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Review

The why and how of amino acid analytics in cancer diagnostics and therapy☆

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ABSTRACT

Pathological alterations in cell functions are frequently accompanied by metabolic reprogramming including modifications in amino acid metabolism. Amino acid detection is thus integral to the diagnosis of many hereditary metabolic diseases. The development of malignant diseases as metabolic disorders comes along with a complex dysregulation of genetic and epigenetic factors affecting metabolic enzymes. Cancer cells might transiently or permanently become auxotrophic for non-essential or semi-essential amino acids such as asparagine or arginine. Also, transformed cells are often more susceptible to local shortage of essential amino acids such as methionine than normal tissues. This offers new points of attacking unique metabolic features in cancer cells. To better understand these processes, highly sensitive methods for amino acid detection and quantification are required. Our review summarizes the main methodologies for amino acid detection with a particular focus on applications in biomedicine and cancer, provides a historical overview of the methodological pre-requisites in amino acid analytics. We compare classical and modern approaches such as the combination of gas chromatography and liquid chromatography with mass spectrometry (GC–MS/LC–MS). The latter is increasingly applied in clinical routine. We therefore illustrate an LC–MS workflow for analyzing arginine and methionine as well as their precursors and analogs in biological material. Pitfalls during protocol development are discussed, but LC–MS emerges as a reliable and sensitive tool for the detection of amino acids in biological matrices. Quantification is challenging, but of particular interest in cancer research as targeting arginine and methionine turnover in cancer cells represent novel treatment strategies.

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Abbreviations: AA, amino acid/amino acids; AAD, amino acid detection; ADI, arginine deiminase; ADT, arginine deprivation therapy; ALL, acute lymphoblastic leucemia; APCI, atmospheric pressure chemical ionization; APPI, atmospheric pressure photo ionization; AQC, aminoquinolyl-N-hydroxysuccinimidyl carbonate (AQC); CE, capillary electrophoresis; CI, chemical ionization; dabsyl-Cl, 4-(4-dimethylaminophenylazo)benzene sulfonyl chloride; dansyl-Cl, 5-(dimethylamino)naphthalene-1-sulfonyl chloride; EFSA, European Food Safety Authority; EI, electron impact ionization; ESI, electrospray ionization; Fmoc-Cl, fluorenylmethyloxycarbonyl chloride; GBM, glioblastoma multiforme; GC, gas chromatography; HCA, heterocyclic amines; HILIC, hydrophilic interaction liquid chromatography; HPLC, high performance liquid chromatography; LC–MS, liquid chromatography mass spectrometry; LLOQ, lower limit of quantification; LOD, limit of detection; MR, maillard reaction; MRM, multiple reaction monitoring; MS, mass spectrometry; MS/MTR, methionine synthase/5-methyltetrahydrofolate-homocysteine methyltransferase; MTAP, methylthioadenosine phosphorylase; OPA, *o*-phthalaldehyde; PET, positron emission tomography; PITC, phenylisothiocyanate; PKU, phenylketonuria; RP, reversed phase; RPLC, reversed phase high performance liquid chromatography; SPE, solid phase extraction; TFA, trifluoroacetic acid; UHPLC, ultra high performance liquid chromatography; VOCs, volatile organic compounds.

☆ This comprehensive review aims at presenting and discussing the amino acid detection tools of interest in biomedical science and cancer research but does not claim to cover the entire field and literature, respectively. The authors apologize to those researchers whose work has not been mentioned due to restrictions in space and time.

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Contents

1. From food chemistry to biomedicine: why to detect AAs

1.1. Background

Amino acids (AAs) – both containing amine (-NH2) or carboxylic acid (COOH) functional groups – were already described in the early 19th century commenced with the isolation of asparagine from *Asparagus sativus* (Vauquelin and Robiquet, 1806). It took another six decades to elucidate the structure of asparagine (Kolbe, 1862). Today, the presence and structure of more than 300 AAs are known (Wu, 2009) including the 21 proteinogenic AAs (selenocysteine and the 20 canonical AAs) which are required for protein biosynthesis in living organisms (Gao et al., 2015). Free and protein/peptide-bound AAs occur ubiquitously in the biosphere, in microorganisms, plants and animals, and are thus an integral nutritional component in species-appropriate food. AAs are specified as essential, semi-essential or non-essential depending on their actual metabolic availability within the (human) body and the divergent necessity for exogenous supply. All AAs except glycine have an asymmetric (α-) carbon with carboxylic or amino groups and are optically active; their nonpolar, polar and unloaded or loaded side chain is crucial for chemical verification and defines the AA classification.

Due to the omnipresence as well as the high variability of AA pattern in various matrices, AA detection (AAD) has become an integral part in life science. The quantification of AAs is primarily based on chromatographic technologies. Attributes important for chromatographic detection are the ampholytic character of AAs leading to a zwitter ion at the individual isoelectric point (IP), as well as the exclusive presence of sulphur in methionine and cysteine, which – amongst others – defines three-dimensional protein folding via the formation of disulfide bonds (Chaimbault et al., 1999; Wu, 2009). Methods of choice for AAD are high performance liquid chromatography (HPLC), capillary electrophoresis (CE) and gas chromatography (GC) (Krumpochova et al., 2015; Otter, 2012; Poinsot et al., 2010; Rigas, 2013), all of which can nowadays be combined with mass spectrometry (MS) to increase the sensitivity of detection as will be highlighted in more detail later in this essay.

The –omics era of the 21st century is unconceivable without sensitive and selective state-of-the-art AA analytics, in particular with the expansion from genomics to proteomics and most recently metabolomics approaches (Arapitsas et al., 2016; Becker et al., 2012; Jehmlich et al., 2015; Possemato et al., 2011; Prabhu et al., 2014). However, the field of applications for both classical as well as modern AA detection techniques is diverse as outlined in Fig. 1. It ranges from biological disciplines including zoology (Preston, 1993; Wu et al., 2016) marine research (Bermudez et al., 2015) and anthropology (Kaal et al., 2016), where samples as diverse as sediments (Larsen et al., 2015), tissues (Wu et al., 2016) and archeological materials (age determination) are monitored, to the use in biotechnology and pharmaceutical research and industry, e.g. for quality control and drug design (Holzgrabe et al., 2010; Ilisz et al., 2006; Peura et al., 2013; Vlaardingerbroek et al., 2013). AAD can be performed in diverse liquid and solid matrices including geological samples, bacteria and plant masses, DNA/protein or RNA/protein extracts, blood, serum and plasma, urine and stool as well as tissue and biopsy samples. Indeed, body fluids are of particular interest in biomedicine and clinical chemistry.

1.2. Linking food chemistry and public health

Food chemistry is a major area of application for AAD. The AA composition of particular food products is for example analyzed to calculate a protein digestibility-corrected AA score (PDCAAS) as measure for nutritional protein quality based on the amino acid profile and the human requirements for essential AAs (Bellomaria et al., 2016; Rutherfurd et al., 2015; Sarwar, 1984; Schaafsma, 2000). At the same time, the AA composition and abundance may affect food quality and thus needs to be monitored already during production. As an example, free AA and ammonium are the main nitrogen source for alcoholic fermentation by yeast. Reduced AA concentrations can lead to malfermentation whereas the excess of AAs might result in microbiological instability, both counterproductive for high quality wine production. Here, AAs as well as specific noxious derivatives, such as biogenic amines that serve as an indication for microbiological deterioration, are routinely determined via HPLC and CE (Acunha et al., 2016; Ortega-Heras et al., 2014; Wang et al., 2014). Biogenic amines are decarboxylated AAs and nitrogenous organic compounds that can act as neurotransmitters and precursors for hormones and vitamins (Karovicova and

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