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PROSPECTS OF APTAMER APPLICATION IN DIAGNOSTICS OF BACTERIAL INFECTIONS

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ABSTRACT

Nucleic acid aptamers are a promising platform for the development of a wide range of diagnostic and therapeutic agents and environmental monitoring tools. The properties of aptamers make it possible to consider them as synthetic analogs of antibodies. At the same time, aptamers have a number of important advantages over antibodies, which makes them an effective tool for the development of new-generation diagnostic tools that provide high sensitivity and specificity of detection with a high degree of reproducibility and controllability of properties and low production costs. In particular, technologies for the detection of biomolecules and whole microorganisms, created on the basis of aptamers, can be used to solve the problems of highly sensitive express diagnostics of bacterial pathogens. This review summarizes the achievements of aptamer technologies in the field of detection of bacterial pathogens and their components and discusses the prospects for their practical use.

Keywords: aptamers, combinatorial libraries, PCR, diagnosticums, pathogens, toxins.

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INTRODUCTION

The use of new methods for the diagnosis, prevention and treatment of bacterial infections has made it possible to significantly reduce their negative impact on humans, known from the past. Nevertheless, mortality from infectious diseases remains high throughout the world, ranking first in developing countries and second only to cancer and cardiovascular diseases in countries with developed or transitional economies. [12]. Despite the existing arsenal of molecular, biochemical and microbiological methods of detection and its constant development, there are a number of problems in clinical diagnostics, the solution of which is extremely important for increasing the effectiveness of the fight against bacterial pathogens. One of them is the etiological decoding of the infection. Determination of the species of the pathogen is carried out by microbiological and biochemical methods and requires a significant amount of time associated with the need to isolate and cultivate the microorganism. In some cases, etiological decoding is considered inappropriate, since it postpones the start of therapy [1]. Thus, the main requirement for new diagnostic methods for identifying pathogens is the possibility of rapid, highly sensitive (1–10 pg / ml or less for molecules, for example, for toxins and 1–20 cells / ml for bacteria) target detection without preliminary enrichment and cultivation of microorganisms. One of the promising directions for creating highly sensitive test systems for express diagnostics of infections is the use of aptamers. Aptamers are fragments of nucleic acids or polypeptides obtained as a result of artificially directed “evolution in vitro” and specifically binding selected target molecules with high affinity [11, 12]. This review will look at nucleic acid aptamers and their potential for the rapid diagnosis of bacterial infections.

Rapid diagnostic methods and prospects for the use of aptamers

The main methods of rapid specific diagnosis of bacterial pathogens, widely used in clinical practice, are currently polymerase chain reaction (PCR) and various detection methods using specific antibodies, the most common of which is enzyme-linked immunosorbent assay (ELISA). Despite the widespread use of these methods, in their modern form they have a number of disadvantages that limit their effectiveness as a means of express diagnostics and rapid etiological decoding of the pathogen. The sensitivity of classical ELISA using colorimetric detection, as a rule, does not exceed 1 ng / ml of the target. Secondary antibodies and conjugates based on avidin and its derivatives used in sandwich ELISA systems are often a source of a nonspecific signal. This limits the possibilities of increasing the efficiency of the method by increasing the sensitivity of secondary reactions in ELISA, for example,

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using chemiluminescence detection. PCR is a very sensitive and specific method of analysis; theoretically, the presence of only a few copies of the pathogen genome in the sample is sufficient to detect a target DNA. [21]. PCR often requires enrichment of detectable targets (analytes) in the sample using affinity labels or selective media [19], which significantly increases the detection time, or another virulence factor in the process of the disease Thus, the key components of the system for rapid diagnosis and early etiological decoding of infection are: 1) a detecting agent that provides high affinity and specificity of binding to the target; 2) a system for detecting and or amplifying a signal from a detecting agent, providing the determination of an analyte at a concentration of 5–50 pg/ml (or 10–100 cells (CFU)/ml) and less. Aptamers are one of the most promising modern tools for highly sensitive express diagnostics. The advantages of aptamers over antibodies include the low cost of chemical synthesis, the ease of introducing a wide range of labels and functional groups directly during synthesis, the absence of a drop in affinity due to irreversible denaturation of active structures, the possibility of using the internal structural features of the aptamer itself to create, for example, a fluorescent reporter, which changes the intensity of fluorescence upon interaction with a target [7, 12], a high density of immobilization in an oriented position on a solid phase compared to antibodies, and a number of other properties [20]. In contrast to antibodies, aptamers can be obtained to completely non-immunogenic targets and even to small, ubiquitous molecules, for example, to ATP [6].

Technology of selection of target-directed aptamers

The aptamer selection technology developed in the early 90s of the XX century was named SELEX (Systematic Evolution of Ligands by Exponential Enrichment) [8, 12, 14, 18]. The SELEX method is a typical representative of combinatorial library screening methods. The higher the complexity of the library, the higher the probability of finding a high-affinity ligand for the selected target. The initial diversity of the library of “nucleic” aptamers far exceeds the complexity of the phage and ribosomal libraries. Reproduction of NK aptamers is carried out in a system consisting of a buffer solution, DNA exchange enzymes and nucleotide triphosphates. For amplification of the main alternative types of combinatorial libraries, living systems or their multicomponent fractions in vitro are required. A large number of undefined components and interference with vital processes in systems have a selective effect on the amplification efficiency of individual library members. Thus, screening of aptamer libraries is the most efficient way to obtain high-affinity ligands for biomolecules.

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Systems for the detection of bacteria and their components on aptamer-based

The development of methods for aptamer diagnostics of bacteria, bacterial toxins and virulence factors began in the last 4–5 years; The number of studies in this area is still relatively small, but the results achieved indicate the significant potential of aptamers for the development of diagnostic systems and approaches to detection in the field of microbiology and infectious diseases.

Aptamers specific to whole bacterial cells and methods for detecting pathogens based on them

Aptamers specific to spore-forming bacilli were among the first representatives of this class of molecules, selected using living cells. It is pertinent to note that the selection of aptamers for whole bacteria is technologically somewhat simpler than the selection of aptamers specific to biomolecules, since bacteria are essentially a natural affinity sorbent that can be separated from aptamer molecules in solution by simple centrifugation, while aptamers bound to bacteria will be deposited. Bacteria fixed, for example, with formaldehyde, are very resistant to the harsh conditions of evolution of the bound DNA, which makes it possible to select high-affinity aptamers. Spores of bacilli, in particular B. anthracis, can withstand boiling and remain viable; therefore, they are a convenient model for studying methods of selection of high-affinity aptamers under the most severe conditions. Aptamers selected for anthrax pathogen spores showed such a high affinity for the target that they could not be eluted in physiological solutions when heated to 99°C, but dissociated from the complex with spores in deionized water [2]. Aptamers for B. thuringensis spores allowed the detection of only about 103 microorganisms, which is possibly related to the choice of the detection method (fluorescent quantum dots), the sensitivity of which is lower than that of electrochemiluminescence. At the same time, the sensitivity of this method is higher than that of other methods of fluorescence detection of bacilli spores [19]. An interesting approach was used to create a system for the detection of whole bacteria Staphylococcus aureus based on aptamers. The authors used both positive selection on pathogen cells and negative selection using closely related non-pathogenic staphylococci [6]. Five aptamers were obtained that effectively detect pathogenic staphylococcus aureus against the background of various, including closely related, bacteria. Since the nonspecific binding of these aptamers turned out to be very low, they were used simultaneously to increase the efficiency of selection of various isolates of Staphylococcus aureus. As a rule, in works on obtaining diagnostic aptamers specific to whole bacteria, deconvolution of an individual target molecule is not performed, since this is associated with significant costs without a

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guarantee of identification and it is impossible to determine in advance whether this or that target will be present in 100% of pathogen isolates or only in some of them. Detection of several targets simultaneously, possible due to the high selectivity of aptamers, significantly increases the probability of successful detection of the pathogen. The described technique makes it possible to detect single bacteria in smears obtained directly from the patient. The potential selectivity of a pair of different aptamers obtained for the same type of microorganisms can be determined by the method of competitive inhibition, in which an excess of aptamer A, which does not contain a label, prevents the binding of labeled aptamer A to the bacterium, but does not prevent the binding of aptamers B, C, E, etc. labeled with dyes with different fluorescence wavelengths. In addition to using several aptamers simultaneously for selective detection of a target of the same type, selection of one group-specific aptamer is also possible. Such molecules were obtained to identify M-type streptococci, which prevail in Canada [16]. Interestingly, the obtained aptamers bound all or almost all streptococcus strains selected for selection with constants ranging from 1–13 nM, while the binding of aptamers to M-type strains that did not participate in selection was much less efficient. Thus, selection of aptamers on whole bacterial cells can be used not only to obtain panspecific diagnostics, but also to develop methods for fine differentiation of pathogen subtypes and isolates. The use of aptamers specific for a specific serovar of a pathogen is considered using the example of Salmonella typhimurium [28]. These aptamers were previously selected for binding to the bacterial outer membrane protein (OMP) fraction [24] and proved to be effective for binding to whole cells and purifying them by magnetic separation from complex mixtures containing closely related bacteria. The authors of the work show the effectiveness of aptamers as a tool that provides adequate sensitivity of real-time PCR in the analysis of complex mixtures of microorganisms, in which the amplification efficiency of the target DNA can decrease by several orders of magnitude. The sensitivity of the method of aptamer magnetic purification on microspheres, coupled with real-time PCR, was 1 bacterium (CFU) per PCR reaction [23]. Research on the selection of aptamers for one of the main causative agents of nosocomial infections, Pseudomonas aeruginosa, was aimed at developing a method for detecting pathogen cells using fluorescently labeled aptamers. It was shown that the most efficiently binding aptamer (Kd about 20 nM) made it possible to efficiently identify target cells by fluorescence microscopy. This method is fast (1.5–2 h), as well as inexpensive and technically uncomplicated, which makes its use attractive for diagnostics in a standard clinical laboratory [20]. Detection of pathogens using

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aptamers obtained by selection on whole bacteria can be very effective in cases where the cultivation of bacteria is problematic. Aptamers selected for binding either to a fraction of the outer membrane proteins of the pathogen [4] or to whole cells [10] were able to detect approximately 2 to 250 bacteria / ml, depending on the type of sample used for analysis. This enables efficient detection of clinical specimens for the presence of Campylobacter jejuni using a standard fluorometer or fluorescence microscope [4]. In addition, the protein nature of the target with which it binds was shown for the aptamer selected for interaction with whole cells. In conclusion, it is pertinent to note that aptamers recognizing targets on the surface of living cells are capable of blocking infection [7, 16]. Aptamers specific to bacterial lipopolysaccharides exhibited a protective anti-inflammatory effect *in vivo* [11]. Thus, aptamers specific to receptors that recognize targets in the host organism or binding virulence factors can be considered not only as potential diagnostic tools, but also as candidates for the development of new therapies.

Detection of molecular targets of microbial origin using aptamers

A significant number of works in the field of aptamers specific to bacterial pathogens are devoted to biomolecular targets, which are either virulence factors or molecular markers of a particular microorganism, or have other unique properties that make them a target for creating a specific diagnostic method. Within the framework of these studies, aptamers specific to the components of the anthrax lethal toxin [8], botulinum toxin [16], cholera and staphylococcal toxins [3], soluble antigens of the causative agent of tularemia [17], tuberculosis [14], lipopolysaccharides of the cell wall of *E. coli* O111: H4 [9]. The sensitivity level of detection of pathogens using these aptamers was close to the detection sensitivity level achieved by the ELISA method, or slightly exceeded it. In some cases, it was possible to achieve a higher detection sensitivity (10 pg for electrochemiluminescence detection of staphylococcal enterotoxin [3]), however, no regularities affecting the detection sensitivity with the use of aptamers were identified in this work. Soluble components of cells, in particular the total proteins of the outer membrane, were used to create methods for the detection of whole cells based on aptamers. For example, aptamers obtained for the outer membrane proteins of Salmonella enterica serovar typhimurium have been used as agents allowing efficient isolation of a pathogen from complex natural mixtures for subsequent PCR detection. Interestingly, both a mixture of aptamers obtained by selection and a number of individual aptamers obtained by deconvolution of the mixture could be effectively used as a tool for affinity purification. A mixture

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of aptamers can be effectively used to detect not only Salmonella typhimurium, but also other Salmonella [12].

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Aptamer PCR and Prospects for Increasing the Sensitivity of Biomolecule

Detection Methods for the detection of whole bacterial cells based on aptamers in a number of cases have reached a very high level of sensitivity, making it possible to determine 1–100 cells/ml in clinical samples and various complex natural mixtures. At the same time, the sensitivity of methods for detecting individual biomolecules is limited by signal generation methods, which, in the case of traditional methods of fluorescence, chemiluminescence, or enzymatic detection in solution or on a solid phase, are at a level from several nanograms to hundreds of picograms per 1 ml of the samples under study. [21, 24]. One of the most promising ways to create methods for detecting low concentrations of toxins and other

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biomolecules characteristic of the early stage of infection is associated with the use of aptamers as substitutes for antibodies in immuno-PCR (IPCR). The classical IPCR method is one of the most sensitive methods for the detection of biomolecules; it allows the determination of subfemtogram amounts of substances, including pathogens and toxins [13, 14, 17, 18, 25, 28.]. The principle of IPCR coincides with the principle of ELISA: in the same way as in ELISA, the antigen is recognized by the antibody, after which the signal is amplified due to the activity of the enzyme. If in ELISA the enzyme is conjugated with a primary or secondary antibody, then in IPCR with an antibody a DNA fragment (usually 80–300 nt long) is conjugated, which is amplified by thermostable DNA polymerase. The high efficiency of PCR provides the sensitivity of IPCR 2–4 orders of magnitude higher than the sensitivity of classical ELISA. At the same time, technological problems of IPCR still complicate the development of clinical diagnostic systems based on this technology. In particular, the preparation of covalent or non-covalent (based on avidinbiotin [24]) antibody – DNA conjugates is a technically difficult procedure, some conjugates initiate nonspecific DNA binding and amplification, the large size of antibodies and conjugates reduces the concentration of these molecules on the solid phase, reducing sensitivity. Applied to IPCR, aptamers combine the properties of both antibodies and reporter DNA. In fact, in the presence of an aptamer specific to a given target, antibodies, conjugation procedures, as well as some of the procedures during the test, become unnecessary, which leads to a significant simplification of the detection method, reduction of the analysis time and a decrease in the background level. Aptamers and prospects for biosensor detection of pathogens and toxins Biosensors are being developed as portable automated devices that ensure the detection of biological targets in the environment and minimize the operator's actions for preparing samples and setting up a reaction. In some cases (for example, detection of a pathogen in air or water), a biosensor is considered as a completely autonomous device signaling the appearance of a pathogen or toxin. The development of biosensors is aimed at creating devices that can be used in the field or close to them. Artificially synthesized (often together with functional groups providing immobilization and detection) aptamers are much more convenient and efficient molecules in terms of creating a sensor and uniformity of its physicochemical properties than antibodies and other biosynthetic products [27]. And although at present aptasensors are exclusively laboratory developments, in the future they can be used as a basis for devices that provide the detection of small and ultra-small amounts of a target [30].

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CONCLUSION

The use of aptamers is promising for creating systems for diagnosing bacterial pathogens, monitoring pathogenesis and therapy of infections, studying bacteria in the environment, including in food and drinking water sources. Aptamers are actually artificial analogs of antibodies and, at the same time, have a number of important advantages over them. Despite the relatively recent beginning of the study of aptamers as potential means of diagnosing infectious diseases and analyzing bacterial contamination of the environment, a fairly clear picture of the development of aptamer technologies as applied to clinical microbiology has now emerged. It is not excluded that in the very near future the clinic will have systems for detecting living cells of microorganisms based on aptamers. The development of aptameric biosensors suitable for use in clinical practice is likely to occur in the longer term, but the potential of this technology is very high due to the autonomy and portability of sensor devices. In general, the properties of aptamers considered in this review make them the most important component of diagnostic systems for the near future.

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