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Original article

BIOINFORMATIC ANALYSIS OF THE GENETIC MECHANISM OF BIOMINERALIZATION OF BIOGENIC MAGNETIC NANOPARTICLES IN BACTERIA CAPABLE OF TUMOR-SPECIFIC ACCUMULATION

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Background. Current methods of targeted cancer therapy are not always effective enough and can lead to side effects, such as an increased risk of autoimmune diseases. It is known that some bacteria are capable of specific accumulation in malignant tumors, and therefore can be used as an alternative means of targeted drug delivery. However, the genetic mechanism of tumor-specific accumulation of bacteria is not fully understood and needs to be studied in more detail.
Objective. This work aims to identify, by methods of comparative genomics methods, magnetically controlled bacteria among those for which tumor-specific accumulation has already been experimentally shown.
Methods. To identify magnetically controlled bacterial strains, i.e., bacteria that biomineralize biogenic magnetic nanoparticles (BMN), the method of comparative genomics was used, namely: pairwise alignment of proteomes with amino acid sequences of Mam-proteins of required for biomineralization of BMN in magnetotactic bacteria *Magnetospirillum gryphiswaldense* MSR-1. Sequence alignments were performed in the BLAST program of the US National Center for Biotechnology Information (NCBI).
Results. The conducted bioinformatic analysis showed that strains of bacteria in which the ability to accumulate specifically in tumors has been experimentally proven are potential producers of BMN of different types. Among them there are potential producers of intracellular crystalline BMN, potential producers of intracellular amorphous BMN, and extracellular crystalline BMN
Conclusions. It is expedient to use bacteria-producing BMN as gene vectors and systems of targeted drug delivery to tumors that biomineralize BMN.
Keywords: cancer therapy; biogenic magnetic nanoparticles; biomineralization; Mam-proteins; bacterial colonization; cancerous tumors; genetic vector; targeted drug delivery system.

Introduction

The search for new methods for cancer therapy remains one of the main tasks of medicine and biotechnology. Traditional treatments for cancer, such as chemotherapy and radiation therapy, are characterized by low patient survival due to a lack of tumor specificity, leading to undesirable side effects on healthy cells and therefore limiting therapeutic doses. There are targeted therapies that use accelerated cell growth as a marker of tumors to achieve targeted therapy, but they are ineffective because usually, only 3–5% of tumor cells are in the growth phase at the same time [1]. It is also known that some types of tumors are characterized by high levels of expression to the transferrin receptor (TfrR). Based on this, TfrR conjugates have been developed with several anticancer drugs that have been successfully internalized into tumor cells of the breast, lung, brain, and some types of lymphoma, but cannot be used for other cancers [2]. Monoclonal antibodies to various receptors on the surface of cancer cells are most widely used in targeted drug delivery systems: TfrR, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and CD receptors. The use of drugs of this type shows high efficiency – therapeutic response in 78% of cases and 45.5% of stable remission [3], but at the same time increases the likelihood of autoimmune reactions [4].

Currently, the use of bacteria in the targeted delivery of chemotherapeutics and the creation of vectors for gene therapy is considered promising [5–7]. The first bacteria to be found to affect cancer cells are of the genus *Clostridium*. As early as 1813, tumors were regression in patients who developed concomitant "gas gangrene" caused by *Clostridium perfringens* [8]. Tumor-specific accumulation in the body was later demonstrated for many other bacterial genus, including *Bifidobacterium*, *Shigella*, *Salmonela*; and for such species of bacteria as: *Vibrio cholerae, Listeria monocytogenes, Pseudomonas aeruginosa*, etc. [6].

Bacterial colonization of tumors was originally attributed to the hypoxic nature of solid tumors (low O_2). Hypoxia is caused by the rapid growth of tumor cells and insufficient blood supply and is a fairly well-studied phenomenon. In [9], bacterial colonization of tumors is explained by the fact that the anaerobic nature of hypoxic and necrotic areas in tumors promotes the growth of anaerobic and facultative anaerobic bacteria. In addition, areas of necrosis may also provide nutrients, such as purines, to further promote bacterial growth [6]. Therefore, bacterial chemotaxis to chemoattractant compounds present in necrotic areas (eg, aspartate, serine, citrate, ribose, or galactose) produced by tumor cells is also considered a contributing factor to the accumulation of bacteria in tumors [10]. However, with new studies [11, 12] it is becoming increasingly clear that other elements of the unique microenvironment of tumors, including the formation of neovasculature, may be involved in this mechanism. As tumors develop, they promote the formation of new blood vessels (neoangiogenesis). However, these newly formed vessels are severely disorganized with incomplete endothelial layers and blind ends, which leads to "leakage" of vessels and sluggish blood flow. This feature of the structure can allow circulating bacteria to enter and be located in tumor tissues [11]. Another factor that contributes to the accumulation of bacteria in tumors may be the local suppression of immunity [13]. In addition, showed [14] that the delivery of genes and drugs to tumors can be carried out by intravenous administration and for some species of bacteria by oral administration of symbiotic nonpathogenic or attenuated pathogenic strains.

It is already clear that tumor-specific accumulation of bacteria can be used for targeted therapies, such as the use of bacterial vectors or targeted drug delivery systems (DDS) [15]. However, understanding the exact mechanisms that lead to bacterial colonization of the tumor is of great importance in terms of optimizing treatment methods, and therefore this phenomenon requires more detailed study.

In paper [16] suggested the hypothesis of magnetocarcinogenesis that exposure to weak magnetic fields can lead to cancer development. Studies have shown [17, 18] that tumor cells are characterized by the ability to enhance the formation of biogenic magnetic nanoparticles (BMN) formation. This "unique" feature of the tumor distinguishes it from normal surrounding tissue, and therefore may also be a factor in the recognition of bacteria by specific accumulation.

BMN are iron-containing compounds, most often nanocrystals of ferrites – magnetite (Fe_3O_4), maghemite (Fe_2O_3), greygite (Fe_3S_4), etc., which are formed in the process of biomineralization, ie genetic control of BMN synthesis [19, 20]. The most studied phenomenon of biomineralization is in magnetotactic bacteria (MTB) *Magnetospirillum gryphiswaldense MSR-1*, in which this process is controlled by numerous Mam-proteins, among which MamA, MamB, MamM, MamE, MamO are indispensable for the biomineralization of BMN [21]. Due to their natural magnetically controlled properties, magnetotactic bacteria are widely studied as vectors for targeted drug delivery to tumors [22, 23], but magnetotactic bacteria are difficult to cultivate and maintain their viability, as their habitat is significantly different from the internal environment of humans or animals [24], so the search for bacteria with natural magnetically controlled properties, characterized by the tumor-specific accumulation in tumors, is a very important task.

The work aims to identify, by methods of comparative genomics, magnetically controlled bacteria – potential producers of BMN among those for which tumor-specific has already been experimentally shown.

Materials and methods

The study used the methods of comparative genomics, namely: pairwise alignment in the program "BLAST" of the US National Center for Biotechnology Information (NCBI) [21]. The amino acid sequences of Mam proteins necessary for the process of biomineralization in the magnetotactic bacteria *Magnetospirillum gryphiswaldense MSR-1* are compared analogously to [21, 24], with proteomes of bacteria those for which tumor-specific has already been experimentally shown. For some strains, the ability to tumor-specific accumulation has been experimentally demonstrated, are shown in Table 1.

To assess the coincidence of amino acid sequences of proteins in alignments, the following values were taken into account: E-value – an indicator of statistical significance of alignment, indicating the level of randomness factor in the coincidence of amino acid residues of comparable proteins; Ident (%) – the number of identical amino acid residues in the pairwise alignment of the specified protein sequences; Length – the length of the alignment (must be at least 100 amino acid residues) [21]. In addition to checking these parameters of amino acid chain sequence matches to determine homology, the functions of the studied proteins were also compared.

Table 1: Strains of bacteria in which the ability to tumor-specific accumulation was experimentally detected

Bacterial Strain	Biological Target: Cancer Cells/Cell Lines	Input method	References
Clostridium butyricum M 55	Vascular glioblastomas	Intracarotid injection	[25]
Clostridium novyi-NT	Bearing human colorectal cancer xenografts (HCT116), human biliary cancer HuCC-T1, the mouse melanoma B16, mouse colon cancer CT26	Intravenous injection	[25]
Bifidobacterium longum	S180 osteosarcoma	Intravenous injection	[6]
Bifidobacterium breve UCC2003	B16-F10 murine melanoma tumors, MCF7 human breast tumor xenografts, or C57 mice bearing s.c. Lewis lung carcinoma tumors	Intravenous injection	[14]
Salmonella typhimurium VNP20009	MDA-MB-361 (human breast carcinoma), WiDr (human colon carcinoma), and B16-F10 (mouse melanoma)	Intravenous injection	[26]
Escherichia coli K-12	Syngeneic murine 4T1 breast cancer model	Intravenous injection	[14, 27]
Escherichia coli Nissle 1917 (EcN)	Tumor tissues transplanted by xenotransplanted SW620 or HT29 cells (SW620 tumor tissues)	Intravenous injection	[28]
Vibrio cholerae	C6 glioma	Intravenous injection	[11]
Listeria monocytogenes	Human breast xenografts MCF-7, tumors of epithelial carcinoma of the human colon (Caco-2)	Intravenous injection, orally	[13, 29]
Shigella flexneri	4T1 tumor xenograft – and a transgenic MMTV-HER2 – breast cancer model	Intravenous injection	[30]
Pseudomonas aeruginosa PA103	Tumor cell lines MCF-7, MDA-MB-231, EMT6, 4T1, MCA, B16 murine melanoma, A375 human melanoma, Calu-3, LLC1, SK-OV-3, and HeLa	Subcutaneous injection	[31]
Staphylococcus aureus	Hypopharyngeal FaDu carcinoma or colorectal carcinoma CT26	Intravenous injection	[32]
Salmonella choleraesuis	B16F10 melanoma model	Intraperitoneal injection	[33]
Fusobacterium nucleatum ATCC 25586	Adenocarcinoma cells of the colon-2 (Caco-2)	The application as a bacterial vector	[34]
Bacillus subtilis	Human breast cell lines, MCF-7 and MDA-MB-231	The application as a bacterial vector	[35, 36]

Results

Alignment of Mam-proteins required for biomineralization (MamA, MamB, MamM, MamO, MamE, MamK) in the magnetotactic bacterium *Magnetospirillum gryphiswaldense* MSR-1 with bacterial proteomes capable of accumulating in cancerous tumors was performed according to information in the NCBI database as of June 2022. To indicate the degree of genome decoding in the NCBI database in Table 2 use the following designations taken from the database, which explain the level of genome assembly: Complete – the genome of the organism is completely deciphered; Chromosome – the genome of the organism is deciphered by ¾; Scaffold – the genome of the organism is deciphered by ½; Contig – the genome of the organism is deciphered by ¼.

Table 2: Alignment between Mam proteins of MTB *M. gryphiswaldense* MSR-1 and genomes of bacteria with proven tumor-specific accumulation

Bacterial Strain	Level of genome assembly	E-value; Ident,%; Length, aa					
		• Mam-proteins *Magnetospirillum gryphiswaldense MSR-1* CAM78034.1					
		MamA	MamB	MamM	MamO	MamE	MamK
Clostridium butyricum 5521 (M-55)	Contig	**7e-09 19.89% 186**	**5e-36 28% 260**	**8e-39 31.56% 244**	**1e-13 28.65% 178**	**3e-35 43.58% 179**	**3e-12 26.47% 306**
Clostridium novyi-NT	Complete	**9e-06 23.13% 134**	**6e-37 27% 269**	**7e-31 30.92% 262**	**2e-09 25.86% 174**	**1e-33 40.11% 182**	**8e-13 27.36% 307**
Bifidobacterium longum	Complete	5e-10 35,56% 90	**0.003 21% 263**	**6e-13 22.96% 257**	**3e-06 28.28% 145**	**5e-26 40.88% 181**	1.1 26.52% 181
Bifidobacterium breve UCC2003	Complete	0.50 53.57% 28	0.14 27% 88	0.13 32.50% 40	**2e-07 28.97% 145**	**1e-27 41.44% 181**	0.094 33.33% 39
Salmonella enterica ser. typhimurium VNP20009	Complete	**7e-04 23.68% 152**	**3e-35 31% 276**	**3e-27 26.87% 268**	**5e-14 28.90% 173**	**7e-37 42.77% 173**	0.005 24.42% 303
Escherichia coli K12	Complete	**3e-04 22.22% 171**	**6e-19 29% 204**	**8e-14 22.96% 257**	**4e-13 28.90% 173**	**2e-38 39.70% 199**	**0.002 24.09% 303**
Escherichia coli Nissle 1917	Complete	0.033 23.91% 138	**1e-18 27.05% 244**	**1e-14 22.96% 257**	**5e-14 28.90% 173**	**2e-38 40.70% 199**	**3e-04 24.09% 303**
Vibrio cholera	Complete	**2e-05 27.35% 117**	**2e-15 26% 240**	**3e-13 24.32% 259**	**4e-11 28.90% 173**	**7e-39 48.26% 172**	1.9 23.31% 326
Listeria monocytogenes 10403S	Complete	**5e-08 23.36% 107**	**1e-32 28% 265**	**1e-37 31.89% 254**	**0.007 31.37% 51**	**4e-23 37.22% 180**	**2e-14 27.10% 310**
Shigella flexneri	Complete	**0.003 22.22% 171**	**1e-17 28% 247**	**4e-14 22.78% 259**	**2e-13 29.48% 173**	**2e-37 39.70% 199**	**0.006 24.09% 303**
Pseudomonas aeruginosa PA103	Scaffold	0.068 34.21% 38	**2e-11 23% 263**	**1e-11 24.56% 281**	**4e-08 25.73% 171**	**4e-34 43.68% 174**	0.026 33.68% 95
Staphylococcus aureus	Complete	**6e-08 23.67% 169**	**1e-20 25% 277**	**2e-35 29.18% 257**	**8e-09 29.59% 169**	**4e-26 40.80% 174**	0.20 22.67% 172
Salmonella enterica ser. choleraesuis	Chromosome	**3e-04 25.16% 155**	**3e-41 34% 257**	**2e-35 32.55% 255**	**7e-13 28.90% 173**	**9e-36 42.77% 173**	**1e-06 25.78% 322**
Fusobacterium nucleatum ATCC 51190	Complete	**2e-09 24.86% 185**	**5e-21 28% 224**	**1e-16 24.46% 233**	2.4 31.58% 38	0.96 27.19% 114	**3e-09 26.71% 337**
Bacillus subtilis	Complete	**3e-08 27.42% 124**	**7e-46 33.33% 285**	**2e-36 31.73% 249**	**2e-10 28.05% 164**	**2e-37 48.21% 168**	**4e-10 25.41% 303**

The results show that 14 of the 15 microorganisms studied are potential producers of BMN, as evidenced by the corresponding values of statistical significance of matches (E-value) and the percentage of identical amino acid residues (Ident), as well as the common functions of proteins. Thus according to classification [37] *Clostridium butyricum* 5521 (M-55), *Clostridium novyi*-NT, *Salmonella enterica ser. typhimurium* VNP20009 *Escherichia coli K12*, *Listeria monocytogenes* 10403S, *Bacillus subtilis*, *Vibrio cholerae*, *Staphylococcus aureus Bifidobacterium longum*, *Salmonella enterica ser.*

choleraesuis are potential producers of intracellular crystalline BMN, *Shigella flexneri*, *Pseudomonas aeruginosa* PA103, *Escherichia coli* Nissle 1917 are potential producers of intracellular amorphous BMN, *Fusobacterium nucleatum* ATCC 51190 – of extracellular crystalline BMN. At the same time, the proteins of the *bacterium Bifidobacterium breve* UCC2003 in Table 2 have the same functions as their homologs in magnetotactic bacteria. That is why the *bacterium Bifidobacterium breve* UCC2003 can also be the potential producer of BMN.

Several bacteria are experimentally proved producers of BMN *Escherichia coli Nissle 1917* [38], *E. coli ATCC 25922* [39], *Pseudomonas aeruginosa* VKM B-552, *Escherichia coli* VKM B-126 [40].

Discussion

Thus, the results of the bioinformatics analysis show that almost all bacteria for which the ability to specifically accumulate in tumors has been experimentally demonstrated are potential producers of biogenic magnetic nanoparticles. Bacteria are thought to accumulate in tumors due to the favorable (hypoxic) environment of tumor tissue that supports bacterial colonization and growth (known as tissue tropism), protecting the host's immune system [35]. However, according to the results of the bioinformatics analysis, it can be concluded that the natural magnetic properties of bacterial cells may be one of the mechanisms of tumor-specific accumulation.

According to the calculations of [41], the strength of the magnetodipole interaction between the intracellular chains of BMN cancer and bacterial cells is approximately 10^{-7}–10^{-8} N and, having a close order of magnitude with the forces of specific antigen-antibody binding, even slightly exceeds their value. This means that the forces of magnetodipole interaction between the BMN of bacteria and the BMN of tumor cells enough to keep the bacteria in the tumor.

This is confirmed by the works [22, 23, 42], which show the effectiveness of using magnetotaxis bacteria as vectors for drug delivery due to their natural magnetic properties. But there are limitations in the wide application of MTB, such as: complex technology of cultivation, possible activity loss or alteration due modification, poorly defined pharmacokinetics, potential immunogenicity, low magnetosome isolation efficiency [23]. Therefore, a search was made in this work is the search for easy-to-cultivate and widespread application of bacteria with natural magnetic properties.

Therefore, the ability of bacteria to synthesize BMN is an important parameter for their transport and fixation in tumor tissues and can be used to create vectors or targeted drug delivery systems based on the studied microorganisms.

The use of bacteria with natural magnetically controlled properties is advantageous due to the more homogeneous distribution of the magnetic susceptibility of individual bacterial cells than when magneto-targeting vectors are labeled with artificial magnetic nanoparticles. This minimizes the possible blockage of capillaries, as it is known that BMN are localized in the walls of capillaries in humans [38, 43]. At the work [38] shows the ability of bacteria *Escherichia coli Nissle 1917* to move in a gradient magnetic field of permanent magnets without artificial magnetic marking, which in practice demonstrates the presence of natural magnetic properties of this organism.

Conclusions

Bioinformatic analysis, with using comparative genomics shows that bacteria that have been experimentally shown to have a specific accumulation in tumors, and for which deciphered data on NCBI-based genomes and proteomes have been presented, are potential producers of biogenic magnetic nanoparticles of various types. Among them there are potential producers of intracellular crystalline BMN, potential producers of intracellular amorphous BMN, extracellular crystalline BMN

Thus, to create vectors or a targeted delivery system for the treatment of cancer based on microorganisms, it is necessary to consider not only their ability to survive in anaerobic conditions and chemotaxis to compounds of necrotic regions, as previously thought but also the ability to synthesize BMN. The ability to synthesize BMN is an important factor for the direction and localization in tumors of vectors or targeted delivery systems using magnetic technology, it is also necessary to take into account the presence of BMN in the capillary walls in the development of magnetically controlled dosage forms.

Interest disclosure

The authors have no conflicts of interest to declare.

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БІОІНФОРМАТИЧНИЙ АНАЛІЗ ГЕНЕТИЧНОГО МЕХАНІЗМУ БІОМІНЕРАЛІЗАЦІЇ БІОГЕННИХ МАГНІТНИХ НАНОЧАСТИНОК У БАКТЕРІЯХ, ЗДАТНИХ ДО ПУХЛИНОСПЕЦИФІЧНОГО НАКОПИЧЕННЯ

Проблематика. Існуючі на сьогодні методи таргетної терапії раку не завжди виявляють достатню ефективність лікування та можуть призводити до появи побічних ефектів, наприклад до підвищення ризику аутоімунних захворювань. Відомо, що деякі бактерії здатні до специфічного накопичення в злоякісних пухлинах, а отже, можуть бути використані як альтернативний засіб спрямованої доставки лікарських засобів (ЛЗ). Однак генетичний механізм пухлиноспецифічного накопичення бактерій не є остаточно з'ясованим і потребує більш детального вивчення.

Мета. Метою роботи є виявлення методами порівняльної геноміки магнітокерованих бактерій серед тих, для яких вже було експериментально показано пухлиноспецифічне накопичення.

Методика реалізації. Для виявлення магнітокерованих бактеріальних штамів, тобто бактерій, що біомінералізують біогенні магнітні наночастинки (БМН), використовувалися методи порівняльної геноміки: попарне вирівнювання протеомів з амінокис-

лотними послідовностями обов'язкових для біомінералізації Mam-білків магнітотаксисної бактерії *Magnetospirillum gryphiswaldense* MSR-1. Вирівнювання послідовностей проводилися у програмі "BLAST" Національного центру біотехнологічної інформації США (NCBI).

Результати. Проведений біоінформаційний аналіз показав, що штами бактерій, у яких експериментально доведено здатність до специфічного накопичення у пухлинах, є потенційними продуцентами БМН різних типів. Серед них присутні потенційні продуценти внутрішньоклітинних кристалічних БМН, потенційні продуценти внутрішньоклітинних аморфних БМН і позаклітинних кристалічних БМН

Висновки. Бактерії-продуценти БМН доцільно використовувати як генні вектори і системи адресної доставки ЛЗ до пухлин, що біомінералізують БМН.

Ключові слова: терапія раку; біогенні магнітні наночастинки; біомінералізація; Mam-білки; бактеріальна колонізація; ракові пухлини; генний вектор; система адресної доставки ліків.