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Review

Mass spectrometry-based tag and its application to high efficient peptide analysis – A review

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ABSTRACT

Chemical derivatization is a very promising technique for improving analysis of peptides by mass spectrometry (MS). Thereinto, development of novel tags compatible with MS and/or MS/MS has always been the focus point of study. In this review, the recent reported tags for derivatization of thiol groups of cysteine, carboxyl groups, and amino groups on peptides as well as peptides with post-translational modifications (PTMs) are summarized. Moreover, the tags used for derivatization of glycans or oligosaccharides released from glycoproteins are also reviewed.

Contents

1. Introduction

Since the completion of human genome sequencing, the human genome project has been entering into the post-genomic era [1,2], of which proteomics, as an infant research paradigm, has been paid much more attention [3]. The major approach used for proteome research is the bottom-up or shotgun strategy. In a typical procedure, proteins are firstly digested into peptides,

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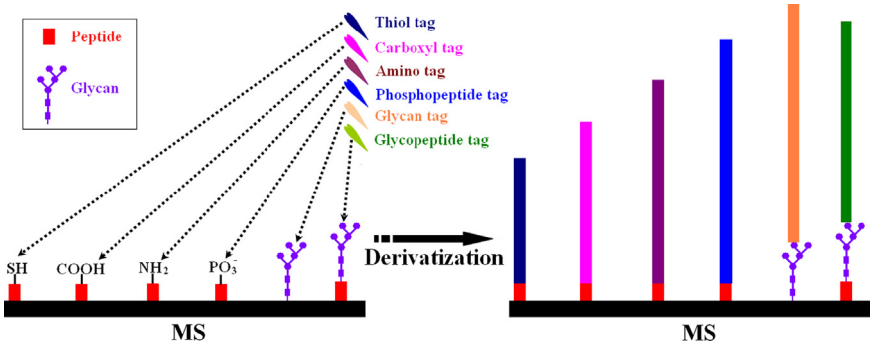

Fig. 1. Schematic diagram of the review.

followed by multi-dimensional high performance liquid chromatography (HPLC) for peptides separation and tandem mass spectrometry (MS/MS) for peptides sequencing [4–6]. Obviously, MS-based technique has become an important tool in proteome research. Especially, with the emergence and wide usefulness of soft ionization techniques, such as matrix-assisted laser desorption/ionization (MALDI) and electrospray ionization (ESI), MS has been evolving into an indispensable technology for qualitative and quantitative analysis of proteins or peptides [7,8].

However, many proteins, such as the drug targets or biomarkers, are often present in low concentration in real protein samples [9,10]. Thus, it is very difficult to detect these proteins in a diverse "sea" of complex proteins. Moreover, the ionization efficiency of peptides in MS is often structure-dependent. Thus, many peptides, such as phosphopeptides and glycopeptides, are difficult to ionize in MS [11,12]. Therefore, improving analysis of these peptides is crucial for further in-depth proteome research.

Chemical derivatization [13–16] is a very promising method for improvement of ionization and detection of these samples. It could even retrospect to the early 1960s when trifluoroacetic anhydride and methanol were used for rapid acylation and esterification of naturally occurring amino acids so as to improve the determination of amino acid ratios in peptides as well as qualitative determination of amino acids in proteins [17]. In the past few decades, numerous tags have been developed and further used for derivatization of thiols groups of cysteine, carboxyl groups, and amino groups on peptides as well as peptides with post-translational modifications (PTMs). In this review, these tags are systematically summarized and further classified according to the target reactive groups on peptides. Furthermore, tags developed for labeling of glycans or oligosaccharides released from glycoproteins are also introduced. The representative scheme of this review is shown in Fig. 1.

2. Characteristics of the developed tags

In the late-1990s, Krause et al. [18] analyzed the mycobacteria proteome by combining with two-dimensional electrophoresis (2-DE) for proteins separation and MALDI- time-of-flight (TOF) MS for peptides identification. Interestingly, 94% of the most sensitive peaks were found to be arginine-containing peptides. It could be attributed to the excellent basicity of guanidine groups of the arginine side chain, which could promote peptide ionization in liquid and/or gas phase, yielding high MS signal. Pashkova and Chiappetta [19,20] further provided evidence that hydrophobic peptides are more likely to co-crystallize with the hydrophobic matrix, allowing more sensitive identification by MALDI source. In ESI–MS, peptides with strong basicity and high hydrophobicity are also more inclined to protonate and ionize during the desolvation process, achieving high-efficiency peptide analysis [21]. Obviously, basicity and hydrophobicity are crucial factors for peptide analysis by MS.

Thus, most of the tags were designed with the following structures: (1) guanidine group, tertiary amines, or quaternary ammonium moieties with high basicity; (2) hydrophobic chains or aromatic groups with strong hydrophobicity; and (3) reactive groups for targeted peptide labeling. In fact, many tags were designed with all of the above-mentioned characteristics.

3. Derivatization of unmodified peptides

3.1. Thiol group of cysteine

Cysteine is an attractive target for peptide labeling due to its high reactivity, low abundance, and universal distribution in a variety of proteomes [22]. Many hydrophobic tags and quaternary ammonium tags were reported for derivatization of thiol group, as summarized in Table 1.

Ueberheide et al. [23] firstly applied N,N-dimethyl-2-chloroethylamine to derivatize thiol groups of toxins so as to increase the charge state of these peptides prior to electron-transfer dissociation (ETD) MS/MS analysis. Totally 31 intact individual toxins were successfully sequenced from crude venom sample from Conus textile.

Li et al. [24] synthesized a novel maleimidyl-containing tag, 1-[3-(4-maleimidylphenoxy)propyl]trimethylammonium bromide, for labeling of cysteine-containing peptides. The reaction was allowed to proceed for 2 h at 37 °C with a derivatization yield close to 100%. Furthermore, the ionization efficiency increased over 100-fold for peptides with less polar residues via MALDI-TOF MS analysis, while the ionization efficiency for peptides with more polar residues could increase only 3–5-fold.

(3-Acrylamidopropyl)trimethylammonium chloride (APTA) was initially used for derivatization and enrichment of cysteine-containing peptides by Ren et al. prior to MS analysis [25]. Vasicek and Brodbelt [26] further evaluated the effect of APTA derivatization on the ETD efficiency of peptides. The results indicated that both the charge states and ETD dissociation efficiency for all the peptides simultaneously increased, outperforming the commonly used tag iodoacetamide (IAA) and N,N-dimethyl-2-chloro-ethylamine [23]. The method was further used for analysis of tryptic digest of bovine serum albumin (BSA), and the SEQUEST score was increased to 3700 from 582 via derivatization. The main drawback of APTA derivatization was relatively low labeling efficiency. It was estimated to be about 70% by comparing the summed area of APTA derivatized products to the summered area of both derivatized products and the native peptides.

In fact, most of the reported tags were functionalized with iodoacetamide group. Muddiaman's group developed a variety of these types of tags to increase the MS response of cysteine-containing peptides. 2-Iodo-N-octylacetamide [27] was firstly