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Perspective

Mass Spectrometry-Based Biosensing and Biopsy Technology

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Abstract: Sensitive and accurate detection of biomolecules by multiplexed methods is important for disease diagnosis, drug research, and biochemical analysis. Mass spectrometry has the advantages of high sensitivity, high throughput, and high resolution, making it ideal for biomolecular sensing. As a result of the development of atmospheric pressure mass spectrometry, researchers have been able to use a variety of means to identify target biomolecules and recognize the converted signals by mass spectrometry. In this review, three main approaches and tools are summarized for mass spectrometry sensing and biopsy techniques, including array biosensing, probe/pen-based mass spectrometry, and other biosensor–mass spectrometry coupling techniques. Portability and practicality of relevant mass spectrometry sensing methods are reviewed, together with possible future directions to promote the advancement of mass spectrometry for target identification of biomolecules and rapid detection of real biological samples.

Keywords: biomolecules detection; mass spectrometry; biosensors; biometrics; clinical mass spectrometry; ambient ionization mass spectrometry

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1. Introduction

A biosensor is an analytical device consisting of a sensing element and a signal transducer. In a general biosensing process, a biological signal is recognized and amplified by a sensing element, converted into a readable state by a signal transducer, and further processed into a digital signal. The role of the sensing element is to recognize target substances, mainly including antibodies, enzymes, nucleic acids, cells, and other biological substances, and also some synthetic substances similar to biological substances, such as aptamers, peptides, and MIPs (molecularly imprinted polymers) [1]. The function of a signal transducer is to convert the interaction between a sensing element and a target molecule into an identifiable signal [2]. For example, enzymes catalyze chemical reactions with specific substances and transform them into electrical signals; biological antibodies capture specific antigens and convert them into optical signals through labeled fluorescence [3].

Mass spectrometry is a method to analyze target compounds based on their mass-to-charge ratio. Mass spectrometry separates and detects the composition of substances by the mass difference of the atoms, molecules, or molecular fragments of the substance through the principle that charged particles are able to deflect in an electromagnetic field [4]. It typically consists of four parts: injection system, ion source, mass analyzer, and detector. With the advantages of high sensitivity, high resolution, and wide analytical range, mass spectrometry can be used with specificity for chemical analysis in food, drugs, cellular components, blood, and other fields [5]. For a classical biosensor system, mass spectrometry is an excellent signal transducer. In addition, researchers have modified the ion source or injection method of a mass spectrometry system to give it the ability to specifically detect certain biomolecules or to enhance the signal response to certain biomolecules; this process is used as a sensing element to form a mass spectrometry-based biochemical sensing

system [6]. Especially after the first ambient ionization technique (Desorption Electrospray Ionization, DESI) reported by Cooks in 2004 [7], ambient ionization mass spectrometry (AMS) techniques have undergone rapid development, allowing the adaptation of multiple types of mass spectrometry interfaces in the open air [8,9], greatly enhancing the application of mass spectrometry in the field of biochemical sensing.

Depending on the device structure and ionization mechanism, mass spectrometry-based biosensing technologies can be broadly divided into 1. biochip and mass tag-based mass spectrometry sensing technology, 2. probe (pen) based mass spectrometry, and 3. integrating other biosensing technologies for mass spectrometry biosensors. Biochip-based mass spectrometry sensing techniques enable targeted screening by coupling biomolecules on a substrate, often in combination with matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) [10], which has been an effective tool for studying biomolecules since its introduction in 1987. Probe-based mass spectrometry biosensing techniques are more in situ, in vivo, and clinical. Researchers collect biological samples through probes or pens of different materials and structures, then conduct direct mass spectrometric detection online [11]. In addition, the successful integration of biospecific interaction analysis based on other biosensors (surface plasmon resonance (SPR), microfluidics) and mass spectrometry produces a powerful technique that couples the benefits of sensitive affinity capture with the ability to characterize interacting molecules [12].

It is worth noting that the concept of mass spectrometry biosensing was proposed and generalized by Ju's group in 2021 [6], and this review expands and summarizes the concept from different perspectives. The concept of mass spectrometry biosensors tends to be less frequently mentioned, and this review classifies key technologies that improve the mass spectrometric response of biochemical molecules or make them measurable by mass spectrometry, as mass spectrometry-based biosensors. This review critically reviews mass spectrometry-based biosensing technologies divided into three main sections. The first part has an emphasis on explanations of biochip and mass tag-based mass spectrometry sensing technology, including applications of microarray mass spectrometry and nanomaterial mass tags, such as MALDI for biomolecular arrays. The second part covers various probes, probe pen techniques for in situ biomass sensing, and the latest clinical references. The third part covers some integrated techniques of biosensing and mass spectrometry.

2. Biochip and Mass Tag-Based Mass Spectrometry Sensing Technology

Laser desorption-based mass spectrometry techniques include matrix-assisted laser desorption ionization (MALDI), surface-assisted laser desorption ionization (SALDI), and ambient ionization mass spectrometry (AMS) techniques using UV or IR pulsed laser ablation. All these techniques facilitate the desorption of the sample through a laser, and the biosensing process is accomplished by transferring energy or electrons to the target molecule through a specific matrix (small molecule, polymer, nanomaterial, etc.) to achieve an increase in the signal intensity of the target biomolecule (Figure 1). Research on the use of MALDI to measure biomolecules dates back to the 1990s [13] and was awarded the Nobel Prize in 2002. Over the next 30 years, a number of variants of the technique were developed, and they are used in various biochemical analyses [14–16]. With the development of laser desorption-based mass spectrometry, researchers have found that the use of microarray biochips can effectively target and detect biomolecules, including DNA, RNA, peptides, sugars, proteins, etc. [6].

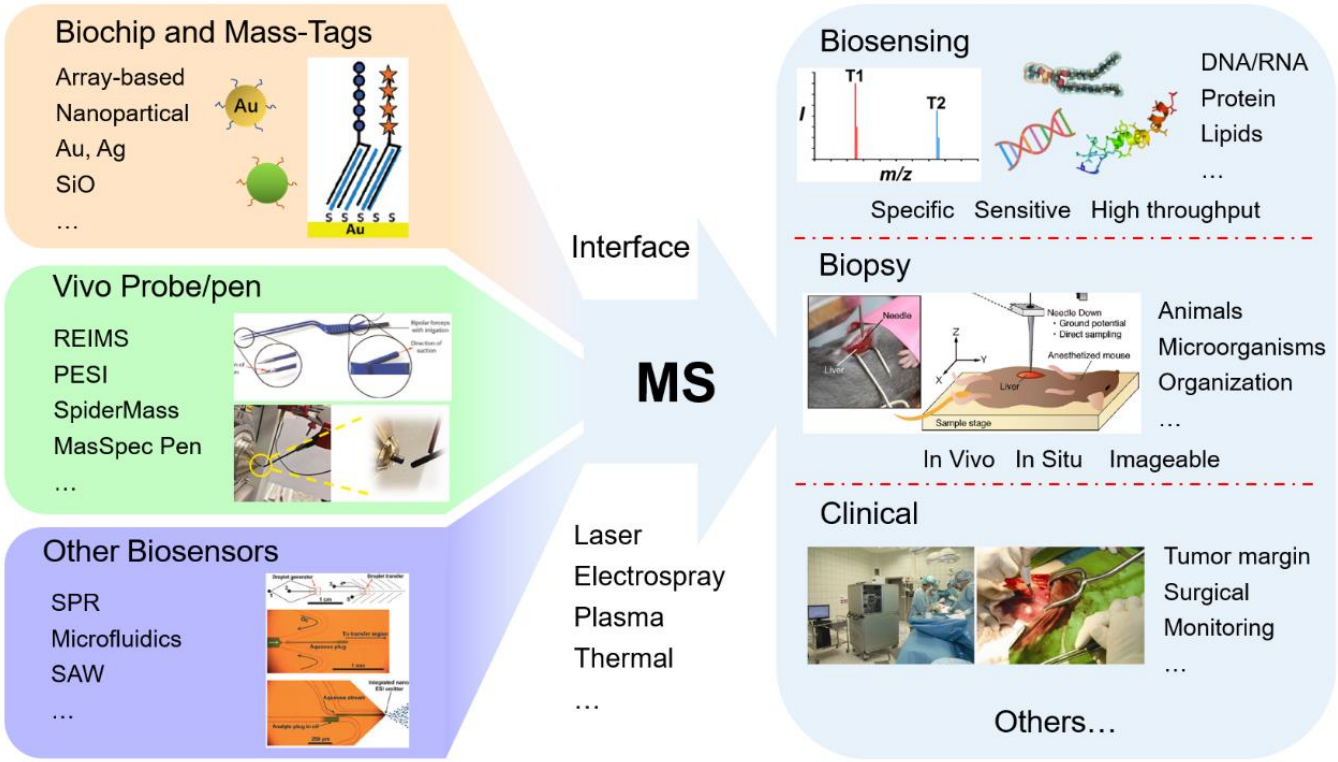

Figure 1. Schematic representation of different sensing technologies (biochip [17], in vivo probe [18,19], microfluidic [20], etc.) combined with mass spectrometry for different detection scenarios (biopsy [21], clinical [18], etc.). Copyright with permission from Wiley, Royal Society of Chemistry, American Chemical Society.

In 2002, Mrksich's group discovered that when MALDI-MS combined with self-assembled monolayers (SAMs) that are engineered to give specific interactions with biomolecules, it is well suited for characterizing biological activities [10]. They first formed SAM (self-assembled monolayers)-Au chips using oligoethylene glycol groups of alkanethiols and peptides, proteins, or carbohydrates to achieve recognition of specific biomolecules, named SAMDI-MS. Then they used SAMDI to provide ligands that interact with target proteins and enzymes for enzyme activity studies and applied this method to screen a chemical library against protease activity of anthrax lethal factor [13,22]. Becker et al. used MS to detect Ras-protein-receptor interactions on protein-oligonucleotide affixes attached to in silico sheets by DNA-directed immobilization in 2005 [23]. In 2007, Mrksich et al. expressed a membrane scaffold protein (MSP) with a hexahistidine (his_6) tag at its N terminus and prepared nanodiscs containing rhodopsin protein and the lipid 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (POPC) based on the self-assembly of lipid molecules within the membrane scaffold protein, producing a circular patch of a soluble lipid bilayer that can immobilize transmembrane proteins for the screening and characterization of transmembrane proteins [24]. Yeo et al. used gold particles carrying small molecules as reporters for target proteins based on the oligoethylene glycol SAM target protein microarray and analyzed by LDI-TOF-MS. As the number of small molecules far exceeded the number of cooperating target proteins, the biosignal was amplified, enabling ultrahigh sensitivity detection in the attomolar range [25]. In 2009, Min et al. used the MALDI laser for selective desorption on the SAMs chip surface to create patterns of cell adhesion ligands on SAMs with simple control over the ligand density [26].

After 2010, with the development of experimental instrumentation, more research groups are involved in the field. Beloqui et al. immobilized lipid-labeled oligosaccharide fragments onto MALDI sample plates by hydrophobic interactions compatible with the solution-like enzyme activity on the chip, allowing easy sample cleanup and subsequent

enzymatic interaction analysis by MALDI-TOF [12]. In subsequent work, they chose commercially available ITO-coated glass sheets. Silylation with 3-aminopropyl-triethoxysilane (APTES), followed by coupling with NHS-activated stearic acid, formed a hydrophobic support layer that immobilized lipid-labeled biomolecules through hydrophobic interactions, achieving highly sensitive detection of peptides, sugars, and other biomolecules [27]. In the same year, Kuo et al. analyzed deacetylase activity in cell lysates using peptide arrays and SAMDI-MS [28]. Li et al. devised a method for detecting protein kinase A (PKA) phosphorylated cysteine peptides using the nanostructure initiator mass spectrometry (NIMS) technique [29]. Hong et al. used anti-Bcr on gold nanoparticles (AuNPs) and anti-Abl on biochips to capture the Bcr/Abl chimeric protein and quantified them in cells by LDI-TOF-MS [30]. Both et al. investigated the application of peptide microarrays in sugar donor promiscuity of pp-a-GanT2 using the SAM chip tandem IM-MS technique [31]. In 2015, Ju et al. proposed a peptide-encoded microplate for MALDI-TOF-MS analysis of protease activity with a low detection limit of 2.3 nM as well as good selectivity [32]. Lorey et al. proposed a new method for the analysis of antibody arrays using laser desorption/ionization mass spectrometry (LDI-MS) with "mass-labeled" specific small reporter molecules to detect immunocapture proteins in human plasma, with detection limits much lower than clinical methods [33]. Hu et al. proposed a MALDI-MS patterning strategy for the convenient visualization of multiple enzyme activities by caspase-activity patterned chip (Casp-PC) with ITO surface peptide arrays [34], and on this basis, they proposed a quantitative method for a variety of enzyme proteins [35]. Xu et al. established an array-based electrospray accelerated chip spray ionization device where gold nano-ions and target proteins form an immune sandwich on an indium tin oxide glass chip for the identification of membrane proteins in blood [36], and the throughput of the method was improved in subsequent studies and applied to screening for cancer markers [37]. Mrksich et al. used cysteine-terminated peptides to covalently capture metabolites bound to CoA and immobilize them on self-assembled monolayer arrays. Thus, the captured metabolites were rapidly separated from the complex mixture and directly quantified by SAMDI-MS [38–40]. Gunnarsson et al. performed multiplex DNA detection using random arrays to capture the binding of DNA-modified liposomes to surface-immobilized probe DNA, forming sequences encoding unique target DNA sequences, and analyzed them with SIMS-TOF [41]. Li et al. used peptide arrays of ITO slides for the study of thrombin activity and screening of potential inhibitors [42].

In addition to microarray biochip mass spectrometry (Figure 2), the development of nanomaterials has contributed to the refinement of mass spectrometry sensing techniques These techniques currently utilize nanomaterials directly or small molecules as mass tags and are categorized as nanomaterial-based mass tags (MT) mass spectrometry. Several nanomaterials, including AuNPs, AgNPs, PtNPs [43–45], quantum dots [46], and metal nanoclusters, can be effectively bound to specific biological moieties. This capability enables the targeted labeling of biomolecules, allowing in situ multiplexed mass spectrometry analysis of proteins [47], glycans [48], and other biomolecules [49] within biological systems [50–52]. It should be noted that Min's team has recently provided an exhaustive review on the topic of MT-encoded MS [53], thus this review will not delve into the field in greater depth.

Overall, compared to traditional biomolecular analysis processes, biochip and mass tag-based mass spectrometry sensing technology are characterized by high specificity analysis, and highly sensitive detection of targeted biomolecules can be achieved through mass tag amplification. However, there are limitations to this technology. For instance, the preparation and pre-processing of bioarray chips are complex and time-consuming. Antibodies utilized for specific recognition are susceptible to inactivation and damage during the experimental process, resulting in a lack of robustness and making them challenging to recover for multiple analyses. Therefore, shortening the pre-processing steps and enhancing the reliability and stability of sensing labels may represent the new direction for development.

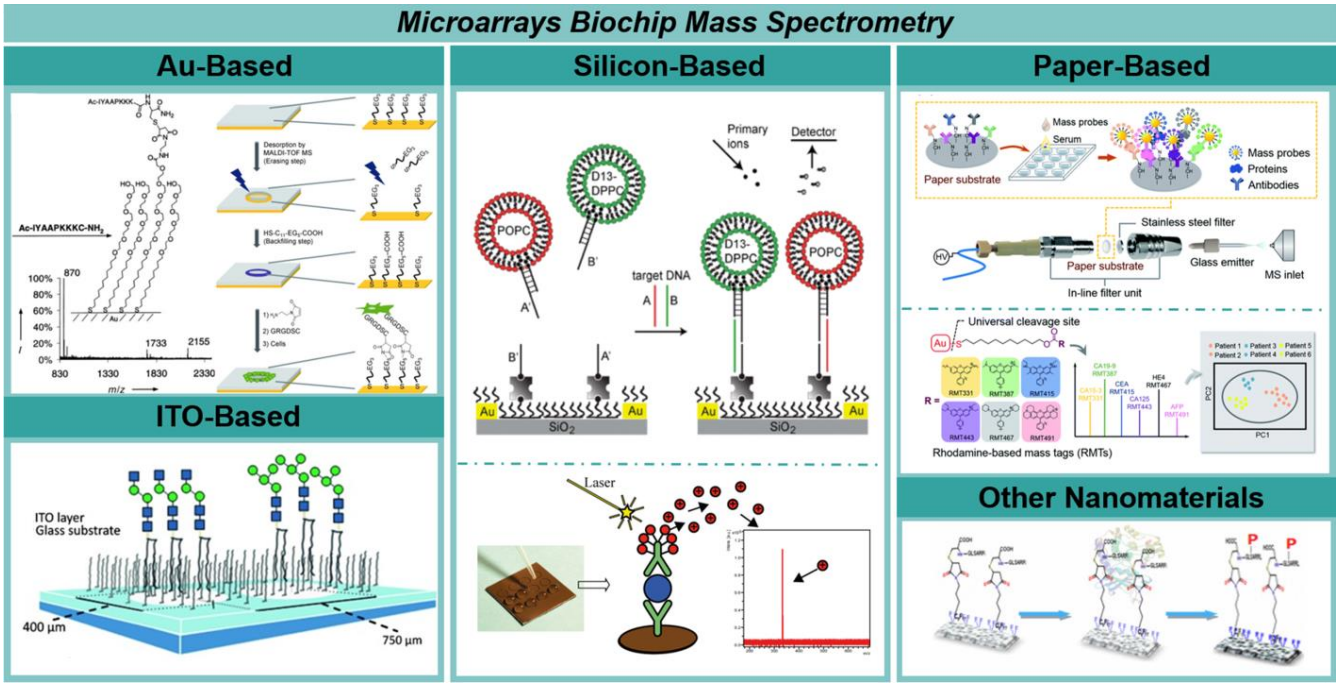

Figure 2. Biochips on different substrates, including Au-based [10,26], ITO-based [27], silicon-based [33,41], paper-based [37], and other nanomaterials-based [29]. Copyright with permission from Wiley, Elsevier, Royal Society of Chemistry, American Chemical Society.

3. Probe/Pen-Based Mass Spectrometry Sensing Technology

With the development of atmospheric pressure mass spectrometry, several in vivo mass spectrometry techniques are available for the detection of specific chemical information contained in different tissues. Such techniques often require a tip or a smaller area to keep the organism with low or no destruction. It is challenging to extract enough chemical information from biological tissues at a low loss to access mass spectrometry for accurate identification with high efficiency and throughput. We classify such online mass spectrometry techniques into biosensing and provide a categorical overview of the following two aspects: in vivo probe mass spectrometry (e.g., probe electrospray ionization, PESI) and pen-based mass spectrometry modalities (e.g., rapid evaporative ionization mass spectrometry (REIMS), MasSpec Pen, and SpiderMass).

3.1. In Vivo Probe Mass Spectrometry

Since the introduction of probe electrospray ionization technology in 2007 [54], researchers have found that the use of probes can cause less damage to the organism while extracting the target compound. PESI is widely used for in vivo non-destructive biological mass spectrometry [55,56]. Chen et al. applied PESI directly to various biological samples such as urine, mouse brain, mouse liver, and fruit, demonstrating that PESI is a practical non-invasive biomolecular detection technique [57]. Yoshimura et al. performed a real-time analysis of in vivo mice using PESI, revealing differences in hepatocyte lipid composition between normal and steatotic mice, with no significant postoperative damage in the in vivo mice [17]. Hsu et al. took advantage of the ultra-fine size of the probe tip to directly extract and ionize a mixture of metabolites from live microbial colonies grown in Petri dishes without any sample pretreatment [58]. Gong et al. used a 1 μm tungsten probe inserted directly into live cells to enrich for metabolites and used PESI for elution and ionization, resulting in the detection of single-cell metabolites [59]. Deng et al. designed a surface-coated probe nanoelectrospray ionization mass spectrometry (SCP-nanoESI-MS) based on SPEM for the analysis of target compounds in individual small organisms and fish; probe tips are at the micron level and exhibit good linearity in the analysis of real

samples [60–62]. Zaitsu et al. applied PESI to the analysis of intact endogenous metabolites in the liver and brain of living mice and achieved the detection of multiple metabolites, including organic acids, sugars, and amino acids in 2015 [63]. Zaitsu et al. constructed a high-throughput metabolic mass spectrometry platform by PESI, screened 72 metabolites in mouse liver and brain, and built data processing software; in subsequent work, they used the platform to analyze extracellular neurotransmitters in mouse brain with excellent linearity and precision [64,65]. The in vivo online detection capability of PESI technology has been well established and is of great value in the study of real-time metabolomics, but the problems of low sampling efficiency of PESI probes, difficulties in the analysis of large molecules, and lack of specific identification limit the wider application of the technology.

In addition to the classical PESI technique, numerous new material-based, solid-phase microextraction (SPME)-based, and plasma-based in vivo probe mass spectrometry techniques have been proposed in the last 5 years. Ngernsutivorakul et al. combined a sampling probe with a microfluidic chip to achieve a 1000-fold increase in resolution over ordinary microdialysis probes, enabling real-time chemical monitoring in vivo [66]. Lendor et al. performed chemical biopsies of the brain by synthesizing SPME probes with functionalized hydrophilic layers, allowing quantitative analysis of multiple neurotransmitters [67]. The method is also combined with Paternò–Büchi (PB) reactions for in vivo, in situ, and microscale analysis of lipid species and C=C location isomers in complex biological tissues [68]. Lu et al. coupled a metal microprobe to a dielectric barrier discharge ionization (DBDI) with a limit of detection as low as 8 pg/mL, and then they achieved the monitoring of drug residues in different organs of live fish using this method [69]. Bogusiewicz et al. first used SPME probe MS technology for biopsy sampling of the human brain, followed by metabolic and lipidomic analysis, demonstrating higher concentrations and diversity of metabolites in the white matter [70]. Mendes et al. performed direct analysis of fruit and mouse brains using inexpensive and environmentally friendly pencil graphite rods as probes for mass spectrometry biosensing [15]. Cheng et al. coupled SPME with nanoESI-MS, achieved by surface-coated acupuncture needles, for the in vivo detection of small molecules, proteins, and peptides in plants [71].

3.2. Pen/knife-Like Mass Spectrometry Sensing Technology

Real clinical testing has placed higher demands on key components of mass spectrometry sensing, and a number of new AMS technologies have been developed to meet scenarios such as tumor margin detection during surgery. One of the more widely used is rapid evaporative ionization mass spectrometry (REIMS), which is often integrated into the clinic as a smart knife. This device cauterizes biological tissue (e.g., tumor margins) by heating the tip and continuously collects a plume for chemical information acquisition [72]. Balog et al. used this technique to analyze various tissue samples from over 300 patients, reflecting the lipidomic profile among different histological tumor types and between primary and metastatic tumors [14]. Golf et al. constructed the REIMS imaging platform for differentiating healthy/cancerous tissues and different bacterial/Fungi strains and built a spectral library [73–75]. Manoli et al. combined REIMS technology with an ultrasonic scalpel for real-time monitoring of lipid profiles during laparoscopic operations [76]. Overall, REIMS focuses on lipids with limitations in the detection of biochemical molecules such as sugars and peptides. In addition, due to the destructive nature of cauterized tissue and the relatively low spatial resolution, a high level of professionalism is required of the operator.

Based on the limitations of REIMS, a series of new clinical biosensing mass spectrometry techniques have been proposed. Fatou et al. proposed a new instrument named SpiderMass for real-time in vivo mass spectrometry detection with a miniature probe designed based on infrared laser ablation that is much less damaging than REIMS, enabling minimally invasive in vivo online analysis [77]. Fatou et al. performed a real-time in vivo pharmacokinetic study by SpiderMass, revealing the potential for DMPK (drug metabolism and pharmacokinetics) and ADME (absorption, distribution, metabolism, and excretion)

analysis with the technique [78]. Subsequently, SpiderMass and the variants have been used in a variety of scenarios such as biofluidics, tumor margins, tissue biopsy, and skin cancer [79–82]. Ogrinc et al. combined a SpiderMass probe with a high-precision robotic arm to enable mass spectrometry imaging on arbitrary sample surfaces, paving the way for surgical applications of excised edges [83]. Although the SpiderMass technology reduces damage to biological tissue compared to REIMS, laser desorption still damages the sample to some extent.

Therefore, a gentler in situ sampling technique called MasSpec Pen has been proposed, which uses discrete droplets to collect chemical information from the tissue surface, and since only droplets are used as a medium, the method is completely non-destructive to the tissue. Using this technique, Zhang et al. analyzed 253 tissue samples from human cancer patients and a variety of metabolites, lipids, and proteins were identified as potential cancer biomarkers [84–86]. The MasSpec Pen was also transferred to the operating room, performing tumor margin prediction during 18 pancreatic surgeries with an accuracy of 93.8% [87].

The studies referenced above have shown that a simple modification of the ion source section can result in a mass spectrometry-based in vivo biosensing system for clinical, cancer detection, tissue biopsy, and various other scenarios (Figure 3). Notwithstanding the numerous inherent advantages associated with these techniques, they are not without limitations. Firstly, their utilization necessitates a certain proficiency level in manipulation skills. Secondly, most of these techniques are limited by the mode of ionization, where the ionization capacity depends on the proton affinity potential, so only polar molecules can be recognized.

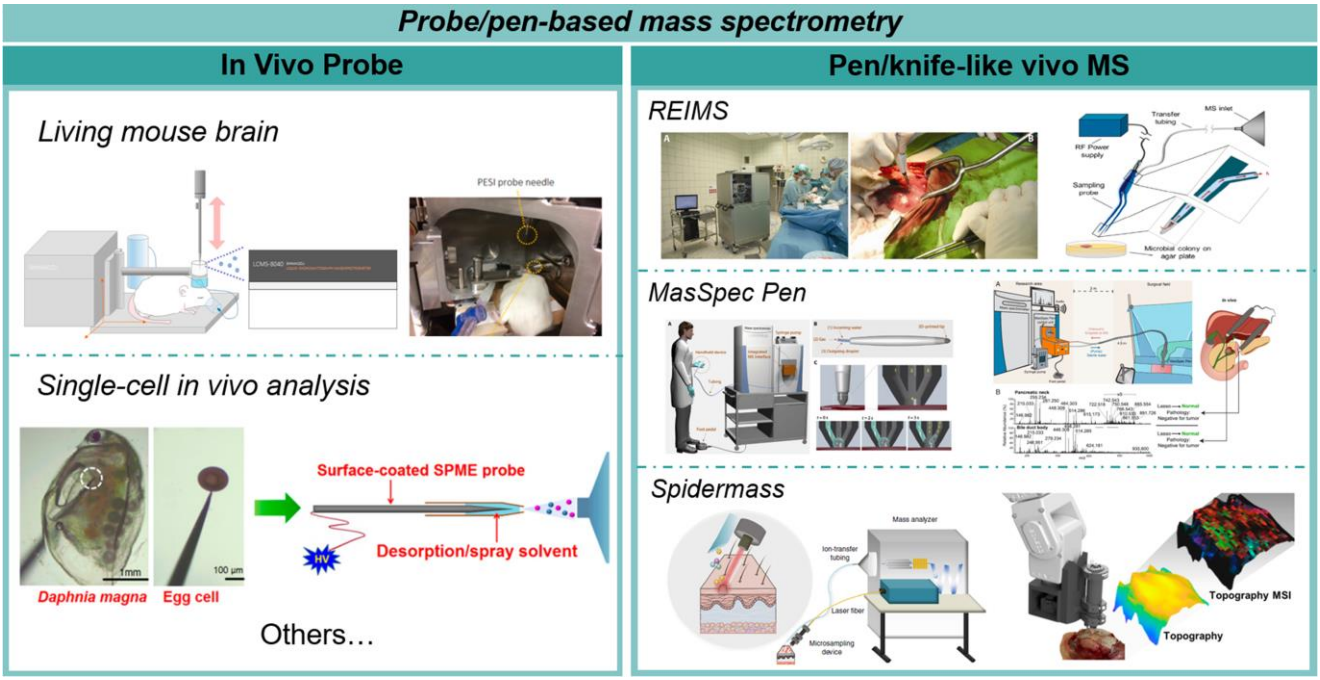

Figure 3. Highlights of in vivo analysis using MS biosensor techniques. Probe mass spectrometry, mainly PESI, for biopsies of various organisms [59,60,66] is shown on the left panel. The right panel shows pen/knife-like in vivo MS technology including REIMS [14], MasSpec Pen [84], and SpiderMass [80,83]. Copyright with permission from Wiley, Elsevier, American Chemical Society.

4. Integration of Mass Spectrometry with Other Biosensors

In recent years, some classical biosensing systems have been coupled with mass spectrometry to achieve complementary performance and functionality. The flexible modification of the interface between mass spectrometry sampling and ion source has given rise to many new coupling methods, with the main difference being whether direct coupling, indirect coupling, online, offline, etc. This chapter focuses on the integration methods between various biosensors with mass spectrometry and their applications.

One of the more widely integrated sensors with mass spectrometry is the surface plasmon resonance (SPR), and MS can provide molecular information that perfectly complements the SPR sensors [12,88]. A common offline coupling approach is to elute biomolecules on the SPR sensing chip into the mass spectrometry test. For example, Hamaloglu et al. used SPR and MALDI-MS together for the detection of Fab-anti-HSA (human serum albumin) on MUA (Mercaptoundecanoic acid) molecules array platforms [89]. Yang et al. used the SPR technique to screen TNF (Tumor Necrosis Factor) from angelicae pubescentis radix extracts, followed by quantitation and evaluation via UPLC-MS/MS [90]. Castells et al. used SPR and an approach that combines limited proteolysis mass spectrometry to analyze in detail glycan−protein interactions [91]. Compared to such offline techniques, the online coupling interface between mass spectrometry and SPR can improve detection speed and avoid sample denaturation, generating greater interest among researchers. Marchesini et al. online coupled SPR-based inhibition biosensor immunoassay (iBIA) with nano-liquid-chromatography electrospray ionization time-of-flight mass spectrometry (nano-LC ESI TOF MS) for effective screening of small molecules in organisms [92]. Zhang et al. proposed an interface for online coupled SPR with direct analysis in real time (DART) MS, and in subsequent work, a direct online coupling technology between dielectric barrier discharge (DBD)-MS and SPR was proposed for the study of various interaction of biomolecules [93,94]. Mihoc et al. used proteolytic epitope extraction mass spectrometry combined with SPR biosensor analysis to determine the molecular epitope structures and affinity of equine heme-myoglobin and apo-myoglobin to a monoclonal antibody [95]. Joshi et al. developed a method to simplify the coupling of SPR and MS by direct biochip spraying, which can selectively capture target small molecules on the SPR surface and nebulize them directly into the mass spectrometry under high voltage [96]. The combination of SPR and mass spectrometry provides protein specific binding recognition ability and highly sensitive, precise qualitative analysis ability, providing an ideal analytical tool for studying the interactions of biomolecules.

In addition to SPR, various other types of biosensors also exhibit different complementary advantages in coupling with mass spectrometry (Figure 4). For example, microfluidic chips are widely used in conjunction with nano ESI to provide excellent performance in reaction monitoring, sensitivity enhancement, biomolecule extraction, etc. [15,97–100]. Surface acoustic wave (SAW) devices are used for sample delivery and assisted ionization to enable a real-time, high-throughput quantitative and qualitative analysis of heavy metals and various biomolecules in human serum [101,102].

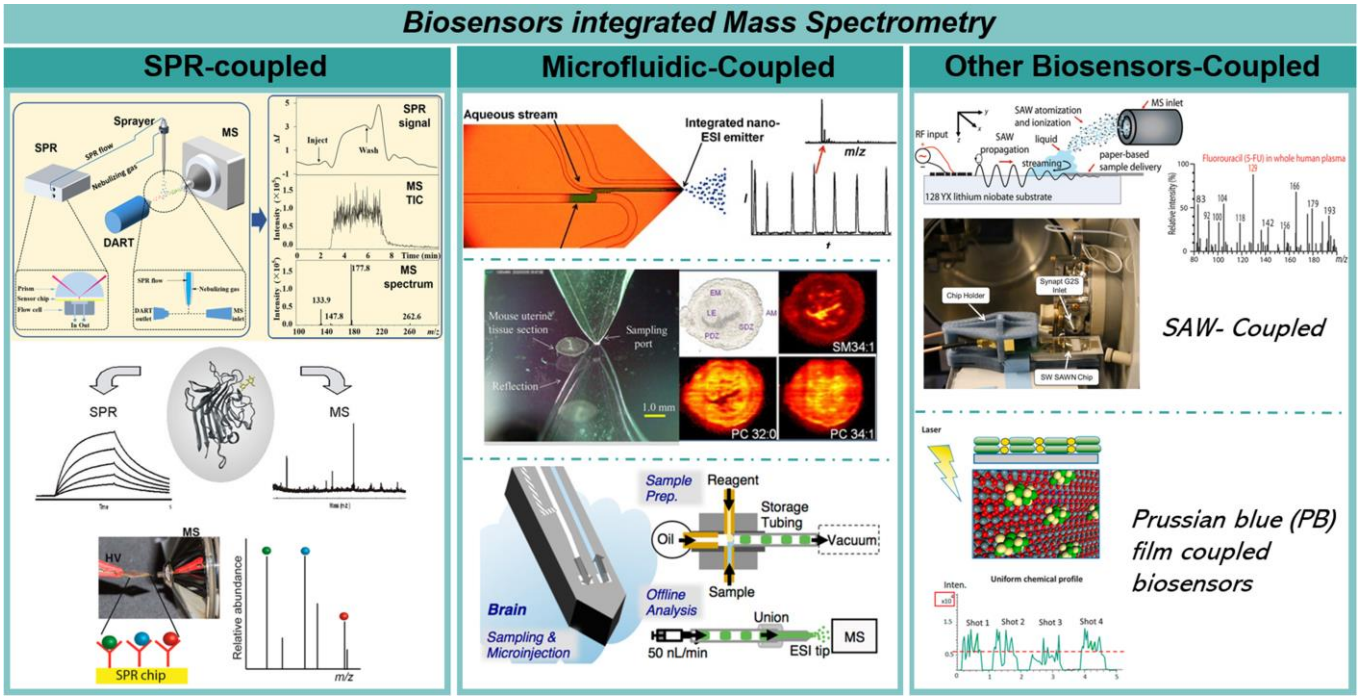

Figure 4. Highlights of different sensor technologies coupled with mass spectrometry including online and offline integration of SPR technology [91,93,96], combination of microfluidic sensing chips [16,66,100], and integration of other biosensors [101–104]. Copyright with permission from Wiley, Elsevier, Royal Society of Chemistry, American Chemical Society.

5. Conclusions

This review details several types of research in the direction of mass spectrometry-based biosensing and summarizes advanced sensing techniques in combination with mass spectrometry, including biochips, mass labels, in vivo probes, clinical biopsies, etc. Given the advantages of mass spectrometry in molecular recognition, each type of technology can exploit its specificity, such as mass-label type technology with flexible target recognition capability and in vivo probe/pen technology for clinical biopsy capability, while the coupling with other sensors can produce functional complementarity. Although mass spectrometry has the above-mentioned advantages, it still has the problems of large instrument size and poor portability, and it cannot completely replace electrochemical and optical sensors. The 21st century is the era of cross-disciplinary development, and combining various analytical methods to form a richer, more sensitive, and faster biosensing system may become the new development direction. In addition, new mass spectrometry sensing systems with greater sensitivity, better robustness, and higher throughput will be introduced and applied in various fields of chemical analysis.

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