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Prospects for the use of *Bacillus anthracis* toxin in cancer therapy

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SUMMARY
Cancer is one of the major causes of death in pet animals and humans worldwide. The contraindications and side effects associated with conventional cancer therapies heighten the importance of research aimed at finding new ways to combat cancer. One of the promising methods for the treatment of oncological diseases is the use of components of bacterial toxins, in particular the toxins of *Bacillus anthracis*, the causative agent of anthrax. Lethal factor is the main virulence factor of the anthrax pathogen, which is a zinc-dependent metalloprotease, the substrate for which is intracellular MAPK signaling pathways widely present in cancer cells. This review focuses on discussing the experience of foreign researchers in the application of *Bacillus anthracis* lethal factor in cancer therapy. The paper presents data from the studies that characterize the structure and functions of the lethal factor, reflect the results of its application on cancer cells both as a part of anthrax toxin and as a separate unit, reveal its therapeutic potential. The analysis of literature demonstrated good prospects for the potential use of the lethal factor to combat such types of cancer as liver, lung, colon, breast, pancreatic, ovarian, prostate, stomach and nervous system cancers. However, despite the impressive results, further in-depth research is needed in this area concerning selection of optimum doses of the lethal factor, determination of sensitivity of different types of cancer to it, investigation of its effects on other body tissues and interaction with the immune system during therapy.

Keywords: review, anthrax, *Bacillus anthracis*, cancer, oncology, lethal factor

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Перспективы применения токсина *Bacillus anthracis* в терапии онкологических заболеваний

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РЕЗЮМЕ
Онкологические заболевания – одна из ведущих причин смертности домашних непродуктивных животных, а также людей во всем мире. Противопоказания и побочные эффекты традиционных методов лечения рака актуализируют исследования, направленные на поиск новых способов борьбы с такого рода заболеваниями. Одним из перспективных методов лечения онкологии является применение компонентов бактериальных токсинов, в том числе токсинов возбудителя сибирской язвы – *Bacillus anthracis*. Летальный фактор – главный фактор вирулентности возбудителя сибирской язвы, представляющий из себя цинк-зависимую металлопротеазу, субстратом которой являются внутриклеточные сигнальные пути МАРК, широко представленные в раковых клетках. Данный обзор сосредоточен на обсуждении опыта зарубежных исследователей по применению летального фактора *Bacillus anthracis* в терапии онкологических заболеваний. В работе представлены данные исследований, характеризующие структуру и функции летального фактора, отражающие результаты его воздействия на онкологические клетки как в составе токсина возбудителя сибирской язвы, так и в виде отдельной единицы,

раскрывающие его терапевтический потенциал. Анализ литературных источников продемонстрировал перспективность возможного применения летального фактора на таких видах онкологических заболеваний, как рак печени, легких, толстой кишки, груди, поджелудочной железы, яичников, простаты, желудка и нервной системы. Однако, несмотря на впечатляющие результаты, необходимы дальнейшие глубокие исследования в этом направлении, касающиеся подбора оптимальных дозировок летального фактора, определения чувствительности к нему различных видов рака, изучения его воздействия на другие ткани организма и взаимодействия с иммунной системой в процессе терапии.

Ключевые слова: обзор, сибирская язва, *Bacillus anthracis*, рак, онкология, летальный фактор

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INTRODUCTION

Papers published over the past few years provide evidence of an increase in oncology-associated pet mortality [1, 2], which makes such pathologies one of the most pressing challenges in veterinary medicine [3].

Furthermore, oncological diseases are a leading cause of human death worldwide. According to the World Health Organization estimates, they accounted for nearly 10 million deaths in 2020. The most common causes of cancer death were lung cancer (1.8 million), colorectal cancer (935 thousand), liver cancer (830 thousand), stomach cancer (769 thousand), breast cancer (685 thousand) [4].

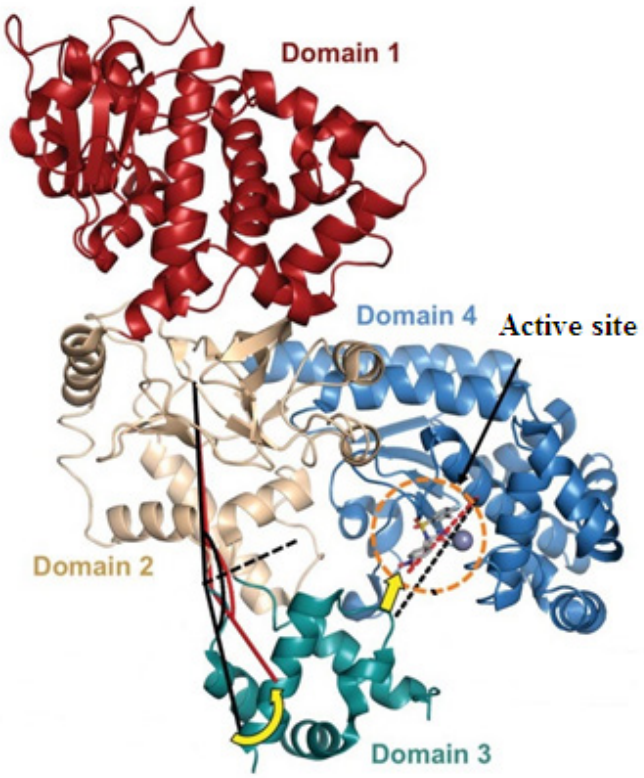

Fig. 1. Structure of B. anthracis lethal factor [21]: domain 1 is responsible for interaction with PA; domain 2 is responsible for LF translocation through the pore formed in the cell membrane; domain 3 is a functionally active subunit; domain 4 is, together with domain 1, responsible for interaction with PA; the active site (circled with an orange dotted line) displays catalytic zinc (gray sphere)

Conventional cancer therapies, in particular radiation, chemotherapy, surgery, though widely applied, are associated with certain limitations and side effects, therefore researchers continue to seek new ways to combat cancer. They are currently exploring the methods of immune therapy, cryotherapy, molecular therapy (gene therapy, RNAi, CRISPR), application of apoptines (viral proteins with selective anti-cancer activity), herbs and plant metabolites [5–12].

At present, one of the promising methods for oncological disease treatment is the use of the components of bacterial toxins [13–15]. Studies on the application of the agent of anthrax for this purpose are not left out [16]. Anthrax is a highly dangerous disease caused by *Bacillus anthracis,* a large gram-positive bacterium. The disease is widely spread worldwide [17, 18]. When inside a susceptible organism, *Bacillus anthracis* secretes two exotoxins – lethal toxin (LeTx) and edema toxin (EdTx), which are responsible for the development of pathological processes in the macroorganism [19]. Over the past decades, based on the thorough studies of mechanisms of action of these toxins, researchers have put forward the idea to investigate the possible application of *B. anthracis* LeTx lethal factor (LF) as a therapeutic in the treatment of oncological diseases [20].

In view of the above, the paper is aimed at reviewing relevant studies on the use of *B. anthracis* toxin lethal factor in cancer therapy.

STRUCTURE AND FUNCTION OF *B. anthracis* LETHAL FACTOR

Lethal factor (LF) is a toxin component secreted by the bacteria. It is a protein with a molecular weight of 90 kDA, which is encoded by *lef* locus on *B. anthracis* pXO1 plasmid. The crystal structure of the protein consists of 4 domains. Domain 1, which is structurally similar to domain 4, is responsible for interaction with protective

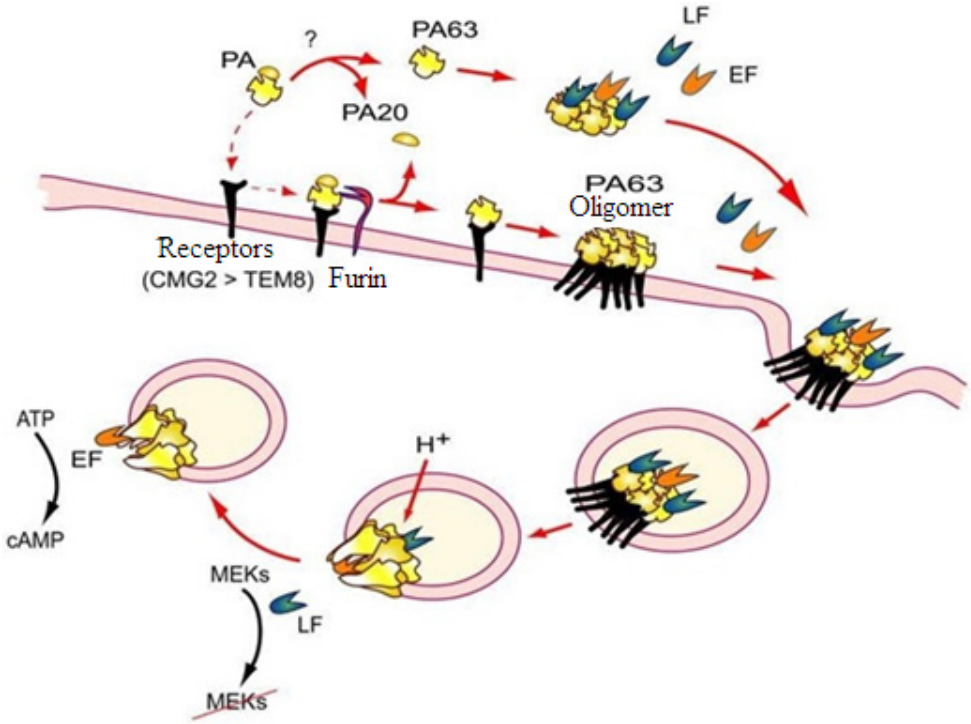

Fig. 2. Mechanism of B. anthracis toxin penetration into the target cell [23]. PA secreted by the agent interacts with its specific receptors on the surface of target cells. Then PA is cleaved by membrane protease (furin) into two peptides (63 kDa and 20 kDa), with subsequent PA_{63} oligomerization, its insertion into the cell membrane and LF or EF attachment to it. The resulting complex (PA + LF and/or PA + EF) enters the cytoplasm through endocytosis. When inside the endosome, the toxin is exposed to acidic environment, which facilitates the formation of PA_{63} oligomer channel in the endosome wall and subsequent LF and/or EF entry into the cell cytosol

antigen (PA), a receptor-binding component of the toxin. Domain 2 is structurally linked with domains 1 and 4 and responsible for translocation through the pore formed in the cell membrane. Domain 3 is an active catalytic subunit responsible for LF functional activity (Fig. 1) [21].

In a classical case, LF penetrates into the target cell by translocation through a pore formed by PA. For this purpose, PA interacts with receptors on the cell surface, which are represented by type I membrane proteins: TEM8 (tumor endothelium marker 8) and CMG2 (capillary morphogenesis protein 2). After that, LF exerts its toxic effect on the cell (Fig. 2) [22, 23].

In 1998, two independent groups of researchers identified MAPK (mitogen-activated protein kinase) signaling pathways as proteolytic substrates for LF. The MAPK signaling pathways are a group of multifunctional intracellular signaling pathways, which control the transcription of genes responsible for metabolism, proliferation and other processes, as well as play a critical role in cancer ontogenesis [24, 25]. These findings encouraged further investigation of *B. anthracis* lethal toxin effect on cancer cells.

STUDIES OF *B. anthracis* LeTx EFFECT ON CELLS OF DIFFERENT TYPES OF CANCER

In 2001, a group of researchers from the USA published their findings regarding *B. anthracis* LeTx effect on fibroblastoma cells. The authors found that a 48-hour exposure to LeTx inhibited the cell proliferation (up to 35%). Following these satisfactory results, N. S. Duesbery et al. investigated LeTx effect on carcinogenicity *in vivo* in the athymic laboratory mouse model. Average tumor weight in

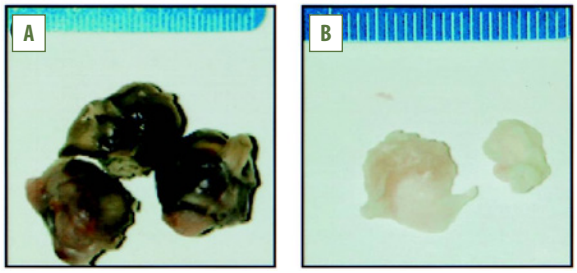

Fig. 3. Fibroblastomas removed from laboratory mice [26]: A – control group; B – test group injected with 2 μg of B. anthracis LeTx during 5 days

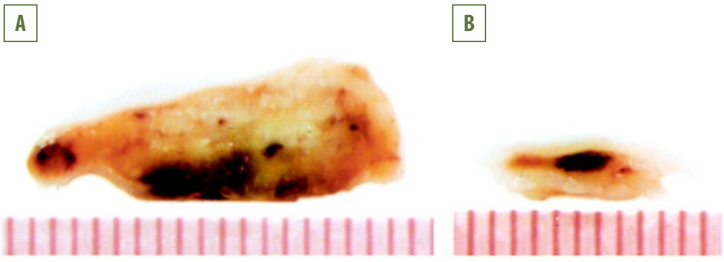

Fig. 4. Melanomas removed from laboratory mice [27]: A – control group; B – test group injected with 2 μg of B. anthracis LeTx during 72 hours

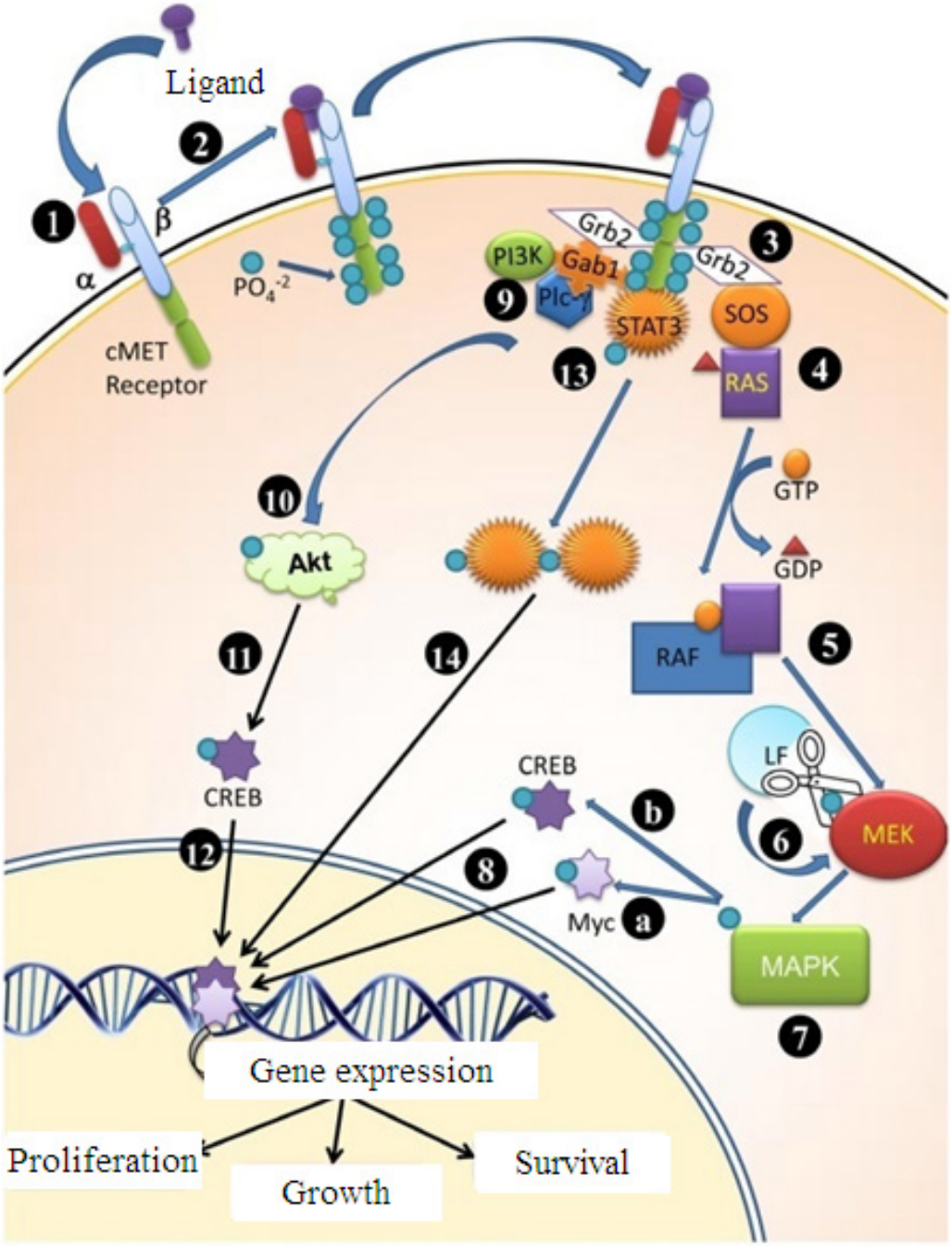

Fig. 5. Plausible mechanism of B. anthracis LF effect on cancer cells expressing c-Met receptor [5]: (1) α-subunit of c-Met receptor is extracellular, while β-subunit is a transmembrane peptide possessing a kinase domain and a docking site for the molecule involved in cell signaling and receptor biological activity; (2) upon ligand binding to c-MET receptor, the tyrosine kinase domain undergoes oxidative phosphorylation; (3) Grb2 (growth factor receptor-bound protein 2) effecter binds to phosphorylated tyrosine kinase and RAS guanine exchange factor SOS; (4) SOS promotes dissociation of GDP (guanosine diphosphate) from Ras and attachment of GTP (guanosine triphosphate) and thereby activates Ras; (5) Ras activates Raf (proteins involved in signaling) and, in turn, (6) phosphorylates MEK, followed by phosphorylation of MAPK; LF cleaves MEK and prevents further signaling required for cell proliferation, survival and growth

the group of mice injected daily with 2 μg of *B. anthracis* LeTx during 5 days was found to decrease by 63% as compared with the control group. Besides, it was found that tumor exposure to LeTx inhibited its angiogenesis (Fig. 3) [26].

Another group of researchers studied LeTx effect on human melanoma cells in the laboratory mouse model [27]. SK-MEL-28 and M14-MEL melanoma cell cultures were administered subcutaneously in the left and right dorsal areas of female athymic mice. After the cell engraftment,

2 μg of *B. anthracis* LeTx were injected in the developed tumors daily, during three days. It was found that, after the treatment, the tumors became necrotized by an average of 31.5–55.2%. Besides, LeTx injection in the tumor on one side only lead to the regression of the tumour on the opposite side, and this is indicative of systemic effect of LeTx (Fig. 4) [27].

The investigation of LeTx effect on melanoma, fibrosarcoma, kidney and lung cancer cells undertaken in the first decade of the XXI century demonstrated the possibility of significant inhibition of cancer cell growth [28–30]. However, alongside with pathological cell destruction, LeTx, being non-specific, caused damage to the normal cells of the organism. Therefore, the use of LeTx in cancer therapy-related studies was limited. This heightened the importance of research aimed at identification of possible specific cell receptors that could interact with LF without intermediary of PA.

POSSIBILITY OF SPECIFIC APPLICATION OF *B. anthracis* LF IN CANCER THERAPY

In 2017, a group of Indian researchers carried out a study that demonstrated the possibility of LF penetration into the cells without binding to PA, but through LF interaction with specific cell receptors. The number of hydrogen bonds and free energy produced during the protein binding to the receptor were adopted as the indicator of intensity of interaction between them. The study revealed, that beside natural binding to PA with 22 hydrogen bonds and a free energy value of -402.60, LF actively interacts with HER3 (human epidermal growth factor 3) receptor with 20 hydrogen bonds and a free energy value of -260.00, and with c-Met receptor (hepatocyte growth factor receptor) with 19 hydrogen bonds and a free energy value of -773.96 [5]. In a healthy organism, c-Met receptor is expressed by stem cells and progenitor cells only, this allows such cells to grow invasively, thus contributing to generation of new tissues in an embryo and regeneration of damaged tissues in an adult. However, in case of oncological disease, this receptor is overexpressed on cancer cells [31, 32]. c-Met receptor is actively expressed in several cancers such as liver, lung, colon, breast, pancreatic, ovarian, prostate, stomach and nervous system cancers [5]. The obtained data showed that LF had stronger affiliation with c-Met, and that was suggestive of its potential for the use in the treatment of oncological diseases with c-Met overexpression on cancer cells.

To confirm this hypothesis, the authors studied LF effect on proliferation of mammary tumor cells (breast cancer is the fifth leading cause of cancer death worldwide). It was found that a 72-hour incubation of mammary tumor cells together with LF at a dose of 50 ng reduced the cell proliferation, on average, by 28.0 ± 1.77%, with absolutely no toxic effect on LeTx-sensitive cells [5]. The study demonstrated the potential of *B. anthracis* LF for the use in the treatment of the oncological diseases characterized by c-Met expression on cancer cells.

At present, it is supposed that the mechanism of *B. anthracis* LF effect on c-Met expressing cancer cells is as follows (Fig. 5). The interaction of the ligand (LF) with the receptor on the cell surface (c-Met) causes conformational changes on the intracellular portion of the receptor, and this, in its turn, activates a cascade of consecutive oxidative phosphorylation reactions. Near the cytoplasmic portion of the receptor, a multi-protein signaling complex is formed, which activates Ras GTPase. Ras binds and activates MAPK/ERK kinase kinase, or MEKK, the main components of which are Raf proteins. MEKK phosphorylates and activates kinase represented by MEK components. MEK, in its turn, phosphorylates MAPK, involved in signaling required for cell proliferation, growth and survival. LF cleaves MEK and prevents further signaling.

CONCLUSION

Oncological diseases are one of the major causes of death in animals and humans. This heightens the importance of research aimed at finding new cancer treatments.

This literature review demonstrates the potential of *B. anthracis* toxin component as a therapeutic in the treatment of oncological diseases. It was found that many types of cancer cells, in particular liver, lung, colon, breast, pancreatic, ovarian, prostate, stomach and nervous system cancer cells, express on their surface an LF-specific tyrosine kinase receptor (c-Met). As a result of interaction with c-Met, LF cleaves intracellular signaling pathways responsible for cell proliferation, growth and survival, thus causing the necrotization of cancer tumors.

However, despite the impressive results of the studies on LF application in oncological disease therapy, further in-depth research is needed in this area concerning:

1) selection of LF doses, its application duration and schedule;

2) *in vitro* and *in vivo* determination of sensitivity of different types of c-Met expressing cancer cells to it;

3) examination of LF effect on other body tissues during therapy;

4) investigation of immune system reactions to LF application.

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