



Streptococcal effective molecules as promising anticancer agents: *pros* and *cons*

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Abstract

Oncological diseases remain the main cause of death and disability of the population worldwide. The most malignant types of cancer include of pancreas, liver and brain tumors. Modern methods of therapy (including chemoradiation, targeted and immune therapy) do not allow achieving the desired effectiveness in this group of patients. In this regard, new approaches to the treatment of oncological diseases are needed.

The **aim** of this review was to discuss the mechanisms of anticancer action of *Streptococcus pyogenes* and other streptococcal species, as well as to consider their cancer-stimulating effects and their limitations.

The review considers the current state of the problem of using bacterial oncotherapy involving streptococci A group (in particular, *S. pyogenes*). The involvement of *S. pyogenes* pathogenicity factors is discussed: M-protein, exotoxins: streptolysins S, O, superantigens, arginine deiminase, etc., as well as molecular mechanisms mediated by the host immune system cells. The authors' own data show that *S. pyogenes* exhibits selective M-protein-mediated cytolytic activity against C6 glioma and pancreatic adenocarcinoma (Panc) tumor cells and no activity against normal fibroblasts. The data on preclinical and clinical application of the streptococcal-based medicine OK-432 for the therapy of oncological diseases are briefly summarized. Tumor-associated properties of streptococci (induction of cytokine storm, proliferation, migration and angiogenesis of vascular epithelial cells, formation of neutrophil extracellular traps in the tumor microenvironment) caused by their interaction with immune cells of the tumor-bearing organism are also discussed.

Conclusion. The research data presented in this review convincingly demonstrate that *S. pyogenes*, with the participation of pathogenicity factors, can directly exert an antitumor effect on cancer cells. However, it should be noted the streptococcal vaccine should be used with caution, taking into account the individual characteristics of the patient's immune system, since *S. pyogenes* can also have effects of the opposite nature, requiring further research.

Keywords: review, *Streptococcus pyogenes*, antitumor mechanisms, pathogenicity factors, immune system, cancer-associated mechanisms, oncolytic effects, bacterial antitumor drugs

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Научный обзор

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Эффе́кторные молекулы стрептококков как перспективные противоопухолевые средства: плюсы и минусы

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Аннотация

Онкологические заболевания остаются одной из основных причин инвалидности и смертности населения во всём мире. К наиболее злокачественным типам рака относятся опухоли поджелудочной железы, печени и головного мозга. Современные методы терапии (в том числе химиолучевая, таргетная, иммунная терапия) не позволяют добиться желаемой эффективности у этой группы пациентов. В этой связи необходимы новые подходы для терапии онкологических заболеваний.

Целью обзора явилось обсуждение механизмов противоопухолевого действия *Streptococcus pyogenes* и других видов стрептококков, а также рассмотрение их опухольстимулирующих эффектов и существующих при этом ограничений.

В обзоре рассмотрено современное состояние проблемы использования бактериальной онкотерапии с участием стрептококков группы А (в частности, *S. pyogenes*). Обсуждается участие факторов патогенности *S. pyogenes*: М-белка, экзотоксинов: стрептолизина S, О, суперантигенов, аргининдеиминазы и др., а также молекулярные механизмы, опосредованные клетками иммунной системы организма-носителя. Собственные данные авторов показывают, что для *S. pyogenes* обнаружена селективная опосредованная М-белком цитолитическая активность в отношении опухолевых клеток глиомы С6 и аденокарциномы поджелудочной железы и её отсутствие на нормальных фибробластах. Кратко суммируются данные по доклиническому и клиническому применению полученного на основе стрептококков препарата ОК-432 для терапии онкологических заболеваний. Обсуждаются и опухоль-ассоциированные свойства стрептококков (индукция секреции цитокинов, пролиферации, миграции и ангиогенеза эпителиальных клеток сосудов, образование внеклеточных ловушек нейтрофилов из микроокружения опухоли), обусловленные их взаимодействием с клетками иммунной системы организма-опухоленосителя.

Заключение. Представленные в обзоре научные данные убедительно показывают, что *S. pyogenes* могут при участии факторов патогенности непосредственно оказывать противоопухолевое действие на раковые клетки. Однако стрептококковую вакцину следует применять с осторожностью, учитывая индивидуальные особенности иммунной системы пациента, поскольку *S. pyogenes* могут оказывать и эффекты противоположного характера, требующие дальнейших исследований.

Ключевые слова: обзор, *Streptococcus pyogenes*, противоопухолевые механизмы, факторы патогенности, иммунная система, опухоль-ассоциированные механизмы, онколитические эффекты, бактериальные противоопухолевые препараты

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

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Introduction

Cancer diseases are one of the main causes of disability and mortality worldwide, second only to cardiovascular pathology [1]. According to the World Health Organization and the International Agency for Research on Cancer (Globocan), 19,976,499 new cases of cancer were globally registered in 2022, of which 9,743,832 were death (48.8%)¹. The World Health Organization predicts that by 2045, cancer incidence and mortality will increase by 55% to reach 31.0 million and 16.7 million cases respectively.

Recent scientific achievements in biology, medicine and oncology have been marked by the discovery of cancer stem cells, horizontal transfer of genetic information (mobile genetic elements), and the emergence of new genetic diagnostic methods: whole-genome and whole-exome sequencing. These and other advances contributed to a paradigm shift from cohort-based to individualized treatment, which led to the emergence of new scientific directions: targeting and immunotherapy, which gave hope for the cure of many types of cancer [2, 3].

On the other hand, all these successes in oncology caused new problems associated with the establishment of molecular and cellular heterogeneity of tumors, the development of multiple drug resistance of cancer cells to therapy, its high toxicity to normal tissues and cells, and the participation of tumor microenvironment cells in cancer progression [4, 5]. These obstacles required reconsideration of existing treatment methods and search for new therapeutic approaches to oncologic diseases.

The use of live bacteria that selectively colonize the tumor represents a promising prospect for cancer therapy that overcomes many problems [6]. Unlike most therapeutic agents, bacteria have multiple mechanisms targeted at inhibiting tumor growth. Microorganisms selectively colonize tumors and proliferate within them, where they initiate anticancer immune responses, which may ultimately increase survival after systemic infection in tumor models of animals [7]. For example, a *Salmonella typhimurium* strain VNP20009 attenuated more than 10,000-fold compared to the wild-type strain has a tumor : liver colonization ratio > 1000 : 1 and exhibits at titers of $1 \times 10^4 - 3 \times 10^6$ CFU/mouse) a strong inhibitory effect (57-95%) on the growth of Lox, DLD-1, A549, WiDr, HTB177, MDA-MB-231 and B16F10 human tumors and the development of pulmonary metastases in mouse tumor models [8, 9]. Furthermore, such bacteria can be further programmed using simple or complex genetic and bioengineering methods for the synthesis and tumor-selective delivery of anticancer drugs [10]. For example, the use of bacteria as transport vectors can increase the poor tumor penetration and activity of preventive drugs for chemotherapy while reducing their systemic toxicity to the

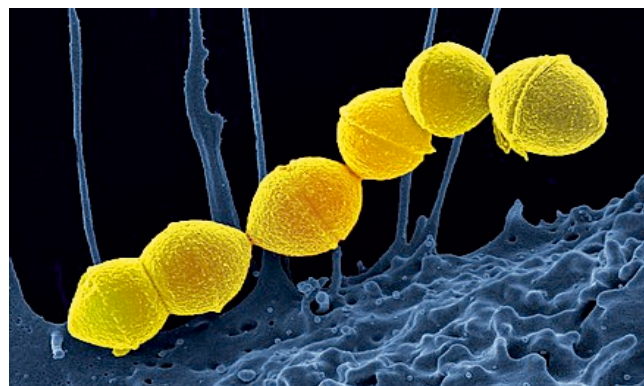


Fig. 1. Electron micrograph of *S. pyogenes*.

Source: *Streptococcus pyogenes*.

URL: https://en.wikipedia.org/wiki/Streptococcus_pyogenes

organism. Bacteria can be used for targeted delivery of chemotherapeutics, cytokines, immunomodulators, enzymes, prodrugs, or small interfering RNAs to tumors [6]. Furthermore, bacteria themselves can synthesize anticancer enzymes, for example, L-asparaginase and methionine-gamma-lyase [11, 12].

Motility is an important property and allows bacteria to penetrate deeper into tumor tissue. In contrast to the passive distribution and limited penetration of chemopreventive agents, bacteria are complex living organisms that can obtain energy from the environment and convert it into kinetic energy of movement, which allows them to move independently deeper into the tumor [13]. Microorganisms are able to influence the tumor microenvironment and produce their own oncolytic metabolites (peptides, bacteriocins), which makes these microbes a promising approach for cancer therapy [14]. Treatment with live bacteria can be used either as monotherapy or in combination with other cancer therapies. Oncolytic bacteria include *Bifidobacteria*, *Clostridium*, *Listeria monocytogenes*, *Salmonella typhimurium*, *Streptococcus bovis* and *S. pyogenes* (Fig. 1) [14].

Since *S. pyogenes* are a group of microorganisms that cause the development of a frequent pathogenic form of group A streptococcal infection in humans and one of the objects studied at the Department of molecular microbiology of the Institute of Experimental Medicine, these bacteria were chosen as the key object for discussion of its anticancer properties in this review.

The aim of the review was to discuss the mechanisms of anticancer action of *S. pyogenes* and other streptococcal species, as well as to consider their tumor-stimulating effects and the limitations that exist in this regard.

Antitumor mechanisms of *Streptococcus pyogenes*

Since 1891, when Dr. W. Coley first used a vaccine based on live *S. pyogenes* and *Serratia marcescens* to treat 10 patients with terminal osteosarcoma and sug-

¹ International Agency for Research of Cancer (Globocan). URL: <https://globocan.iarc.fr>

gested an association between the development of fever and tumor regression [15], several bacterial strains have been studied and selected for testing on patients. In order to understand the pathogenetic mechanisms of the effect of *S. pyogenes* on tumor cells, it is necessary to consider the associated pathogenicity factors of these microorganisms.

Pathogenicity factors

More than 40 pathogenicity factors have been found for *S. pyogenes* [16]. All of them can be divided into microbial cell-associated and extracellular ones.

The streptococcus cell is surrounded by a cell wall formed by the peptidoglycan polymer consisting of N-acetylglucosamine and N-acetylmuramic acid and covalently linked to them by teichoic and lipoteichoic acids [17]. Protein and polysaccharide components are connected to the cell wall (Fig. 2) [18].

The cell wall polysaccharides also include carboxyhydrate antigens formed by group-specific polysaccharide-A, the differences in the structure of which are the basis for the classification of streptococci [20]. Among cell wall proteins, the main pathogenicity factor is M (Emm) protein, which provides resistance of *S. pyogenes* to phagocytosis and multiplication in the blood [21].

The authors of the review showed that both wild-type *GUR* and M-protein mutant *GURSAI* strains (10^6 CU/mL) exerted *in vitro* cytotoxic effect on C6 glioma cells using the xCELLigence system (Fig. 3) [22, 23].

The data of Fig. 3 show that streptococcal strains *GUR*, *GURSAI* demonstrated rapid and strong oncolytic effect against C6 glioma cells. *S. pyogenes* strains *GUR* and *GURSAI* had the slowest cytotoxic effects on C6 glioma cells with the highest cell inhibition rates of 81.8 and 79.3% after 4 and 6 h, respectively. More-

over, the cytotoxic effects of *S. pyogenes* strains *GUR* and *GURSAI* slightly increased over time, reaching growth inhibition rates of 85.0 and 81.5% after 8 h, respectively [22]. Similar results were obtained when *S. pyogenes* strains *GUR* and *GURSAI* were tested on mouse pancreatic adenocarcinoma (Panc) cells in real time (Fig. 4) [23].

The results in Figs. 3, 4 show that both strains inhibited the growth of C6 glioma and Panc cells, and the effect of *GURSAI* strain was weaker than that of *GUR*, which confirms the presence of a cytotoxic effect due to the presence of M-protein as a pathogenicity factor. At the same time, both strains had no cytotoxic effects on normal fibroblast cells in real time (Fig. 5) [23].

S. pyogenes do not synthesize a single M-protein, but there are at least up to 4 groups of M-proteins: FG I (*Mrp*); FG II, M-protein and H-protein; FG III (*Enn*); and FG IV (M-protein). The M and Enn proteins form two groups with 9 subgroups, and the Mrp proteins form 4 groups with 10 subgroups (Fig. 6) [24].

M-proteins are known to consist of α -helical fibrils with a diameter of 50-60 nm located on the bacterial cell wall. These proteins have a super-spiral structure and can form dimers with different polypeptide chain lengths (Fig. 7) [25].

M-proteins as pathogenicity factors contribute to the resistance of *S. pyogenes* to phagocytosis by macrophages and host antibodies [26]. M-proteins can bind blood plasma proteins: immunoglobulins G and A (Fc-fragments), fibrinogen, fibronectin, albumin, plasminogen, C4b-binding protein (C4BP), factor-H and complement proteins [19]. The interaction of M-protein with plasma factors affects the adhesive and invasive properties of *S. pyogenes*, and through alteration of blood coagulation capacity indirectly affects cancer cell viability. This is confirmed by the fact that the state

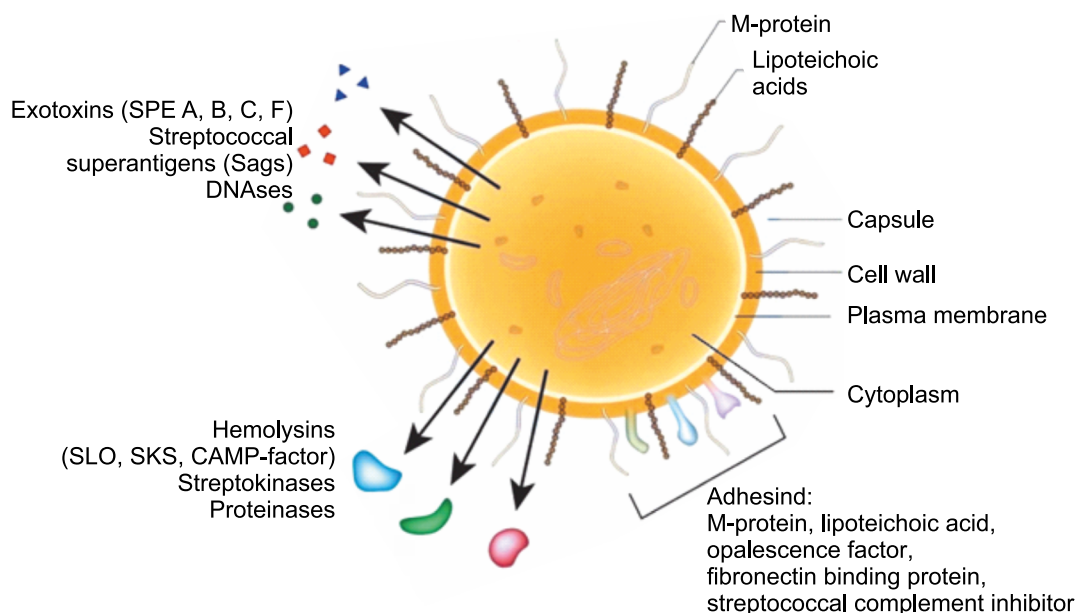


Fig. 2. Schematic representation of the streptococcal cell and the main biologically active products of *S. pyogenes* [19].

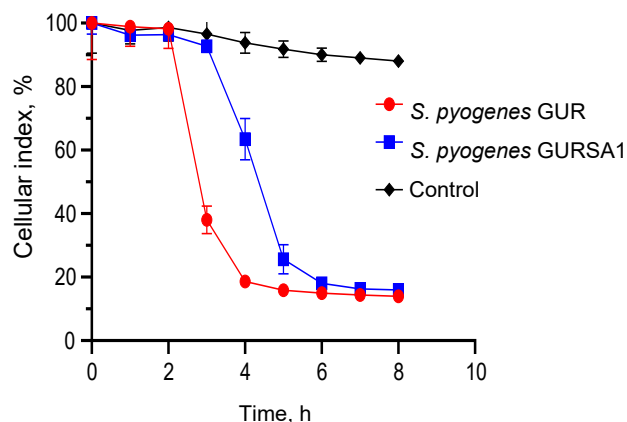


Fig. 3. Effect of *S. pyogenes* strains *GUR*, *GURSA1* on C6 cells in real time using xCELLigence system [23].

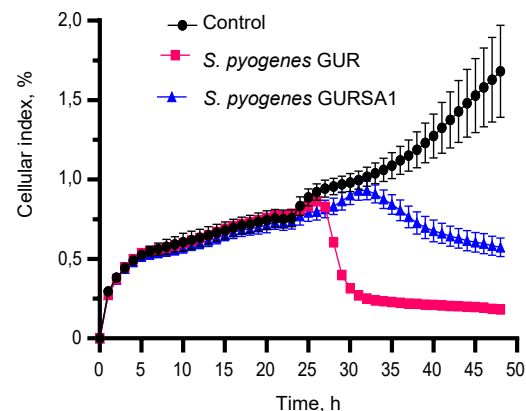


Fig. 4. Effect of *S. pyogenes* strains *GUR*, *GURSA1* on Panc cells in real time using xCELLigence system [23].

of blood hypercoagulability as a component of tumor microenvironment promotes cancer progression [27].

The other pathogenicity factors of *S. pyogenes* have been studied to a lesser extent. They include: exotoxins streptolysins S, O, superantigens, serine and cysteine proteinases, streptokinase, arginine deiminase, endo- β -N-acetylglucosaminidase, nicotinamide dinucleotide, etc. [19]. For example, arginine deiminase (ADI) consists of 2 domains, the first of which is formed by 5 $\beta\beta\alpha\beta$ sites repeating around a pseudo-5-fold axis containing the active center. The second domain is a 4-domain helical chain (**Fig. 8**).

ADI was first isolated from the *Su* strain (3 $\mu\text{g}/\text{mL}$), which is capable of inhibiting the growth of transformed BALB/3T3 fibroblast cells [29]. ADI is localized in the cell wall of *S. pyogenes*, whereas in *S. suis* the same enzyme is present in the membrane fraction of cells. Its activity is associated with the ability to convert arginine to ammonia and citrulline [30]. On the other hand, arginine utilization enhances the proliferation and growth of some types of tumors such as melanoma, hepatocellular carcinoma and prostate cancer. Since arginine deficiency induces cycle arrest in G_1 -phase can-

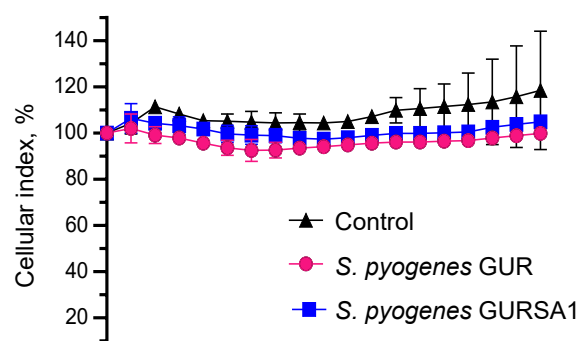


Fig. 5. Effect of *S. pyogenes* strains *GUR*, *GURSA1* on normal fibroblast cells in real time using xCELLigence system [23].

cer cells, activation of mTOR- and GCN2-kinase genes in them, which trigger autophagy and apoptosis [31, 32], T. Fiedler et al. studied the efficacy of ADI therapy (3.5–350.0 IU/mL) and its combinations with cytostatic drugs: chloroquine (5 and 20 μM), hydroxamic acid suberoylanilide (SAHA; 0.25 and 0.5 μM) or palomide 529 (dual TORC1/TORC2 inhibitor; 7.5 μM) to inhibit the growth of 12 glioblastoma (GBM) cell lines *in vitro* and *in vivo* on male *NMRI Foxn1nu* mice weighing 20–

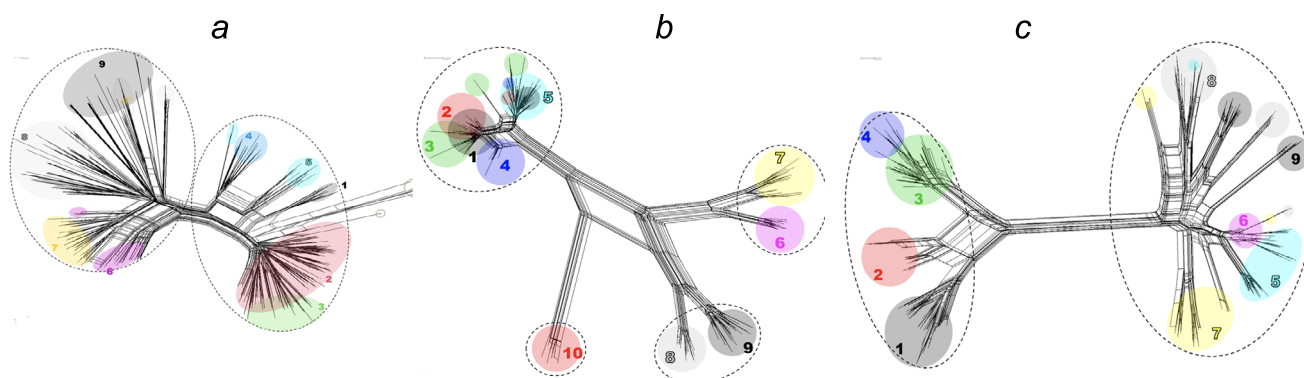


Fig. 6. Genetic network analysis of SplitsTree, including 537 genetic sequences with the allocation of clusters of M proteins [24].

a — M protein; b — Mrp (221 sequences); c — Enn proteins (262 sequences). Black dotted ellipses denote two groups of M proteins, green dotted ellipses denote chimeric M proteins, and colored ellipses denote subgroups of M proteins.

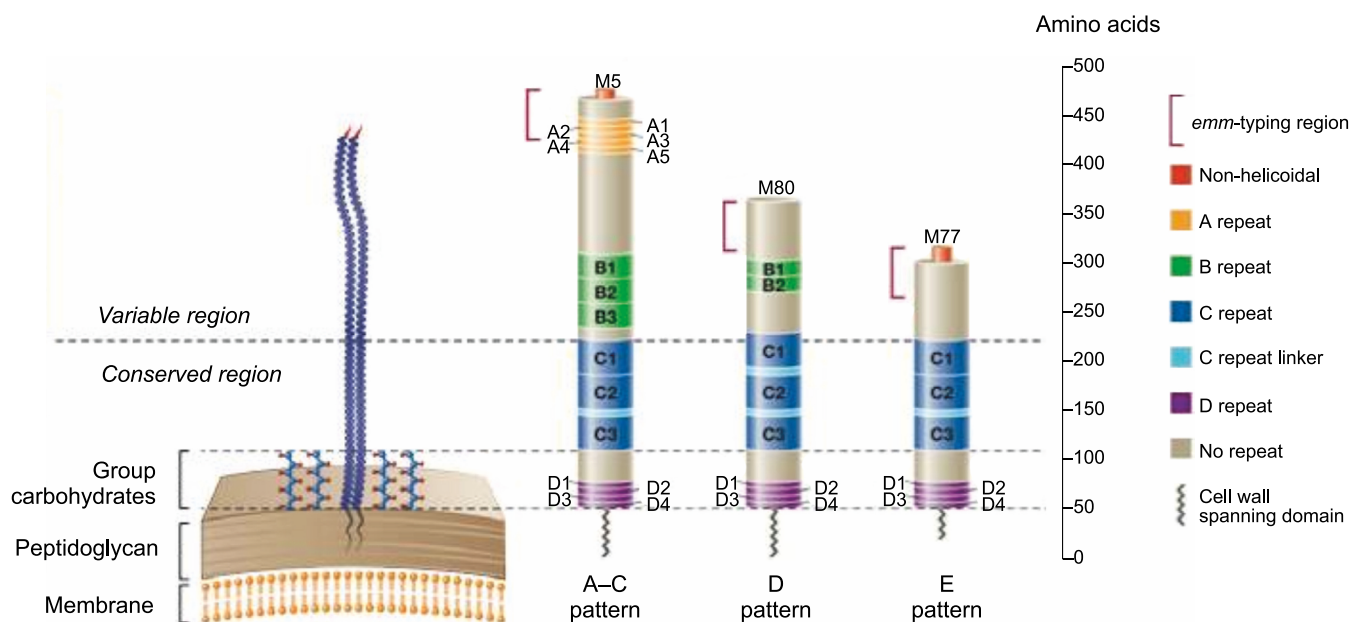


Fig. 7. Three M (emm) proteins (M5, M80, and M77) [25].

The length of the M protein and the size of the repeat and non-repeat domains are shown to the scale. The A–C emm patterns are the longest M proteins with a hypervariable domain of 230 amino acids. The D and E structured M proteins have hypervariable domains consist from 150 and 100 residues, respectively. The “A” repeats are absent from the vast majority of M proteins belonging to the D and E pattern groups. The “B” repeats are present in most A–C and D M proteins, but are absent from the E–M subtypes of M proteins

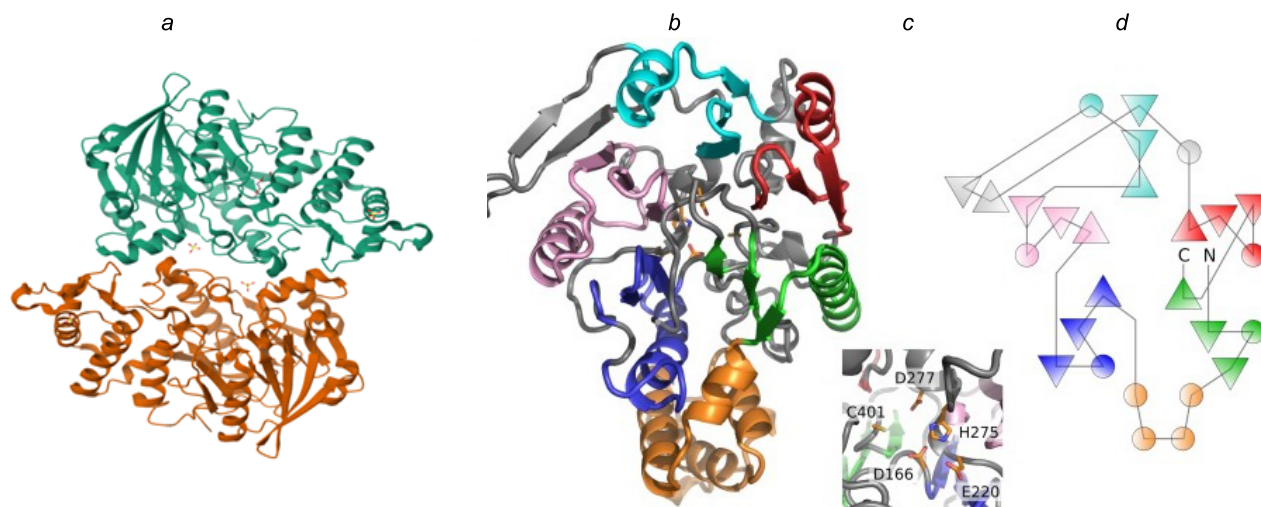


Fig. 8. Structure of arginine deaminase from *S. pyogenes* (a); crystal structure illustrating the connecting regions (b): green, blue, pink, light blue and red colors, respectively; residues of the ADI active site (c), and the ADI topological diagram (d) [28].

25 g [33]. ADI administration inhibited GBM growth in 50% of tested lines (**Fig. 9**).

In cell lines for which ADI reduced cell proliferation, its combinations with chemotherapy agents were tested. Synergistic effects were observed on HROG02, HROG05 and HROG10 66% GBM cells with growth inhibition of up to 70% using the combination of ADI with Palomid 529. Similar anticancer effects (60% cell death) were established after adding chloroquine to ADI. The reason for the anticancer effects of ADI was epigenetic suppression of arginine synthesis pathway genes (argininosuccinate synthetase *ASS1* and argininosuccinate lyase *ASL*). In an *in vivo* model,

ADI (250 U/kg wt) and its combination with SAHA (25 mg/kg wt) inhibited 70% of HROG05 heterograft tumor size compared to control (**Fig. 9, b**) [32].

C. Maletzki et al. found that ADI (35 mU/mL) induced the expression of heat shock and arginine metabolism protein genes (*ASS1*, *ASL*, *ArgI*, *CPSI*, *OTC*) in HROG02, HROG05, HROG52, HROG63 cells of GBM patients (**Fig. 10**) [34]. As in a previous study, ADI administration stimulated autophagy and senescence of tumor cells. Combinations of ADI with curcumin, resveratrol, quinacrine and sorafenib for 3 days enhanced the cytotoxicity of the enzyme by activating autophagy.

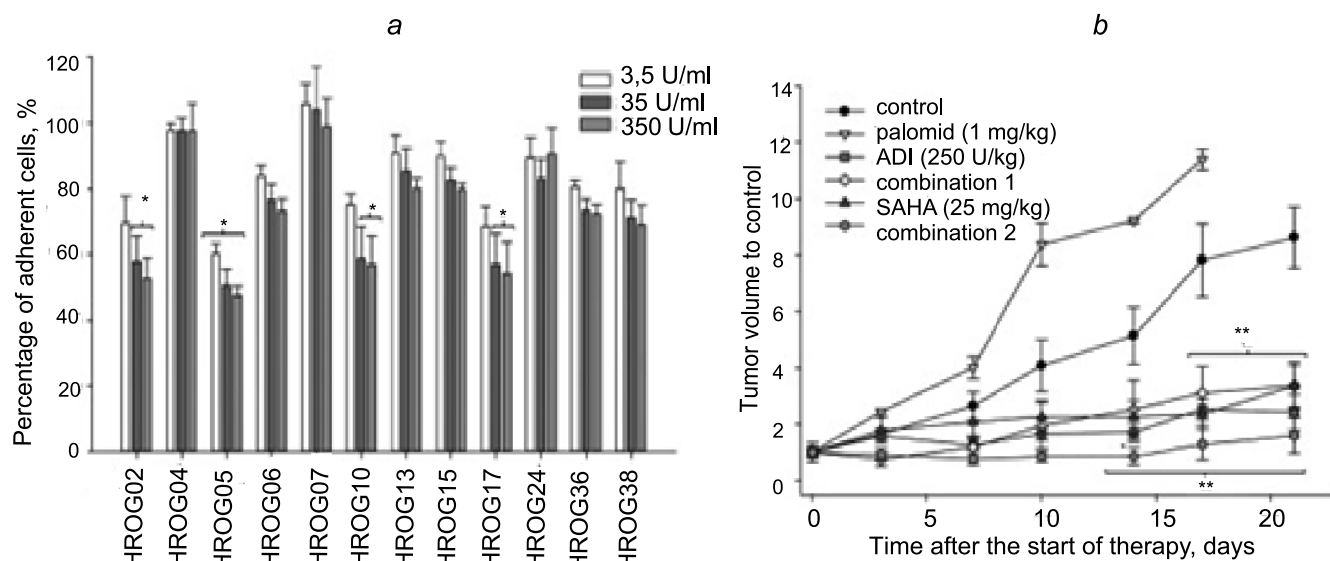


Fig. 9. Crystal violet staining of the GBM cells after ADI incubation during 72 h (a) and tumor growth curve (b). Tumor volumes are given as x-fold increase compared to day 0 [33].

Other pathogenicity factors of *S. pyogenes* include: cholesterol-dependent cytolysins and streptolysin O (SLO). S.C. Feil et al. determined the three-dimensional structure of this enzyme (**Fig. 11**) [35].

The SLO molecule consists of 571 amino acids, which form 4 domains having a β -folded structure. The first N-terminal domain (70 amino acids) is cleaved off by proteolysis by streptococcal proteases after secretion. In addition to the domains, SLO contains 2 transmembrane regions, TMH1 (residues 259–288) and TMH2 (residues 359–386), which have an α -helical structure. SLO includes the 11-amino acid sequence ECTGLAWWW, rich in tryptophan residues, which promotes the incorporation of the molecule into cell membranes [35]. As a result of oligo- and polymerization, SLOs form large pores in cell membranes. These mechanisms lead to structural damage, severe ATP depletion and cell death by necrosis. Consequently, this mechanism of action of SLO can be used for cytolysis of cancer cells. In this regard, C. Gruber et al. using RNA trans-splicing developed 3'-pre-trans-splicing molecules (PTM) containing an embedded *SLO* gene in the target gene of matrix metalloproteinase-9 (*MMP9*) in highly aggressive squamous cell carcinoma cells [36]. This technique allowed the replacement of a tumor-specific transcript with a peptide/toxin encoding gene, resulting in cell death. A fluorescent tag was used to visualize the transcript (**Fig. 12**).

Trans-splicing between the 50th and 30th nucleotides of *MMP9* and *PTM* genes resulted in the formation of mRNA encoding a full-length GFP-protein containing a DsRed tag. Transfection of HEK293 human squamous cell carcinoma and embryonic kidney HEK293 cancer cells with *SLO-PTM* induced death in them due to SLO expression (**Fig. 13**).

Thus, the use of SLO is a new approach in bacterial therapy of human malignant tumors [37]. In other *Streptococcus* species, such as *S. bovis* those belonging to group D, bacteriocin bovicin HC5 synthesized in ribosomes has been found [37]. This cationic peptide has a cytolytic effect against MCF-7 breast adenocarcinoma and HepG2 hepatocellular carcinoma cells [38].

Mediated mechanisms of *S. pyogenes*' anticancer action

In addition to direct cytolytic action on tumor cells, *S. pyogenes* in the body can also exert cytostatic anticancer effects mediated by immune cells and factors. Once in the body, streptococci are perceived by the immune system as foreign and trigger an inflammatory response. During this reaction, a cytokine and chemokine storm develops due to increased levels of tumor necrosis factor- α (TNF- α), interferon- γ , interleukins (IL-1 β , IL-6, IL-10), monocyte chemoattractant protein-1 [38]. In addition to these changes, Y.H. Liu et al. found that during infection with the A20 strain of *S. pyogenes*, the patient's brain cells expressed glial fibrillary acidic protein, inducible nitric oxide synthase, components of nicotinamideadenine dinucleotide phosphate oxidase, all at a high level, which stimulated the production of reactive oxygen species. Myeloperoxidase secreted by activated macrophages and neutrophils was also expressed in the cortex and hippocampus of infected mice (**Fig. 14**) [39].

Increased levels of IL-10 and IL-12 in blood activate CD18⁺-monocytes and CD11c⁺CD123⁺-plasmacytoid and CD11c⁺CD123⁻-myeloid dendritic cells (DCs) through the Toll-like receptor (TLR) signaling pathway [40]. T.G. Loof et al. showed that when KTL3 was stimulated by *S. pyogenes* strain through TLR4 activation

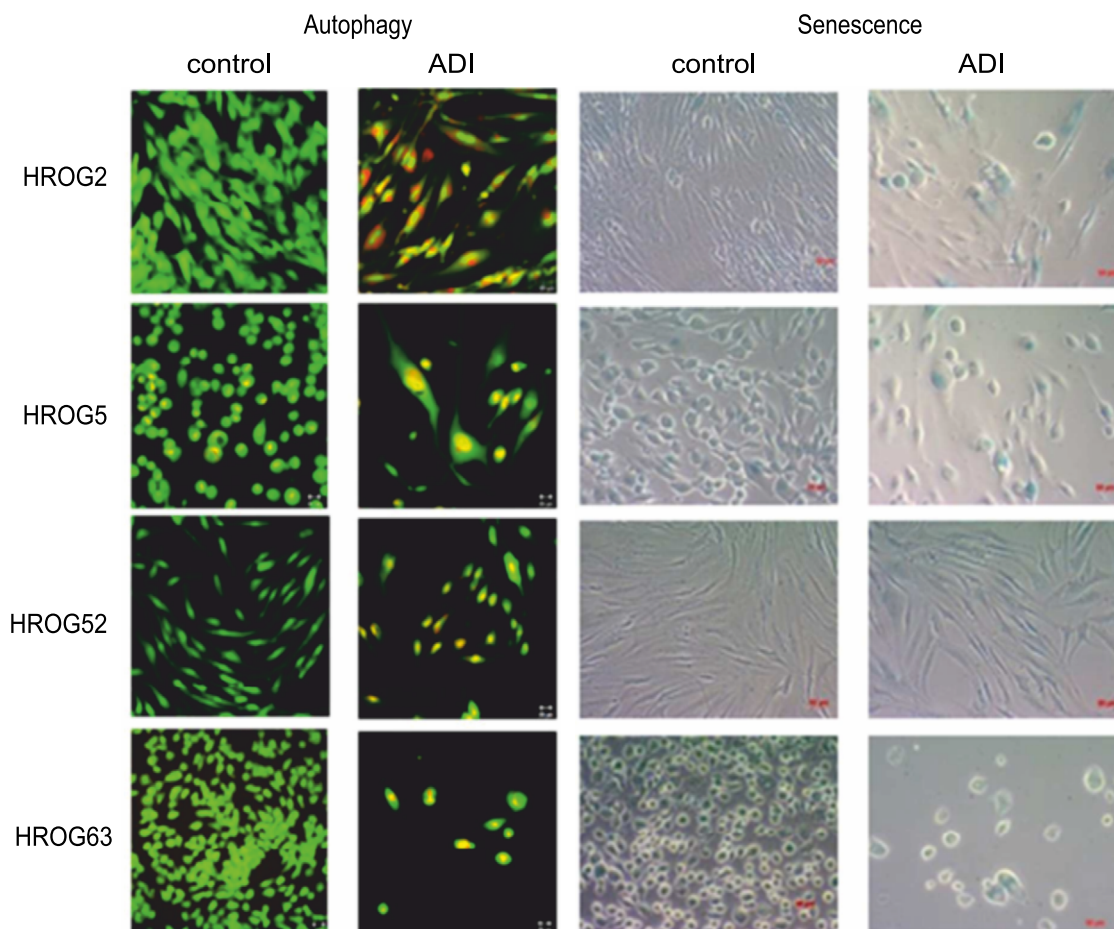


Fig. 10. ADI treatment induces autophagy and senescence in GBM cells [34].

Acridine orange (orange) and calcein AM (green) staining. Analysis was conducted on a laser scanning microscope (Zeiss) using a 20x objective.

in MyD88-DCs, the expression of costimulatory molecules CD40, CD80, CD86 and the production of inflammatory cytokines were decreased in them [41, 42]. Activation of receptors and CD54, CD70, CD83, CCR7 molecules triggers p38MAPK, ERK, JNK, PI3K/Akt/NF- κ B signaling cascades in DCs that enhance their proliferation and differentiation [43, 44]. Recently, X. Chen et al. found that TLR4 also stimulates the cGAS-STING/NF- κ B signaling pathway, which mediates DC maturation and IL-6 secretion [45]. These results suggest that *S. pyogenes* through stimulation of monocytes, macrophages, may exhibit their anticancer effects.

Furthermore, *S. pyogenes* stimulate a subpopulation of interferon-producing DCs and natural killers. Activation of these cells enhances processing, tumor antigen presentation, TNF- α -induced TRAIL- and Fas-ligand-dependent apoptosis [46]. In turn, plasmacytoid myeloid DCs activate tumor-specific cytotoxic CD8⁺, CD4⁺-T-lymphocytes and their secretion of cytokines [40, 47]. According to the study of W. Li et al. factors involved in DC activation in hepatocellular carcinoma are presented in Fig. 15.

The key pathogenicity factor, M-protein or acidic streptococcal glycoprotein (SAGP) binds to an

IAP-specific coupled receptor, which activates proteintyrosine phosphatase dephosphorylates epidermal growth factor and blocks the p42/44MAPK-signaling cascade, thereby inhibiting proliferation of A431 epidermoid carcinoma cells [48]. *S. pyogenes* secrete exotoxins SpeB, SpeA, which have cysteine protease ac-

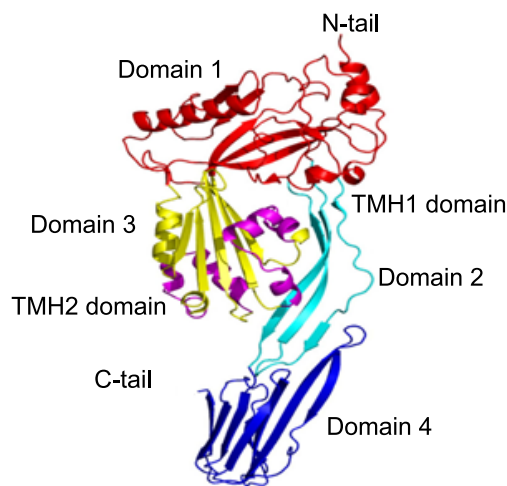


Fig. 11. Strepolisin O molecular structure [35].

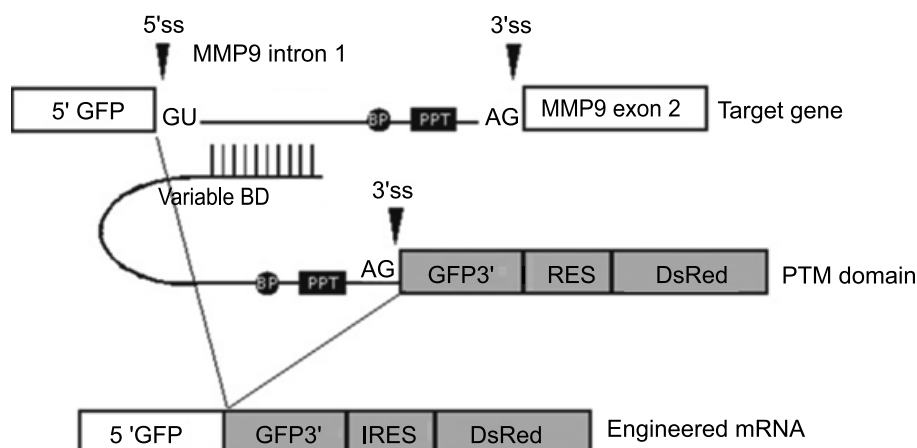


Fig. 12. Schematic representation of the fluorescent trans-splicing assay system [36]. PTM is the engineered mRNA linked via an antisense BD domain to *MMP9* intron 1. BP is the branch point; PPT is the polypyrimidine sequence.

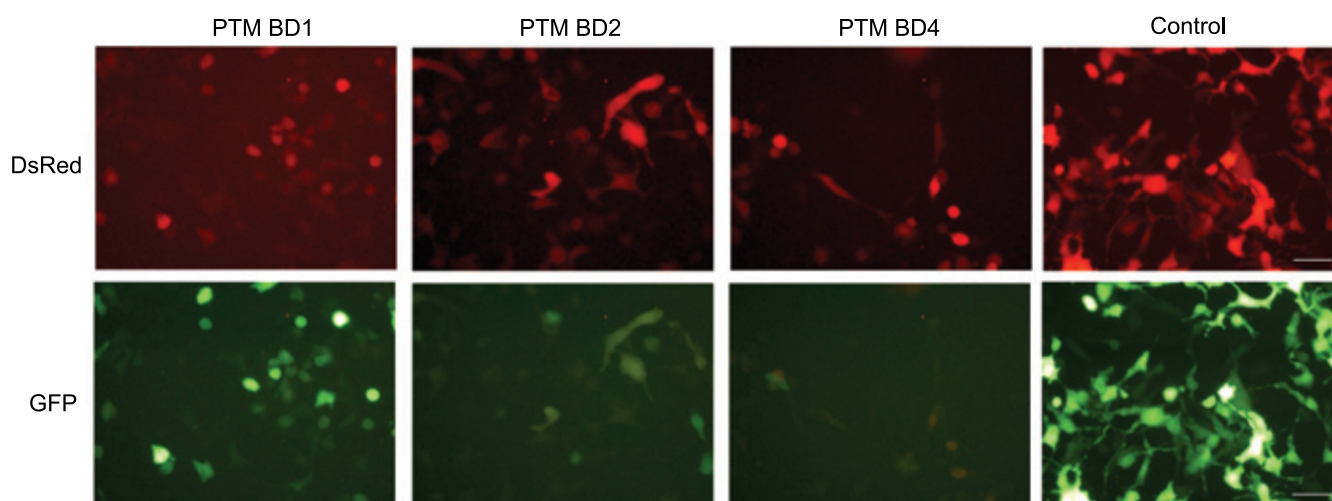


Fig. 13. Fluorescence microscopy of transfected HEK293 cells [36].

Control was transfected with a construct containing DsRed dye and full-length cDNA of GFP. Cells expressing GFP indicate trans-splicing in the target gene and the PTM carrying one of the three BD domains (BD1, BD2, and BD4). Scale bar is 20 mm.

tivity and inactivate inflammatory factors IL-8, C5a, cathelicidin LL-37, and inhibit neutrophil chemotaxis [26, 47, 49, 50]. DNAases SpnA and SdaI of *S. pyogenes* suppress the formation of neutrophil extracellular traps, SpeB suppresses the activity of antimicrobial chemokines (Fig. 16). Furthermore, SpeB promote the formation of gazdermin D, which forms pores, induces pyroptosis, inhibits IL-1 β and H-kininogen, which exert potent proinflammatory effects [47]. Consequently, secretion of streptococcal exotoxins can inhibit tumor growth and development.

Not only live streptococci have cytotoxic activity, but also the preparation OK-432 (picibanil, NSC-B116209; Fig. 16) obtained on their basis, the administration of which (0.001–1.0 μ g/mL) caused CD56⁺NK activation. This resulted in growth inhibition by 7–14 days of MADB106 mammary carcinoma in an F344 rats' intraperitoneal model [51]. OK-432 admin-

istration promoted the activation of T-helper lymphocytes and leukocytes by increasing the number of neutrophils [26]. In the review by Y. Ryoma et al. summarize the mechanisms of anticancer activity of OK-432, showing that picibacil induces direct anticancer action by inhibiting RNA synthesis and cell cycle arrest. Also OK-432 stimulates the synthesis of TNF- α , perforin and interferon- γ , which activate the expression of intercellular adhesion molecules (ICAM-1), HLA-DR and eventually apoptosis of cancer cells [52]. OK-432 stimulates the production of IL-8, macrophage factors (G-CSF, GM-CSF) that enhance proliferation and maturation of granulocytes, monocytes, lymphocytes and platelets [52]. Recent results convincingly demonstrate that collagen-like protein-1 (Sc11) of *S. pyogenes* inhibits the formation of neutrophil extracellular traps in a rat model with Panc02 pancreatic ductal adenocarcinoma [53].

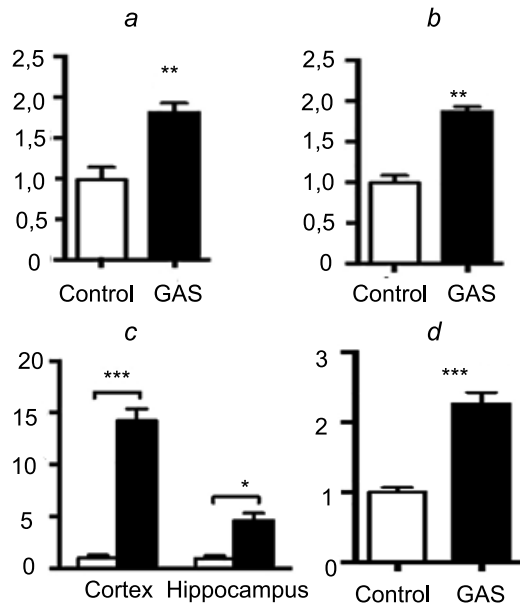


Fig. 14. Changes in GFAP (a), iNOS (b), MPO (c) and MMP-9 (d) levels in the brain during infection with *S. pyogenes* strain A20 in a patient [39].

In this regard, it is interesting to note that streptococci can infect the tumor, forming biofilms on it. Streptococcal infection activates the body's immune system, which increases the number of neutrophils and lymphocytes in the focus of infection [14, 54]. Thus, bacterial components can enhance the interaction between the tumor and the immune system, acting as adjuvants, promoting the presentation of tumor antigens and activation of the immune system [55].

Preclinical and clinical studies

The results of *in vitro* and *in vivo* experiments with *S. pyogenes*, which established their anticancer effects and mechanisms, stimulated further preclinical and clinical trials with these microorganisms. For example, T. Iwai et al. recently conducted a preclinical study to evaluate the efficacy of intratumoral administration of OK-432 or its combination with radiofrequency ablation on 4–5 weeks old male Sprague-Dawley rats ($n = 145$; 80–90 g) with metastatic osteosarcoma [55]. The animals were divided into 4 groups to evaluate overall survival and tumor size: control (no treatment), radiof-

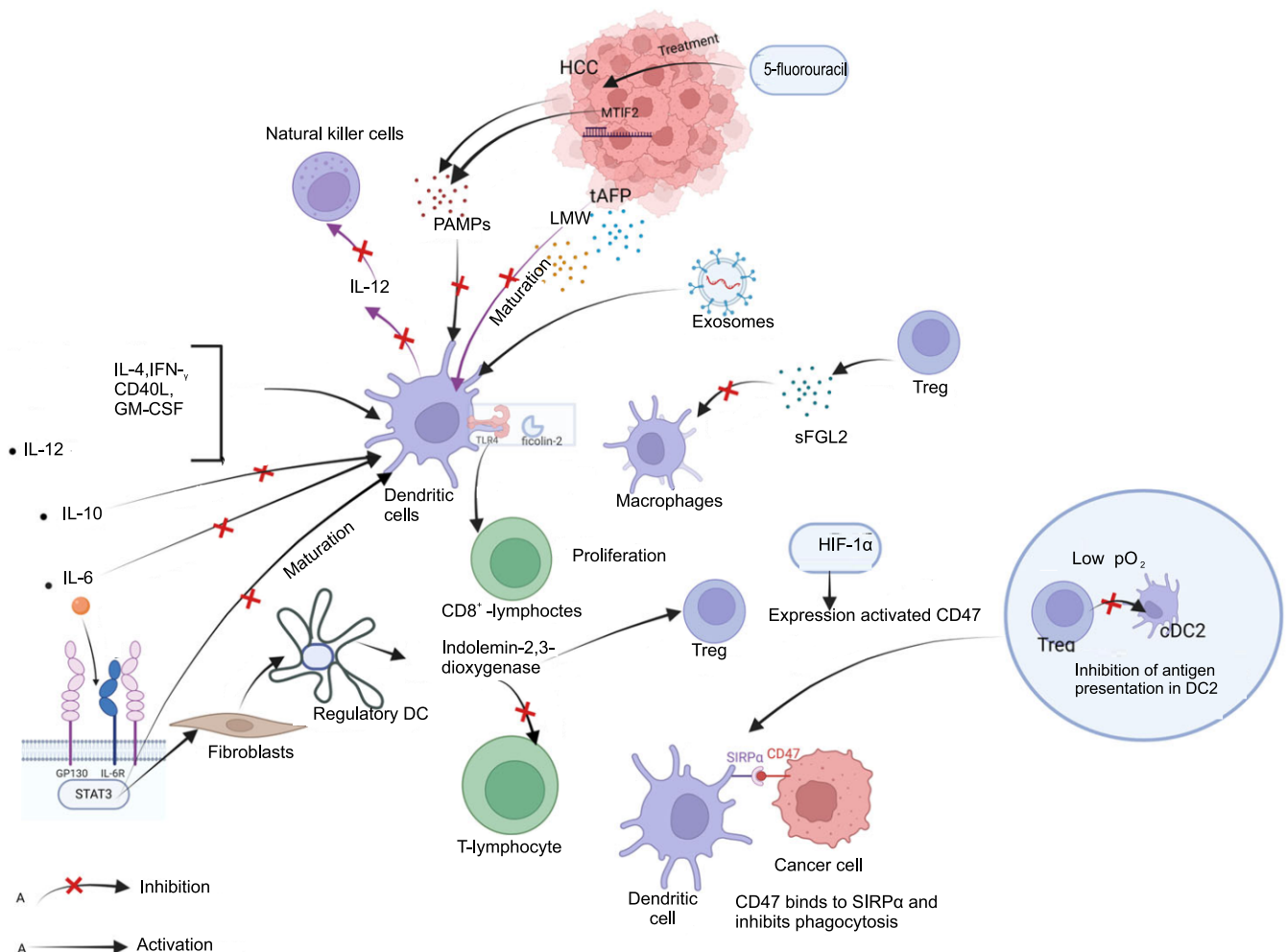
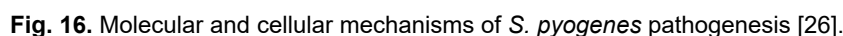
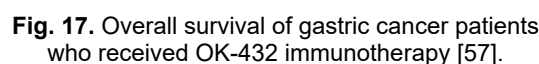


Fig. 15. Mechanisms of streptococcal activation of DCs targeted at inhibiting of hepatocellular carcinoma growth [47].



Japanese scientists M.S. Oba et al. conducted a meta-analysis including 14 studies involving 796 patients with stage III or IV gastric cancer after surgical resection to evaluate the efficacy of OK-432 immunotherapy compared to standard chemotherapy. The primary endpoint was overall survival [57]. The control and OK-432 groups included 726 and 796 patients, respectively. The median overall survival was 42.6 months for the OK-432 group and 32.3 months for the control group. The overall hazard ratio was 0.88 (95% confidence interval 0.77-1.00; $p = 0.050$; **Fig. 17**) [57]. The authors conclude that immunotherapy



with OK-432 may be effective for patients with gastric cancer in stages III or IV after surgery [57].

In an earlier study, the same authors, summarizing 6 randomized trials involving 1522 patients with gastric cancer, showed that systemic administration of OK-432 had a significant effect on increasing life expectancy (OR = 0.81; 95% CI = 0.65–0.99; $p = 0.044$) and 3-year survival. This rate was 67.5 and 62.6% in the immunochemotherapy and chemotherapy groups, respectively [58].

It should be noted that mild adverse reactions such as: fatigue, anorexia, local inflammation, hyperemia, chest and abdominal pain were observed during clinical use of OK-432. The most frequent symptom was fever controlled with antipyretic therapy. Intracranial pressure was rarely reported. Only a few patients experienced fatal outcomes due to the development of embolism, acute nephritis, hemorrhage, and improperly dosed injections of the drug [59]. Serious side effects require identification of their causes and relationship to the cur-

rent therapy, perhaps they were due to incorrect dosage or development of individual intolerance to the drug.

Mechanisms of cancer-stimulating effects of *S. pyogenes*

In the process of studying the anticancer effect of *S. pyogenes*, data of the opposite nature were gradually accumulated. For example, D. Kong et al. studied the effects of OK-432 (sapilin) in patients with breast cancer and found increased secretion of cytokines IL-1 α , IL-6, fibroblast growth factor- β , vascular endothelial growth factor and transforming growth factor- β 1 in drainage fluids. Furthermore, its administration enhanced proliferation, migration and angiogenesis of HUVEC, HFL1 epithelial cells, fibroblasts and collagen deposition [60]. These results indicate that *S. pyogenes* through activation of proliferation, migration and angiogenesis of epithelial cells and fibroblasts can stimulate the development of breast cancer. Exotoxins SpnA, SpeB and serine protease SpyCEP of *S. pyogenes* take part in

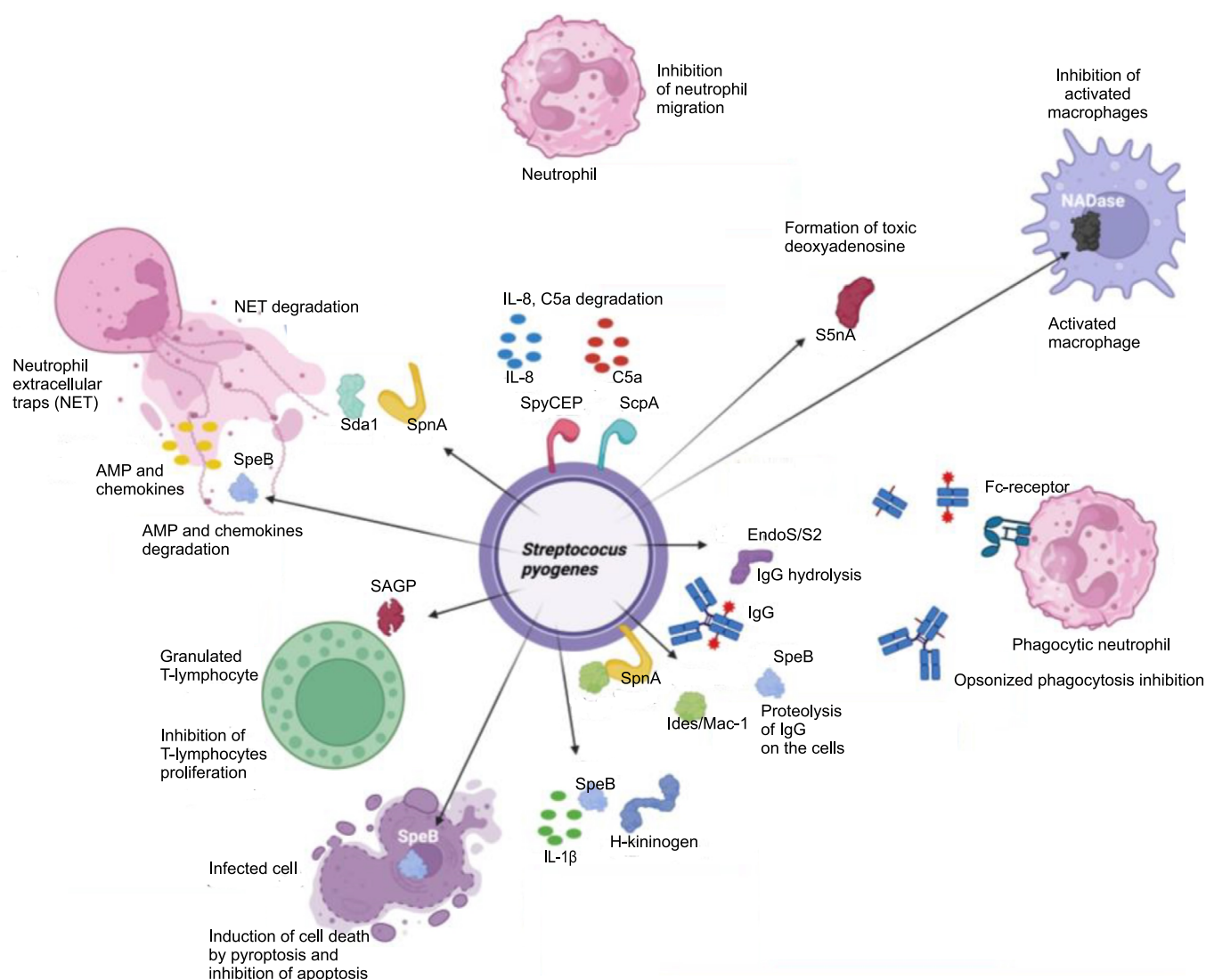


Fig. 18. Total scheme of the *S. pyogenes* effects to immune cells [61].

the degradation of IL-8, IL-1 β , complement factor C5a, which inhibit the migration (chemotaxis) of neutrophils (Fig. 18). In turn, SpeB induces IgG proteolysis, degradation of antimicrobial peptides, chemokines, which promotes the formation of neutrophil extracellular traps and cancer development [61].

NADase S5nA inhibits phagocytic activity of macrophages against tumor cells, inhibits IgG proteolysis and antibody-mediated killing of cancer cells by neutrophils (opsonophagocytosis). The peptidases EndoS/S2, IdeS/Mac-1 and Mac-2, SpeB are involved in the hydrolysis of glycans and ubiquitin-binding proteins that inhibit apoptosis, and M-protein (SAGP) suppresses T-lymphocyte proliferation [61]. All these events indirectly stimulate the cell cycle, proliferation, migration of tumor cells observed predominantly in chronic streptococcal infection in cancer patients.

Conclusions

Contrary to established views, streptococcal infection or fever may not always be undesirable in cancer patients and does not always lead to a decrease in immune system reserves in the cancer patient. The research evidence presented in that review strongly suggests that *S. pyogenes* can, with the involvement of pathogenicity factors, directly exert anticancer effects on cancer cells. Furthermore, these bacteria stimulate

interleukins, chemokines of the host immune system cells (neutrophils, T-, B-lymphocytes, macrophages, dendritic cells), which, in turn, participate in anticancer immune responses.

Modern oncological therapeutic methods (chemotherapy, radiation therapy) have a number of disadvantages associated with non-selectivity of action on cancer cells, as well as, due to cellular and molecular-genetic heterogeneity of tumors, the development of therapeutic resistance, which leads to the inability to monitor the effectiveness of treatment in dynamics. All these problems cause high oncological morbidity and mortality, progression of oncological diseases with the emergence of more resistant forms of tumors with a high rate of metastasis.

Thus, it is necessary to improve cancer therapy regimens using new approaches that include selective anticancer activity combined with minimal toxicity to normal tissues of the body, as well as the ability to overcome the constant dynamic molecular and genetic changes in neoplastic cells. The use of *S. pyogenes* as a therapeutic strategy in cancer patients meets all of these criteria. However, it should be noted that streptococcal vaccine should be used with caution, taking into account the individual characteristics of the patient's immune system, because *S. pyogenes* may have opposite effects that require further research.

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