REVIEWS

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Treatment approaches to pulmonary lymphangioleomyomatosis: From surgical extirpation to molecular biology

I.V. Polovnikov, G.Yu. Yukina, E.G. Sukhorukova

Pavlov First Saint Petersburg State Medical University,
Bld. 6, 8, Lev Tolstoy Str., Saint Petersburg, Russia, 197022

E-mail: policrats@mail.ru

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The aim of the work was to collect and systematize the data on the treatment approaches to pulmonary lymphangioleiomyomatosis (LAM) based on insights into the pathogenesis of the disease.

Materials and methods. 70 original sources have been selected from analyzed 1 157 articles and monographs (including duplicates). The search for the sources was carried out in the databases of PubMed, eLibrary.ru, Cyberleninka for a fifty-year period of publications (from 1973 to August 2023), with an emphasis on more current publications and the ones in highly rated scientific journals.

Results. The review presents the treatment approaches to LAM, based both on clinical observations of the disease course and on the experimental data on its probable pathogenesis. The collected data are presented in the chronological order, starting from radical methods based on the idea of an unconditional connection between the development of LAM and the female sex hormones. Special attention has been paid to the drugs from the group of mTOR inhibitors, including their safety profile. In addition, the results of the studies demonstrating new promising methods of the LAM drug therapy, both combining the use of mTOR inhibitors with other drugs, and the ones based on the isolated use of alternative groups of drugs, are presented in the work.

Conclusion. The currently used methods of the drug therapy and the proposed new methods are aimed at only treating an already established disease, and the effective drug prevention of LAM now seems almost impossible due to the lack of a complete understanding about its pathogenesis and, more importantly, its etiology. This issue is the most relevant in determining further prospects for the development of pharmacotherapeutic approaches to LAM.

Keywords: lymphangioleiomyomatosis; treatment; biochemistry; pathogenesis; etiology

Abbreviations: LAM — lymphangioleiomyomatosis; TSC — tuberous sclerosis complex; VEGF-D — vascular endothelial growth factor D; MIAA — methylimidazoleacetic acid; iNOS — inducible NO synthase; SGCs — systemic glucocorticosteroids; TB — tuberous sclerosis; Cox2 — cyclooxygenase-2; RAAS — renin-angiotensin-aldosterone system; ACE — angiotensin-converting enzyme; AGT — angiotensinogen; Ang1 — angiotensin 1; Ang2 — angiotensin 2; AT-R — angiotensin receptor; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; IL — interleukin; MMPs — matrix metalloproteinases; MCP1 — monocyte chemoattractant protein 1; PKB — protein kinase B; ERK — extracellular signal-regulated kinases; TGFβ — transforming growth factor beta; SASP — senescence-associated secretory phenotype; CatK — Cathepsin K; SREBP — sterol regulatory element-binding protein; CAs — carbonic anhydrases; NBC — bicarbonate Sodium (Natrium) cotransporter; SPHK1 — sphingosine kinase 1.

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Подходы к лечению лимфангиолейомиоматоза лёгких: от радикальной хирургии до молекулярной биологии

И.В. Половников, Г.Ю. Юкина, Е.Г. Сухорукова

Федеральное государственное образовательное учреждение высшего образования
«Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова»
Министерства здравоохранения Российской Федерации,
197022, Россия, Санкт-Петербург, ул. Льва Толстого, д. 6–8

E-mail: policrats@mail.ru

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Цель. Сбор и систематизация данных о подходах к лечению лимфангиолейомиоматоза (ЛАМ) лёгких, основанных на представлениях о патогенезе заболевания.

Материалы и методы. Проанализировано 1157 статей и монографий (включая дубли), из которых отобраны 70 оригинальных источников. Поиск источников осуществляли в базах PubMed, eliabrary.ru, CyberLeninka. Глубина поиска составила 50 лет — с 1973 г. по август 2023 г. Авторы акцентировали внимание на актуальных публикациях в высокорейтинговых научных журналах.

Результаты. В обзоре представлены подходы к лечению ЛАМ, основанные как на клинических наблюдениях за течением заболевания, так и на экспериментальных данных о вероятном его патогенезе. Собранные данные представлены в хронологическом порядке, начиная с радикальных методов, основанных на представлениях о безусловной связи развития ЛАМ с воздействием женских половых гормонов. Отдельное внимание уделено препаратам из группы ингибиторов mTOR, в том числе их профилю безопасности. Помимо этого, приведены результаты исследований, демонстрирующих новые перспективные методы лекарственной терапии ЛАМ, сочетающие в себе как применение ингибиторов mTOR с другими препаратами, так и основанных на изолированном использовании альтернативных групп медикаментов.

Заключение. Используемые на настоящий момент методы лекарственной терапии и предлагаемые новые методы направлены лишь на лечение уже сформировавшегося заболевания, а проведение эффективной медикаментозной профилактики ЛАМ сейчас представляется практически невозможным ввиду отсутствия полного понимания патогенеза заболевания и, что более важно, — его этиологии. Данный вопрос является наиболее актуальным в определении дальнейших перспектив развития фармакотерапевтических подходов к ЛАМ.

Ключевые слова: лимфангиолейомиоматоз; лечение; биохимия; патогенез; этиология

Список сокращений: ЛАМ — лимфангиолейомиоматоз; TSC — комплекс туберозного склероза; VEGF-D — фактор роста эндотелия сосудов D; MIAA — метилимидазолускусная кислота; ЖБАЛ — жидкость, полученная при проведении бронхоальвеолярного лаважа; iNOS — индуцибельная NO-синтаза; СГКС — системные глюкокортикостероиды; ТС — туберозный склероз; ЦОГ2 — циклооксигеназа 2 типа; РААС — ренин-ангиотензин-альдостероновая система; АПФ — ангиотензин превращающий фермент; АТГ — ангиотензиноген; Анг1 — ангиотензин 1; Анг2 — ангиотензин 2; Анг-R — рецепторы к ангиотензину; иАПФ — ингибитор ангиотензин превращающего фермента; АРБ — ангиотензина рецепторов блокатор; ИЛ — интерлейкин; ММП — матриксные металлопротеиназы; МХБ1 — моноцитов хемоаттрактантный белок 1 типа; ПК-В — протеинкиназа типа В; ERK — киназы, регулируемые внеклеточными сигналами; TGFβ — трансформирующий фактор роста бета; SASP — секреторный фенотип, связанный со старением; CatK — катепсин К; SREBP — белок связывающий регуляторный элемент стерола; СА — карбангидраза; NBC — контранспортёр бикарбонат-анионов и катионов натрия; SPHK1 — сфингозин киназа 1.

INTRODUCTION

Lymphangioleiomyomatosis (LAM)[1] is a rare disease affecting lungs, kidneys and pelvic organs, classified by WHO as a mesenchymal tumor and considered a metastatic low-grade neoplasm that originates from cells (LAM cells) with a biallelic mutation in the gene of a tuberous sclerosis complex (TSC) [1,2]. Previously, there had been a well-established belief that this disease affected only women [3], but in recent years there have been described several cases of LAM in men [4]. Nevertheless, the incidence even among females, whose proportion among patients with LAM prevails significantly, varies from 3.35 to 7.76 cases per 1 million women [5].

The issue of treating LAM is relevant, but it is better

[1] Ilkovich MM. Diffuse and parenchymal lung diseases. Moscow: GEOTAR-Media; 2021. DOI: 10.33029/9704-5908-9-DPL-2021-1-440. Russian

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to highlight briefly the main reliable biochemical markers that are identified during a laboratory LAM diagnosis and reflecting its pathogenesis (at least partly), before the immersion into therapy approaches.

The main biochemical marker in blood plasma, that is associated with lung damage by LAM, is vascular endothelial growth factor D (VEGF-D). The generally accepted concentration of it is 800 pg/mL [6, 7]. However, a meta-analysis of researches on the diagnostic effectiveness of the VEGF-D concentration in blood plasma in LAM with the PROSPERO design (protocol No. CRD42020164137) and with the QUADAS-2 method (Quality Assessment of Diagnostic Accuracy Studies, version 2) shows that the determination of VEGF-D has a high specificity and a moderate sensitivity for a LAM diagnosis. It means that a high concentration of VEGF-D confirms a LAM diagnosis, while a low concentration does not exclude it. Moreover, there was noted that the variability of VEGF-D concentration from 440 to 1239 pg/mL is permissible due to the possible influence of a number of factors on this indicator (including a sample preparation and other aspects of the analysis) [8]. Along with VEGF-D, it is proposed to use the methylimidazoleacetic acid (MIAA), that is declared as a histamine metabolite [9].

Currently, in the routine practice of a LAM diagnosis, there is a concentration determation of metalloproteinases type 2 (mainly in the blood serum) and type 9 (both in the blood serum and urine), which is more applicable for assessing the effectiveness of therapy, but not for a primary diagnosis [10–12]. Herewith, the researchers develop and test molecular “nanosensors”, that allow the assessment of the enzyme activity in real time by determining the level of specific “sensory markers” in the urine. The essence of the “nanosensors” action is in their specific interaction with metalloproteinases, whereupon the specific compound is eliminated from the body through the urine [13]. This may be interesting not only to be used in clinical practice, but also in scientific research.

It has also been shown that in LAM patients, the blood plasma concentration of osteopontin is significantly higher in comparison with healthy people, which is explained by the participation of this protein in the process of a signal transmission from CD44v6 receptors [14].

Moreover, three serum proteins can be identified as potential diagnostic markers: fibronectin, von Willebrand factor and kallikrein III [15]. A recent study of the blood plasma of patients with an established LAM diagnosis is interesting due to using a nuclear magnetic resonance method to identify a wide range of biochemical markers. Based on the results of this study, the authors identified two potential blood plasma LAM markers — methionine and acetic acid [16].

It has also been shown that in the LAM patients, concentrations of the cytokines CCL2 (MCP-1), CXCL1 (GRO1) and CXCL5 (ENA-78) that are determined in the fluid obtained during the bronchoalveolar lavage, is higher. The main difficulty in introducing the identified markers into the routine practice is the standardization of methods for collecting that fluid due to the impossibility of accurately determining the degree of the material dilution [17].

A surfactant analysis in the mice demonstrates a significant activity increase in the inducible NO synthase (iNOS) in the lungs of the animals with a mutation in TSC2 that results in the nitrosylation of surfactant protein D [18], an established regulator of the alveolar macrophages activity [19].

It is also advisable to focus on the biochemical features that underlie various treatment approaches to LAM during their consideration.

THE AIM of the work was to collect and systematize the data on the treatment approaches to pulmonary lymphangioleiomyomatosis (LAM) based on insights into the pathogenesis of the disease.

MATERIALS AND METHODS

The selection of the sources was accorded to the algorithm presented at Figure 1. As a result, 70 original sources have been selected from analyzed 1 157 articles and monographs (including duplicates).

The search for the sources was carried out in the databases of PubMed, eLibrary.ru, CyberLeninka for a fifty-year period of publications — from 1973 to August 2023, with an emphasis on more current publications and publications in highly rated scientific journals. The keywords used for the search were as follows: “lymphangioleiomyomatosis” / “лимфангиолейомиоматоз” isolated and in combination with “pulmonary / лёгкие”, “(bio)marker” / “(био)маркер”, “immunology” / “иммунология”, “gene” / “ген”, “diagnosis” / “диагностика”, “therapy” / “терапия”, “experiment” / “эксперимент”, “animal model” / “модель животного”.

A primary analysis of the sources (*n*=1157) was based on a screening of their abstracts. As a result, 541 sources including original studies, clinical observations, a retrospective analysis of the clinical observations data, a meta-analysis of the experimental studies and clinical observations, monographs and their individual chapters wholly or partially directly related to LAM, were selected. Next, duplicates (*n*=29) were excluded and a screening of the sources (*n* = 512) was carried out. As a result, the review includes only the sources that contained information about: biochemical and/or genetic characteristics of changes, approaches to their treatment (correction). The criteria for non-inclusion were: isolated extrapulmonary LAM

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manifestations, a clinical LAM picture (symptoms and semiotics), functional studies, methods of radiation and ultrasound examinations, approaches to collecting biological materials for the examination.

To analyze the selected sources, a descriptive and analytical method was used.

The review also includes three more sources containing information necessary to clarify individual concepts, definitions, research and diagnostic methods related to the topic of the review.

RESULTS AND DISCUSSION

The drug therapy approaches are based both on the clinical observations and on the data on the biochemical changes occurring in LAM. The data below are structured chronologically and, where it is possible, are grouped by the similarity of the action mechanism.

Radical and hormonal kinds of therapy

Due to the predominant LAM manifestation in women and due to the positive clinical experience, one of the first ideas for the "targeted" LAM therapy was a major surgery at the early stages of identifying the symptoms of the disease [20]. But later on, probably due to the widespread introduction of the hormone replacement therapy into the clinical practice and for humanistic reasons, this method got less preferable than the drug therapy.

The world experience in the LAM treatment with sex hormones shows conflicting data. Several studies *in vitro* demonstrated the effectiveness of estrogen and progesterone receptor blockers on the LAM cells development [21, 22]. An *in vivo* experiment on Eker rat uterine leiomyoma cells (line ELT3) showed the inducing effect of estradiol on metastasis of TSC2-deficient cells through matrix metalloproteinase 2. Whereas the use of fulvestrant inhibited estradiol-induced lung metastases and increased the survival of the mice with xenografts tumors treated with estradiol [22]. This consists with retrospective clinical observations [23]. However, the current results of the clinical observations indicate only a variable effectiveness of such therapy and only in women whose clinical LAM picture was dependent on the menstrual cycle phase [24], and the clinical studies actually proved the ineffectiveness of the hormonal therapy, in particular the analogue of a gonadotropin-releasing hormone [25]. Herewith, to refuse the application of estrogen-based oral contraceptives due to the fact that their effect on the growth of LAM cells has been proven experimentally [22] and by clinical observations [26], seems reasonable.

Regarding the use of systemic glucocorticosteroids (SGCs), the situation is even more ambiguous. Although LAM is called "steroid-sensitive cancer" [27], we are usually talking about estrogens and progesterone are usually in the focus of the discussion, and no data have been found on clinical observations of the SGCs effect on the course of LAM or on the experimental study of this effect. Symptomatic LAM therapy usually includes the use of inhaled glucocorticosteroids, long-acting beta-2-adrenergic agonists and anticholinergics; however, the tactics of their use need to be studied in more detail [28], and no data have been found on their effect on pathogenesis either.

In the context of the therapy effectiveness of LAM as a disease directly related to sex hormones, the question about the metastatic nature of LAM cells is still relevant. A genetic analysis of LAM cells demonstrates their similarity to myometrial cells, from which the authors who have studied this issue conclude that they are likely to have a metastatic nature. Herewith, they note that there is need for further research. However, they point out that even if the development of LAM cells is determined as *in situ*, it will be possible to use the PBX1/HOXD11 markers as targets for a specific kind of therapy by the drugs that are an alternative to mTOR inhibitors that characterize myometrial cells [29]. This is serine-threonine protein kinase, acting as a subunit of intracellular multimolecular signaling complexes that regulate the cell growth well-known since 1991. More details about this group of drugs will be discussed below.

mTOR inhibitors

The key link in the LAM pathogenesis is considered mTOR. Its constitutive activation is a result of mutation in TSC-genes (typical for LAM-cells) that leads to a proliferation stimulation of mutant cells, and the leading pathogenetic drug therapy is its inhibitors — sirolimus and everolimus [1]. But there are also the data on the non-drug inhibition of mTOR, based on the artificial deficiency of amino acids, demonstrated *in vitro* in cell cultures [30].

A retrospective analysis of the clinical data from the patients with verified LAM included in the Chinese LAM registry from 10 May 2017 to 31August 2020 (n=399), demonstrates that the use of sirolimus significantly reduces the risk of recurrent pneumothorax in the LAM patients. However, the authors keep the question about the significance of pneumothorax to start sirolimus therapy, and note that this requires a further study [31]. On the other hand, it has been shown that even relatively low sirolimus doses (with plasma concentrations below 5 ng/ml) demonstrate a clinical efficacy comparable to the use of high doses of this drug (with plasma concentrations of 5–15 ng/mL) [32]. In general, the use of sirolimus demonstrates a satisfactory safety profile according to a retrospective analysis of adverse events caused by the use of the drug in patients included in the LAM registry of Peking Union Medical College Hospital (PUMCH), Beijing, China (n=142) [33].

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

Based on the same registry, there is a retrospective study of the course of pregnancy against the background of taking Sirolimus at the established diagnosis of LAM (*n*=30). Based on its results, the authors draw a non-confident conclusion that although the use of sirolimus is probably associated with a high risk of a spontaneous abortion. In their study, this connection is not observed reliably [34]. Herewith, there is a clinical observation of a woman at the established diagnosis of LAM, who endured successfully two pregnancies, the second during therapy with sirolimus, gave birth to two healthy children and demonstrated a clinical stability of the disease [35].

The presence of a risk of adverse events caused by taking mTOR inhibitors, including a combination with another method of treating LAM (a lung transplantation) and in the context of an increase of a risk of developing infectious diseases due to a weakened immune response [36] forces further research into their effectiveness and the search for alternative treatment methods.

Regarding the effect on the prognosis of a lung transplantation, the data on the relative safety of the sirolimus and everolimus use both in the period up to and after the lung transplantation, have been previously published [37]. However, the results of the recent survey (2022) of several centers where a lung transplantation is carried out demonstrate that now it is impossible to unequivocally conclude both about the need to continue therapy with mTOR inhibitors in patients included in the waiting list for a lung transplant, and about the impact of taking these drugs on “an anastomotic failure” after a lung transplantation [38].

Regarding the issue of increasing the risk of developing infectious diseases, the greatest interest nowadays is the condition of patients on therapy with mTOR inhibitors in the context of the ongoing COVID-19 pandemic. It was shown that patients with tuberous sclerosis (TS) and LAM on therapy with mTOR inhibitors did not have a higher risk of contracting COVID-19 [39]. In the outcomes of COVID-19 in the patients at the previously established diagnosis of LAM, there are no significant differences between those who were treated with mTOR inhibitors and those who received other therapy, either [40]. A case of a 29-year-old patient at the previously established diagnosis of LAM, who fell ill with COVID-19 and tolerated it relatively satisfactorily on Sirolimus therapy, has been also described in detail [41].

In addition, the development of bronchial hyperreactivity induced by sirolimus has been described, with a description of the supposed pathogenesis of this adverse event development [42].

Overall, it remains an open question as to whether such therapy is necessary or at least defining clear criteria for the need of it. This describes the clinical case of a 36-year-old patient with a verified diagnosis of LAM after a series of spontaneous pneumothoraxes, but after that the course of the disease independently stabilized without taking any specific therapy [43]. This can point out the invalidity of the thesis about mTOR being not the only one key link in the LAM pathogenesis.

The search for new treatment approaches to LAM can be divided into two directions — the isolated use of alternative drugs or their combination with mTOR inhibitors.

mTOR inhibitors in combination

Statins

As far back as 2007, an experiment demonstrated the effectiveness of a combination of mTOR inhibitors and statin drugs (in particular atorvastatin), including by inhibition of prenylation of the GTP-binding protein RHEB, which is involved in the regulation of the cell cycle [44]. Later, experiments *in vitro* [45] and *in vivo* [46] demonstrated the effectiveness of the combination of mTOR inhibitors with Simvastatin, and its greater effectiveness was noted in comparison with atorvastatin [47].

In clinical studies of the proposed combination of simvastin+sirolimus and simvastin+everolimus, multidirectional dynamics is noted: on the one hand, it is possible to achieve a stabilization of the lung diffusion capacity and lungs volumes; on the other hand, a decrease of the speed criteria of the external respiration function [48].

Hydroxychloraquine

The combined effects of mTOR inhibitors and hydroxychloroquine are studied actively. Their extreme similarity in their effect on polyamine metabolism was shown in an *in vitro* experiment on the cells obtained from LAM patients. In this regard, the authors also propose to consider the assessment of polyamine metabolism as a biochemical criterion for the effectiveness of the LAM therapy, and point out that the safety of the combined use of drugs has already been proven, but a therapeutic effect assessment requires a further study [49].

Bisphosphonates

Another option for mTOR therapy “adding-on” is the use of bisphosphonates, particularly zoledronic acid, based on clinical observations. The same combination demonstrates its effectiveness in an *in vivo* experiment on a LAM model in female mice with a subcutaneous injection of TSC-deficient cells [50].

Phytoalexin

Another combination is phytoalexin Resveratrol, which demonstrates a wide range of clinical effects [51]. Clinical trials have demonstrated its safety in combination

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with sirolimus, but its efficacy evaluation in comparison with monotherapy requires further research [52].

Alternative to mTOR inhibitors

In the context of the "isolated" LAM therapy, first, it is necessary to mention the drugs effect on VEGF. An *in vivo* experiment on female mice after the intranasal administration of a suspension of cells obtained from the chylous effusion of a patient with an established diagnosis of LAM, demonstrated the effectiveness of the intramuscular administration of antibodies to VEGF receptors [53]. The similar data were presented in another *in vivo* experimental model in female mice after the injection into the tail vein of a suspension of cells obtained from the renal tubular cystadenoma of TCS2-mutant mice [54].

As the tissues affected by the LAM cells show a deficiency of the collagen type IVa5, their effect on the activity of the LAM cells was appreciated in an *in vitro* experiment on the heterogeneous LAM cells and in an *in vivo* experiment, when the tumor cells of the line LNM35 AAV-EGFP-expressing were engrafted into the ears of the female mice. The results of the study demonstrate a decrease in the cells proliferative activity in response to the use of the protein, that is named by the authors as Lamstatin. Its active center, CP17, is represented by the following amino acid composition — VCNFASRNDYSYWLSTP between amino acids 66 and 82 in the collagen chain [55].

Because of the established effect of the matrix metalloproteinases (MMPs) inhibition by doxycycline, its use in the treatment of LAM was explored. Despite its high effectiveness according to the laboratory studies [8], later on, its ineffectiveness in the LAM treatment was proven by a systematic clinical analysis [56].

Based on the previously established data that the LAM cells express cyclooxygenase-2 (COX-2), and the use of celicoxib in an *in vivo* experiment on the mice demonstrates its effectiveness [57], in 2020, a safety study of this drug in the LAM patients, who had not previously received the treatment, was carried out with positive results. The clinical effectiveness of the drug was not assessed [58].

It was revealed that LAM cells have a local renin-angiotensin-aldosterone system (RAAS) (Fig. 2), and a retrospective analysis of the clinical cases showed that the patients with therapy by angiotensin-converting enzyme (ACE) inhibitor drugs are less prone to a decreased lung function [59]. However, it should be separately noted that determining the level of ACE, a well-known since the end of the last century marker for the diagnosis of sarcoidosis [60], — has been recognized as uninformative for the LAM diagnosis [11].

An *in vitro* experiment on the ELT3V-line cells showed that the exposure to an angiotensin II receptor inhibitor (Losartan) regulates a synthetic activity of TSC2-deficient cells, causing their death by changing the level of expression of the Klotho protein, which is probably involved in aging processes [61]. Moreover, in an *in vitro* experiment on the cells obtained from the chylous effusion of a LAM patient, it was demonstrated that LAM cells in general have a secretory phenotype associated with aging senescence-associated secretory phenotype (SASP), that manifests itself in the activation of β-galactosidase and in increasing the secretion in Cathepsin K (CatK), IL-6 and IL-8. SASP can play a key role in the migration of LAM cells and the transformation of granulomas into cysts. In this light, the identified molecules can be targeted for specific LAM therapy, aimed at reducing the risk of a cystic transformation of the lungs and its progression [62]. It has also been shown that the main producers of one of the SASP — CatK — components are fibroblasts that are associated with LAM, and its activation is possible only at a relatively low pH level (<7.0). The necessary "acidification" of the environment is ensured by the LAM cells themselves by an increased expression of membrane transport proteins that ensure the export of hydrogen cations and the manifestation of the Warburg effect, which is caused by the mTOR dysregulation (Fig. 3) [63]. In addition, "aging" of LAM cells also manifests itself in lipid metabolism changes by SREBP (sterol regulatory element-binding protein), which is an mTOR effector [64].

An *in vitro* experiment on heterogeneous cell cultures and on mice with subcutaneous injections of ELT3-V3-line cells showed that TSC2 deficiency causes an abnormal sphingolipid metabolism, which can be a target for other specific LAM therapy. In particular, these are the enzyme sphingosine kinase 1 (SPHK1), the receptor complex S1PR3, and the phosphorylated sphingosine S1Pthat "binds" them. The effectiveness of PF-543 hydrochloride in inhibiting SPHK1 and the effectiveness of the S1PR3 antagonist (TY52156) have been demonstrated in suppressing the tumor activity of TSC2-deficient cells, in particular, that of LAM cells (Fig. 4) [65].

As has been shown, that the tissues affected by LAM have increased the expression of PD-L1 (CD274), a ligand that suppresses the T-cell immune response. The authors believe that this fact can explain the situation when the immune system is not aggressive towards LAM cells. An *in vivo* experiment demonstrated a statistically significantly better survival of mice that had been treated by PD-L1 inhibitors, which can also form the basis of an alternative route for the treatment of LAM [66], including a form of inhaled drugs[2].

[2] Amosu M.M., McCright J.C., Yang B.E., de Oro Fernandez J.G., Moore K.A., Gadde HS. Inhaled CpG increases survival and synergizes with checkpoint inhibition in lymphangioleiomyomatosis. bioRxiv. 2023;2023.02.06.527331. Preprint. DOI: 10.1101/2023.02.06.527331

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(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

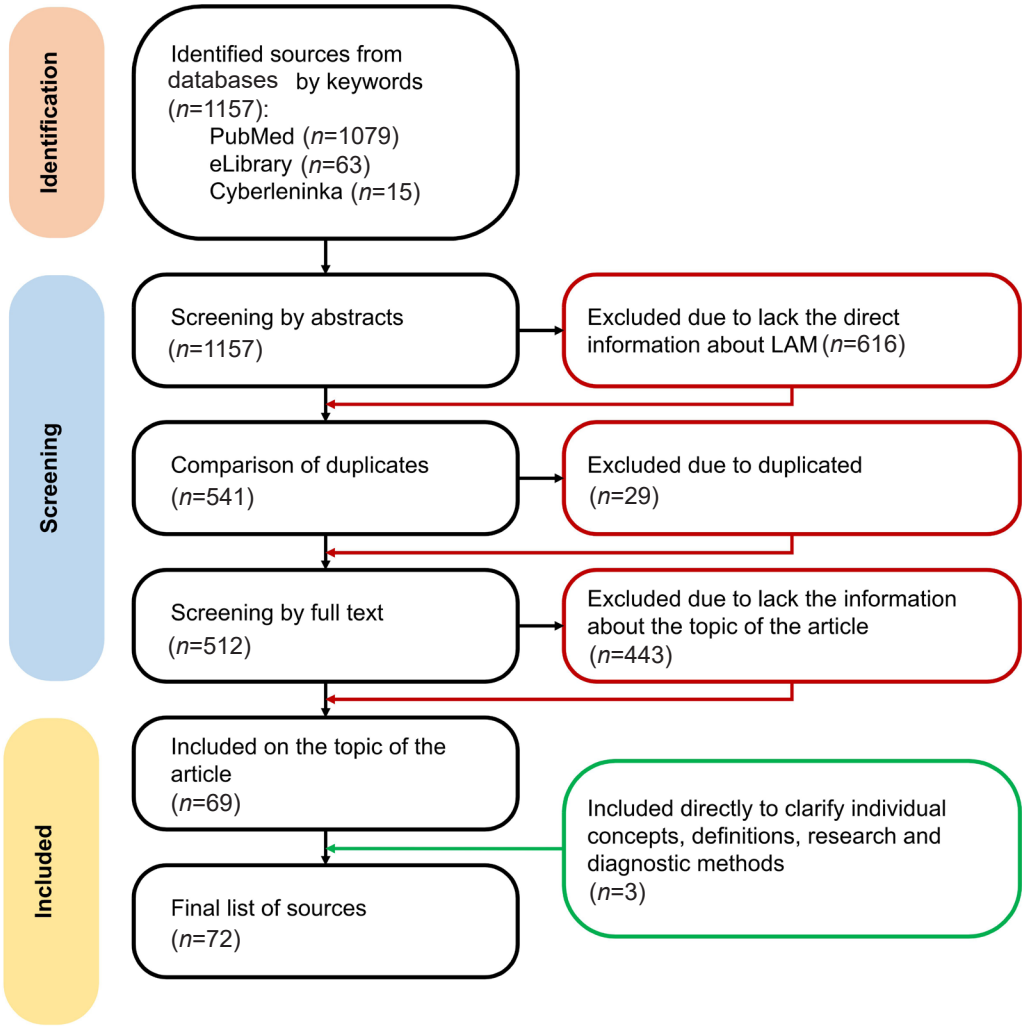

Figure 1 – Scheme for selecting sources to be included in the review.

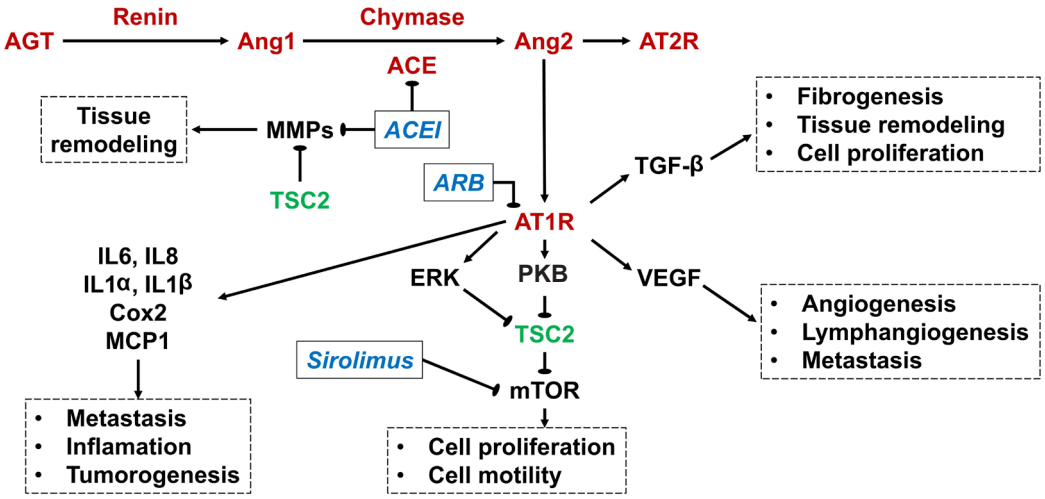

Figure 2 – Local renin-angiotensin-aldosterone system of LAM cells and its targets for drug therapy.

Notes: Adopted from [59]. AGT — angiotensinogen; Ang1 — angiotensin 1; Ang2 — angiotensin 2; AT*R — angiotensin receptor (1; 2 types); ACE — angiotensin-converting enzyme; ACEI — ACE inhibitor; ARB — angiotensin receptor blocker; Cox2 — cyclooxygenase-2; IL* — interleukin (1; 6; 8 types); MMPs — matrix metalloproteinases; MCP1 — monocyte chemoattractant protein 1; PKB — protein kinase B; TSC2 — gene of tuberous sclerosis complex; mTOR — mechanistic/mammalian target of rapamycin; TGFβ — transforming growth factor beta; VEGF — vascular endothelial growth factor.

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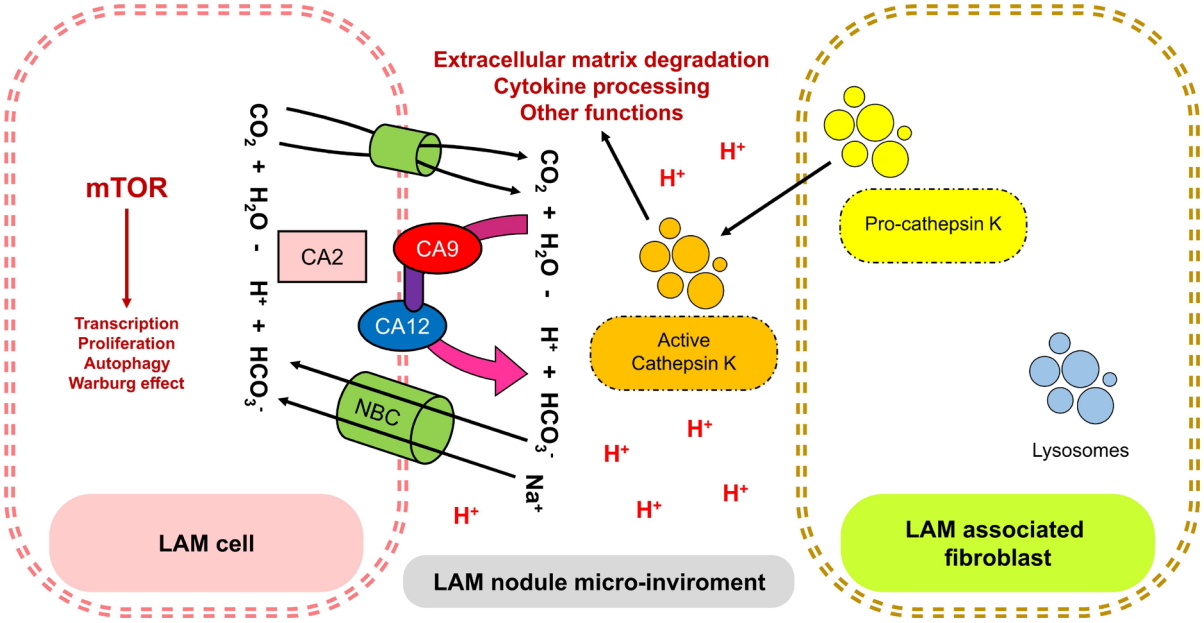

Figure 3 – The mechanism of Cathepsin K activation in LAM cells micro-environment.
Notes: Adapted from data in [63]. CA* — carbonic anhydrases (2, 9, 12 types); NBC — bicarbonate Sodium (Natrium) cotransporter.

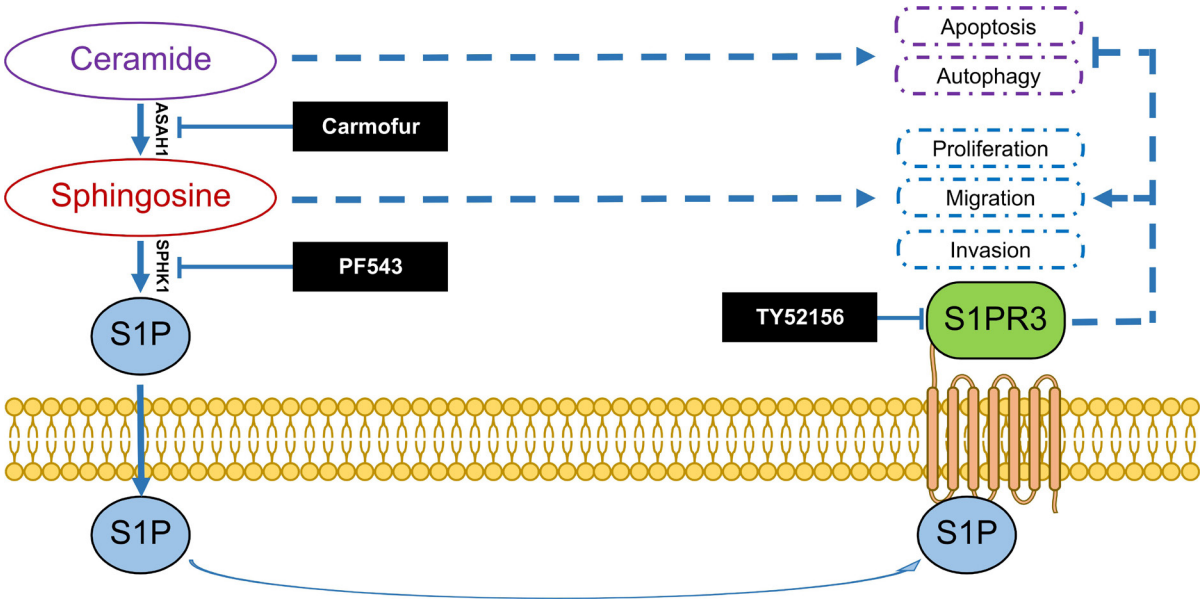

Figure 4 – Abnormal sphingolipid metabolism in LAM cells with potential targets for drug therapy.
Notes: Adapted from data in [65]. Explanations are in the text.

Another potential target for the LAM therapy is Galectin-3, a tumor growth factor, an elevated amount of which was found in LAM cells [67].

In June 2023, a great study of the cytostatic drug Sorafenib was published. It was carried out on a cell culture obtained from the human lungs affected by LAM and extirpated during the transplantation. The cells were cultured and then engrafted into the cell culture obtained from healthy lungs that mimicked the own lung tissue and a stromal component. As a result, the invasion of LAM cells and the effect of the specified cytostatic drug on this process were assessed. Finally, the invasion of LAM cells and the effect of the indicated cytostatic drug on this process were estimated. A pronounced inhibitory effect of Sorafenib on the invasion process was observed, which the authors associate with VEGF, transforming growth factor beta (TGFβ) signaling and the Wnt signaling pathway[3].

According to the recent study, the genes *IGF1*, *SERPINE1*, and *CXCL12* have been recognized as key links in the pathogenesis of the inflammatory response

[3] Koc-Gunel S., Gautam L.K., Calvert B.A. Sorafenib inhibits invasion of multicellular organoids that mimic Lymphangioleiomyomatosis nodules. Preprint. DOI: 10.1101/2023.06.12.544372

and intense LAM proliferation. The results of the research can form the basis for a new pathogenetic LAM therapy [68].

In addition, in the *in vitro* experiment on ELT3-V3-line cell cultures that had been obtained from Eker rat uterine leiomyoma and ELT3-T3-line cells, it was shown that in the LAM cells there was a violation of the expression of glutaredoxin-1. As a result, a cell apoptosis was inhibited, which provoked a tumor growth. The mechanism of the identified changes was described and it had been proven that it was not associated with mTOR. It is assumed that the use of the drugs that normalize the production of glutaredoxin-1 can create a new treatment approach to LAM [69].

Concluding the discussion of the LAM therapy, it is worth mentioning the survival trends of patients. Overall, based on the analysis of the outcomes of the LAM patients at Asian Medical Center (Seoul, Republic of Korea) from July 2001 to February 2020, and compared with the data from other studies, there is a trend towards an increase in the percentage of a ten-year survival of the patients: approximately 80% in 2000–2001, 86% in 2007, 90.9% in 2020 [70].

CONCLUSION

In the search for the treatment approaches to LAM, the researchers have traveled a truly thorny path from radical and even barbaric methods that cripple the body of an already ill person, to the methods based on a deep understanding of molecular biology and having a relatively more acceptable safety profile. However, all currently used methods of the drug therapy and the proposed new methods are aimed at only treating an already established disease, and an effective drug prevention of LAM now seems almost impossible due to the lack of a complete understanding about its pathogenesis and, more importantly, its etiology.

This issue is the most relevant in determining further prospects for the development of pharmacotherapeutic approaches to LAM.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Ilya V. Polovnikov — creation of the idea, work with the key aim and objectives, data collection, analysis and interpretation, writing the manuscript, preparing the article for the publication, collection and reworking of data visualization; Galina Y. Yukina — work with the key aim and objectives, data collection, analysis and interpretation, preparing the article for the publication, provision an access to the databases for analysis; Elena G. Sukhorukova — work with the key aim and objectives, data collection, analysis and interpretation, critical revision of the data visualization. All the authors have made equial and equivalent contributions to the preparation of the publication.

All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

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AUTHORS

Ilya V. Polovnikov – pulmonologist, senior laboratory assistant of the department of pathological anatomy with a pathology clinical department, Pavlov First Saint Petersburg State Medical University. ORCID ID: 0000-0002-8633-8496. E-mail: policrats@mail.ru

Galina Yu. Yukina – Candidate of sciences (Biology), associate professor, head of the scientific laboratory of pathomorphology of the scientific and clinical center of pathomorphology, Pavlov First Saint Petersburg State Medical University. ORCID ID: 0000-0001-8888-4135E-mail: pipson@inbox.ru

Elena G. Sukhorukova – Candidate of sciences (Medicine), senior researcher at the scientific laboratory of pathomorphology of the scientific and clinical center of pathomorphology, Pavlov First Saint Petersburg State Medical University. ORCID ID: 0000-0001-5521-7248. E-mail: len48@inbox.ru