3D-LC

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Three-dimensional liquid chromatography (3D-LC) is the consecutive combination of 3 independent LC techniques to decrease the complexity of proteome digest samples. 3D-LC systems can be performed in an online or offline manner. Ideally, each dimension in a 3D-LC system is completely orthogonal to the others.

Bottom-up proteomics separation 3D-LC

1. Introduction

Proteomics is the study of proteomes, aiming at globally characterizing all proteins in any given cell [1]. The simultaneous separation of a large number of peptides in a bottom-up proteomic sample raises great challenges to both liquid chromatography (LC) and mass spectrometry (MS). Regarding LC, various multidimensional (MD) separation approaches have been developed to decrease the complexity of samples, by which, peptides are consecutively separated by two or more independent separation mechanisms [2][3]. After the development of the first two-dimensional LC (2D-LC) system [4], various combinations of MD-LC have been reported. Some 3D-LC systems have been used in bottom-up proteomics. They can be classified into offline, online, and combined systems.

2. Recent Developments and Applications of 3D-LC

2.1. Offline 3D-LC Systems

At the early stage of 3D-LC, several 3D-LC systems were developed by modification of MudPIT. Most of them were based on the combination of SCX and RPLC [5] two RPLC implemented under extremely different pH conditions (usually high pH and low pH) [6]. The success of some HILIC-RPLC 2D-LC platforms resulted in their further utilization in 3D strategies [7][8]. Setups and performance of some outstanding 3D-LC systems are summarized in Table 1 of the article.

Generally, offline 3D-LC systems suffer from sample loss due to nonspecific adsorption of samples to tube or other surfaces as well as the additional sample handling. They usually require a large amount of samples in the peptide level [9]. Therefore, a number of studies have integrated the fractionation step into the sample preparation procedure in the same device. These integrated devices could minimize the sample loss, enable a small amount of sample, and ensure high efficient digestion and fractionation, such as StageTips [10], in-StageTip (iST) [11], 3D-SISPROT [9], mixed-mode-SISPROT [12].

2.2. Online 3D-LC Systems

Some online 3D-LC systems have been developed with an attempt to reduce sample loss, labor intensity, and time. They are relatively sophisticated in instruments and typically limited in total sample capacity. In the early stage, after developing MudPIT as the first 2D-LC system, Yates' group continued to design a 3-phase MudPIT column packed with RP-SCX-RP. It could be considered the first 3D-LC setup for proteomic analysis [13]. Besides packing 3-phasic columns, some groups have developed online 3D-LC platforms by modifying setups of HPLC/UPLC systems [14][15][16]. The performance of some online 3D-LC systems is outlined in Table 2 of the article.

2.3. Combined Offline-Online 3D-LC Systems

A 3D-LC strategy can be performed using a mixed online and offline system. The sample is either pre-fractionated with the first dimension prior to an online 2D-LC separation or fractionated with an online 2D-LC platform and then separated with the third dimension coupled with MS/MS analysis. Table 3 of the article summarizes major features of these two combined 3D-LC platforms.

3. The Power of 3D-LC Compared to 1D- and 2D-LC

Performance comparisons among 3D-LC, 2D-LC, and 1D-LC systems have been reported in some studies, which are summarized in Table 5 of the article.

4. Outlook and Concluding Remarks

Up to date, the outstanding performance of 3D-LC is undeniable. We believe that 3D-LC systems will be continuously developed, improved, and applied in the future. The development of 3D-LC combined with major improvements in the sensitivity and the resolution of MS/MS analysis will enable increasingly wider proteome identification. Basic 2D-LC combinations such as SCX-RP and RP-RP will be fundamental for future 3D-LC systems. In addition, other LC modes, including HILIC, ERLIC, mixed SCX-SAX will be continuously combined and investigated. The options of 3D-LC strategies will therefore expand. Offline and online 3D-LC systems will be developed simultaneously since they possess their unique advantages. Combined systems may still be developed, taking advantage of the state-of-the-rat 2D-LC strategies. Finally, integrated devices that enable many steps in sample preparation and fractionation will continuously demonstrate their utility and be incorporated in many 3D-LC platforms. Particularly, with the wide-spreading of automated sample handling platforms, these devices will be the future of high throughput sample preparation for 3D-LC.

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