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CORRELATION OF HYPERACTIVATION OF THE mTOR SIGNALING PATHWAY, AGING PROCESSES AND COVID-19 PATHOGENESIS (LITERATURE REVIEW)

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Abstract. One of the most pressing problems of modern healthcare is the aging of the world's population and the spread of diseases associated with aging. One of the promising areas that can shed light on the solution of this problem today is the study of the intracellular signaling pathway mTOR (Mechanical target of rapamycin) and drugs that can inhibit it. The mTOR signaling pathway is the most important regulator of cellular metabolism and immune response, and its hyperactivation contributes to the development of a cytokine storm, carcinogenesis and actually the aging of the body itself. Another challenge for humanity is the ongoing COVID-19 pandemic, in connection with which the search for new methods of antiviral therapy has become of great importance. There are various theories explaining the connection between hyperactivation of the mTOR pathway, aging of the body and the "COVID-19 vulnerability syndrome" of older people, which partly explains the high mortality from SARS-CoV-2 among the elderly population. In this regard, proposals are being put forward for the use of mTOR pathway inhibitors (such as rapamycin and metformin) for the treatment of various viral diseases (including COVID-19), as well as for the treatment of age-related diseases. Researchers have shown the connection of the mTOR signaling pathway with such phenomena as hyperinflammation, cytokine storm, obesity and atherosclerosis, type 2 diabetes mellitus (type 2 diabetes), a decrease in the ability of stem cells to differentiate and a decrease in acquired immunity. Its effect on excessive synthesis of adhesion molecules, activation of leukocytes, suppression of apoptosis, lipid peroxidation, excessive activation of inflammatory cells, as well as viral replication, which in turn increases the vulnerability of the body to COVID-19, is considered. At the same time, mTOR can stimulate the function of NK cells, as well as the production of interferon-α and anti-inflammatory cytokines, activate the ULK1/miR122 pathway, which, on the contrary, positively affects the body's resistance to viral infection. The complex and diverse interrelations between all these processes are creatively reworked by the authors and presented in the form of visual generalizing schemes and cognitive maps presented in the article. The urgent task at the moment is to translate this theoretical knowledge into practical ones and to develop new treatment regimens and methods based on inhibitors of the mTOR signaling pathway.

Key words: COVID-19; SARS-CoV-2; mTOR; cytokine storm; aging; aging-related diseases; "COVID-19 vulnerability syndrome"; rapamycin; antiviral therapy; anti-aging therapy.

ВЗАИМОСВЯЗЬ ГИПЕРАКТИВАЦИИ СИГНАЛЬНОГО ПУТИ mTOR, ПРОЦЕССОВ СТАРЕНИЯ И ПАТОГЕНЕЗА COVID-19 (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. Одной из наиболее актуальных проблем современного здравоохранения является старение населения планеты и распространение ассоциированных со старением заболеваний. Одним из перспективных направлений, способных пролить свет на решение данной проблемы, на сегодняшний день является изучение внутриклеточного сигнального пути mTOR (Mechanistic target of rapamycin) и препаратов, способных его ингибировать. Сигнальный путь mTOR является важнейшим регулятором клеточного метаболизма и иммунного ответа, а его гиперактивация способствует развитию цитокинового шторма, канцерогенезу и собственно самому старению организма. Другим вызовом для человечества является продолжающаяся пандемия COVID-19, в связи с которой огромное значение приобрели поиски новых методов противовирусной терапии. Существуют различные теории, объясняющие связь гиперактивации пути mTOR, старения организма и «синдрома уязвимости к COVID-19» у пожилых людей, что отчасти объясняет высокую смертность от SARS-CoV-2 среди пожилого населения. В связи с этим выдвигаются предложения по использованию ингибиторов пути mTOR (таких как рапамицин и метформин) для лечения различных вирусных заболеваний (в том числе COVID-19), а также для лечения заболеваний, ассоциированных с возрастом. Исследователями показана связь сигнального пути mTOR с такими явлениями, как гипервоспаление, цитокиновый шторм, ожирение и атеросклероз, сахарный диабет второго типа (СД 2-го типа), снижение способности стволовых клеток к дифференцировке и снижение приобретенного иммунитета. Рассмотрено его влияние на избыточный синтез молекул адгезии, активацию лейкоцитов, подавление апоптоза, перекисное окисление липидов, избыточную активацию воспалительных клеток, а также репликацию вирусов, что, в свою очередь, повышает уязвимость организма к COVID-19. В то же время mTOR может стимулировать функцию NK-клеток, а также выработку интерферона-α и противовоспалительных цитокинов, активировать путь ULK1/miR122, что, напротив, положительно влияет на устойчивость организма к вирусной инфекции. Сложные и разнообразные взаимосвязи между всеми этими процессами творчески переработаны авторами и представлены в статье в виде наглядных обобщающих схем и когнитивных карт. Актуальной задачей на данный момент является перевод этих теоретических знаний в практические и разработка новых схем и методов лечения на основе ингибиторов сигнального пути mTOR.

Ключевые слова: COVID-19; SARS-CoV-2; mTOR; цитокиновый шторм; старение; ассоциированные со старением заболевания; «синдром уязвимости к COVID-19»; рапамицин; противовирусная терапия; антивозрастная терапия.

RELEVANCE

Scientific and technological advances, particularly in the sphere of medicine, over the past few decades have helped humans to cope with many previously untreatable diseases and significantly increased average life expectancy. However, this undeniable achievement has had a downside: in virtually all developed and developing countries of the world, the proportion of the elderly population is increasing, posing a serious challenge to their health systems. In addition, the priority now is not just to increase life expectancy, but to achieve healthy and active longevity while maintaining its high quality. The most promising research in this direction to date is the work on the intracellular mTOR signalling pathway and rapamycin drugs capable of inhibiting it. It was found that rapamycin, originally used for antifungal, antitumour and immunosuppressive therapy, is one of the few drugs capable of prolonging the life of all groups of control organisms. Research about that sheds light on the pathogenesis of many aging-associated diseases, and thus opens up new possibilities for their treatment, which may help to fight the aging in the future.

In addition, a pandemic of a new COVID-19 coronavirus infection caused by SARS-CoV-2 virus, reported in December 2019, is ongoing worldwide. The situation is exacerbated by the adherence of these patients to hospital-acquired infections caused by hospital-acquired antibiotic-resistant strains, particularly *Klebsiella pneumoniae* [7]. COVID-19 is widely recognised to be most severe in elderly patients, and proposals have been made to use rapamycin preparations to treat this disease. However, it appears that the spectrum of action of these drugs is much broader, which probably makes it possible to use them in the future to treat other viral diseases and prevent future pandemics, the danger of which has now become much more seriously considered, whether it is new strains of SARS-CoV-2, Ebola and monkeypox viruses or other pathogens.

COVID-19 AND THE CYTOKINE STORM

It is known that COVID-19 can occur in the form of a mild acute respiratory infection or extremely severe infection. In most people, the disease ends in recovery, with no specific treatment measures required. Complications of severe cases may include “severe acute respiratory syndrome” — SARS, often incorrectly called as atipical pneumonia. Pneumonia rapidly progresses to respiratory failure, leading to death. The most vulnerable group is the elderly (a possible explanation will be given later), but young people are also at the risk group [8, 10, 23].

Severe cases of COVID-19 extremely often lead to immunological dysregulation, the so-called cytokine storm. It is the cause of multi-organ failure and subsequent mortality. It is not known whether this phenomenon is based on the immune hyperactivity or the inability to eliminate the inflammatory response due to ongoing virus replication [3, 6, 11, 23, 24].

It is known that the concept of cytokine storm includes three main criteria [12]:

1) the increase in the levels of circulating cytokines;
2) the presence of acute systemic inflammatory symptoms;
3) secondary organ dysfunction due to inflammation of greater intensity than organ disfunction with a normal pathogen response (if it is present) or induced by cytokines (in the absence of the pathogen) [12].

Thus, a cytokine storm is an excessive immune response that causes side effects that may exceed the direct benefit of that immune response [4, 12, 24].

The pathogenesis of cytokine storm is summarised in Figure 1 in the form of a summarising scheme. It should be noted that a great many of the pathways and processes presented in the scheme can be inhibited by appropriate drugs, which will thus prevent the development of cytokine storm, favourably affecting the course of the disease. One of such drugs is rapamycin (sirolimus), which inhibits the mTOR signalling pathway [1, 23].

RAPAMYCIN — HISTORICAL BACKGROUND

In 1964, on Easter Island (Rapa Nui), a Canadian expedition led by Suren N. Sehgal (an Indian-born Canadian scientist) collected soil samples to identify new antimicrobial agents. In a sample containing bacteria of *Streptomyces hygroscopicus* species (Fig. 2), a substance was detected that was a product of their vital activity and was later named rapamycin after the place of detection [31]. Another common name of rapamycin is sirolimus. By its structure, it is a macrolipid (Fig. 3), and the technology of its biosynthesis has now been mastered. In the course of tests, it was found out that rapamycin has unique antifungal, immunosuppressive and antitumour properties, which are now actively used in the clinic (particularly in organ transplantation and cancer therapy). However, when scientists tried to find out the reason for these actions, it turned out that it is much more fundamental than it was seen at first [28, 31].

WHAT IS mTOR?

In 1994, a protein was discovered that is a direct target of rapamycin action — Mechanistic (formerly mammalian) target of rapamycin (abbreviated as mTOR). The mTOR protein is a serine/threonine protein kinase of the PI3K-related kinase family, which forms the catalytic subunit of two different protein complexes: mTORC1 and mTORC2 (Fig. 4). These enzymes change the conformation (and hence function) of other proteins by phosphorylating them, thus forming the intracellular mTOR signalling network [28, 31].

The mTORC1 complex consists of the mTOR regulatory-associated protein (RAPTOR), the rapamycin targeting complex subunit LST8 (mLST8), the proline-rich substrate Akt 40 kDa (PRAS40) and the mTOR-interacting protein containing the DEP domain (DEPTOR).

The mTORC2 complex also contains mLST8 and DEPTOR and, in addition, a RAPTOR-independent protein, a TOR companion (RICTOR), the mSIN1 protein and a RICTOR-observed protein (PROTOR) [28, 31].

mTOR FUNCTIONS ON CELLULAR AND SUBCELLULAR LEVELS

It was found that mTORC1 plays a key 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, and oxygen; under the action of growth factors (including steroid hormones). Stress and DNA damage, on the contrary, inhibit mTORC1 activity. 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 (Fig. 5) [31, 34].

mTORC2, in turn, is also activated by growth factors (including insulin) and stimulates the rearrangement of cytoskeleton, cell migration, ion transport, regulates glucose metabolism and suppresses apoptosis. Thus, it is responsible for cell survival and tissue proliferation (Fig. 6) [31, 34].

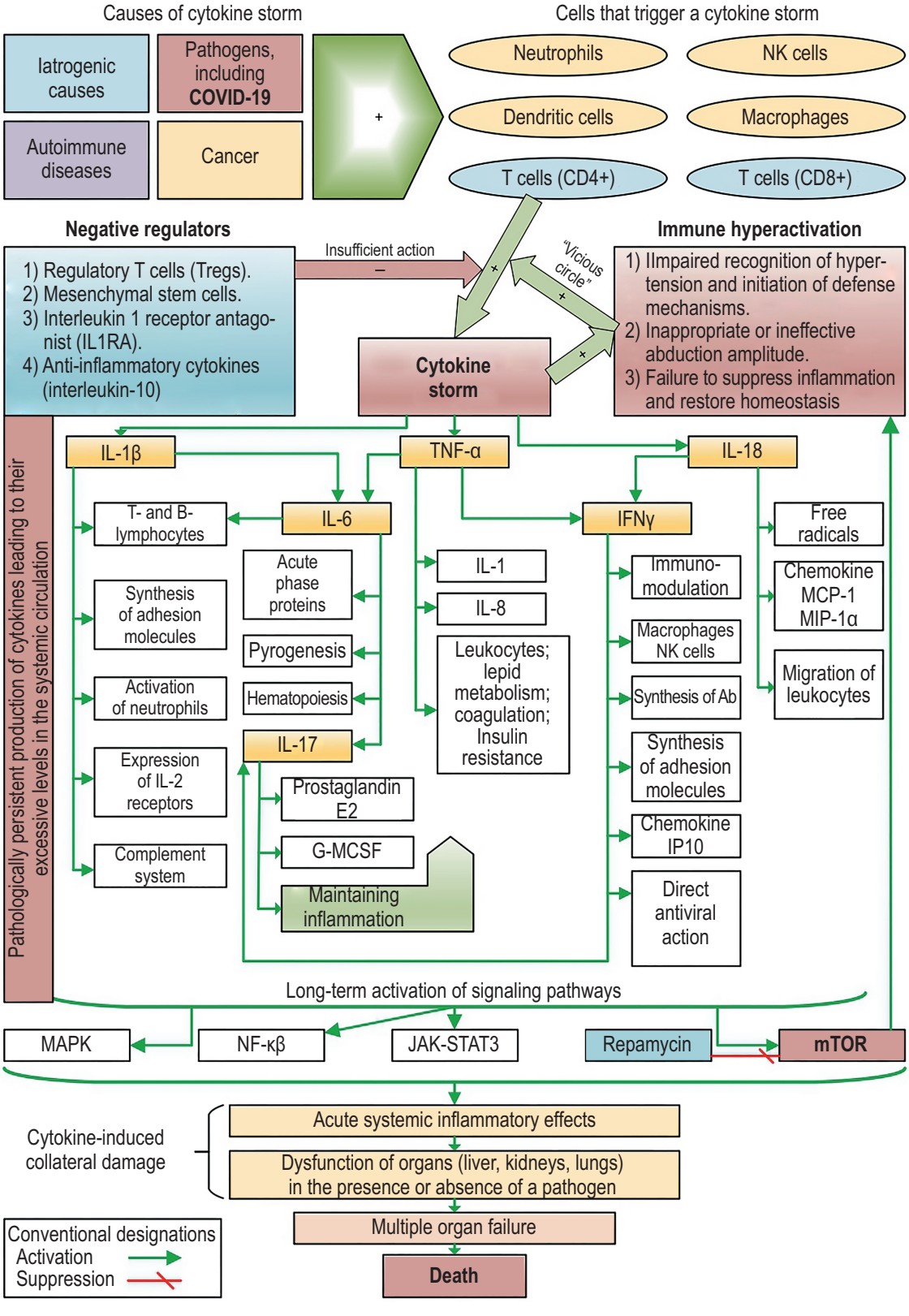

Fig. 1. Pathogenesis of cytokine storm (compiled by Baranov I.A.). IL — interleukin; TNF — tumor necrosis factor; IFN — interferon; G-MCSF — granulocyte-macrophage colony-stimulating factor; NK cells — natural killers; MAPK — mitogen-activated protein kinase; NF-kB — nuclear factor kappa-light-chain-enhancer of activated B cells; mTOR — mammalian target of rapamycin

Рис. 1. Патогенез цитокинового шторма (составлено Барановым И.А.).

Fig. 2. *Streptomyces hygroscopicus* **(https://upload.wikimedia.org/wikipedia/commons/thumb/b/be/Streptomyces_hygroscopicus.JPG/1200px-Streptomyces_hygroscopicus.JPG)**
Рис. 2. *Streptomyces hygroscopicus*

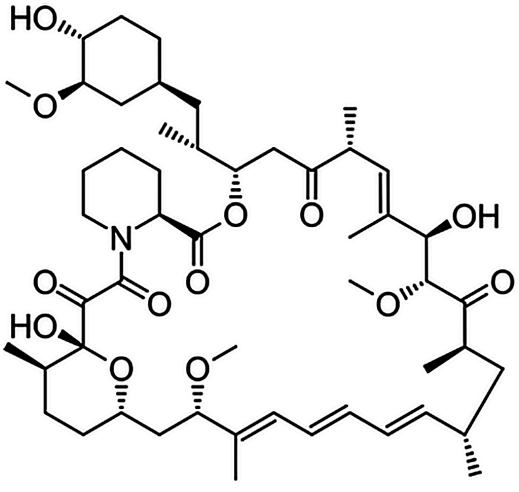

Fig. 3. Chemical structure of rapamycin (https://upload.wikimedia.org/wikipedia/commons/thumb/0/0f/Sirolimus.svg/1024px-Sirolimus.svg.png)
Рис. 3. Химическая структура рапамицина

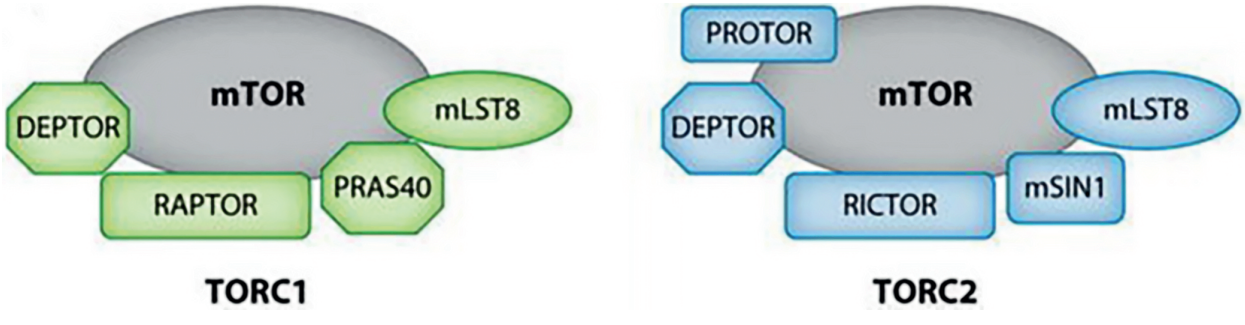

Fig. 4. Schematic structure of the complex mTORC1 and mTORC2. Raptor — regulatory-associated protein of mTOR; mLST8 — mammalian lethal with SEC13 protein 8; PRAS40 — proline-rich AKT1 substrate; DEPTOR — DEP domain-containing; mTOR — interacting protein; RICTOR — rapamycin-insensitive companion of MTOR; mSIN1 — mammalian stress-activated protein kinase interacting protein 1; PROTOR — protein observed with Rictor (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3616892/bin/nihms448316f2.jpg)
Рис. 4. Схематичное строение комплексов mTORC1 и mTORC2.

THE RELATIONSHIP BETWEEN mTOR, AGING AND COVID-19

Theories explaining the link between the mTOR pathway and aging

So what links the three phenomena of aging, vulnerability to COVID-19, and the mTOR signalling pathway (Fig. 7)?

Let us first focus on the connection between the mTOR pathway and aging processes. It is important to note that this signalling pathway is specific 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 lifetime of such organisms as yeast (>100%), nematodes, Drosophila and mice (10–20 %), and also slows down aging of various human cell cultures. The fact that a similar effect in all model organisms is caused only by

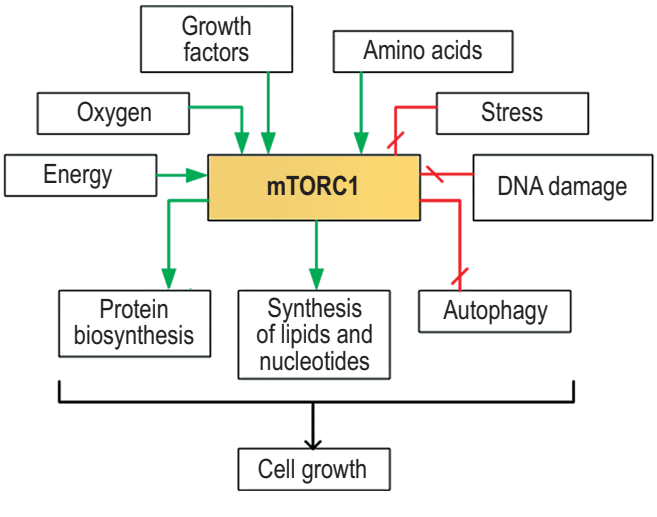

Fig. 5. mTORC1 functions (compiled by Baranov I.A.)
Рис. 5. Функции mTORC1 (составлено Барановым И.А.)

caloric restriction without malnutrition [5, 34] suggests that these phenomena are interrelated. This is the basis for one of the theories explaining the link between the mTOR pathway and the aging of the organism. Indeed, in the wild, animals face serious difficulties in obtaining food. In their lives, “calm” periods alternate with periods of stress, hence the activity of mTOR has a wave-like character. It is this cyclical pattern, fixed by evolution, that is normal. However, modern humans or laboratory animals are protected from the stress of malnutrition, so the activity of mTOR in their organisms is disturbed. Given the extensive influence of this signalling pathway, we can conclude that this imbalance is the cause of various age-related diseases and aging. This is confirmed by the detection of increased mTOR concentration in the cells of aging organisms [5, 34].

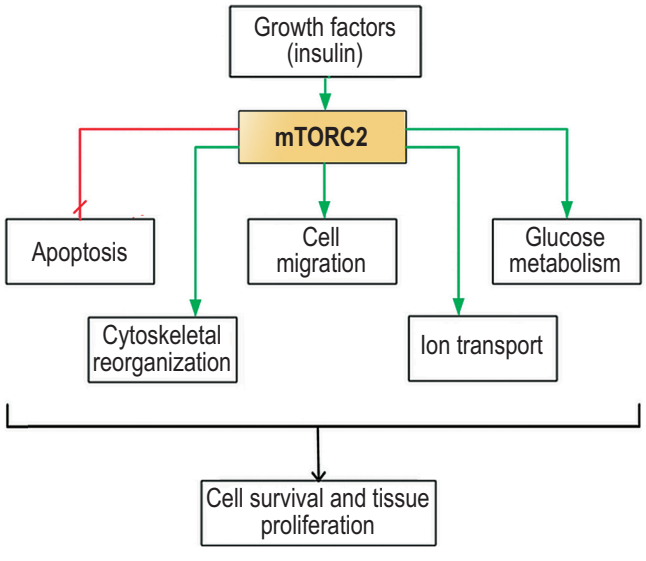

Fig. 6. **mTORC2 functions (compiled by Baranov I.A.)**
Рис. 6. **Функции mTORC2 (составлено Барановым И.А.)**

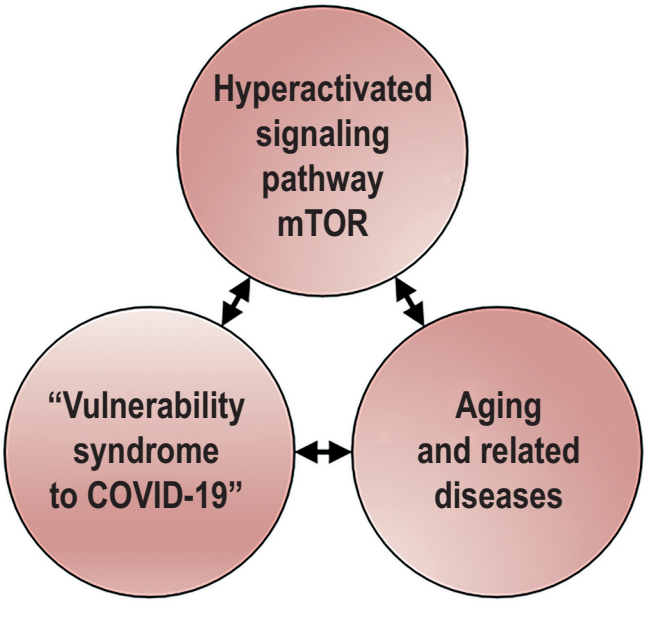

Fig. 7. **The fundamental relationship of processes (compiled by Baranov I.A.)**
Рис. 7. **Принципиальная взаимосвязь процессов (составлено Барановым И.А.)**

Another (apparently more plausible) theory is called the ‘quasi-programmed aging’ theory. “Quasi” means “similar” or “seeming but not actually so”. Quasi-programmed aging is not a programme, but a continuation of developmental programmes that were not switched off when they ended. They continue to function aimlessly, leading to age-related diseases, secondary organ failure and death. An illustrative example is the increase in blood pressure in children as they grow older. Up to a certain point, this rise corresponds to normal cardiovascular development and body growth, but as they age, growth ceases and blood pressure does not stop rising, gradually leading to hypertension. Hypertension, in turn, is the most common age-related disease and can cause damage to various organ systems: a stroke, heart attack, renal failure, etc. [9].

The same is true for the mTOR signalling pathway. As mentioned above, mTOR is normally responsible, among other things, for cell growth. However, having fulfilled its programme, mTOR continues to act, which leads to the so-called cellular hyperfunction. Such enhanced work, as a rule, is destructive for the cell, and at the level of the organism is manifested as aging. Thus, quasi-programmed aging is associated with the excess of optimal cellular and systemic functions, which eventually leads to the loss of these functions through cell exhaustion and organ damage (Fig. 8) [9].

Hyperactivation of the mTOR pathway as a cause of aging

The consequences of excessive activation of the mTOR pathway at the cellular and organismal level are schematically presented in Fig. 9.

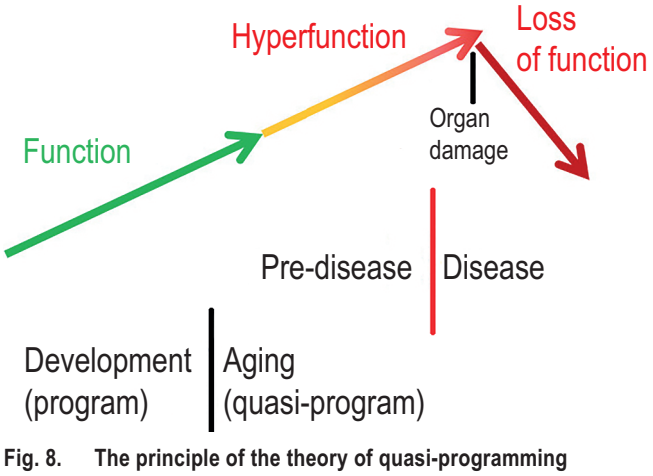

Fig. 8. **The principle of the theory of quasi-programming**
Рис. 8. **Принцип теории квазипрограммирования**

It is shown that hyperactivated mTOR through a number of intermediate links 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, anaemia, joint disease and hair loss, age-related skin hyperpigmentation. In addition, suppression of apoptosis and DNA repair and stimulation of proliferation may contribute to carcinogenesis. The role of mTOR hyperactivation in the pathogenesis of type 2 DM, obesity, atherosclerosis, and chronic inflammation is great [2, 5, 34].

Thus, it is obvious that mTOR pathway hyperactivation leads to a huge number of aging-associated diseases, and they are the very essence of aging and ultimately the cause of death. Aging and aging-associated diseases are inseparable, and thus, it can be argued that it is the hyperactivated mTOR pathway that causes them [2, 5, 34].

Thus, it is obvious that mTOR pathway hyperactivation leads to a huge number of aging-associated diseases, and they are the very essence of aging and ultimately the cause of death. Aging and aging-associated diseases are inseparable, and thus, it can be argued that it is the hyperactivated mTOR pathway that causes them [2, 5, 34].

There is no doubt that research into the mTOR signalling pathway is of great importance due to its incredible breadth of action. However, rapamycin will never be a "pill for old age", because it is impossible to predict the side effects of switching off such an important component of homeostasis maintenance. Nevertheless, this does not mean that further research in this area will be hopeless. By discovering more and more new ways of interaction of mechanisms of cell metabolism regulation, we are coming closer to understanding the pathogenesis of various diseases (including the "COVID-19 vulnerability syndrome"). And with this understanding comes the methods of the disease treatment [1, 34].

Cytokine storm as hyperfunction, vulnerability to COVID-19 as an age-related syndrome

The mTOR signalling pathway in mammals has now been shown to be a central regulator of immune responses. In particular, mTOR appears to function as a central node in the signalling cascade that directs the integration of various environmental factors into the immune microenvironment. mTOR plays a role in the regulation of various immune cells including neutrophils, mast cells, natural killer cells, macrophages, dendritic cells (DC), T cells and B cells. It is this property that allows rapamycin and its analogues to be used as immunosuppressive drugs in organ transplantation [25, 28]. Unfortunately, it is not possible to consider this issue in more detail in the scope of this review. Therefore, we will briefly highlight only the key points.

All immune reactions can be divided into innate reactions, which are mainly carried out by neutrophils, macrophages and NK-cells, which react to the pathogen quickly but nonspecifically, and acquired reactions, carried out by T- and B-lymphocytes, which develop more slowly but act specifically and form immunological memory.

As practice shows, in elderly people immune reactions to SARS-CoV-2 remain at the level of innate immunity, with insufficient development of adaptive immunity. The cause of this phenomenon is the same as that of aging — the hyperactivated mTOR signalling pathway. Just as hypertension can be thought of as hyperfunction of vascular smooth muscle cells, the "COVID-19 vulnerability syndrome" can be thought of as hyperfunction of immune cells of innate immunity. It is as a result of an inadequate mTOR-mediated immune response that cytokine storm, hypercoagulability and damage to the lungs and distant organs develop, which are the main causes of mortality in this disease. Increased pro-inflammatory activity of the innate immune system is a precautionary measure against potential age-related inflammatory diseases, but it is such precaution that can be fatal [9, 28].

In addition, the hyperactivated mTOR pathway can cause immunosenescence — a suppression of adaptive immunity. This occurs because mTOR stimulates cell proliferation, thus reducing the number of naive T- and B-lymphocytes, and thus the response to new antigens. This is supported by studies on the increased efficacy of vaccines when used in conjunction with rapalogues. Thus, rapamycin analogues seem to "rejuvenate" immunity [9, 28, 34].

Obviously, the cause-and-effect relationship is bidirectional: hyperinflammation serves as both a cause and a consequence of immunosenescence; thus, two processes are mutually dependent on each other [9].

From the above, it can be concluded that ageing and vulnerability to COVID-19 are indeed closely linked, as confirmed by statistics.

In all studies conducted in all countries, COVID-19 mortality increases exponentially with age. Although figures may vary somewhat between studies, for example due to differences in outcome assessment methods or therapeutic interventions, one thing is certain: the mortality rate increases exponentially with age [9, 29]. Mortality is particularly high in patients with pre-existing diseases. In Italy, 99% of patients who died had at least one comorbid disease. And as we have already learnt, it is the set of diseases associated with aging that defines old age itself. Of course, vulnerability to COVID-19 is related to biological age, but it is most often close to the chronological (passport) age [9].

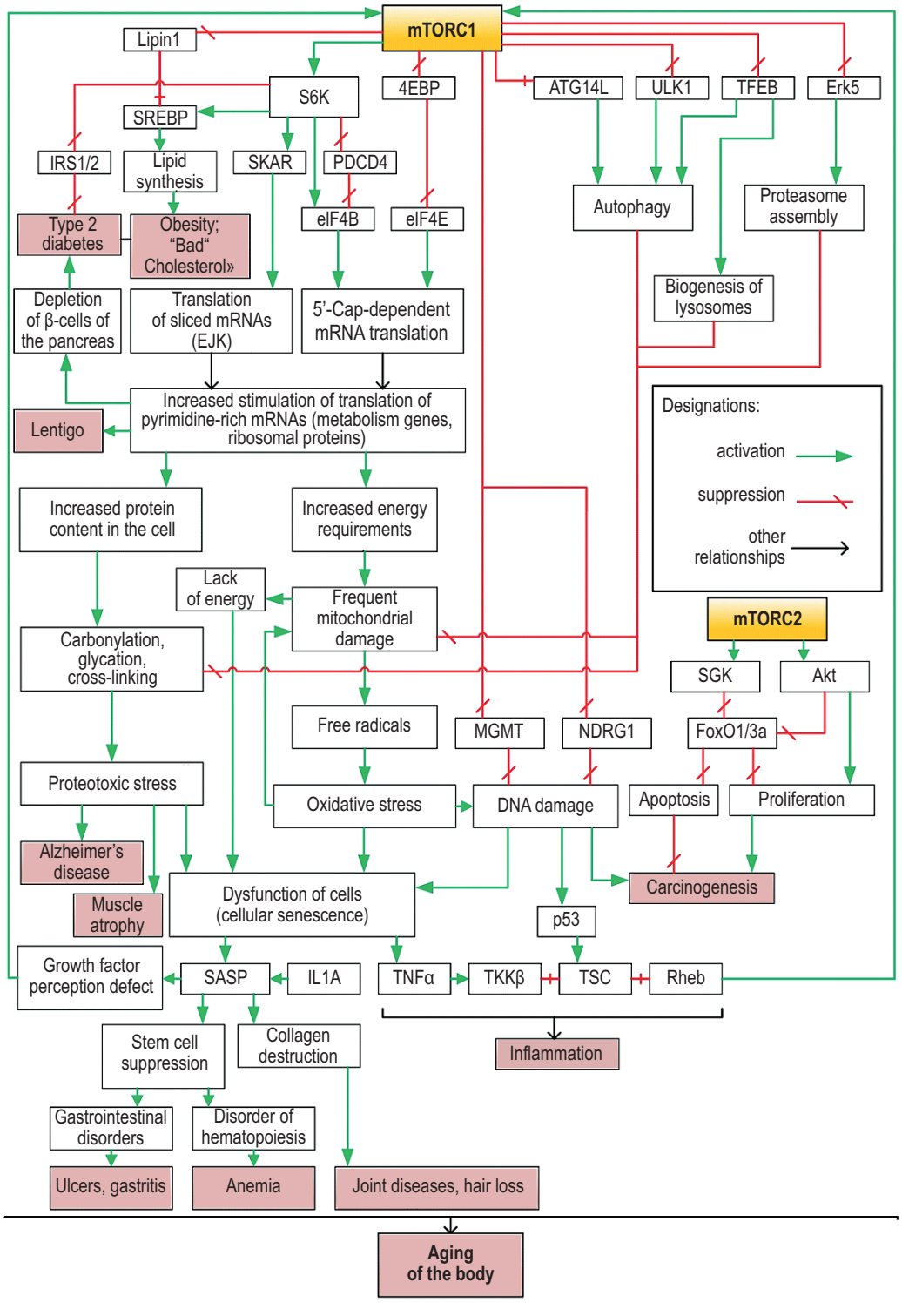

Fig. 9. **The scheme of the relationship between mTOR and the aging of the body (compiled by Baranov I.A.).** DM — Diabetes mellitus; S6K — Ribosomal S6 Kinase; 4EBP — Eukaryotic Translation Initiation; Factor 4E Binding Protein; SREBP — Sterol regulatory element-binding proteins; SKAR — a component of exon-junction complexes; PDCD4 — Programmed cell death protein 4; eIF4B — eukaryotic translation initiation factor 4B; eIF4E — eukaryotic translation initiation factor 4E; IRS1/2 — insulin receptor substrate 1/2; ATG14L — autophagy related 14; ULK1 — unc-51 like autophagy activating kinase 1; TFEB — Transcription factor EB; ERK5 — Extracellular signal-regulated kinase 5; SGK — serum/glucocorticoid regulated kinase; Akt — RAC-alpha serine/threonine-protein kinase; FoxO1/3a — forkhead box O1/3a; p53 — transformation-related protein 53; SASP — senescence-associated secretory phenotype; IL1A — Interleukin-1 alpha; TNFα — tumor necrosis factor alpha; TSC — tuberous sclerosis complex; Rheb — Ras homolog enriched in brain

Рис. 9. **Схема связи mTOR и старения организма (составлено Барановым И.А.)**

Ageing can be measured as an increase in the probability of death with age. Mortality rates increase exponentially from age 8–9. Men have a higher "normal" age-specific mortality rate than women because men age more rapidly (this is due to a higher metabolic rate, and therefore a higher level of mTOR activity) [9, 34].

The mortality rate from COVID-19 coincides with the "expected" mortality rate associated with aging (Fig. 10). The odds of dying from COVID-19 are proportional to the odds of dying from aging itself at any age. COVID-19 only, figuratively speaking, doubles them [9]. The only discrepancy between natural mortality and mortality from COVID-19 occurs before the age of 8 years. Before this time, mortality remains high, particularly from infectious diseases, but not from COVID-19. This further supports the fact that the main cause of mortality due to it is not the deficiency but the hyperactivation of the immune response [11, 12, 21].

Thus, it becomes obvious that three phenomena are closely linked: the mTOR pathway hyperactivation, aging, and vulnerability to COVID-19 (Fig. 7).

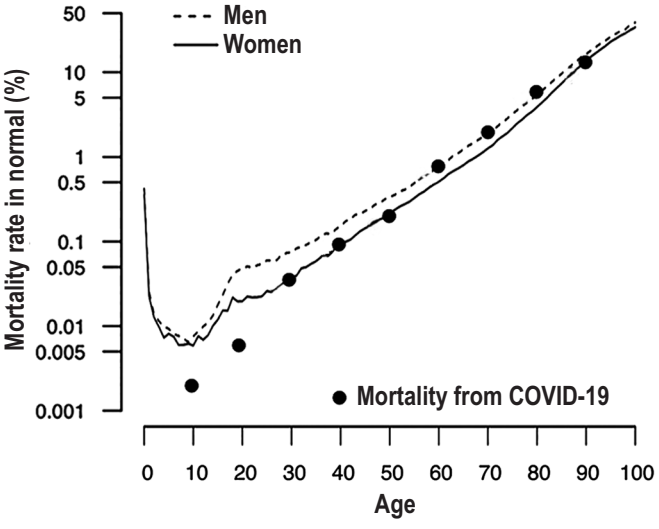

Fig. 10. A graph of the dependence of mortality from COVID-19 on the age of patients (according to the Office for National Statistics for England and Wales for 2016–2018) (https://medium.com/wintoncentre/how-much-normal-risk-does-covid-represent-4539118e1196)

Рис. 10. График зависимости смертности от COVID-19 от возраста пациентов (по данным Управления национальной статистики по Англии и Уэльсу за 2016–2018 годы)

POTENTIAL USE OF RAPAMYCIN AS THE ANTIVIRAL THERAPY

Anti-ageing therapy as prevention of COVID-19

Currently, knowledge of the close relationship between the pathogenesis of viral diseases and the mTOR signalling pathway serves as a basis for the development of methods for their treatment using rapamycin analogues. One of the promising directions is the use of rapamycin analogues in so-called anti-aging therapy.

Scientific and technological progress (including in the sphere of medicine) over the last decades has significantly increased the life expectancy of people. However, this has not solved the problem of ageing. Ageing-associated diseases are becoming more frequent, the quality of life of the elderly is suffering, and the percentage of the population unable to work is increasing.

The use of rapamycin (sirolimus) as an anti-aging agent, it would seem, could solve this problem. However, as mentioned above, this is likely to be impossible in the near future due to unpredictable side effects [20]. Nevertheless, some private western clinics already prescribe "off-label" rapamycin to their patients for this purpose. The efficacy and safety of such therapy remain to be investigated.

At the same time, simple caloric restriction has already been shown to be effective. It also reduces the activity of the mTOR signalling pathway and thereby successfully combats type 2 DM and obesity, which, in turn, are among the main risk factors for death in COVID-19 [9, 34]. Rapamycin is also already used in the therapy of these diseases, it is a matter of selecting doses and treatment regimens.

Nevertheless, a regimen of rapamycin analogues for life extension and healthy aging, developed sometime in the future, would also overcome the age-dependent vulnerability to COVID-19.

In theory, continuous rapamycin treatment would have slowed the increase in vulnerability to COVID-19 with age. The increase would still remain logarithmic, but with a different slope. Such a trend is depicted in a hypothetical graph (Fig. 11) [9].

However, there are other, perhaps less impressive but more feasible considerations for the use of rapamycin in the therapy of novel coronavirus infection in the foreseeable future.

OTHER POSSIBILITIES FOR THE USE OF DRUGS AFFECTING mTOR ACTIVITY AS ANTIVIRAL THERAPY

The use of rapamycin as an immunosuppressor and the role of mTOR in the development of cytokine storm have been mentioned previously. A number of considerations are being made about the possible use of this knowledge for the development of treatments for COVID-19. Relatively recently, a novel cytokine IL-37 [26] was discovered that can suppress innate and acquired immunity through inhibition of the mTOR pathway and activation of AMPK (AMP-regulated protein kinase) [11]. AMPK is activated when the AMP/ATP ratio increases in the cell and is one of the negative

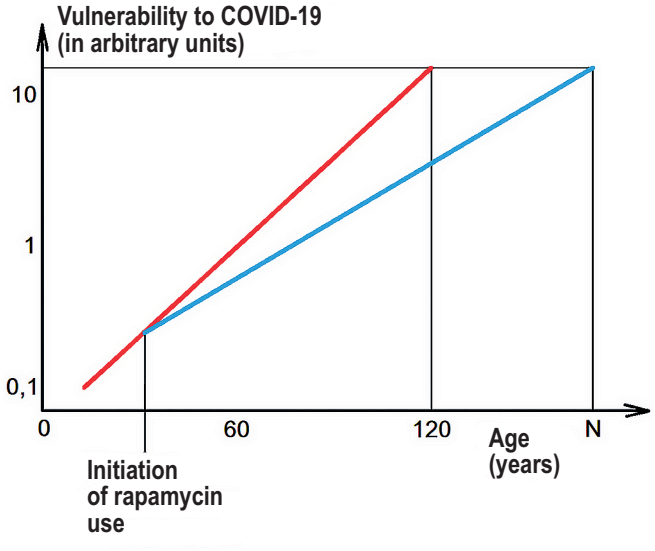

Fig. 11. A hypothetical graph of the dependence of vulnerability to COVID-19 on age under normal conditions and in conditions of anti-aging therapy

Рис. 11. Гипотетический график зависимости уязвимости к COVID-19 от возраста в обычных условиях и в условиях антивозрастной терапии

regulators of mTOR, activating its main inhibitor, the tuberous sclerosis complex (TSK), as discussed above [19].

IL-37 inhibits class II major histocompatibility complex molecules and the release of inflammatory cytokines such as IL-1β, IL-6, IL-17, TNF-α and chemokine IP10. Thus, IL-37 may be considered as a novel target for anti-inflammatory therapy, particularly in COVID-19 [11].

In addition, it has been shown that the use of drugs that activate AMPK and therefore inhibit mTOR (such as metformin) can prevent cell damage by reducing the production of adhesion molecules (they control leukocyte migration and adhesion) [27]. Metformin itself is actively used in the treatment of type 2 DM. It normalises the glucose tolerance and prevents the development of complications. Indeed, in both type 2 DM and cytokine storm the mTOR pathway is hyperactivated. The commonality of these phenomena is confirmed by statistics — COVID-19 is much more severe in patients with type 2 DM [14, 23].

In addition, metformin, can activate autophagy and thus protect cells from apoptosis by inhibiting mTOR activity [17]. However, decreased mTOR activity can stimulate apoptosis through the mTORC2 complex [22]. The result depends on the specific body tissue, conditions, etc.

Another property of metformin is its ability to limit lipid peroxidation in the brain and spinal cord and reduce caspase activity during toxic exposures, which can lead to excessive activation of inflammatory cells [23]. All of the above makes it another unique drug as another potential anti-aging agent, which has already been shown in many studies [15].

However, metformin use may also reduce the efficacy of influenza vaccination (and presumably COVID-19), by decreasing interferon-α production, mediated by decreased mTOR activity [30].

Recent studies have suggested that hydroxychloroquine may be used as adjuvant therapy to metformin in the treatment of type 2 DM by improving glycaemic control. It also appears to be suitable for antiviral treatment [23].

However, in some cases, mTOR activation can paradoxically have an anti-inflammatory effect. For example, treatment of a cell with alpha-lipoic acid, which activates mTOR, protects it from the action of reactive oxygen species. This occurs through stimulation of the mTORC2 complex, which suppresses apoptosis and increases cell survival. In the same study, an increase in the level of anti-inflammatory cytokine IL-10 and a decrease in inflammatory cytokines in the cells was observed [18].

In addition to the immunomodulation described above, mTOR may also have a link to direct antiviral activity. In particular, it has been shown that mTOR can stimulate translation of West Nile virus proteins through the 4EBP/eIF4E pathway described above [33]. This appears to be the same for the influenza A virus [32]. However, this effect may vary depending on the specific virus. For example, active mTORC1 suppresses hepatitis C virus RNA replication but may promote its packaging and exit from the cell [16]. The relationship of mTOR to the life cycle of SARS-CoV-2 remains to be established.

At the same time, mTOR can stimulate the activity of NK cells, which are necessary for the destruction of cells affected by the virus [25].

Recent studies have also shown the possibility of using rapamycin in the therapy of HIV. It is assumed that the drug can slow down the spread of the virus in the body by inhibiting the formation of CCR5 receptors and activating autophagy [13].

For a more visual presentation of the presented material, a summarising scheme has been drawn up (Fig. 12). It should be noted that many of the above relationships can be corrected by one or another methods and drugs. Studies of them represent the basis for the development of new methods of COVID-19 treatment.

CONCLUSION

Thus, the above data indicate the great biological importance of the mTOR signalling pathway in many vital processes of the organism, which determine its immunity, the course and outcome of infectious diseases, the presence of acquired diseases, as well as the duration and quality of life. Hyperactivation of this pathway can explain the processes of premature aging and high vulnerability of the elderly to COVID-19.

The ability of rapamycin and metformin to inhibit mTOR is an additional explanation for their positive effects on the

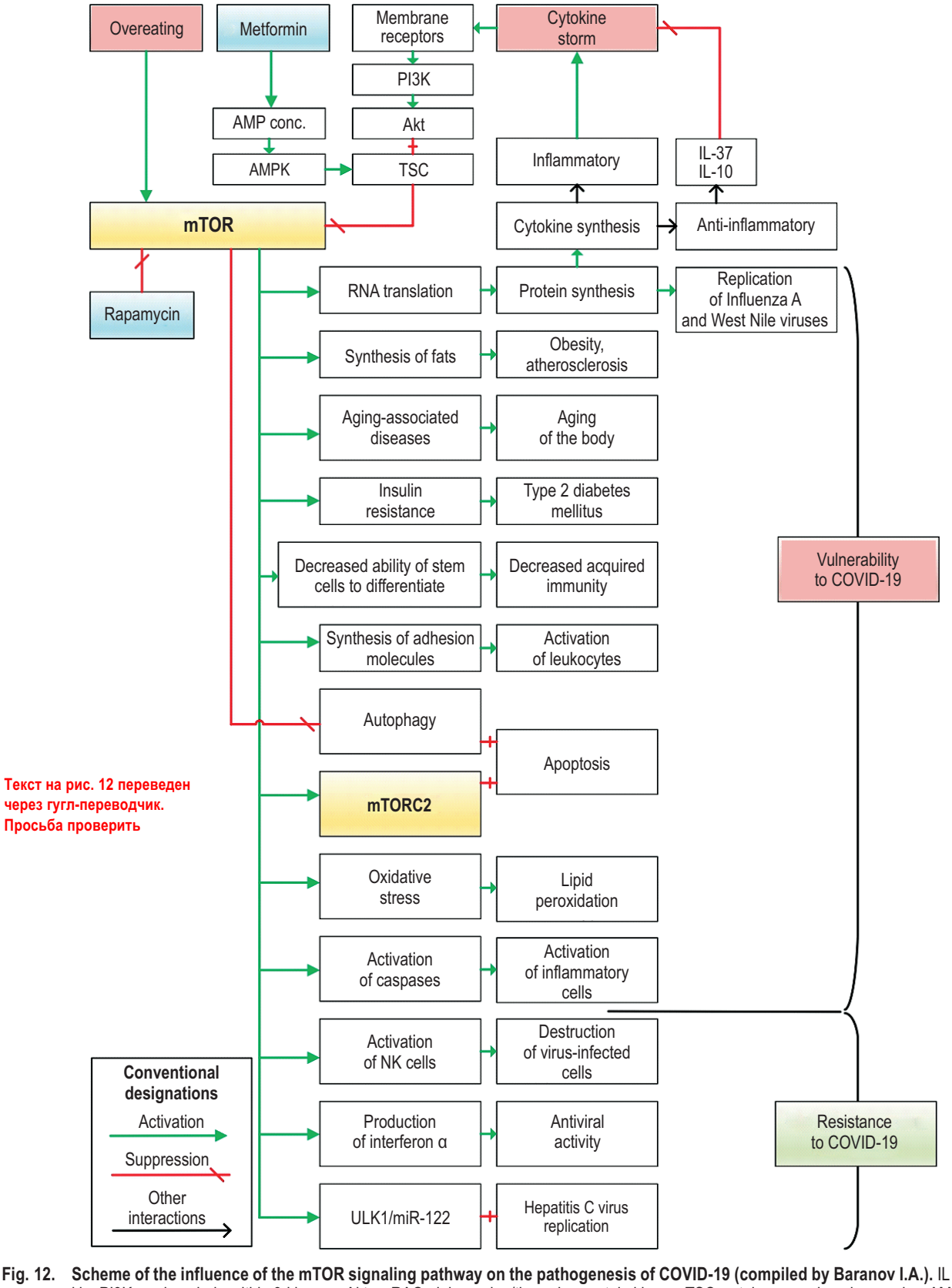

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Fig. 12. Scheme of the influence of the mTOR signaling pathway on the pathogenesis of COVID-19 (compiled by Baranov I.A.). IL — interleukin; PI3K — phosphoinositide 3-kinases; Akt — RAC-alpha serine/threonine-protein kinase; TSC — tuberous sclerosis complex; AMPK — AMP activated protein kinase; miR — 122-MicroRNA-122; ULK1 — unc-51 like autophagy activating kinase 1

Рис. 12. Схема влияния сигнального пути mTOR на патогенез COVID-19 (составлено Барановым И.А.)

longevity of animal and human cells in vitro. It is obvious that further study of the mTOR signalling pathway holds great potential for understanding the pathogenesis of not only infectious diseases, but also many diseases associated with aging, and opens new opportunities for their treatment. The development of new drugs based on rapamycin analogues and other mTOR inhibitors for its fine regulation, as well as the development of methods and regimens for the treatment of aging-associated diseases on their basis, may in the future lead to the achievement of humanity's dream — to increase life expectancy with the maximal preservation of health and ability to work.

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.

Competing interests. The authors declare that they have no competing interests.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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