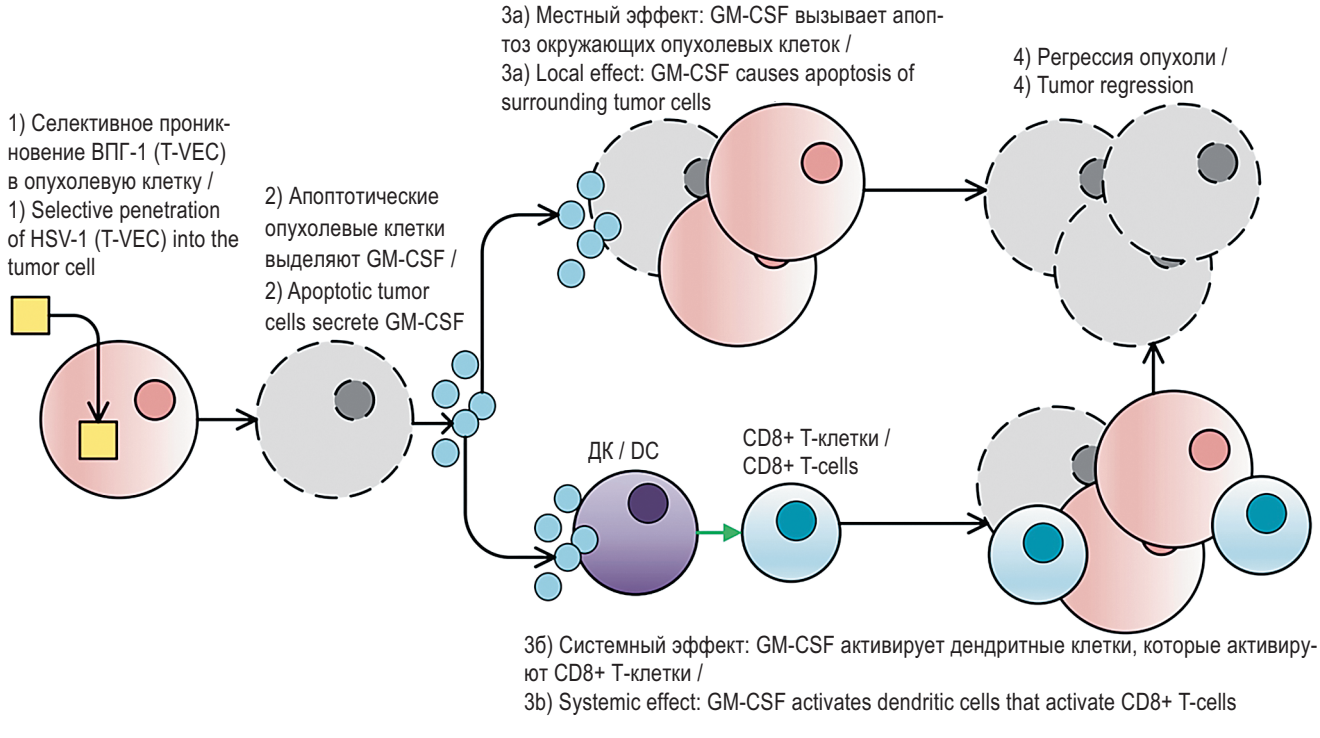

Fig. 4. Mechanism of action of T-VEC. HSV-1 — herpes simplex virus 1; T-VEC — talimogene laherparepvec; GM-CSF — granulocyte–macrophage colony stimulating factor; DC — dendritic cells

Рис. 4. Механизм действия препарата T-VEC. ВПГ-1 — вирус простого герпеса 1; T-VEC — талимоген лахерпарепвек; GM-CSF — гранулоцитарно-макрофагальный колониестимулирующий фактор; ДК — дендритные клетки

3) modified viruses which carry transgenes encoding cytokines or enzymes (a transgene is a DNA fragment transferred by genetic engineering manipulations into the genome of an organism in order to modify it).

It should be noted, that representatives of the first generation have not been practically used in clinical practice and are rather of research interest [15].

A representative of the third generation is, for example, a modified Herpes Simplex Virus — with the *GM-CSF* gene introduced into it, as well as reduced neurotoxicity (drug T-VEC) [30]. The *GM-CSF* gene encodes a protein of the same name — granulocyte-macrophage-colony stimulating factor.

That drug based on oncolytic viruses was first approved for melanoma treatment in the European Union, the USA and Australia. It is proposed to use it for other types of tumors as well. Let us briefly consider its mechanism of action (Fig. 4) [22].

The first step is the administration of the drug and selective penetration of the virus into the tumor cell (1) [22]. Then the affected cell starts to synthesize *GM-CSF* and release it during apoptosis (2) [22]. *GM-CSF* exhibits its action at two levels. At the local level, it induces apoptosis of surrounding tumor cells (3a) [22]. The systemic effect is the activation of CD8+ T cells by stimulating dendritic cells, which enhances antitumor immunity with long-term immunological memory (3b) [22]. All this leads to apoptosis and lysis of tumor cells and, ultimately, to regression of the tumor itself (4) [22].

However, the development of drugs based on individual oncolytic viruses has revealed a number of difficulties, including the toxic effect of viruses on the macroorganism, low bioavailability, difficulties in monitoring transgenes carried, the need for a special design of clinical trials, biosafety problems associated with virus persistence, etc. This explains the fact that over 60 years of research, only a few drugs have been approved for clinical use [22, 23].

Thus, it becomes obvious that both oncolytic virus-based and rapamycin-based drugs are extremely promising in the treatment of malignant neoplasms, but both have a number of drawbacks that limit their efficacy and clinical application. In this regard, proposals are made for their combined use, the rationality of which will be discussed further.

RATIONAL COMBINATION OF ONCOLYTIC VIRUSES AND RAPAMYCIN ANALOGS

In 2005, researchers found that everolimus increased the efficacy of oncolytic viruses in colorectal cancer therapy, but exactly how it increased treatment efficacy was not entirely clear [20]. In 2007, rapamycin was found to increase myxoma virus tropism to human cancer cells and thus enhance oncolytic virus therapy [26, 39].

The study showed that the wild strain of myxoma virus carries the *M-T5* gene encoding a protein of the same name that activates Akt (kinase), which in turn suppresses apoptosis and stimulates cell proliferation, promoting virus replication. A close analog of *M-T5*, the PIKE-A protein, which also activates Akt, was found in humans [26, 39, 42]. PIKE-A, and consequently Akt, is known to have

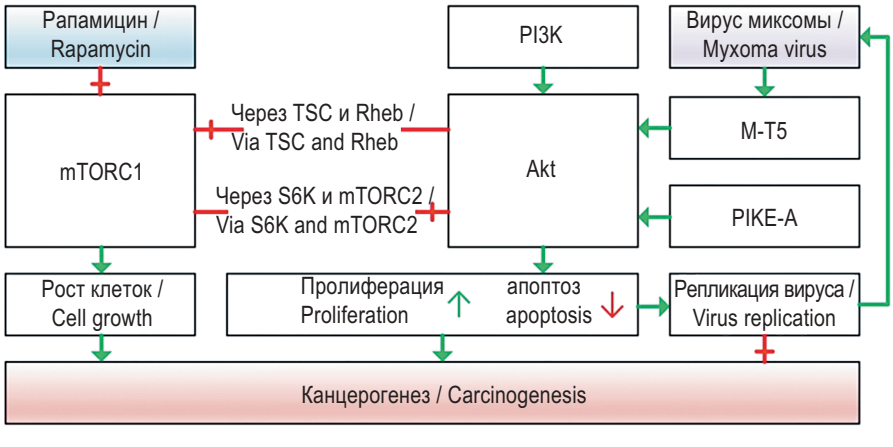

Fig. 5. **Scheme of combined use of rapamycin and oncolytic myxoma virus (compiled by Baranov I.A.). TSC — tuberous sclerosis complex; Rheb — Ras homolog enriched in brain; S6K — Ribosomal S6 kinase; Akt — RAC-alpha serine/threonine-protein kinase; PI3K — phosphoinositide 3-kinases; M-T5 — ankyrin repeat M-T5; PIKE-A — PI3-kinase enhancer activating AKT**

Рис. 5. **Схема сочетанного применения рапамицина и онколитического вируса миксомы (составлено Барановым И.А.). TSC — комплекс туберозного склероза; Rheb — гомолог Ras, обогащенный в мозге; S6K — рибосомальная S6-киназа; Akt — RAC-альфа серин/треонин-протеинкиназа; PI3K — фосфоинозитид-3-киназы; M-T5 — анкириновый повтор M-T5; PIKE-A — PI3-киназный энхансер, активирующий AKT**

increased activity in a number of malignant tumors. Myxoma virus strains devoid of the *M-T5* gene have been artificially produced. Such strains have increased oncotropism and practically do not affect healthy cells. At the same time, there are tumors with low Akt activity, against which these strains are ineffective [29, 39, 43].

It turned out that mTORC1 and Akt are in a complex antagonistic relationship mediated through a number of intermediates. Thus, rapamycin, inhibiting mTORC1, stimulates Akt activity according to the "principle of negative feedback" [12]. This explains the fact of increased efficacy of myxoma virus therapy in combination with rapamycin and is also consistent with the above-mentioned fact that rapamycin monotherapy has a cytostatic effect on tumors. Thus, rapamycin and myxoma virus is a very promising synergistic combination. Rapamycin stimulates replication of the virus in cells affected by it, while in unaffected cells it shows its usual effect by inhibiting cell growth [26, 39]. This relationship is presented in the form of a scheme (Fig. 5).

Later, this combination was also applied to smallpox virus, HSV, vesicular stomatitis virus, and ad-enovirus [46].

In addition, rapamycin can stimulate the replication of oncolytic viruses by disrupting mTORC1-dependent production of type I interferon (IFN), which has antiviral properties [9]. At the same time, we should not forget that type I IFN also has antitumor effects, which makes the selection of rational doses of drugs extremely important. It has also been shown that catalytic inhibitors of mTORC1 and mTORC2 (but not the rapamycin) enhance HSV replication in cancer cells along the eIF4E/4EBP axis [45].

It should be noted that combinations of oncolytic viruses with rapamycin have already been tested. It has proven itself in a number of studies both in vitro (on human tumor cell cultures) [26, 28] and *in vivo* (on laboratory mice) [26].

However, it is necessary to keep in mind the immunosuppressive function of rapamycin. Inadequate doses of rapamycin may not only level the antitumor immunity enhanced by oncolytic viruses, but also make the macroorganism vulnerable to the viruses themselves [1]. In addition, a number of pathways have been shown through which the antiviral effect of rapamycin can be realized. Among them are activation of natural killer cells, stimulation of interferon-α production, etc. [34]. This should be taken into account during the combination of rapamycin with oncolytic viruses and prevent them from antagonizing each other.

CONCLUSION

Both oncolytic viruses and rapamycin were discovered more than half a century ago, but their clinical use is currently limited. This is due to a number of their side effects, the difficulty of drug dosing, the need for special clinical trial designs, etc. At the same time, the possibility of overcoming the disadvantages and improving the effectiveness of treatment may lie in the combined use of drugs from these two groups. Such combined regimens have already been tested and have proven themselves in a number of studies. The mechanism of synergistic effect of combined therapy is primarily due to the ability of rapamycin to increase the tropism of a number of oncolytic viruses to tumor cells and stimulate their replication, disrupting mTORC1-dependent production of type I IFN. In addition, catalytic inhibitors of mTORC1 and mTORC2 enhance herpes simplex virus replication in cancer cells via the eIF4E/4EBP axis. Further research should be directed toward the selection of specific combinations and effective dosages of drugs based on rapamycin or other inhibitors of mTOR and oncolytic viruses, which may help mankind to take another step in the direction of the final victory over cancer.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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REFERENCES

1. Baranov I.A., Gladin D.P., Kozlova N.S. Vzaimosvyaz' giperaktivacii signal'nogo puti mTOR, processov stareniya i patogeneza COVID-19 (obzor literatury). [Relationship of hyperactivation of the mTOR signaling pathway, aging processes and COVID-19 pathogenesis (literature review)]. Rossijskie biomedicinskie issledovaniya. 2023; 8(2): 64–77. (in Russian).

2. Baranov I.A., Melieva Z.Yu., Melieva F.Yu. Patologicheskaya anatomiya tuberoznogo skleroza. [Pathological anatomy of tuberous sclerosis]. Internauka. 2022; 38-1(261): 15–20. (in Russian).
3. Borodkina A.V., Deryabin P.I., Gryukova A.A., Nikol`skij N.N. "Social`naya zhizn`" stareyushhix kletok: chto takoe SASP i zachem ego izuchat`? ["Social life" of senescent cells: what is SASP and why study it?] Acta Naturae (russkoyazy`chnaya versiya). 2018; 1(36). (in Russian).
4. Davydov M.I., Gancev Sh.H., Vel'sher L.Z. i dr. Onkologiya. [Oncology]. Moskva: GEOTAR-Media Publ., 2010. (in Russian).
5. Dement'eva E.A., Gurina O.P. Immunologicheskie izmeneniya, soprovozhdayushchie razvitie eksperimental'nogo neoplasticheskogo processa. [Immunological changes accompanying the development of the experimental neoplastic process]. Pediatr. 2015; 6(2): 96–108. DOI: 10.17816/PED6296-108. (in Russian).
6. Imyanitov E.N., Hanson K.P. Molekulyarnaya onkologiya: klinicheskie aspekty. [Molecular oncology: clinical aspects]. Sankt-Peterburg: Izdatel'skij dom SPbMAPO; 2007. (in Russian).
7. Moskalev A.A. 120 let zhizni — tol`ko nachalo. Kak pobedit` starenie? [120 years of life is just the beginning. How to beat aging? 2nd edition]. 2-e izdanie. Moskva: E`ksmo Publ.; 2018. (in Russian).
8. Selezneva A.A., Kozlova N.S. Mikrobiota i rak: soyuzniki ili vragi? [Microbiota and cancer: allies or enemies?]. Zdorov'e — osnova chelovecheskogo potenciala: problemy i puti ih resheniya. 2022; 17(2): 774–81. (in Russian).
9. Alain T., Lun X., Martineau Y. et al. Vesicular stomatitis virus oncolysis is potentiated by impairing mTORC1-dependent type I IFN production. Proc Natl Acad Sci USA. 2010; 107(4): 1576–81. DOI: 10.1073/pnas.0912344107. Epub 2010 Jan 4.
10. Blagosklonny M.V. Cancer prevention with rapamycin. Oncotarget. 2023; 14: 342–50. DOI: 10.18632/oncotarget.28410.
11. Blagosklonny M.V. From causes of aging to death from COVID-19. Aging (Albany NY). 2020; 12(11): 10004–21. DOI: 10.18632/aging.103493. Epub 2020 Jun 12.
12. Chen X.G., Liu F., Song X.F. et al. Rapamycin regulates Akt and ERK phosphorylation through mTORC1 and mTORC2 signaling pathways. Mol Carcinog. 2010; 49(6): 603–10. DOI: 10.1002/mc.20628.
13. Dominick G., Bowman J., Li X. et al. mTOR regulates the expression of DNA damage response enzymes in long-lived Snell dwarf, GHRKO, and PAPPA-KO mice. Aging Cell. 2017; 16(1): 52–60. DOI: 10.1111/acel.12525. Epub 2016 Sep 13.
14. Dorrello N.V., Peschiaroli A., Guardavaccaro D. et al. S6K1- and betaTRCP-mediated degradation of PDCD4 promotes protein translation and cell growth. Science. 2006; 314(5798): 467–71. DOI: 10.1126/science.1130276.
15. Fukuhara H., Ino Y., Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. Cancer Sci. 2016; 107(10): 1373–9. DOI: 10.1111/cas.13027. Epub 2016 Sep 9.
16. García-Martínez J.M., Alessi D.R. mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). Biochem J. 2008; 416(3): 375–85. DOI: 10.1042/BJ20081668.
17. Grabiner B.C., Nardi V., Birsoy K. et al. A diverse array of cancer-associated MTOR mutations are hyperactivating and can predict rapamycin sensitivity. Cancer Discov. 2014; 4(5): 554–63. DOI: 10.1158/2159-8290.CD-13-0929. Epub 2014 Mar 14.
18. Granville C.A., Warfel N., Tsurutani J. et al. Identification of a highly effective rapamycin schedule that markedly reduces the size, multiplicity, and phenotypic progression of tobacco carcinogen-induced murine lung tumors. Clin Cancer Res. 2007; 13(7): 2281–9. DOI: 10.1158/1078-0432.CCR-06-2570.
19. Holz M.K., Ballif B.A., Gygi S.P., Blenis J. mTOR and S6K1 mediate assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. Cell. 2005; 123(4): 569–80. DOI: 10.1016/j.cell.2005.10.024.
20. Homicsko K., Lukashev A., Iggo R.D. RAD001 (everolimus) improves the efficacy of replicating adenoviruses that target colon cancer. Cancer Res. 2005; 65(15): 6882–90. DOI: 10.1158/0008-5472.CAN-05-0309.
21. Huang S. mTOR Signaling in Metabolism and Cancer. Cells. 2020; 9(10): 2278. DOI: 10.3390/cells9102278.
22. Javanbakht M., Tahmasebzadeh S., Cegolon L. et al. Oncolytic viruses: A novel treatment strategy for breast cancer. Genes Dis. 2021; 10(2): 430–46. DOI: 10.1016/j.gendis.2021.11.011.
23. Kaufman H.L., Kohlhapp F.J., Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat Rev Drug Discov. 2015; 14(9): 642–62. DOI: 10.1038/nrd4663. Erratum in: Nat Rev Drug Discov. 2016; 15(9): 660.
24. Kim J., Kundu M., Viollet B., Guan K.L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol. 2011; 13(2): 132–41. DOI: 10.1038/ncb2152. Epub 2011 Jan 23.
25. Laberge R.M., Sun Y., Orjalo A.V. et al. MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. Nat Cell Biol. 2015; 17(8): 1049–61. DOI: 10.1038/ncb3195. Epub 2015 Jul 6. Erratum in: Nat Cell Biol. 2021; 23(5): 564–5.
26. Lun X.Q., Zhou H., Alain T. et al. Targeting human medulloblastoma: oncolytic virotherapy with myxoma virus is enhanced by rapamycin. Cancer Res. 2007; 67(18): 8818–27. DOI: 10.1158/0008-5472.CAN-07-1214.
27. Ma X.M., Yoon S.O., Richardson C.J. et al. SKAR links pre-mRNA splicing to mTOR/S6K1-mediated enhanced translation efficiency of spliced mRNAs. Cell. 2008; 133(2): 303–13. DOI: 10.1016/j.cell.2008.02.031.
28. Mafi S., Mansoori B., Taeb S. et al. mTOR-Mediated Regulation of Immune Responses in Cancer and Tumor Microenvironment. Front Immunol. 2022; 12: 774103. DOI: 10.3389/fimmu.2021.774103.
29. Martina J.A., Chen Y., Gucek M., Puertollano R. MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB. Autophagy. 2012; 8(6): 903–14. DOI: 10.4161/auto.19653. Epub 2012 May 11.
30. Melcher A., Parato K., Rooney C.M., Bell J.C. Thunder and lightning: immunotherapy and oncolytic viruses collide. Mol Ther. 2011; 19(6): 1008–16. DOI: 10.1038/mt.2011.65. Epub 2011 Apr 19.
31. Mukhopadhyay S., Frias M.A., Chatterjee A. et al. The Enigma of Rapamycin Dosage. Mol Cancer Ther. 2016; 15(3): 347–53. DOI: 10.1158/1535-7163.MCT-15-0720. Epub 2016 Feb 25.
32. Popova N.V., Jücker M. The Role of mTOR Signaling as a Therapeutic Target in Cancer. Int J Mol Sci. 2021; 22(4): 1743. DOI: 10.3390/ijms22041743.

33. Powell J.D., Pollizzi K.N., Heikamp E.B., Horton M.R. Regulation of immune responses by mTOR. Annu Rev Immunol. 2012; 30: 39–68. DOI: 10.1146/annurev-immunol-020711-075024. Epub 2011 Nov 29.
34. Powell J.D., Pollizzi K.N., Heikamp E.B., Horton M.R. Regulation of immune responses by mTOR. Annu Rev Immunol. 2012; 30: 39–68. DOI: 10.1146/annurev-immunol-020711-075024. Epub 2011 Nov 29.
35. Rousseau A., Bertolotti A. An evolutionarily conserved pathway controls proteasome homeostasis. Nature. 2016; 536(7615): 184–9. DOI: 10.1038/nature18943. Epub 2016 Jul 27.
36. Sarbassov D.D., Guertin D.A., Ali S.M., Sabatini D.M. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005; 307(5712): 1098–101. DOI: 10.1126/science.1106148.
37. Saxton R.A., Sabatini D.M. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017; 168(6): 960–76. DOI: 10.1016/j.cell.2017.02.004. Erratum in: Cell. 2017; 169(2): 361–71.
38. Sokolenko A.P., Imyanitov E.N. Molecular diagnostics in clinical oncology. Frontiers in Molecular Biosciences. 2018; 5(AUG.): 76. DOI 10.3389/fmolb.2018.00076.
39. Stanford M.M., Barrett J.W., Nazarian S.H. et al. Oncolytic virotherapy synergism with signaling inhibitors: Rapamycin increases myxoma virus tropism for human tumor cells. J Virol. 2007; 81(3): 1251–60. DOI: 10.1128/JVI.01408-06. Epub 2006 Nov 15.
40. Strong J.E., Coffey M.C., Tang D. et al. The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by reovirus. EMBO J. 1998; 17(12): 3351–62. DOI: 10.1093/emboj/17.12.3351.
41. Thoreen C.C., Chantranupong L., Keys H.R. et al. A unifying model for mTORC1-mediated regulation of mRNA translation. Nature. 2012; 485(7396): 109–13. DOI: 10.1038/nature11083.
42. Weichhart T. mTOR as Regulator of Lifespan, Aging, and Cellular Senescence: A Mini-Review. Gerontology. 2018; 64(2): 127–34. DOI: 10.1159/000484629. Epub 2017 Dec 1.
43. Werden S.J., Barrett J.W., Wang G. et al. M-T5, the ankyrin repeat, host range protein of myxoma virus, activates Akt and can be functionally replaced by cellular PIKE-A. J Virol. 2007; 81(5): 2340–8. DOI: 10.1128/JVI.01310-06. Epub 2006 Dec 6.
44. Yu Z., Chan M.K., O-charoenrat P. et al. Enhanced nectin-1 expression and herpes oncolytic sensitivity in highly migratory and invasive carcinoma. Clin Cancer Res. 2005; 11(13): 4889–97. DOI: 10.1158/1078-0432.CCR-05-0309.
45. Zakaria C., Sean P., Hoang H.D. et al. Active-site mTOR inhibitors augment HSV1-dICP0 infection in cancer cells via dysregulated eIF4E/4E-BP axis. PLoS Pathog. 2018; 14(8): e1007264. DOI: 10.1371/journal.ppat.1007264.
46. Zhu Z., McGray A.J.R., Jiang W. et al. Improving cancer immunotherapy by rationally combining oncolytic virus with modulators targeting key signaling pathways. Mol Cancer. 2022; 21(1): 196. DOI: 10.1186/s12943-022-01664-z.

ЛИТЕРАТУРА

1. Баранов И.А., Гладин Д.П., Козлова Н.С. Взаимосвязь гиперактивации сигнального пути mTOR, процессов старения и патогенеза COVID-19 (обзор литературы). Российские биомедицинские исследования. 2023; 8(2): 64–77.
2. Баранов И.А., Мелиева З.Ю., Мелиева Ф.Ю. Патологическая анатомия туберозного склероза. Интернаука. 2022; 38-1(261): 15–20.
3. Бородкина А.В., Дерябин П.И., Грюкова А.А., Никольский Н.Н. «Социальная жизнь» стареющих клеток: что такое SASP и зачем его изучать? Acta Naturae (русскоязычная версия). 2018; 1(36).
4. Давыдов М.И., Ганцев Ш.Х., Вельшер Л.З. и др. Онкология. М.: ГЭОТАР-Медиа; 2010.
5. Дементьева Е.А., Гурина О.П. Иммунологические изменения, сопровождающие развитие экспериментального неопластического процесса. Педиатр. 2015; 6(2): 96–108. DOI: 10.17816/PED6296-108.
6. Имянитов Е.Н., Хансон К.П. Молекулярная онкология: клинические аспекты. СПб.: Издательский дом СПбМАПО; 2007.
7. Москалев А.А. 120 лет жизни — только начало. Как победить старение? 2-е издание. М.: Эксмо; 2018.
8. Селезнева А.А., Козлова Н.С. Микробиота и рак: союзники или враги? Здоровье — основа человеческого потенциала: проблемы и пути их решения. 2022; 17(2): 774–81.
9. Alain T., Lun X., Martineau Y. et al. Vesicular stomatitis virus oncolysis is potentiated by impairing mTORC1-dependent type I IFN production. Proc Natl Acad Sci USA. 2010; 107(4): 1576–81. DOI: 10.1073/pnas.0912344107. Epub 2010 Jan 4.
10. Blagosklonny M.V. Cancer prevention with rapamycin. Oncotarget. 2023; 14: 342–50. DOI: 10.18632/oncotarget.28410.
11. Blagosklonny M.V. From causes of aging to death from COVID-19. Aging (Albany NY). 2020; 12(11): 10004–21. DOI: 10.18632/aging.103493. Epub 2020 Jun 12.
12. Chen X.G., Liu F., Song X.F. et al. Rapamycin regulates Akt and ERK phosphorylation through mTORC1 and mTORC2 signaling pathways. Mol Carcinog. 2010; 49(6): 603–10. DOI: 10.1002/mc.20628.
13. Dominick G., Bowman J., Li X. et al. mTOR regulates the expression of DNA damage response enzymes in long-lived Snell dwarf, GHRKO, and PAPPA-KO mice. Aging Cell. 2017; 16(1): 52–60. DOI: 10.1111/acel.12525. Epub 2016 Sep 13.
14. Dorrello N.V., Peschiaroli A., Guardavaccaro D. et al. S6K1- and betaTRCP-mediated degradation of PDCD4 promotes protein translation and cell growth. Science. 2006; 314(5798): 467–71. DOI: 10.1126/science.1130276.
15. Fukuhara H., Ino Y., Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. Cancer Sci. 2016; 107(10): 1373–9. DOI: 10.1111/cas.13027. Epub 2016 Sep 9.
16. García-Martínez J.M., Alessi D.R. mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). Biochem J. 2008; 416(3): 375–85. DOI: 10.1042/BJ20081668.
17. Grabiner B.C., Nardi V., Birsoy K. et al. A diverse array of cancer-associated MTOR mutations are hyperactivating and can predict rapamycin sensitivity. Cancer Discov. 2014; 4(5): 554–63. DOI: 10.1158/2159-8290.CD-13-0929. Epub 2014 Mar 14.
18. Granville C.A., Warfel N., Tsurutani J. et al. Identification of a highly effective rapamycin schedule that markedly reduces the size, multiplicity, and phenotypic progression of tobacco carcinogen-induced murine lung tumors. Clin Cancer Res. 2007; 13(7): 2281–9. DOI: 10.1158/1078-0432.CCR-06-2570.

19. Holz M.K., Ballif B.A., Gygi S.P., Blenis J. mTOR and S6K1 mediate assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. Cell. 2005; 123(4): 569–80. DOI: 10.1016/j.cell.2005.10.024.
20. Homicsko K., Lukashev A., Iggo R.D. RAD001 (everolimus) improves the efficacy of replicating adenoviruses that target colon cancer. Cancer Res. 2005; 65(15): 6882–90. DOI: 10.1158/0008-5472.CAN-05-0309.
21. Huang S. mTOR Signaling in Metabolism and Cancer. Cells. 2020; 9(10): 2278. DOI: 10.3390/cells9102278.
22. Javanbakht M., Tahmasebzadeh S., Cegolon L. et al. Oncolytic viruses: A novel treatment strategy for breast cancer. Genes Dis. 2021; 10(2): 430–46. DOI: 10.1016/j.gendis.2021.11.011.
23. Kaufman H.L., Kohlhapp F.J., Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat Rev Drug Discov. 2015; 14(9): 642–62. DOI: 10.1038/nrd4663. Erratum in: Nat Rev Drug Discov. 2016; 15(9): 660.
24. Kim J., Kundu M., Viollet B., Guan K.L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol. 2011; 13(2): 132–41. DOI: 10.1038/ncb2152. Epub 2011 Jan 23.
25. Laberge R.M., Sun Y., Orjalo A.V. et al. MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. Nat Cell Biol. 2015; 17(8): 1049–61. DOI: 10.1038/ncb3195. Epub 2015 Jul 6. Erratum in: Nat Cell Biol. 2021; 23(5): 564–5.
26. Lun X.Q., Zhou H., Alain T. et al. Targeting human medulloblastoma: oncolytic virotherapy with myxoma virus is enhanced by rapamycin. Cancer Res. 2007; 67(18): 8818–27. DOI: 10.1158/0008-5472.CAN-07-1214.
27. Ma X.M., Yoon S.O., Richardson C.J. et al. SKAR links pre-mRNA splicing to mTOR/S6K1-mediated enhanced translation efficiency of spliced mRNAs. Cell. 2008; 133(2): 303–13. DOI: 10.1016/j.cell.2008.02.031.
28. Mafi S., Mansoori B., Taeb S. et al. mTOR-Mediated Regulation of Immune Responses in Cancer and Tumor Microenvironment. Front Immunol. 2022; 12: 774103. DOI: 10.3389/fimmu.2021.774103.
29. Martina J.A., Chen Y., Gucek M., Puertollano R. MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB. Autophagy. 2012; 8(6): 903–14. DOI: 10.4161/auto.19653. Epub 2012 May 11.
30. Melcher A., Parato K., Rooney C.M., Bell J.C. Thunder and lightning: immunotherapy and oncolytic viruses collide. Mol Ther. 2011; 19(6): 1008–16. DOI: 10.1038/mt.2011.65. Epub 2011 Apr 19.
31. Mukhopadhyay S., Frias M.A., Chatterjee A. et al. The Enigma of Rapamycin Dosage. Mol Cancer Ther. 2016; 15(3): 347–53. DOI: 10.1158/1535-7163.MCT-15-0720. Epub 2016 Feb 25.
32. Popova N.V., Jücker M. The Role of mTOR Signaling as a Therapeutic Target in Cancer. Int J Mol Sci. 2021; 22(4): 1743. DOI: 10.3390/ijms22041743.
33. Powell J.D., Pollizzi K.N., Heikamp E.B., Horton M.R. Regulation of immune responses by mTOR. Annu Rev Immunol. 2012; 30: 39–68. DOI: 10.1146/annurev-immunol-020711-075024. Epub 2011 Nov 29.
34. Powell J.D., Pollizzi K.N., Heikamp E.B., Horton M.R. Regulation of immune responses by mTOR. Annu Rev Immunol. 2012; 30: 39–68. DOI: 10.1146/annurev-immunol-020711-075024. Epub 2011 Nov 29.
35. Rousseau A., Bertolotti A. An evolutionarily conserved pathway controls proteasome homeostasis. Nature. 2016; 536(7615): 184–9. DOI: 10.1038/nature18943. Epub 2016 Jul 27.
36. Sarbassov D.D., Guertin D.A., Ali S.M., Sabatini D.M. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005; 307(5712): 1098–101. DOI: 10.1126/science.1106148.
37. Saxton R.A., Sabatini D.M. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017; 168(6): 960–76. DOI: 10.1016/j.cell.2017.02.004. Erratum in: Cell. 2017; 169(2): 361–71.
38. Sokolenko A.P., Imyanitov E.N. Molecular diagnostics in clinical oncology. Frontiers in Molecular Biosciences. 2018; 5(AUG.): 76. DOI 10.3389/fmolb.2018.00076.
39. Stanford M.M., Barrett J.W., Nazarian S.H. et al. Oncolytic virotherapy synergism with signaling inhibitors: Rapamycin increases myxoma virus tropism for human tumor cells. J Virol. 2007; 81(3): 1251–60. DOI: 10.1128/JVI.01408-06. Epub 2006 Nov 15.
40. Strong J.E., Coffey M.C., Tang D. et al. The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by reovirus. EMBO J. 1998; 17(12): 3351–62. DOI: 10.1093/emboj/17.12.3351.
41. Thoreen C.C., Chantranupong L., Keys H.R. et al. A unifying model for mTORC1-mediated regulation of mRNA translation. Nature. 2012; 485(7396): 109–13. DOI: 10.1038/nature11083.
42. Weichhart T. mTOR as Regulator of Lifespan, Aging, and Cellular Senescence: A Mini-Review. Gerontology. 2018; 64(2): 127–34. DOI: 10.1159/000484629. Epub 2017 Dec 1.
43. Werden S.J., Barrett J.W., Wang G. et al. M-T5, the ankyrin repeat, host range protein of myxoma virus, activates Akt and can be functionally replaced by cellular PIKE-A. J Virol. 2007; 81(5): 2340–8. DOI: 10.1128/JVI.01310-06. Epub 2006 Dec 6.
44. Yu Z., Chan M.K., O-charoenrat P. et al. Enhanced nectin-1 expression and herpes oncolytic sensitivity in highly migratory and invasive carcinoma. Clin Cancer Res. 2005; 11(13): 4889–97. DOI: 10.1158/1078-0432.CCR-05-0309.
45. Zakaria C., Sean P., Hoang H.D. et al. Active-site mTOR inhibitors augment HSV1-dICP0 infection in cancer cells via dysregulated eIF4E/4E-BP axis. PLoS Pathog. 2018; 14(8): e1007264. DOI: 10.1371/journal.ppat.1007264.
46. Zhu Z., McGray A.J.R., Jiang W. et al. Improving cancer immunotherapy by rationally combining oncolytic virus with modulators targeting key signaling pathways. Mol Cancer. 2022; 21(1): 196. DOI: 10.1186/s12943-022-01664-z.