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REVIEW

Serum Amyloid A Protein in Clinical Cancer Diagnosis

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Abstract The serum amyloid A (SAA) protein is an acute phase protein that is synthesized under the regulation of inflammatory cytokines during both acute and chronic inflammation. It is suggested that the SAA increases correlate with many types of carcinogenesis and neoplastic diseases. Th changes in SAA in serum could therefore indicate the progress and malignancy of the disease, as well as the host responses. The present paper reviewed the rationale of using SAA as potential cancer biomarker in clinical diagnosis, including the contribution and involvement of SAA in cancer growth and development. Then we discussed the current applications of SAA in diagnosis and tracing of different types of cancers. Finally the proteomics techniques, especially the SELDI-TOF MS to identify SAA in serum from patients were appreciated as an important manner in clinical diagnosis.

Keywords Serum amyloid A · SAA · Cancer diagnosis · Proteomics · Inflammation · SELDI-TOF MS

Accurate clinical diagnosis largely relies on the complexity of the disease (or the biomarker specificity) and the sensitivity of the diagnostic approaches. In cancer patients multiple changes in the proteome occur before the evident syndromes, which might only appear in late phases of some malignant cancers [1,2]. Therefore the early diagnosis of cancer is of great importance and the identification of reliable biomarkers at the first convenience significantly saves lives [3]. The fact that the levels of many proteins would change at the same time in the serum in response to inflammatory signaling cascades suggests that the proteomic technique with high sensitivity is needed for this purpose. Also, due to the complexity of tumorigenesis, many molecules associated with inflammation pathways could be detected in the serum during the development of multiple cancers, which decreases the specificity of the diagnosis [3–6]. Generally the biomarkers could be classified into two systems: early biomarkers with less specificity but high sensitivity; biomarkers with high specificity, which are often detected only in late phases of cancers. It is still possible to quantify the changes of early biomarkers to enhance its specificity in early cancer diagnosis in practice, though this is depending on different populations.

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Contribution of SAA in Cancer Development

Serum amyloid A (SAA) protein could be considered as one of the early biomarkers though the detection of SAA expands over the disease development and progression phases. SAA is a protein with 104 amino acids, and the genes SAA1 and SAA2 share 95% of homology [7]. SAA protein increases significantly in the acute phase of inflammation, and shows better sensitivity in compared to other common acute phase proteins, such as the C-reactive protein (CRP), at least in some circumstances [8]. It is suggested that the levels of SAA is associated with amount of dead cells and tissues, and therefore the inflammation severity. In most cases the level of SAA protein peaks at the third day of inflammation onset and return to the baseline after another 4 days. In the chronic inflammation cases such as the tumor development, SAA level would increase substantially in a continuous period [9], which then

contribute to the secondary amyloidosis during cancergenesis [10–12]. The SAA concentration is also correlated with prognosis of inflammation diseases, as well as the tumor grading [13–16], suggesting that SAA could be used to monitor the tumor development and progression.

SAA level is low in healthy control in spite of a little bit variations among individuals due to the differences in clinical backgrounds and subclinical inflammation cases [17,18]. In most cases of carcinoma diseases, the serum SAA level elevated, acting as non-specific biomarkers and independent correlated factors of the prognosis. However, this does not underestimate the diagnostic potential of serum SAA level measurement. Firstly, the acute phase of SAA increase in inflammation disorders could generally suggest the nature of the disease, and narrow down the arsenal of diseases. Secondly, with more specific analysis, the amplitude and the time course of SAA level change in the serum could still indicate the nature of the disease, for example, either regional or disseminated [19–22].

One potential mechanism underlying the contribution of SAA to cancer development is the fact that SAA acts like a extracellular matrix (ECM) adhesion molecule [23,24], and the interaction with ECM alter the binding of different cell types of the ECM, therefore initiate series of cellular changes in prior to the tumor development. The SAA-ECM complex could play roles in the inflammation reaction as well, for example, enhancing the TNF-α secretion from the T lymphocytes in a dose dependent manner [25]. The changes in ECM trigger the intracellular signaling pathways, and finally modify the cell adhesion, migration, activation as well as secretion of inflammatory molecules [25–30]. Taken together, SAA is involved in the link between chronic inflammation and tumor initiation, as well as the following tumor progression.

The Changes of SAA in Different Types of Cancers

Previous studies showed the elevation of serum SAA in different types of cancers in different phases, including hepatic cancer, gastric cancer, lung cancer, ovarian cancer, renal cancer, breast cancer, endometrial cancer, uterine serous papillary cancer, colon cancer, pancreatic cancer, prostate cancer, nasopharyngeal cancer and so on [11,20,21,31–67]. These studies all pointed out the possibility of using SAA as biomarker for specific types of cancers under given circumstances, with varied sensitivity and specificity in different population and subpopulations. The intriguing feature of these studies is to extract the change of SAA out of thousands of other serum proteins from the samples of patients, which was achieved with the progress of SELDI-TOF MS or MALDI-TOF MS technique in recent decade.

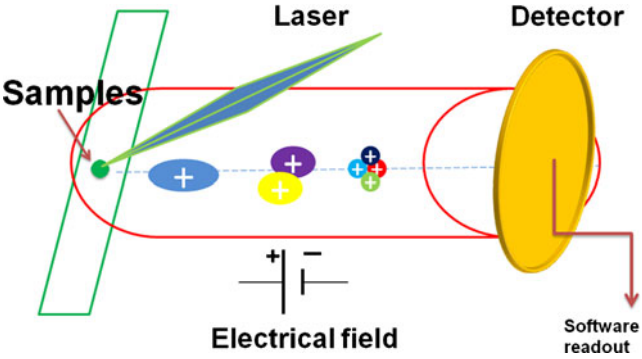

Fig. 1 The laser ionized peptides from crystals of the sample and matrix mixture (*green spot*). Then these ions (in different colors, suggesting for different m/z ratio) were accelerated through an external electric field and down into the flight tube (*red tube*). Finally the detector (*yellow plate*) would measure ions as they reach the end of the tube, with software readout the data

SELDI-TOF MS and SAA Identification

The surface-enhanced laser desorption/ionization time of flight mass spectrometry (SELDI-TOF MS) technique was firstly introduced in 1993 [68], and was commercialized by Ciphergen Biosystems in 1997 as the ProteinChip system. SELDI-TOF-MS is one variation of matrix-assisted laser desorption/ionization (MALDI), which uses a target modified to reach biochemical affinity with the sample proteins. The two systems have the following differences: In MALDI, the sample is mixed with the matrix molecule in

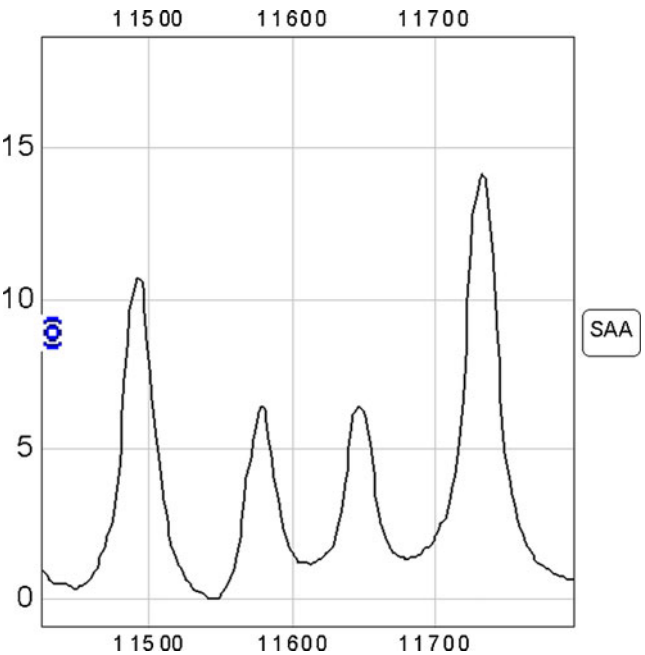

Fig. 2 SELDI-TOF MS identification of SAA from human serum samples

solution and a small amount of the mixture was deposited on the surface to dry. After the solvent evaporated, the sample and matrix would co-crystallize; in the case of SELDI, the mixture is spotted on a chemically modified surface with binding affinity. Therefore some proteins in the samples would bind to the modified surface without the need to dry, and the non-binded proteins could be washed off. Then the matrix is applied to the surface for crystallization with the sample peptides.

Samples spotted on a SELDI surface are analyzed with time-of-flight mass spectrometry (TOF-MS) approach [69], in which process the laser ionized peptides from crystals of the sample and matrix mixture. Then these ions were accelerated through an electric field and down into the flight tube. Finally the detector would measure the captured ions at the end of the tube (Fig. 1). The mass-to-charge ratio of each ion are determined from the length of the tube, the kinetic energy given to ions by the electric field, and the time taken to travel the length of the tube. Some surfaces that are normally adopted include CM10 (weak-positive ion exchange), H50 (hydrophobic surface, similar to C6-C12 reverse phase chromatography), IMAC30 (metal-binding surface), and Q10 (strong anion exchanger). Surfaces can also be modified or functionalized with antibodies, other proteins with proper binding properties, or even DNA. All there variations expand the exact application of this technique in detecting serum samples in practices.

Both SELDI-TOF MS and MALDI-TOF MS contributed to the progresses of SAA identification from serum samples of cancer patents described above [4,42,43,46,54,55,62,70–76]. It is still yet to test how much quantitatively the SAA level could be measured in order to accurately monitor the progression of a specific tumor upon diagnosis or during clinical treatment, for example (Fig. 2).

Summary

In summary, SAA plays important roles in response to acute inflammation in the body, and in chronic inflammation cases, SAA contributes to the tumor initiation and progression with multiple signaling pathways, including the interaction with ECM. The changes of SAA level in serum were found to be associated with many types of diseases with inflammation, especially in early and late phases of cancers. Though currently it lacks the SAA-targeting therapy to cancer in clinical treatment, the SAA level increase could be considered as a potential biomarker for these types of diseases and disorders, with varied specificity and sensitivity. We believe that SAA based early cancer diagnosis will a powerful technique in clinical practices in coming decade, which would rely on further progresses in the bioinformatics tools for analyses of the proteomics data.

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