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STUDYING THE GEROPROTECTIVE EFFECTS OF INHIBITORS SUPPRESSING AGING-ASSOCIATED SIGNALING CASCADES IN MODEL ORGANISMS

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ИССЛЕДОВАНИЕ ГЕРОПРОТЕКТОРНЫХ СВОЙСТВ ИНГИБИТОРОВ АКТИВНОСТИ СВЯЗАННЫХ СО СТАРЕНИЕМ СИГНАЛЬНЫХ КАСКАДОВ НА МОДЕЛЬНЫХ ОРГАНИЗМАХ

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According to DrugAge (<http://genomics.senescence.info/drugs/>) and Geroprotectors.org (<http://geroprotectors.org/>) databases nowadays more than 200 compounds which elongate lifespan of model organisms exist. One of the most promising approaches constitutes aging-associated pathways (insulin/IGF-1, mTOR, NF-κB, PI3k, etc.) as main targets for new perspective geroprotectors' screening. In the current review we summarized the data touching upon geroprotectors that target signaling pathways which are involved in stress-response, metabolism, growth and proliferation, inflammation, apoptosis, etc. Some our results on *Drosophila melanogaster* and *Caenorhabditis elegans* models confirm the effectiveness of pathways of aging inhibition approach to the search for new geroprotectors.

Keywords: longevity, aging, geroprotector, signaling cascades pathways, model organisms

Согласно базам данных DrugAge (<http://genomics.senescence.info/drugs/>) и Geroprotectors.org (<http://geroprotectors.org/>) на сегодня известно более 200 соединений, увеличивающих продолжительность жизни модельных организмов. Одним из многообещающих экспериментальных подходов для поиска новых эффективных геропротекторных средств может быть скрининг соединений, мишенями которых являются белки, участвующие в старение-ассоциированных сигнальных путях (инсулин/IGF-1, mTOR, NF-κB, PI3k и др.). В настоящем обзоре обобщены сведения о геропротекторах, модулирующих активность внутриклеточных сигнальных путей, вовлеченных в стресс-ответ, обмен веществ, рост клеток и организма, воспаление, апоптоз и др. Рассмотрены данные литературы и результаты собственных исследований по использованию таргетного подхода на примере моделей *Drosophila melanogaster* и *Caenorhabditis elegans*.

Ключевые слова: долголетие, старение, геропротекторы, сигнальные каскады, модельные организмы

The studies in model organisms such as budding yeast *Saccharomyces cerevisiae*, soil roundworm (nematode) *Caenorhabditis elegans*, fruit fly *Drosophila melanogaster*, and house mouse *Mus musculus* have established that longevity is genetically controlled. According to GenAge database there are about 2000 genes associated with aging and longevity in model organisms [58]. Mutations

of pro-aging genes lead to substantial life extension in yeast, nematode, fruit fly, and house mouse (Table 1). Over expression of pro-longevity genes demonstrates the same effects on lifespan [47]. Though, manipulations with human hereditary apparatus are not possible now, this fact results in the search of alternative approaches to health span and lifespan extension.

Table 1

The list of maximum effects observed on model organisms (top mutations in pro-aging genes and experimental overexpression of anti-aging genes)

Model organism	Geneproduct (signaling pathway)	Life span extension	References
Mutations			
Budding yeast <i>Saccharomyces cerevisiae</i>	Double mutant of RAS2 (Ras/cAMP/PKA/Rim15/Msn2/4) and SCH9 (Tor/Sch9/Rim15/Gis1)	10-fold (M and Max, in combination with calorie restriction)	[57]
Nematode <i>Caenorhabditis elegans</i>	AGE-1/PI3K _{CS} (silences multiple signaling pathways partially mediated by the DAF-16/FOXO transcription factor)	10-fold (M and Max)	[2, 52]
Fruitfly <i>Drosophila melanogaster</i>	INDY/SLC13A5 (transporter of Krebs cycle intermediates with the highest affinity for citrate)	1.8-fold (M and Max)	[49]
House mouse <i>Mus musculus</i>	Prop-1 (control of adenohipophyseal development)	1.6-fold (M and Max)	[6]
Over expression			
Budding yeast <i>Saccharomyces cerevisiae</i>	MCA1, Ca ²⁺ -dependent cysteine protease (proteostatic stress)	56 % (M)	[25]
Nematode <i>Caenorhabditis elegans</i>	TKR-1, tyrosine kinase receptor-1 (activation of the DAF-16/FOXO transcription factor)	65 % (M and Max)	[43]
Fruitfly <i>Drosophila melanogaster</i>	D-GADD45 (DNA-damage response)	102 % (M), 50 % (Max)	[45]
House mouse <i>Mus musculus</i>	hNAG-1/hGDF15 (energy metabolism and insulin/IGF-1/mTOR signaling)	43 % (M)	[55]

The note: M – median lifespan; Max – maximum lifespan.

Pharmaceutical impact on longevity- and aging-associated gene products allows one to increase the lifespan of model organisms without DNA editing, which opens it for use on humans. To date there is an opportunity to select the pharmacological inhibitors for pro-aging factors and also it is possible to sort out the inhibitors which activate expression of pro-longevity genes by suppression of its negative regulators. So-called «target approach» is probably the syntheses of the genetics of aging and longevity, modern drug design and advances in translational medicine (using model organisms) [37].

The pharmacological agents that decrease the rate of aging and extend lifespan are called geroprotectors [36–38]. The term «geroprotector» (literally «protecting from aging») was first coined by the Nobel Prize laureate Ilya Mechnikov, an outstanding Russian and French scientist, in 1910 [35], but those times the concept had not been widely used before enough empirical data was accumulated. First attempts of life extension via pharmacological treatment were described in the pioneer investigations of Thomas Gardner experiments performed on mice [15, 18] and on flies [16, 17] in 1940s. The elevation of researchers' interest to anti-aging drugs took place in 1960s, which was connected to endeavours of «Free Radical Theory

of Aging» (by Denham Harman [21]) evaluation, as well as with discovery of phenomenon of longevity hormesis [44]. At the present day, according to Geroprotectors.org (<http://geroprotectors.org/>) [36] and DrugAge (<http://genomics.senescence.info/drugs/>) [4] databases, found more than 200 geroprotectors. However the lifespan-extending effects of pharmacological interventions surpass the threshold of 20–40 % very seldom, mutations of aging genes and over expression of longevity genes usually have more significant impact. The increment of median lifespan often depends on model complexity; the simplest model shows typically great effects (Table 2).

Table 2

Lifespan-extending effects of rapamycin (mTOR inhibitor) in different model organisms

Model organism	Life span extension	References
Budding yeast <i>Saccharomyces cerevisiae</i>	100 % (M and Max)	[46]
Nematode <i>Caenorhabditis elegans</i>	20 % (M and Max)	[48]
Fruitfly <i>Drosophila melanogaster</i>	5 % (M)	[41]
House mouse <i>Mus musculus</i>	60 % (M)	[8]

The note: M – median lifespan; Max – maximum lifespan.

Recently, the system of criteria for geroprotector identification and classification were proposed [37, 38]. The main criteria are (1) the ability to prolong life, in addition, a potential geroprotector should (2) return the biomarkers of aging to the state characteristic of a young organism; (3) the dose providing effective use must be fundamentally lower than the toxic dose with (4) minimal side effects at therapeutic dosage, and, finally, (5) the quality of life in patients treating with geroprotectors should increase, and the physical, mental, emotional state should improve. Secondary criteria are worthy of mention either: (1) the geroprotector should be aimed at evolutionarily conservative targets; (2) the hormetic effect must, in consequence, be reproduced on different models, despite the likely absence of a specific target; (3) the potential geroprotector is obliged to reduce the rate of development of age-related pathologies and (4) has to increase resistance to environmental challenges.

Taking into account the existence of compounds which extend lifespan of model organisms, we have to admit that in most cases a specific mechanism has not been clarified, so the concrete target is typically unknown or there is a wide variety of targets impacted by the chemical. Target approach is an alternative to non specialized methods of aging therapy.

The target approach. The products of genes that affect longevity and aging represent potential targets for pharmacological intervention [9, 37]. The candidate geroprotectors may be selected from a libraries of natural and synthetic compounds or discovered by computer-assisted molecular design approaches [22]. The main advantage of the drug design approach is an extensive toolkit, allowing to conduct a theoretical selection of compounds that can affect the molecule of interest. Thus, online services and commercial packages that carry out molecular docking through a wide range of mathematical methods are widely spread [7, 19, 31, 34]. Another powerful tool for anti-aging therapy selection is a set of algorithms that implement machine learning on big data [5].

The goal of target approach is in simplified experimental design, which implies the formula «one drug – one target – one mechanism» [33]. The specific inhibitors of PI3K (LY-294002 and wortmannin) and TOR (rapamycin) kinases, pro-inflammatory transcription factor NF- κ B (pyrrolidindithiocarbamate and QNZ), and inducible NO synthase iNOS (1400W) have been shown to increase *Drosophila* lifespan [11, 39, 42]. High specificity of small molecules is rather rare in pharmacology, thus, the observed effects could be determined by the interaction with the target of interest. The genuine high affinity and specificity may be only reached after numerous changes have been made in the molecule design. However, safety and bioavailability of the hypothetical compound cannot be guaranteed. The shortcomings of the target approach undoubtedly include its application to the most part of approved pharmaceuticals, so far as the list of each potential targets is long [50].

It is worth noting that there are revolutionary inhibitors which have an ultimate affinity to its targets, the majority of these drugs are antibodies and nanoantibodies, unfortunately, and the usage is limited by the size. The smallest antibodies are able to inhibit only targets on the cell membrane [54]. However recently presented modular strategy enables to create functional cell-permeable nanobodies capable of targeted manipulation of intracellular antigens in living cells [24].

Using traditional method «one drug – one target» it is difficult to observe an outstanding lifespan extension effect with a single geroprotector. The aging is multifactorial process involving a complex interplay of individual proteins and entire signaling pathways [40]. In the light of low efficacy of monotherapy of aging in model animals, researchers are interested in synergistic effects of combined inhibitors targeting multiple components within the different signaling pathways (Table 3). The drugs that interact with multiple targets might give better results also [53]. The increasing of molecular specificity of compounds might reduce the side effects of potential geroprotectors.

Pharmaceutical targeting of aging-associated signaling pathways. Model organisms have been used not only to identify individual aging genes and proteins related to ageing and longevity but also entire signal transduction pathways, that are known to be evolutionary conserved from invertebrate to mammals. The following signaling pathways are involved in regulating the aging process: insulin/IGF-1, PI3K, TOR, MAPK, AMPK, PKC, NF- κ B, TGF- β , Notch, and WNT [40]. Under favorable environmental conditions, these signaling cascades control energy balance, cellular plasticity, and the mechanisms supporting homeostasis, growth, and reproduction. However, under harmful conditions, the hormonal stimulation of growth is blocked, while stress-resistance proteins are activated. Number of known geroprotectors can stimulate stress-resistance and promote longevity via mechanisms of hormesis [44]. Among them both natural products and man-made drugs may be found [14, 29, 36]. For example in *Drosophila* the lifespan-extending effect of the low methyl esterified pectins is mediated by intracellular pathways that involve NF- κ B signaling and activation of stress response genes including DNA repair (*D-GADD45*, *mei-9*, *spn-B*), apoptosis (*wrinkled/hid*), and heat shock response (*hsp70Aa*) genes [51]. Carotenoid fucoxanthin increases lifespan in *Drosophila melanogaster* and *Caenorhabditis elegans* and upregulates the expression of stress response genes involved in oxidative stress (*sod1*, *Keap1*, *CncC/Nrf2*, *GclC*), DNA repair (*D-GADD45*, *mei-9*, *spn-B*, *p53*), heat shock response (*hsp70Aa*), and some longevity-associated genes (*dSir2/SIRT1* and *JNK*) [30]. Enhanced longevity

by non-steroidal anti-inflammatory drugs in multiple species (*Saccharomyces cerevisiae*, *Caenorhabditis elegans* and *Drosophila melanogaster*) may occurs through inhibition of Tat2p, a known target of TOR involved in tryptophan import in the cells [12, 23]. Thus the one more promising approach for development a new geroprotectors may be the screening of compound libraries on chemicals with the ability to activate stress response pathways.

Table 3

Increasing lifespan by drug synergy

Model organism	Combination of geroprotectors	Targets (signaling pathways)	Life span extension	References
Budding yeast <i>Saccharomyces cerevisiae</i>	Rapamycin and myriocin	Tor (Tor/Sch9/Rim15/Gis1) and Pkh1/2 (sphingolipid/Pkh1/2/Sch9)	2.4 fold (M and Max)	[28]
Fission yeast <i>Schizosaccharomyces pombe</i>	Rapamycin and myriocin	Tor (Tor/Sch9/Rim15/Gis1) and Pkh1/2 (sphingolipid/Pkh1/2/Sch9)	9.6 fold (M and Max)	[27]
Nematode <i>Caenorhabditis elegans</i>	Rapamycin, rifampicin, and allantoin	TOR (TOR/S6K/4E-BP), JNK (JNK-1/DAF-16), and calorie restriction mimetic	96.6 % (A) 76.3 % (Max)	[13]
Nematode <i>Caenorhabditis elegans</i>	Rifampicin, Psora-4, and allantoin	TOR (TOR/S6K/4E-BP), K-channel, and calorie restriction mimetic	89.5 % (A) 76.1 % (Max)	[13]
Fruitfly <i>Drosophila melanogaster</i>	Rapamycin and wortmannin	Tor (Tor/S6K/4E-BP) and PI3K (PI3K/AKT/FOXO)	14.6 % (M), 23.4 % (Max)	[11]

The note: A – average lifespan; M – median lifespan; Max – maximum lifespan.

The current progresses in pharmacological correction of aging-associated signaling pathways to increase lifespan are presented in figure. However particular signaling pathways (for example, WNT and Notch) are involved in a very complex network of pathways and have pleiotropic effects on longevity, and it is difficult to apply the pharmacological approach for correction of their activity for lifespan increase [3, 20].

Using the groups of geroprotectors or multitarget drugs provide a new opportunity for inhibition of critical links that allow the functioning of the extensive pathological processes associated with aging, for example inflammation [32, 56]. It is also proposed to compare the signaling pathways activated in the course of aging with pathways active in cancer, due to the presence of similarities between the lists of genes and participating proteins. Aging/Cancer pathways may be targeted by precise anticancer drugs [26]. Another powerful approach is to use computational tools to carry out signaling pathway analysis of gene expression between young and old cells. Based on the signaling pathway results, known compounds may be screened and

Fig. The integral scheme of anti-aging treatment has lifespan in its core, the most studied and perspective pathways and processes to be inhibited or activated lay around the central node. In the outer circle you see the pharmacological groups of drugs and compound which form these groups. The scheme is based on materials of DrugAge (<http://genomics.senescence.info/drugs/>) [4] and Geroprotectors.org (<http://geroprotectors.org/>) [36] databases

ranked, in order to identify the best compounds to target those pathways and restore a «young» cellular profile [1]. Using this approach six substances, that demonstrate lifespan-extending effects in animal models, were tested for geroprotective effects in senescent human fibroblast cultures. PD-98059, a highly selective MEK1 inhibitor, showed both life-prolonging and rejuvenating effects. Natural compounds like N-acetyl-L-cysteine, Myricetin and Epigallocatechin gallate also improved several senescence-associated properties [1].

However, there is a concept which stands apart, Mikhail Blagosklonny suggests to concentrate the attention on mTOR signaling pathway and inhibit it using rapalogs. When a stable effect is obtained it is suggested to use IGF targeting drugs, angiotensin 2 blockers, beta-adrenoblockers, statins, COX-2 inhibitors, PDE5 inhibitors either. In addition, he proposes the development of anti-aging pharmaceuticals that implies a systemic approach

to aspects of design, combination and evaluation of geroprotectors and complex geroprotector therapies. [10].

Thus, the usage of drugs targeting aging-associated pathways makes the synergistic effect on lifespan of model organisms possible.

Conclusions. Notwithstanding the 70 years of research history, geroprotectors significantly pass up genetic approaches. The search of compounds having high geroprotective activity is one of the hottest issues of contemporary biogerontology and medicine. Using the target approach it is possible to boost the specificity of geroprotectors to their molecular targets and improve the particular effects. Considering the multifactorial origin of aging the combinations of different specific inhibitors as well as multitarget drugs have to be used.

The computer-assisted molecular design approaches will play a growing role in the discovery of new geroprotectors. A new opportunity for predicting lifespan-extending chemical compounds provides the using of a computational tools and predictive machine learning methods [1, 5].

Using of lifespan-extending compounds for a long time and even throughout the whole lifetime can dramatically increase the risk of side effects. Recent studies in mice suggests

that reduction in side effects can be achieved by short-term treatment, which is sufficient to increase life expectancy but is insufficient for development of adverse effects [8].

Eventually the development of new highly effective geroprotectors with using the model organisms will give the opportunity to slow down ageing, postpone onset of age-related diseases, and increase the maximum lifespan in human.

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NITROUS OXIDE. SHOULD IT STILL BE USED IN PEDIATRIC MEDICINE? (PART 1)

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ЗАКИСЬ АЗОТА. НУЖНА ЛИ ОНА НАМ ПРИ ПРОВЕДЕНИИ АНЕСТЕЗИИ У ДЕТЕЙ? (ЧАСТЬ I)

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Nitrous oxide (N₂O) has been used in medicine for more than 165 years. By incidence was the analgesic effect recognized by Howard Wells. Originally was it thought to be a clean and anesthetic not causing a single adverse effect, and therefore was it considered the safest anesthetic. However, around 1956 was it recognized that some patients, after prolonged exposure developed, mostly transient, megaloblastic anemia and neurological disorders. Gradually became adverse effects more known. This resulted in discussions in the literature on the safety of N₂O. Since the 1990's are there indications that N₂O administration in children during the period of brain development and in elderly persons has neurotoxic effects. This lead to the conclusion of many that N₂O should no longer be used in medicine. However, other physicians have the opinion that there is no reason to stop the use of N₂O.

Keywords: *pediatric anesthesia, children surgery, anesthesia associated complications in children, drugs adverse reactions*

Закись азота (N₂O) применяется в медицинских целях более 165 лет. Ее анагетический эффект был случайно обнаружен Говардом Веллсом. Изначально считалось, что это достаточно безопасный анестетик, не вызывающий побочных реакций. Однако начиная с середины 1950-х годов было замечено, что у ряда пациентов, получавших этот анестетик, развивались преходящие неврологические расстройства и мегалобластическая анемия. Постепенно все большее количество побочных эффектов данного препарата было замечено при его практическом применении. В 1990-х годах было показано, что его использование у детей в период развития головного мозга, а также у пожилых пациентов приводит к развитию нейротоксических эффектов. Это привело к широкой дискуссии относительно использования закиси азота ввиду его небезопасности для пациентов и персонала, а также к заключению о нецелесообразности использования закиси азота. Однако не менее обширная когорта медицинских профессионалов не видит оснований для прекращения применения закиси азота в своей практике.

Ключевые слова: *педиатрическая анестезия, детская хирургия, осложнения анестезии у детей, побочные эффекты лекарственных средств*