TARGETED DELIVERY OF ANTI-TUBERCULOSIS AND PHOTOSENSITIZING AGENTS TO TUMOR-ASSOCIATED AND *M. TUBERCULOSIS*-INFECTED MACROPHAGES USING NANOCARRIERS

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Abstract

Tuberculosis remains a leading cause of mortality among infectious diseases, with drug resistance posing a major challenge to effective treatment. Macrophages serve as the primary cellular reservoir for *M. tuberculosis* (MTB), which upon interaction with this pathogen may acquire a complex phenotype with predominantly anti-inflammatory, immunosuppressive properties and establish a metabolically privileged niche that supports intracellular persistence and survival of MTB. In this review, the phenotype of such macrophages is referred to as M2 (alternatively activated macrophages). This review systematizes current strategies for targeted delivery of anti-tuberculosis agents to MTB-infected macrophages using macromolecular and nanoscale carriers. Passive and active targeting approaches are examined, including the engineering of vector properties through ligand conjugation to M2 macrophage receptors. Strategies for reprogramming macrophage functional phenotype and the development of nanoscale biomimetics are discussed. Special emphasis is placed on targeted delivery of photosensitizers to infected cells for antimicrobial photodynamic therapy. The summarized evidence indicates that combined nanotherapeutic approaches, integrating direct antimicrobial activity with modulation of local immune responses, offer promising strategies for overcoming drug resistance and achieving eradication of MTB.

Key words: Mycobacterium tuberculosis, macrophage, drug resistance, nanoparticle, targeted delivery, antimicrobial photodynamic therapy.

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НАПРАВЛЕННАЯ ДОСТАВКА ПРОТИВОТУБЕРКУЛЕЗНЫХ И ФОТОСЕНСИБИЛИЗИРУЮЩИХ ПРЕПАРАТОВ В ОПУХОЛЬ-АССОЦИИРОВАННЫЕ И *M. TUBERCULOSIS*-ИНФИЦИРОВАННЫЕ МАКРОФАГИ С ИСПОЛЬЗОВАНИЕМ НАНОНОСИТЕЛЕЙ

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Резюме

Туберкулёз остаётся одной из важнейших глобальных проблем общественного здравоохранения, входя в первую десятку основных причин, уносящих человеческие жизни и занимая первое место по смертности среди всех инфекционных заболеваний. При этом наиболее сложной проблемой туберкулеза, как и множества других инфекционных заболеваний, является лекарственная устойчивость возбудителя**.** Основным клеточным резервуаром *M. tuberculosis* (МБТ) являются макрофаги – клетки врожденной иммунной системы, которые во взаимодействии с данным патогеном могут приобретать сложный фенотип с преимущественно антивоспалительными, иммуносупрессивными свойствами и формируют метаболически привилегированную среду, способствующую выживанию и внутриклеточной персистенции МБТ. В настоящем обзоре фенотип таких макрофагов обозначен как М2 (альтернативно активированные макрофаги). В обзоре систематизированы современные подходы к таргетной доставке противотуберкулезных препаратов в МБТ-инфицированные макрофаги с использованием высокомолекулярных и наноразмерных носителей. Рассмотрены

стратегии пассивного и активного таргетирования, включая придание частицам векторных свойств лигандами к рецепторам М2-макрофагов, обсуждаются методы перепрограммирования функционального фенотипа макрофагов и использования наноразмерных биомиметиков; особое внимание уделяется направленной доставке в инфицированные клетки фотосенсибилизаторов для антимикробной фотодинамической терапии. Обобщенные данные свидетельствуют, что комбинированные нанотерапевтические подходы, сочетающие прямой антимикробный эффект с модуляцией локального иммунного ответа, открывают новые возможности для преодоления лекарственной устойчивости и эрадикации МБТ.

Ключевые слова: *Mycobacterium tuberculosis*, макрофаг, М2-поляризация, лекарственная устойчивость, наночастица, таргетная доставка, антимикробная фотодинамическая терапия.

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Introduction

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* (MTB) and remains one of the most serious global public health problems. According to the World Health Organization, in 2023, the incidence of TB was approximately 10.8 million people, with mortality at 1.25 million. The problem is compounded by the increasing spread of multidrug resistance (MDR) of the pathogen: in 2023, approximately 400,000 cases of the disease were caused by MDR strains [1]. The problem of drug resistance is driven by the rate of mutations/acquisition of chemoresistance by MTB, which significantly exceeds the rate of generation of new effective anti-tuberculosis drugs. This fact demonstrates the extreme limitation of the therapeutic potential of traditional approaches to the treatment of MDR-TB and necessitates the development of fundamentally new therapeutic methods.

Macrophages (Mφ) play a central role in the pathogenesis of TB, serving as the first line of defense against the pathogen, but also as the primary host cell within which MTB can persist and proliferate. The interaction between MTB and Mφ determines the outcome of the infection: effective activation of Mφ along the classical pro-inflammatory phenotype leads to the destruction of the bacteria, while activation along the anti-inflammatory M2 (alternatively activated macrophages) phenotype creates conditions for pathogen survival [2]. It is evident that the development of interventions targeting Mφ with persistent MTB could become an effective strategy for overcoming drug resistance of the TB pathogen.

Functional phenotype of macrophages in tuberculosis infection

The nature of the macrophage response to MTB is determined by the influence of the microenvironment and mycobacteria on the functional polarization/formation of the functional phenotype of these cells. Despite the plasticity of the functional phenotype of Mφ, the literature generally uses a binary division into predominantly pro- or anti-inflammatory – M1 (classically activated macrophages) or M2 phenotype – depending on the effector molecules produced by these cells, with corresponding differences in transcriptomic signatures [3, 4]. MTB-induced M1 activation of Mφ is necessary for infection control [5]. Markers of M1-type activation include increased expression of iNOS, STAT-4, CCR7 and high levels of production of pro-inflammatory mediators and cytokines, such as TNF-α, IL-6, IL-12, IL-1β, IL-15, IL-23, CXCL-10, COX-2, reactive oxygen and nitrogen metabolites. Furthermore, in M1-Mφ, the autophagy process is activated, effectively destroying MTB [4, 6]. If MTB are not destroyed by anti-infective factors and survive, they induce a shift in the functional phenotype of Mφ towards M2, which are characterized by the production and expression of large amounts of IL-10, TGF-β, IL-1Ra, CCL17, CCL18, CCL22, Arg-1, fizz-1, Ym-1, COX-1, ALOX, etc. [3]. The functional phenotype of M2-Mφ is oriented towards reducing the biocidal-destructive pro-inflammatory response, tissue regeneration, and fibrogenesis. This phenotype is unable to inhibit the growth and spread of intracellular infections, including MTB [2].

MTB during co-evolution with *Homo sapiens* has developed numerous mechanisms for evading the immune response and manipulating the immune response of Mφ to its advantage [7]. MTB-induced M2 polarization creates a tolerant, privileged intracellular environment for MTB persistence and growth, due to low production of pro-inflammatory and high production of anti-inflammatory mediators and cytokines [3, 6, 8, 9, 10]. Furthermore, the M2 phenotype is associated with fibrosis processes that help maintain the structure of MTB-induced granulomas – the primary tissue niche for MTB persistence in infected Mφ [11, 12].

Targeting MTB-infected Mφ in TB therapy can pursue several goals simultaneously: 1) increasing the effectiveness of therapy through direct killing of MTB in their primary intracellular niche due to increased concentration of anti-tuberculosis chemotherapeutic agents [7, 13]; 2) reducing the side effects of anti-tuberculosis chemotherapeutic agents by lowering their concentration outside the targeting zone; 3) the possibility of overcoming drug resistance through the delivery of anti-tuberculosis agents to Mφ with mechanisms of action alternative to

chemotherapeutic agents [14, 15, 16]; 4) increasing the effectiveness of anti-tuberculosis therapy through the repolarization of Mφ from the M2 to the bactericidal M1 phenotype, induction of autophagy in them, and reprogramming of the immune microenvironment towards pathogen destruction [17].

Targeted delivery of nanoparticles to macrophages: influence of size and charge

Nanoscale carriers are most often used for the effective delivery of therapeutic agents to Mφ. Passive targeting is determined by the ability of Mφ to phagocytose particles of a certain size, surface charge, shape, and hydrophilicity, which affects the dispersion and aggregation of particles, as well as their binding to specific receptors [18, 19]. The surface charge of particles significantly influences cellular uptake and biodistribution of polymeric nanoparticles (NPs). It has been shown that with increasing surface charge (positive or negative), NP uptake by Mφ increased [18, 20]. A high NP charge enhances their phagocytosis by Mφ through opsonization, i.e., adsorption of immunoglobulins A/G/M, C3/C4/C5, complement activation products C3b/C4b/iC3b, laminin, fibronectin, C-reactive protein, etc. [21, 22]. When a negatively charged component such as phosphatidylserine is incorporated into NPs with a photosensitizer (PS), the "eat me" signal is significantly enhanced, providing increased recognition and uptake of NPs by Mφ [23]. Conversely, PEG modification of NPs reduces their charge and uptake by Mφ compared to NPs with highly charged coatings [24, 25].

Regarding the size of NPs, C. He *et al.* showed that increasing NP size from 150 to 300 and 500 nm led to an increase in uptake by 1.1 and 1.3 times, respectively, indicating that phagocytes with greater avidity capture larger NPs [18]. This same relationship was confirmed in a study by B. Prietl *et al*., which showed that carboxylpolystyrene particles sized 500-1000 nm induced phagocytosis and respiratory burst significantly more effectively than particles sized 20-200 nm [25]. The literature also mentions NPs with a diameter of about 500 nm, which are well-suited for passive targeting of alveolar Mφ [26].

Receptor-mediated targeting of anti-tuberculosis drugs and biomolecules to MTB-infected macrophages

Active targeting aimed at target cells assumes that the drug carrier has affinity for receptors expressed on these cells or is modified with a specific ligand recognized by corresponding receptors. The literature describes receptor-dependent phagocytosis involving different types of macrophage receptors, such as the mannose receptor, mannose-fucose (CD206) and fucose receptors, scavenger receptors (SR), Fc receptors, folate receptor alpha, hyaluronic acid receptor (CD44), tuftsin receptor, formyl peptide receptor, and others [26].

In TB infection, Mφ acquire an M2-like phenotype and express a number of specific receptors and signaling pathway molecules that promote MTB survival within cells but can also be used as targets for delivering NPs with active agents. These include, in particular, the mannose and mannose-fucose receptors (CD206), which belong to the large family of C-type lectin receptors (CLR) [27, 28].

Mannosylation is the most common strategy for delivering NPs to Mφ via CD206. Examples of mannosylated NPs are given in Table 1.

Although the literature primarily focuses on the CD206 receptor, targeting of Mφ is also achieved through other receptors. For instance, S.S. Soni *et al*. identified the role of SR-A1 in the uptake of cyclodextrin NPs by Mφ [42]. An example of targeted delivery of anti-tuberculosis drugs to Mφ in tuberculosis infection is the conjugate of moxifloxacin with carboxymethylglucan (M-DCMG), where carboxymethylglucan served as a ligand for Mφ SR [43]. Peptide ligands, such as tuftsin, encapsulated in PLGA (poly(D,L-lactide-co-glycolide)) NPs, increase uptake by monocytes/Mφ and suppression of intracellular MTB growth [44]. Another promising approach is based on the use of β-glucans and other carbohydrates as ligand carriers. For example, E. Jaecklein *et al*. presented a strategy for encapsulating anti-tuberculosis drugs or prodrugs in the hydrophobic core of glucan-lipid NPs derived from baker's yeast *Saccharomyces cerevisiae*. Glucan-lipid NPs can be

Таблица 1
Применение стратегии маннозилирования для таргетинга НЧ
Table 1
Application of the mannosylation strategy for targeting NPs

Тип НЧ Type of NPs	Активное вещество Active substance	Основные эффекты Outcomes	Авторы, год Authors, year
PLGA-PEG-Маннозамин PLGA-PEG-Mannosamine	Рифапентин + Изониазид Rifapentine + Isoniazid	↑ фагоцитоз, медленное высвобождение, ↑антибактериальная активность ↑ phagocytosis, sustained release, ↑ antibacterial activity	Peng C. с соавт., (2025) [29] Peng C. et al., (2025) [29]
PLGA-PEG-Маннозамин PLGA-PEG-Mannosamine	Рифапентин Rifapentine	↑ поглощение макрофагами ↑ macrophage uptake	Luan H. с соавт., (2025) [30] Luan H. et al., (2025) [30]

Липидные НЧ-Манноза Lipid NPs-Mannose	Рифампицин Rifampicin	↑ антибактериальное действие (*M. Intracellulare*), подавление биопленок ↑ antibacterial activity (*M. Intracellulare*), biofilm suppression	Chae J. с соавт., (2023) [31] Chae J. et al., (2023) [31]
Гиалуроновая кислота-Манноза/Хитозан Hyaluronic acid- Mannose/ Chitosan	Изониазид Isoniazid	Сродство к CD206/CD44, стимуляция Т-клеточного ответа Affinity for CD206/CD44, stimulation of T-cell response	Mukhtar M. с соавт., (2022) [32] Mukhtar M. et al., (2022) [32]
GO-PEG-Манноза GO-PEG-Mannose	Рифампицин Rifampicin	↑ захват/накопление в макрофагах, pH-зависимое лизосомальное высвобождение, ↑ бактерицидность (БЦЖ/МБТ) ↑ macrophage uptake/accumulation, pH-dependent lysosomal release, ↑ bactericidal activity (BCG/MTB)	Pi J. с соавт., (2019) [33] Pi J. et al., (2019) [33]
Липидные НЧ-Манноза Lipid NPs-Mannose	Изониазид Isoniazid	↑ поглощение альвеолярными макрофагами, рецептор-зависимое (ингибируется маннозой) ↑ alveolar macrophage uptake, receptor-dependent (inhibited by mannose)	Costa A. с соавт., (2018) [34] Costa A. et al., (2018) [34]
Желатиновые НЧ Gelatin NPs	Глицирризин Glycyrrhizin	↑ захват *in vitro*, ↓ бактериальная нагрузка в легких/селезенке у мышей ↑ *in vitro* uptake, ↓ bacterial burden in lungs/spleen of mice	Viswanathan V. с соавт., (2018) [35] Viswanathan V. et al., (2018) [35]
Дендримерные НЧ-Манноза Dendrimer NPs-Mannose	LXR-L LXR-L	↑ накопление в макрофагах бляшек, активация LXR-ABCA1/ABCG1, замедление атеросклероза, ↓ MMP9/NF-κB и некроза без выраженной липогенности в печени ↑ accumulation in plaque macrophages, activation of LXR-ABCA1/ABCG1, atherosclerosis retardation, ↓ MMP9/NF-κB and necrosis without marked hepatolipotoxicity	He H. с соавт., (2018) [36] He H. et al., (2018) [36]
НЧ на основе бычьего сывороточного альбумина-Манноза Bovine serum albumin NPs-Mannose	miRNA KLK12 miRNA KLK12	pH-чувствительное высвобождение, ↓ бактериальная нагрузка/воспаление *in vivo* pH-sensitive release, ↓ bacterial burden/inflammation *in vivo*	Wang Y. с соавт., 2024 [37] Wang Y. et al., 2024 [37]
Внеклеточные везикулы-VSV-G-α-CD206 Extracellular vesicles-VSV-G-α-CD206	Рекомбинантная люцифераза Recombinant luciferase	↑ поглощение CD206+ клетками ↑ uptake by CD206+ cells	Ovchinnikova LA. с соавт., (2024) [38] Ovchinnikova LA. et al., (2024) [38]
Фукоидан/Хитозан-Манноза/Маннан Fucoidan/Chitosan -Mannose/Mannan		Активация THP-1, ↑ IL-1β, IL-6, TNF-α, поляризация в М1-макрофаги THP-1 activation, ↑ IL-1β, IL-6, TNF-α, polarization towards M1 macrophages	Serrasqueiro F. с соавт., (2023) [39] Serrasqueiro F. et al., (2023) [39]
Полимерные НЧ-двухвалентный маннозный PEG-лиганд Polymer NPs-bivalent mannose PEG ligand		Селективное поглощение М2-макрофагами (в 2.4-11.8 раз), рецептор-зависимое (ингибируется маннаном), плотность маннозного лиганда 1% Selective uptake by M2 macrophages (2.4- to 11.8-fold), receptor-dependent (inhibited by mannan), mannose ligand density 1%	Chen P. с соавт., (2020) [40] Chen P. et al., (2020) [40]
Pluronic F127 -Дубильная кислота-Манноза Pluronic F127-Tannic acid-Mannose		Селективное поглощение М2-макрофагами, рецептор-зависимое (ингибируется маннаном) Selective uptake by M2 macrophages, receptor-dependent (inhibited by mannan)	Hatami E. с соавт., (2019) [41] Hatami E. et al., (2019) [41]

PLGA – поли(D,L-лактид-ко-гликолид); PEG – полиэтиленгликоль; LXR-L – агонист рецептора LXR (Liver X Receptor); KLK12 – калликреин-связанная пептидаза 12.
PLGA – poly(D,L-lactide-co-glycolide); PEG – polyethylene glycol; LXR-L – LXR agonist (Liver X Receptor); KLK12 – kallikrein-related peptidase 12.

modified for controlled release of cargo at low pH and intra-macrophagally after recognition of β-1,3-glucans by dectin-1 and CR3 receptors [25, 45].

Receptor-mediated targeting of photosensitizers to macrophages for photodynamic therapy in oncological and other diseases

Photodynamic therapy (PDT) with receptor-mediated targeting of Mφ is a promising approach for treating tumors, atherosclerosis, and infectious diseases, based on the selective delivery of PS to target cells. This approach is particularly often used for the elimination or reprogramming of tumor-associated macrophages (TAMs), as they have an M2-like phenotype and serve as the main source of immunosuppression in tumor tissue, promoting tumor cell growth and metastasis [17, 46, 47]. Studies show that conjugates of PS with proteins (albumin, transferrin, lipoproteins), polysaccharides (dextran, mannan, beta-glucans), as well as nanoparticles binding to specific receptors, ensure high selectivity of PS accumulation in Mφ. It has been shown that conjugates of hematoporphyrin with lipoproteins [48], albumin, or transferrin [49] are actively taken up by Mφ due to high SR expression on them. Modification of PS-binding proteins with maleic acid enhances the selectivity of PS uptake by Mφ via SR-A1 [50, 51]. Since SR-A1 recognizes and binds negatively charged molecules, F. Tang *et al*. conjugated sodium alginate (polyanion) with the PS 1-[4-(2-aminoethyl)phenoxy] zinc(II) phthalocyanine. *In vivo* biodistribution analysis revealed selective accumulation of conjugates in the tumor, with 87% tumor growth inhibition without systemic toxicity [52]. Conjugates of PS with polysaccharides, such as dextran sulfate, also provide targeted delivery to TAMs. Dextran sulfate conjugated with chlorin e6 was predominantly taken up by TAMs with the M2 phenotype expressing SR-A1 receptors and effectively induced tumor cell apoptosis upon laser irradiation [47]. Similarly, mannose-modified compounds provide targeted delivery to TAMs with an M2-like phenotype via CD206. T. Soyama *et al*. synthesized a conjugate of chlorin e6 with mannose, which selectively targeted CD206 highly expressed on M2-TAMs and led to damage and death of tumor cells [53].

By directly eliminating M2-TAMs, PDT increases the proportion of anti-tumor Mφ with an M1-like phenotype and induces immunogenic cell death [54]. Along with the elimination of some cells, DAMP molecules (e.g., calreticulin) are released, and the antigen-presenting function of Mφ is activated [53, 55, 56]. This leads to a reduction in immunosuppression and enhancement of local anti-tumor immunity [53]. Y. Kimura *et al*. showed that PDT using a mannose-chlorin e6 conjugate increased the amount of calreticulin on the surface of cancer cells, enhancing their phagocytosis by Mφ [55]. In the work of X. Chi *et al*., a nanocomposite was synthesized consisting of chlorin e6 and the α2-adrenergic receptor (α2-AR) agonist guanfacine, which, by activating these receptors, can enhance the effectiveness of photoimmunotherapy. It was shown that α2-AR agonists promoted the repolarization of M2-TAMs towards the M1 phenotype through α2-AR-mediated inhibition of adenylate cyclase [56].

Clinical perspectives of PDT are associated not only with oncology but also with the treatment of pathologies such as atherosclerosis [57, 58], infectious diseases [23, 60, 61, 62, 63, 64, 65, 66, 67], and autoimmune processes [59]. In atherosclerotic lesions, Mφ constitute the most numerous cell population, determining all stages of its development [57]. Furthermore, Mφ play a key role in the initiation and progression of rheumatoid arthritis [59]. S.Y. Lee *et al*. synthesized D-mannosamine-PEG-chlorin e6 for PDT of atherosclerosis, which specifically bound to CD206 and penetrated foam cells derived from Mφ, significantly increasing reactive oxygen species generation after irradiation [58]. J. Huang *et al*. developed a dextran-bovine serum albumin conjugate to create a nanoemulsion with chlorin e6 and dexamethasone for SR-A-mediated delivery to Mφ. PDT using this nanoemulsion enhanced reactive oxygen species production, stimulated autophagy in foam cells, increased expression of the cholesterol efflux-associated protein ABCA1, and reduced secretion of pro-inflammatory cytokines [57]. A new PDT method for treating rheumatoid arthritis was proposed by D.N. Dorst *et al*., in which liposomes containing the PS IRDye700DX were delivered to Mφ in inflamed joints. It was shown that PDT using liposomes containing IRDye700DX caused Mφ death *in vitro* and significantly slowed arthritis development in mice with collagen-induced arthritis, providing local elimination of pro-inflammatory Mφ [59].

Receptor-mediated targeting of photosensitizers to MTB-infected macrophages for antibacterial photodynamic and photothermal therapy

Traditional TB chemotherapy faces problems of long treatment duration, toxicity, and the development of MDR strains. The use of TB treatment strategies alternative to chemotherapy, such as PDT, can overcome MDR-MTB through non-specific action on multiple cellular proteins, lipids, and nucleic acids [14, 15, 16]. Anti-tuberculosis therapy targeted at Mφ can be conducted using nanomaterials, which allows increasing the local concentration of drugs in infection foci, reducing systemic toxicity, and providing a synergistic effect through the combination of direct PDT action and PDT-induced immune response [23].

As noted above, Mφ play an important role in the pathogenesis of TB, being the primary cellular reservoir of MTB. To enhance therapeutic efficacy, NPs modified with ligands or membranes capable of selectively binding to macrophage receptors are used. Within the framework of antibacterial PDT and combined approaches, strategies

for targeting PS to MTB-infected Mφ are being particularly actively developed. An example is the work of N. Tian *et al*., who developed nanocomposites with a core made of a metal-organic framework based on zirconium ions and porphyrin ligands, with internal content of synthetic unmethylated CpG oligonucleotides. Phosphatidylserine was used as a surface coating. By stimulating TLR in immune cells, oligonucleotides can induce an anti-mycobacterial Th1- and M1-type immune response. The obtained NPs combined properties necessary simultaneously for PDT and targeted immunotherapy; as a result, the created NPs showed high bactericidal activity against MTB and immunostimulatory properties [23].

In addition to classical PDT, combined approaches combining photodynamic and photothermal effects have been actively developed in recent years. Mannosylated NPs provide highly effective delivery of anti-tuberculosis drugs through interaction with CD206. S. Fan *et al*. developed mannose-modified polydopamine-based mesoporous NPs loaded with rifampicin. These NPs provided selective drug delivery and photothermal bacterial killing in MTB-infected Mφ. At the same time, these NPs induced an immune response and prevented MTB evasion from immune cells, stimulated autophagy, suppressed lipid peroxidation and ferroptosis of MTB-infected Mφ. In a mouse model of cutaneous TB, such combined therapy significantly reduced bacterial load and decreased pathological changes without systemic side effects [60].

One approach to TB therapy uses NPs coated with the membrane of activated Mφ or erythrocytes. This design ensures precise targeting of granulomas and infected tissues, high biocompatibility, and prolonged circulation in the bloodstream. H. Wang *et al*. created biomimetic NPs coated with erythrocyte membranes to increase blood circulation time and selective accumulation in tuberculous granulomas. Inside these NPs contained a PS excited in the near-infrared range, as well as a photothermal agent – Prussian blue. This construct, upon laser irradiation, destroys bacteria, providing simultaneously PS-mediated reactive oxygen species generation and local thermal effects. As a result, in a mouse model of TB infection, a synergistic effect was observed, leading to suppression of bacterial growth and reduction of granulomatous infiltration [61]. The same group of researchers developed NPs containing macrophage membrane-derived microvesicles with chlorin e6. These NPs circulated in the blood for a long time and accumulated in tuberculous granulomas due to the tropism of microvesicles for infection foci. In a mouse model of tuberculous granulomatosis, microvesicles effectively inhibited pathogen growth and spread, demonstrating good biocompatibility and potential for TB treatment with a low risk of drug resistance development [62]. B. Li *et al*. developed PLGA-based NPs encapsulating a photothermal agent with aggregation-induced emission (AIE), coated with membranes from *M. marinum*-activated RAW 264.7 Mφ. The *M. marinum*-induced increased expression of TLR2/4/6 on the membranes of such Mφ provides targeted transport of NPs to tuberculous granulomas. AIE allows fluorescent visualization of tissues in the near-infrared range (1500-1700 nm). In a mouse model of TB infection, intravenous administration of these NPs provided high-contrast visualization of granulomas in the lungs with resolution surpassing CT, and transcutaneous laser irradiation induced a local photothermal effect eliminating the pathogen [63]. Biomimetic AIE NPs allow not only combined photodynamic/photothermal therapy but also high-contrast visualization of granulomas *in vivo*. In a recent study, Yan D *et al*. synthesized AIE NPs coated with membranes of pre-activated Mφ. Using AIE visualization allowed precise detection of small granulomas about 0.2 mm in diameter in the lungs of infected mice. Upon irradiation with a 1064 nm laser, NPs provided photothermal bacterial killing more effectively than chemotherapy [64].

It should be noted that targeted PDT aimed at destroying intracellularly localized pathogens is effective not only against *M. tuberculosis* but also against other pathogens, including *Staphylococcus aureus* [65], including methicillin-resistant strains [66], *Acinetobacter baumannii* [66], *Salmonella enterica* [67], and others.

Conclusion

The increasing prevalence of MDR-TB and the limited effectiveness of chemotherapeutic agents dictate the need to revise treatment strategies towards alternative highly specific pathogen-oriented and immunomodulatory approaches. The data presented in this review show that Mφ with M2-like polarization are not only a central link in MTB persistence but also a promising therapeutic target. The use of nanoscale carriers with passive and active targeting allows not only to ensure a high intracellular concentration of antibacterial drugs but also to implement fundamentally different mechanisms of action. Of particular interest in this context is the targeted delivery of PS, which underlies antimicrobial PDT. Combined approaches integrating PDT with photothermal effects and immunomodulation demonstrate high efficacy in preclinical models, providing synergistic killing of intracellular pathogens and stimulation of anti-infective immunity. It is important to emphasize that the efficacy of many of the platforms considered has already been confirmed *in vivo* in models of TB infection with MDR pathogen.

Nevertheless, the translation of the obtained results into clinical practice requires solving a number of tasks: optimization of the biodistribution and biocompatibility profile of NPs, standardization of targeted delivery protocols for different routes of administration (inhalation, intravenous), as well as studying the long-term effects of modulating the Mφ phenotype on anti-tuberculosis immunity as a whole.

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