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MALDI TOF Mass Spectrometry: The Rise, Relevance and Rapid Adoption

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Abstract:

Traditional methods of testing pathogens, for the identification of bacteria and fungi, are time-consuming and can be subjective calling for expert opining. Even though the first-generation MS Matrices were random, the second-generation structures were systematically modified revolutionizing the technology of testing pathogens. In numerous areas like ganglioside species detection, MALDI proved to be a reliable technique. MALDI TOF Mass Spectrometry proved to be more reliable and easier to use than traditional methods which needed greater expertise. Even in detecting pathogens that could easily escape detection through the traditional methods, MALDI TOF MS proved its utility by solving the problems of Biomass and the throughput. In pandemic-like situations where rapid testing is essential for isolating the patient and developing proper treatment protocols, the adoption of MALDI TOF MS can become indispensable. The article also discusses the applicability and need for the adoption of MALDI TOF MS in the population and resource constraint context of third-world countries.

Introduction

The two popular methods used to study bacterial macromolecules are genomics and proteomics. To derive general information about the bacteria's genome, genomics[i] methods are used and to identify multiple bacterial proteins proteomics[ii] methods are used. The popular methods of proteomics are liquid chromatography-mass spectrometry (LC-MS), two-dimensional gel electrophoresis, and matrix-assisted laser desorption/ionization mass spectrometry (MALDI-TOF MS). As proteomics studies bacterial protein contents providing comprehensive information about the cell, they are very helpful in identifying the bacteria, and hence treatment protocols can be formulated in time by identifying and creating effective drugs and vaccines. Over time MALDI-TOF MS turned into one of the most potent techniques of proteomics. It proved its effectiveness in the detection of various microorganisms such as bacteria[iii], viruses[iv], fungi[v], and parasites[vi].

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The Limitations of the Traditional Methods

Traditional methods of diagnosis involve the workup of bacteria and yeasts. This can include assessing colony and gram stain morphology. Then phenotypic and biochemical testing will be done.

For fungi[vii], generally microscopic and macroscopic morphology is used to distinguish organisms. For identification of the M. tuberculosis complex[viii], traditional methods use DNA probes and other molecular methods. But the assessment of phenotypic traits, including colony morphology and growth rate is necessary for identifying members of the M. tuberculosis complex.

MALDI, its Advent, and Rise

Matrix-assisted laser desorption ionization (MALDI) came into existence in 1985 when Franz Hillenkamp, Michael Karas, and their colleagues found that the amino acid alanine could be ionized more easily if mixed with the amino acid tryptophan and irradiated with a pulsed 266 nm laser. The further development of MALDI and in general 'soft' laser ionization, has made it a star in modern mass spectrometry (MS).

Unlike the first generation, MS Matrices which were random, in the 'second generation' matrices[ix] the structures of established matrix molecules were systematically modified by varying the nature, number, and position of their functional groups. In the next two decades, this technology revolutionized life sciences like no other technology had in decades.

MALDI-TOF imaging mass spectrometry in Enhancing ganglioside species detection

Gangliosides[x] are a set of glycosphingolipids (GSLs)that are aplenty in the nervous system. They can be found in the plasma membrane of all vertebrate cells, aplenty in the brain. They carry most of the sialic acid residues in the brain. Gangliosides play a crucial role in the modulation of membrane proteins and ion channels and are hence crucial for cell signaling and communication among cells.

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Gangliosides are subcategorized based on the number of sialic residues[xi]

Subcategory	Number of sialic residues
monosialogangliosides (GMs)	1
disialogangliosides (GDs)	2
trisialogangliosides (GTs)	3
tetrasialogangliosides (GQs)	4
pentasialogan-gliosides(GPs)	5

Any loss of function mutations in ganglioside biosynthetic enzymes will result in severe neurodegenerative disorders, with onset from childhood. Experimental evidence suggests the possible role of gangliosides in the disease pathogenesis of Huntington's disease (HD), Parkinson's disease (PD), and some forms of epilepsy.

As they play a crucial role in the process of cell recognition and signaling their dysregulation and excess accumulation is identified as an important cause for umpteen lysosomal storage disorders like Tay Sachs, Hunter's, and Gaucher's neurodegenerative diseases including Alzheimer's, Parkinson's, and the Guillain-Barré syndrome. Their role is also identified in cancer including neuroblastoma, melanoma, and stem cells of breast cancer.

For visualizing the spatial distribution of biomolecules on tissue surfaces, Matrix-assisted laser/desorption ionization (MALDI) imaging mass spectrometry (IMS) is a powerful technique. In 2008, after Chen et al. used 2,5-dihydroxybenzoic acid as a matrix to identify them in a Tay-Sachs/Sandhoffdisease mouse model, MALDI IMS evolved as the most preferred method for on-tissue imaging of gangliosides.

After that using buffered washes[xii], novel matrices, and matrix solutions[xiii]for on-tissue derivatization[xiv], gold nanoparticle labeling[xv], and the coupling of different ionization techniques,in the detection of gangliosides, have evolved into more reliable methods through IMS.

MALDI -TOF Mass Spectrometry for better brain tumor classification:

Interpreting pathological observations using traditional methods is often uneasy and subjective to the operator. This makes classification difficult leading to wide variability in clinical outcomes. In recent years umpteen mutations in tumor suppressor genes and oncogenes were discovered by genomic studies.

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The lack of correlation between the genetic alterations and protein expression regulated by different cellular signaling pathways acting on mRNA translation made these methods random and less reliable in clinical practice.

MALDI-TOF MS analysis by Serafim[xvi] et al. led to the development of MALDI-TOF MS technology for the classification of cancer cells[xvii]. In their study, GracianePetrea[xviii] et al. applied MALDI-TOF MS analysis for the characterization of fifteen human cell lines including five different glioblastomas. This establishes that MALDI-TOF MS profiling can be a reliable tool for the classification of cell lines. Proteomic profiles distinguished within the same cell type, as exemplified by primary cutaneous fibroblasts, which are divided into wild-type cells, suggest that proteomic profiles, reflecting proteomic changes in a pathologic tissue, could help for clinical diagnosis.

MALDI-TOF MS in the diagnosis of hard-to-identify pathogenic bacteria[xix]

By using traditional methods, it would be quite difficult to identify or differentiate aerobic bacteria from several taxonomic entities. But MALDI-TOF MS is expected to make the phrase 'hard-to identify' rarely applicable for bacteria.

For lack of characteristic, biochemical reactions of gram-negative non-fermenting aerobic bacteria and a heterogeneous group of microbes, once used to be too difficult to identify. But rapid adaption[xx] of a MALDI-TOF system for an emerging pathogen by expert users proved its usefulness in identifying rare and novel bacteria.

In the case of anaerobic bacteria, classical identification methods were problematic due to the amount of biomass needed and the time consumed due to the inactivity of the bacteria in automated or miniaturized biochemical tests. MALDI-TOF MS addressed and solved both the problems of biomass[xxi] and the time[xxii] required.

In the case of the mycobacterial species, the growing number of possibly clinically relevant species made DNA probe-based assays lacking in coverage and discriminatory power[xxiii]. In this case, MALDI-TOF MS offered new scope for the identification of mycobacteria and evaluations. The databases today have broad coverage of NTM species, making its application much easier.

The unforeseeable but occasional appearance of highly pathogenic bacteria creates the risk of exposure for the laboratory staff. But the rapid identification of a highly pathogenic

microorganism using mass spectrometry not only reduces the time of possible exposure to laboratory staff (reducing their scope for contacting a disease) but also helps in the proper handling of the respective organisms.

MS is not dependent on the indirect detection of analytes. Using an intrinsic physical property, i.e., their molecular weights, MS detects the analyte molecules. This direct detection makes the technique a much-preferred option, especially when MS is applied as a supportive diagnostic tool in clinical applications.

Despite MALDI's superiority in certain areas, in MS, electrospray ionization (ESI) is still preferred by some to MALDI. The easy online coupling to liquid chromatography and formation of multiply charged ions with the associated advantages in structure analysis as well as being a superior match to high-performing mass analyzer technologies made ESI more preferred than MALDI. But MALDI borrowing ideas from ESI is making big strides in areas where ESI previously dominated.

MALDI-TOF-MS for rapid high-throughput screening of COVID-19

In the case of SARS CoV-2, quick detection of the disease and immediate isolation of the infected individuals are crucial for immediate control from further spreading. The need for a reliable, swift, inexpensive, and non-invasive diagnostic tool for detecting the newly emerging strains is quite high.

Numerous studies have established that saliva is a better specimen type than the nasopharyngeal swabs for early detection of SARS-CoV-2. Also, the specimens of saliva can quickly and safely be collected from different populations.

Though RT-PCR is currently considered the reference method, it is well known that it is difficult to accept it as a gold standard. The popular PCR and immunoassay-based methods not only take too much time but also can render some false negatives. Even while using established molecular platforms, public health authorities often require a trade-off between accuracy and throughput.

Prajkta Chivte et al. gathered 60 gargle samples and employed MALDI-TOF mass spectrometry to analyze and compare the resultant spectra against COVID-19 status. To offer a relative view of the saliva and viral proteome[xxiv], they analyzed many standards like isolated human serum immunoglobulins, and controls, such as pre-COVID-19 saliva and heat-inactivated SARS-CoV-2 virus.

To prove the high concurrence with COVID-19 individuals, they established five potential biometric peaks. For the study group the concurrence of these results on nasopharyngeal swabs with RT-qPCR testing was ≥90%. These results from the pilot study suggest that MALDI-TOF could be used as an inexpensive tool for rapid COVID-19 testing.

Matthew M Hernandez et al. used AgenaMassARRAY, a new sensitive RT-PCR/MALDI-TOF mass spectrometry-based assay to trace SARS-CoV-2 in saliva specimens. when compared to matched patient upper respiratory specimens their platform demonstrated high diagnostic sensitivity and specificity[xxv]. They proved that in a large variety of clinical laboratory settings, for SARS-CoV-2 discovery in saliva, the MassARRAY® system is a sensitive and reliable platform that offers scalable throughput.

Meritxell Deulofeu et al. synthesized the analysis made from human nasopharyngeal (NP) samples by MALDI-TOF MS with the use of machine learning (ML).They gathered 236 NP samples in two different viral transport media[xxvi] and analyzed them with minimal sample preparation. ML models with two different techniques were built using the subsequent mass spectra data. The top model built through the above procedure demonstrated high levels of accuracy, sensitivity and specificity, by reaching values higher than 90% in all the cases. Their research[xxvii] proved that the analysis of NP samples by MALDI-TOF MS and ML is not only simple, safe, and fast but is also an economic diagnostic tool to test COVID-19.

Nam K. Tran et al. combined machine learning (ML), with the MALDI-TOF-MS approach to overcome the logistical barriers encountered by the then-existing testing models. Residual nasal swab samples are used[xxviii] for testing and compared against RT-PCR to evaluate the analytical performance of an ML-enhanced MALDI-TOF-MS method for screening COVID-19. They developed two optimized ML models and demonstrated an accuracy of 98.3%, positive percent agreement (PPA), and negative percent agreement (NPA) of 96%. An accuracy of 96.6%, PPA of 98.5%, and NPA of 94% respectively have been achieved. Machine learning enhanced MALDI-TOF-MS for COVID-19 testing exhibited performance comparable to existing commercial SARS-CoV-2 tests.

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Adoption of MALDI Mass Spectrometry in the third world countries:

In third-world countries, antimicrobial resistance makes it difficult to fight infections[xxix]. On the other hand, methods employed to identify these microorganisms are laborious and time-consuming. The size of the population many a time results in a low hospital-to-population ratio. In such a scenario early identification of contagion and appropriate treatment protocolsarecrucial for an early discharge, which can mean a vacant bed for new patient admission. Minimizing throughput time is one way of ensuring the availability of a medical facility to the maximum number of people.

In densely populated countries contagion spreads faster and can turn into a pandemic in no time. To nip such a phenomenon in the bud, early identification and exact identification of the species and its subtype becomes essential, so that the right treatment protocol is employed, and the disease is halted before it progresses. This early identification is essential to stop a geometric progression of disease in the population.

The cost of diagnostic tools employed is also one deterrent when it comes to mass testing. A right balance between speed, accuracy, and cost must be stricken for a technique to be employed successfully at a mass level.

Experiments for microbial detection using MALDI-TOF MS devices are simple, cheap, faster, and highly efficient too. The routine identification of microorganisms in clinical microbiology laboratories is optimized with this technology. This technology that has in a way revolutionized clinical diagnostics in advanced countries, is sooner than later going to replace at least some of the current biochemical methods used in the third world.

Large population testing turned out to be crucial to controlling the COVID pandemic. Karina Helena Morais Cardozo et al. develop a high-throughput targeted proteomics assay to detect SARS-CoV-2 nucleoprotein peptides directly from nasopharyngeal and oropharyngeal swabs.

When the TFC-MS system was applied[xxx], analysis of 4 samples within 10 minutes was made possible, which means that more than 500 samples could be processed per day. This method was validated qualitatively and quantitatively using 985 specimens that were previously analyzed by real-time RT-PCR. The level of detection was up to 84% of the positive cases with up to 97% specificity. The strategy developed by them had high sample stability and hence emerged as a suitable option for SARS-CoV-2 testing in countries with large populations, like those in Southeast Asia.

With greater acceptance and adoption of digitalization in Asian countries, collecting and storing data has become easier and cheaper. With larger populations and huge databases, rapid microbial identification has become fast and cheap.

Conclusion

After its initial rise, MALDI Mass Spectrometry emerged as a leading tool in various fields of biomedical applications. With gangliosides beingcrucial molecules in various neurodegenerative diseases, MALDI spectrometry is a helpful tool in visualizing and gauging the spread of these gangliosides, playing an important role in the mapping of these molecules. Other applications of this spectrometry include accurately classifying different types of brain tumors based on their proteinic profiles as well as diagnosing pathogenic bacteria in a more time-efficient manner. In comparison to MALDI, ESI is preferred in situations where more accuracy is required in structural analysis and when the technology needs to be paired with mass analyzing technologies. While borrowing certain features of ESI, MALSI is still able to act as a leading method in many relevant biomedical areas. One example of this is in the usage of MALDI in detecting SARS CoV-2. MALDI allows the rapid detection of the high-throughput screening pattern signatures of SARS CoV-2 and is faster than the widely used and accepted RT-PCR method. This detection paired with machine learning algorithms that can help identify peaks can be used to analyze data from large populations which is essential in controlling the various waves of the virus. The adoption of technologies such as MALDI in third-world countries is also an active topic of discussion, especially during a pandemic that requires mass testing to happen accurately and efficiently. MALDI is not only rapid in detection but is also affordable, making it an ideal tool to be adopted in countries with large populations and few resources.

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