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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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INTERACTION BETWEEN NATURAL POLYPHENOL RESVERATROL AND IMMUNE SYSTEM: BIOCHEMICAL ASPECTS

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Abstract.

The article explains the biochemical aspects of interaction of natural polyphenol resveratrol and immune system. The molecular mechanisms of action of resveratrol are given. The anti-inflammatory effect of resveratrol is described in detail. The relationship between resveratrol and tumor macrophages was analyzed. It has been shown that resveratrol can have an activating, suppressive and modeling effect on the cells of immune system, as well as exhibit a suppressive effect on inflammatory and tumor processes.

Key words. Resveratrol, immune system, biochemistry, anti-inflammatory effect, antitumor effect, antioxidants, macrophages, lymphocytes, Sirt1.

Introduction.

Resveratrol (trans-3,4,5-trihydroxystilbene) is a natural polyphenol found in red wine, rhubarb, blueberries, many types of red grapes, and peanuts. Resveratrol may exhibit antioxidant (AO), anti-inflammatory, anticancer, antimicrobial, antineurodegenerative, and estrogenic properties. The immunomodulatory role of resveratrol was proposed over 18 years ago in a study that demonstrated how it suppresses spleen cell proliferation induced by concanavalin A (ConA), interleukin-2 (IL-2), or alloantigens, and more effectively prevents the formation of IL-2 and interferon gamma (IFNγ) by lymphocytes and production of tumor necrosis factor alpha (TNF-α) or IL-12 by macrophages. Resveratrol is involved in the activation of macrophages, T cells, and natural killer (NK) cells. In addition, this compound is involved in the suppressive functions of regulatory T-lymphocytes CD4+ and CD25+. Its effects result from its ability to scavenge reactive oxygen species (ROS), inhibit cyclooxygenase (COX), and activate many anti-inflammatory pathways, including the Sirtuin-1 (Sirt1) enzyme. Note that Sirt1 is an enzyme that is located in the cell nucleus; refers to transcription factors that promote cellular regulation (responses to stressors and longevity). Resveratrol, by activating Sirt1, disrupts signaling in the TLR4/NF-κB/STAT chain, which in turn reduces the production of cytokines from inactivated immune cells or pro-inflammatory factors derived from macrophages/mast cells, such as platelet activating factor (PAF), TNF-α and histamine. Given the wide range of positive effects of resveratrol on the body, it is increasingly offered as a dietary supplement. However, pharmacokinetic analysis shows that resveratrol undergoes rapid metabolism in the body. Its bioavailability after oral administration is very low, although absorption reaches 70%, this affects the physiological significance of high concentrations used in in vitro studies. So, in this paper, the molecular mechanisms of interaction between resveratrol and the functioning of the body's immune system will be presented [1-3].

Biochemical aspects of the mechanism of action of resveratrol.

The key function of Resveratrol is to suppress the production of inflammatory factors by activating Sirt1. Sirt1 is an important deacetylase involved in many molecular processes, including metabolism, cancer, embryonic development, and immune tolerance. Sirt1 maintains the tolerance of peripheral T-lymphocytes. Removal of Sirt1 leads to increased T cell activation and spontaneous autoimmune disease. Studies show that the relationship between resveratrol and Sirt1 modulates the structure of Sirt1 and enhances the activity of binding to its substrates [1]. Through its ability to activate Sirt1 and suppress inflammation, resveratrol is able to alleviate inflammatory symptoms in experimental models of autoimmune diseases such as colitis, type 1 diabetes, encephalomyelitis, and rheumatoid arthritis. One of the major substrates of Sirt1 is p65/RelA constituting NF-κB, which is a major regulator of leukocyte activation and inflammatory cytokine signaling. Activation of Sirt1 by resveratrol causes inhibition of RelA acetylation, which in turn reduces NF-κB-induced expression of inflammatory factors such as TNF-α, IL-1β, IL-6, metalloproteinases (MMP)-1 and MMP-3, and Cox -2. Resveratrol-treated cells have been shown to be less sensitive to TNF-α-induced NF-κB signaling and initiation of apoptosis, acting as a dual block in the NF-κB signaling pathway.

It has been established that resveratrol suppresses the expression of p300 and promotes the degradation of the inhibitory protein-κBα (IkBα). However, it is not known whether this is due to Sirt1 activation. Resveratrol targets include AMP-activated protein kinase (AMPK), an important cellular energy sensor that controls Sirt1 activity by regulating cellular levels of available nicotinamide adenine dinucleotide (NAD+). Cyclic adenosine monophosphate (cAMP) levels trigger protein kinase A (PKA), which in turn phosphorylates and activates Sirt1. Evidence that resveratrol function is partially mediated by Sirt1 is supported by the observation that the anti-inflammatory properties of resveratrol are abolished by genetic deletion of Sirt1 or the addition of Sirt1 inhibitors such as Sirtinol [4-6]. Upon subsequent activation of AMPK, an increase in NAD+ levels induces Sirt1 activation, which promotes beneficial metabolic changes primarily through deacetylation and activation of the peroxisome proliferator-activated receptor gamma-coactivator-1-alpha (PGC-1-α).

Anti-inflammatory effect of resveratrol.

Additionally, it has been shown that resveratrol exhibits an anti-inflammatory effect in macrophages [7-13]. Macrophages differentiate from blood monocytes and are involved in both innate and adaptive immunity. These cells constitute a heterogeneous pool of cells with a wide spectrum of biological activity depending on their physical location and external signals received from the tissue microenvironment. Many of these activities seem to differ in nature: anti-inflammatory effects, immunogenic and tolerogenic activities, tissue destruction and repair. Through a broad spectrum of signal recognition receptors (PRS), these immune cells can specifically identify conserved pathogen-associated molecular structures (PAMPs) that are exclusively present on microorganisms such as viruses, bacteria, parasites, and fungi. The main members of the PRS families are transmembrane TLRs, C-type lectin receptors (CLRs), cytoplasmic nucleotide oligomerization domain (NOD)-like receptors (NLRs), and retinoic acid gene I inducible RNA helicase (RIG-I) RIG-I- like receptors (RLRs).

Thus, activated intracellular signaling induces the expression of genes involved in the inflammatory and/or immune response and the recruitment of phagocytic cells to the site of infection.

Due to their ability to recognize pathogens and activate bactericidal activity, macrophages always act at the site of immune defense. They produce anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGFβ) and inhibit TLR-mediated inflammatory pathways. TLRs initiate signaling in innate and adaptive immune pathways. This highly conserved family of transmembrane proteins includes an extracellular domain that recognizes exogenous and endogenous dangerous molecules and an ectodomain that activates downstream pathways. Several lines of evidence suggest that continuous activation or dysregulation of TLR signaling may contribute to the occurrence of chronic pathological conditions. Resveratrol regulates TLR4 expression. Therefore, it can be used for TLR-mediated inflammatory responses and chronic diseases associated with TLR activation, including obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, Crohn's disease, rheumatoid arthritis, cardiovascular and neurodegenerative disorders.

The molecular regulation of the inflammatory response is largely modulated by transcription factors. Resveratrol has been shown to reduce NF-κB activation and Cox-2 expression in lipopolysaccharide (LPS) induced RAW264.7. In addition, it inhibits TANK-binding kinase 1 (TBK1) and receptor-interacting protein 1 (RIP1) in the adapter containing the interleukin-1 toll receptor domain, inducing the interferon complex (TRIF) in myeloid differentiation factor-independent signaling. 88 (MyD88) paths [14,15-17].

Additional studies have shown that resveratrol has an anti-inflammatory effect by attenuating the TLR4-TRAF6, mitogen-activated protein kinase (MAPK), and AKT pathways in LPS-induced macrophages [7,18].

Another signaling pathway associated with inflammation is the endoplasmic reticulum (ER) response. ER stress leads to the activation of inositol-requiring enzyme 1 (IRE1), which is involved in the splicing of X-box-binding protein 1 (Xbp-1) into its functional state and ultimately leads to the suppression of global translation and an increase in chaperone activity.

It is known that if cells fail to reduce the effective scattering area during spectroscopy, they undergo apoptosis. It has been suggested that the IRE1α-Xbp-1 pathway is critical for Toll-like receptor (TLR)-induced production of inflammatory cytokines by macrophages. Xbp-1 was found to be regulated by post-translational acetylation and deacetylation mediated by p300 acetyltransferase and Sirt1 deacetylase, respectively.

More recently, resveratrol has been shown to prevent the increase in acetylated α-tubulin caused by mitochondrial damage in macrophages stimulated by inducers of the nodal receptor family, pyrine domain-containing 3 (NLRP3) inflammasome. Since resveratrol influences the creation of an optimal assembly site for NLRP3 and ASC and in turn inhibits NLRP3-inflammasome activation, it may be an effective drug for the treatment of NLRP3-related inflammatory diseases. Resveratrol has been found to affect not only the transcription of NF-κB elements, but also the transcription of STAT1 and cyclic cAMP-binding protein 1 (CREB1). TNF-α-induced activation of NF-κB elements is also modulated by resveratrol.

LPS was shown to dose-dependently increase extracellular malondialdehyde (MDA) and nitric oxide without affecting their intracellular levels, while resveratrol reversed all of these harmful effects. LPS activation of monocytes and macrophages induces NF-κB-dependent transcription of chemokines such as CXCL8/IL-8, CXCL10/IP-10, CCL2/MCP1, and CCL5/RANTES [19,20]. LPS increases the expression of CD14, interleukin-1 receptor-associated kinase (IRAK1), and a phosphorylated form of the p38 MAPK protein. It has been shown that resveratrol prevents the effect of LPS by reducing the expression of CD14 and IRAK1, and at the same time increases the phosphorylation of the p38 MAPK protein. Further studies have shown that resveratrol reduces the LPS-induced prooxidant effect in the AR42J cell line through a Myd88-dependent signaling pathway. These data indicate that resveratrol exhibits AO properties in a Myd88-dependent pathway without IRAK1 or TRIF-dependent pathways [2,11].

Sirt1 plays a direct regulatory role in macrophage function during inflammation. Production of the pro-inflammatory cytokines TNF-α, IL-6, and IL-1β by macrophages in mice with myeloid-specific Sirt1 knockout increases dramatically in response to infection and inflammation. In addition to pro-inflammatory cytokines, Sirt1 is involved in the expression of cell surface molecules such as intercellular adhesion molecule 1 (ICAM-1) to facilitate macrophage transport during an inflammatory response. Hyperacetylation of the transcription factor NF-κB RelA/p65 was found in macrophages of mice with myeloid-specific Sirt1 knockout, which indicates that the anti-inflammatory activity of Sirt1 in macrophages occurs, among other things, due to the suppression of NF-κB [3].

In addition, resveratrol actively reduces the production of granulocyte-macrophage colony-stimulating factor (GM-CSF), a pro-inflammatory cytokine that acts at the interface between innate and adaptive immunity, essential for the survival/differentiation/activation of pro-inflammatory macrophages and a key marker of atheroma formation [13,21,22].

Some evidence indicates that resveratrol alters cell morphology, gene expression, ligand-receptor interactions, signal transduction pathways, and foam cell formation [15,23].

Resveratrol is also able to modulate the immune response by influencing cellular levels of prostaglandin E2 (PGE2). PGE2 plays an important role in the regulation of the immune response. Resveratrol activates COX-2 in various inflammatory diseases. The cell-specific effect on interleukin production is another important function of resveratrol. In fact, resveratrol has been found to upregulate IL-1β and IL-6 expression in peripheral blood lymphocytes (PBL), but has the opposite effect on macrophages. Increased production of IL-1β and IL-6 characterizes a pro-inflammatory status that promotes the differentiation and function of T-helper lymphocytes, but it is also involved in tissue regeneration. Immune cells exposed to resveratrol in the vascular compartment expressing significant levels of IL-1β or IL-6 are triggered for an adaptive immune response. However, resveratrol only affects immune cells for a limited time due to its short half-life in the blood. These data suggest that resveratrol facilitates the systemic response to injury and moderates the low-grade inflammatory status associated with chronic tissue disease [17,24].

Resveratrol and tumor-associated macrophages (TAMs).

Clinical and experimental evidence suggest that high macrophage infiltration in most human cancers is associated with tumor malignancy, poor prognosis, and tumor recurrence. Macrophages exhibit plasticity in their activation profile when stimulated by various cytokines. They are able to both suppress and promote the growth and spread of cancer, depending on the state of their activation. Macrophages can be activated classically (M1) in the presence of IFN-γ and LPS, while in the presence of IL-4 and IL-13, or indirectly through the induction of Th2 cells towards alternatively activated macrophages (M2). Polarization of macrophages profoundly alters the immune properties of these cells. Polarized M1 macrophages exhibit high levels of proinflammatory cytokines and promote Th1 responses that increase tumor activity and antitumor immunity. The polarization of M1 macrophages is mainly regulated by separate transcriptional networks consisting of the interferon regulatory factor (IRF-1/5), STAT-1/4 and NK-κB. Alternatively, M2-like polarization of macrophages that produce secretory factors that promote tissue remodeling, immune tolerance, and angiogenesis may be associated with tumor progression. M2 polarization is induced by Th2 cytokines such as IL-13 and IL-4 and regulated by transcription factors such as IRF-4, STAT-3/6, PPAR-γ and Krüppel-like factor 4 (KLF-4). Accumulating evidence indicates that macrophages controlling the ability to stimulate or suppress a tumor depend on their subphenotype, which is dynamically switched. TAMs in malignant tumors resemble alternatively activated macrophages (M2-like). They enhance tumor-associated angiogenesis, promote tumor migration and invasion, and lack an antitumor immune response. A high density of TAMs, especially in the M2 subgroup, corresponds to poorer overall survival (OS) in patients with lung cancer, gastric cancer, or breast cancer. TAMs infiltrated into primary tumors or metastatic sites play a critical role in targeting tumor cells from the primary site to distant tissues in various mouse models. TAMs in the peripheral blood can mediate the migration of circulating tumor cells and contribute to their achievement in distant sites of metastasis [5,25].

In an in vitro experimental model investigating the morphology and function of macrophages in relation to the tumor microenvironment, treatment with the synthetic resveratrol analogue HS-1793 was found to significantly increase IFN-γ, which reprogrammed the M2 phenotype [24,26,27]. Thus, it was proved that HS-1793 effectively counteracts the immunosuppressive and tumor-progressive effects of TAMs.

STATs are cytoplasmic transcription factors that act as intracellular effectors of cytokine and growth factor signaling pathways. STAT3, a member of the STAT family, plays a key role in promoting proliferation, differentiation, anti-apoptosis, or cell cycle progression. Constitutive activation of STAT3 is involved in a variety of tumor cells. As previously mentioned, activation of STAT3 in the M2 subset results in tumor-induced immunosuppression and activates STAT3 by inhibiting the expression of mediators required for immune activation against tumor cells.

In several mouse models of carcinogenesis, tumor progression is often associated with a phenotypic switch from M1 to M2 in TAMs. Inhibition of STAT signaling pathways can suppress tumor growth and metastasis by inhibiting M2-like macrophage polarization, which also suggests that TAMs are a possible target in cancer therapy [11,14]. To date, there have been many studies on the role of STAT3 in cancer treatment and its therapeutic applications. In lung cancer cells, resveratrol treatment reduces STAT3 activity and inhibits lung cancer progression by inhibiting protumoral TAM activation. In addition, in a lung cancer xenograft model in a mouse population, resveratrol was shown to significantly inhibit tumor growth by reducing cell proliferation and p-STAT3 expression in tumor tissues. Other studies have shown that both the antitumor and antimetastatic effects of resveratrol were due in part to antilymphangiogenesis through the regulation of M2 macrophage activation and differentiation. In fact, resveratrol inhibited the production of IL-10 monocyte chemoattractant protein-1 (MCP-1) in M2 macrophages, while it stimulated the production of TGFβ1. However, resveratrol inhibited STAT3 phosphorylation without affecting its expression during M2 macrophage differentiation. In addition, resveratrol-treated M2 macrophage conditioned medium inhibited vascular endothelial growth factor C (VEGFC)-induced migration, invasion, and human lymphangiogenesis of human lymphatic endothelial cells (HLEC).

Conclusion.

Thus, by interacting with several molecular targets, resveratrol regulates innate and adaptive immunity. Resveratrol has been shown to dose-dependently modulate immune system function. In low doses, it stimulates the action of the immune system, and in high doses, it causes immunosuppression. The immunomodulatory effect of resveratrol has been established, which is confirmed by a number of studies conducted with the participation of various animal models and cell lines. In addition, resveratrol reduces inflammatory reactions, including the processes of autoimmune genesis, slows down the aging

process of the immune system, in particular, and improves immunological activity against cancer cells, inhibiting tumor growth, metastasis, and the area of lymphatic endothelial cells in tumors.

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