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Application of Novel Molecular Diagnostic Technologies in Precision Detection of Clinical Infectious Diseases

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ABSTRACT

Rapid and accurate identification of infectious diseases is an important aspect in both clinical diagnosis and public health surveillance. The conventional methods for pathogen detection, such as microbial culture and immunological tests, are still useful in medical field but have some disadvantages like low sensitivity, lack of specificity and prolonged waiting time, which cannot satisfy the needs of the present precise medicine. With the development of molecular biology and nanotechnology, new molecular diagnostic techniques have demonstrated great advantages in the detection of infectious diseases. In this research, we systematically investigate the principles and clinical uses of nucleic acid amplification-based techniques (PCR, LAMP, RPA), high-throughput sequencing (NGS), gene chips and CRISPR-based molecular recognition systems. Their influences on improving sensitivity, shortening detection time, enabling multi-pathogen detection and aiding personalized treatment plans are discussed. It is pointed out that the recent molecular diagnostic techniques are promoting the detection of infectious diseases towards high-throughput, point-of-care and intelligent procedures, providing a solid scientific and technological support for precise clinical management and disease prevention.

Introduction

Infectious diseases have significant influences on the health and safety of the world. The complicated origins and diverse transmission ways of these diseases need reliable detecting methods. The present laboratory techniques such as culture and serology can offer valuable medical data; however, they may lead to false negative results at the onset of an infection or in samples with low pathogen concentrations, which will delay the early diagnosis and specific treatment. With the advancement of molecular diagnostic techniques, it is possible to detect

pathogen nucleic acids with high sensitivity and specificity directly. The recent advances, including real-time PCR, isothermal amplification systems, next-generation sequencing (NGS) and CRISPR-based molecular recognition, have reached a new level of rapid, accurate and automatic tests in infectious disease diagnosis. This paper explains the working principles of these techniques, evaluates their clinical applications, and discusses the related problems and future research directions, providing some suggestions for improving clinical laboratories and infectious disease management strategies.

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I. Principles and Development Trends of Novel Molecular Diagnostic Technologies

(1) Nucleic Acid Amplification–Based Molecular Diagnostic Techniques

Nucleic acid amplification is important for the current molecular diagnosis, which can increase the target genetic sequences to a detectable level greatly. Polymerase chain reaction (PCR) is the most effective method for pathogen detection because of its high sensitivity and specificity. The application of real-time quantitative PCR also helps in the automatic monitoring and accurate quantification. However, the reliance on thermocyclers and stable experimental conditions restricts the use of PCR in the point-of-care. Thus, isothermal amplification methods such as loop-mediated isothermal amplification (LAMP) and recombinase polymerase amplification (RPA) have been studied. LAMP can perform rapid amplification at a constant temperature and the results can be observed visually by using colorimetric or fluorescence signals. RPA can operate efficiently at 37°C, which is appropriate for portable detecting devices. The recent combination of digital PCR and microfluidic systems has enhanced the sensitivity and quantitative accuracy, thus enabling the detection of very small amounts of pathogenic substances. These developments lead to the transformation from centralized laboratory tests to nearby and bedside diagnosis.

(2) Applications of High-Throughput Sequencing (NGS) in Infectious Disease Diagnostics

High-throughput sequencing (NGS) can sequence all nucleic acid fragments in a clinical sample without any bias, which is helpful for identifying the whole pathogen. Compared to the targeted assays needing pre-designed primers, NGS can detect thousands of organisms at the same time, thus being very valuable for the diagnosis of mixed infections, rare pathogens or newly emerged infectious diseases. Clinical experiments show that metagenomic NGS (mNGS) can identify rapidly the pathogen in pneumonia, meningitis, endocarditis and sepsis, frequently finding the markers of antibiotic resistance. Automation of the mNGS procedures such as sample extraction, library preparation, sequencing and bioinformatics analysis has greatly shortened the time from several days to less than 48 hours. The obtained pathogen spectrum gives doctors strong evidence to make therapeutic decisions, making NGS an important technique in the comprehensive diagnosis of infectious diseases.

(3) CRISPR Systems and Emerging Molecular Recognition Platforms

Since CRISPR-Cas systems were firstly used for gene alteration, they can also be applied to some new diagnostic methods. The Cas12- and Cas13-based systems detect the target sequences by inducing collateral cleavages, giving out fluorescent or colorimetric signals without the need for complex or any nucleic acid amplification. The SHERLOCK and DETECTR systems have shown excellent ability in detecting SARS-CoV-2, dengue virus and Zika virus etc. The CRISPR diagnostic techniques have quick responses, easy operations and small demands for instruments, suitable for point-of-care tests (POCT). When combined with microfluidic chips and portable detection devices, CRISPR-based systems will become the new type of intelligent and convenient diagnostic tools in this area. The appearance of these systems indicates a progress in mobile and dispersed infectious disease surveillance and timely public health actions.

II. Clinical Applications of Molecular Diagnostics in Infectious Disease Detection

(1) Rapid Pathogen Detection in Respiratory Infections

Respiratory infections are one of the common infectious diseases with various causes and easy transmission. Molecular diagnosis improves the efficiency of detecting both viral and bacterial pneumonia. Real-time PCR can determine the presence of influenza viruses, *Mycoplasma pneumoniae* and SARS-CoV-2 within two hours, which is better than the antigen-based methods. Multiplex PCR systems can detect multiple respiratory pathogens at the same time by using multi-target amplification. Multi-Nucleotide Positioning Sequencing (mNGS) also provides a comprehensive analysis of pulmonary infections, particularly useful for cases where culture is negative or when there are mixed infections. Clinical observations indicate that mNGS has been able to detect the co-infection of *Mycobacterium tuberculosis* and fungi, thus facilitating individualized treatment modifications.

(2) Early Diagnosis of Bloodstream Infections and Sepsis

Timely diagnosis of sepsis is important to decrease the mortality rate. The ordinary blood culture needs more than 48 hours, which may prolong the treatment under certain situations. Molecular diagnosis, especially PCR and NGS, can determine the pathogens in a few hours. Digital PCR has a sensitivity approximately 20 times higher than that

of culture, allowing the detection of pathogens at the single cell level. mNGS on circulating DNA in plasma provides unbiased pathogen identification together with the detection of resistance genes. These techniques are currently extensively used in the intensive care unit (ICU) to help in the individualized antibiotic treatment for critically ill patients.

(3) Precision Detection of Viral and Parasitic Infections

Molecular diagnostics are used for both qualitative analysis and measurement of the viral load in hepatitis B, HIV and SARS-CoV-2 infections. Real-time PCR is usually employed to assess the therapeutic results. CRISPR-based systems show high sensitivity in identifying the low concentrations of viral RNA at the initial stage of an infection or an outbreak. For parasitic diseases, LAMP assays are mainly applied for the detection of malaria and *Toxoplasma gondii* due to their simplicity and small requirement of apparatus. The implementation of different molecular diagnostic techniques leads to a transition from centralized laboratory diagnosis to decentralized and point-of-care monitoring of infectious diseases.

III. Advantages and Limitations of Novel Molecular Diagnostic Technologies

(1) Significant Improvements in Sensitivity and Specificity

Molecular diagnostics can directly detect the pathogen DNA or RNA sequences, which are better than the culture method and the cross-reaction problems in immunoassay. Methods like digital PCR and CRISPR-based detection can examine individual molecules and detect early infections, trace pathogenic substances and unusual carriers. Multi-target amplification, sequence alignment and signal amplification improve the accuracy and reduce the number of wrong results. Next generation sequencing (NGS) is very efficient in identifying the existence of pathogens in complicated samples and is significant for recognizing new or rare pathogens. Consequently, these enhancements have made molecular diagnostics the newest approach for current pathogen detection.

(2) Optimization of Detection Turnaround Time and Operational Efficiency

Unlike the culture methods which need several days to weeks for results, real-time PCR, RPA and LAMP can give the results in 30-60 minutes. The automation in the

molecular next generation sequencing (mNGS) processes shortens the sequencing time to less than 48 hours. The CRISPR based diagnostics operating at a constant temperature can provide the results in approximately 30 minutes on portable instruments, suitable for urgent and resource poor regions. The application of microfluidic chips makes the procedures simpler, increases their automation, reduces the amount of sample required and decreases the possibility of contamination. All these technological improvements accelerate the diagnostic procedure and increase the availability of infectious disease tests.

(3) Challenges in Cost, Standardization, and Clinical Implementation

Although there are several advantages, molecular diagnostics still face some difficulties such as high cost, technical problems and the absence of standard procedures. The application of NGS requires expensive equipment and experienced bioinformatics specialists, which is not appropriate for primary health care centres. Although CRISPR and LAMP methods are more convenient to operate, the issues concerning reagent stability and signal detection still need to be further improved. At present, the insufficient common quality control criteria and cross-platform compatibility make it hard to be accepted in the clinical field. It is necessary to combine the molecular results with the clinical manifestations and epidemiological data, for otherwise an incorrect diagnosis may occur. Hence, it is important to establish standard and traceable quality systems and to reduce the operational costs for the widespread use in the clinics.

IV. Integration of Molecular Diagnostics with Precision Medicine

(1) Individualized Infection Management and Targeted Antimicrobial Therapy

Molecular diagnostics improve the treatment of infectious diseases by providing personalized medical advice. The identification of pathogen types, virulence factors and resistance genes provide useful suggestions for selecting antibiotics and altering antiviral treatments. These data-based techniques prevent the excessive use of broad-spectrum antimicrobials and reduce the appearance of resistant strains. The examination of viral quantities and genetic variations allow for prompt modification of antiviral therapies, which enhances both the efficacy and safety. Thus, molecular diagnostics change the treatment from arbitrary methods to specific strategies.

(2) Integration of Molecular Diagnostics with Artificial Intelligence

Artificial intelligence (AI) improves the efficiency, accuracy and personalization of molecular diagnostic data. Machine learning algorithms can identify pathogens in next generation sequencing (NGS) data, recognize important mutations and forecast resistance traits. The combined risk classification models based on both clinical and molecular data help in the early diagnosis and treatment choices. These techniques promote the establishment of 'intelligent laboratories', converting diagnostic data into intelligent medical information and assisting in the formation of effective management systems for infectious diseases.

(3) Future Trends and Innovation Directions

Future molecular diagnostic methods will be based on the integration of some characteristics like miniaturization and intelligent automation. The CRISPR-based bedside test apparatus, microfluidic equipment and nanosensor techniques are expected to facilitate the rapid, inexpensive and onsite detection. The application of multi-omics, which includes genomics, transcriptomics, metabolomics and proteomics, will give a comprehensive knowledge of the relations between the pathogen and the host, beneficial for the construction of more accurate treatment strategies. With the support of artificial intelligence and cloud computing, molecular diagnostics will progress into intelligent diagnostic systems capable of forecasting, issuing early warnings, performing continuous

surveillance and providing personalized treatment, suggesting a change from the inactive diagnosis to the preventive management of diseases.

Conclusion

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