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REVIEW

Why Do Cancer Cells Produce Serum Amyloid A Acute-Phase Protein?

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Abstract—The level of acute-phase serum amyloid A (SAA) protein in human blood dramatically grows in cancer, often at its early stage, when acute inflammatory signs are not observed. This fact was registered both by immunochemistry and by proteomics methods in different common cancers, such as lung, ovarian, renal, uterine, and nasopharyngeal cancer and in melanoma. It was proposed that SAA is produced by liver in such cases, as in inflammation, high levels of SAA being a part of nonspecific response to tumor. However, that was not always true, because, in many cancers, the protein of interest is produced directly by cancer cells. What is the biological significance of this observation? What preferences do cancer cells obtain due to SAA overexpression? Recent data on melanoma patients have shown that serum amyloid A is able to stimulate immunosuppressive neutrophils to produce interleukin-10 cytokine that suppressed cell immunity. The ability of cancer cells to produce SAA that is acquired during cancer mutagenesis is likely to enhance their resistance to T-cell immunity due to activation of immunosuppressive granulocytes.

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Serum amyloid A (SAA) is a family of three protein-coding human genes and one pseudogene [1]. The best-studied proteins from this family are acute phase serum amyloids – SAA1 and SAA2. Amino acid sequences of these proteins differ by approximately six amino acids out of 107 residues of a mature chain with a molecular weight of about 11.7 kDa. This defines their similar properties and regulation. In the UniProt database, these proteins are put together into one register entry P02735 (www.uniprot.org). In this article, for convenience the term SAA implies all protein products of these two genes.

Already in the beginning of the development of clinical biochemistry, SAA attracted attention as a protein forming depositions in tissues termed amyloid AA in pathological anatomy. The respective disease is called AA amyloidosis or inflammatory amyloidosis. The pathological β-structure of amyloid is currently known to be formed by fragments of a cleaved protein of 7.5 kDa [2]. The ability to aggregate, forming fibrils, is caused by highly hydrophobic nature of the protein sequence – it is associated with high density lipoproteins in blood plasma [3]. Another unique property of SAA is its ability to be rapidly induced during acute and chronic inflammation, while its concentration in blood plasma can increase by three or four orders of magnitude, reaching more than 1 g/liter [4].

Despite the fact that biochemical research concerning amyloid A started a few decades ago, its functions actually remained unknown until recently. Only in recent years has the role of SAA in certain molecular mechanisms related to lipid metabolism and immunity regulation been established [1, 4].

Already in 1979, SAA levels in human blood plasma were noted to significantly increase in cancer cases [5]. This fact raised interest once again in the beginning this century for the development of proteomics diagnostics [6]. In particular, using MALDI-TOF mass spectrometry on blood plasma or serum allows easy detection of SAA concentration higher than 0.3 g/liter without any treatment [7]. Moreover, this simple instrumental approach allows detection of allele variants of acute phase amyloid A and its fragments formed due to proteolysis *in vivo* [7, 8].

We identified mass spectrometric peaks corresponding to acute phase amyloid A forms in blood plasma taken from patients with ovarian cancer [9], in some cases

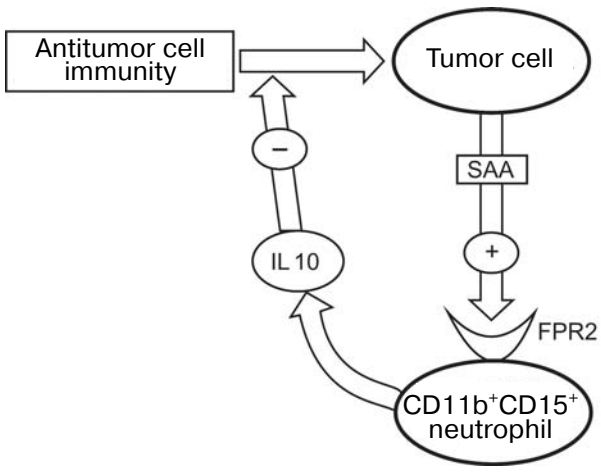
at early stages of the disease [7]. Confirmation of proteomics data with immunoanalysis in some cases revealed an increase in SAA level in plasma up to 1.5 g/liter, which exceeds the value in healthy human plasma by more than three orders of magnitude. Based on these and other data, serum amyloid A was included in the list of ovarian cancer markers that is undergoing tests in Australia to access possible clinical use [10]. High level of SAA in ovarian adenocarcinoma without any other clinical signs of the acute stage of inflammation supposedly furthers amyloidosis AA development in some cases [11].

Acute phase serum amyloid A was characterized by an elevated concentration in blood plasma in many other cancers. It was detected by proteomics as a potential biomarker in lung cancer [12, 13], and it even promoted metastasis in lung carcinoma cell line *in vitro* [13].

Many forms of SAA have been identified in blood plasma in renal cell carcinoma [14]. Later data was obtained that suggested that raised concentration of amyloid A mainly indicates the presence of remote metastases of a certain tumor [15]. Moreover, a high level of SAA in blood plasma was shown to be a prognostic sign of more aggressive, fatal forms of renal cell cancer [16].

An elevated level of SAA was also proposed as a potential biomarker for uterine cancer, in particular endometrial cancer [17] and the most aggressive serous papillary uterine cancer [18]. Elevated concentration of this marker also correlated with recurrences of nasopharyngeal cancer [19].

Moreover, acute phase serum amyloid A turned out to be a perspective marker for predicting high risk of malignant melanoma progression at early stages [20].



Supposed scheme of regulation of antitumor immunity by acute phase serum amyloid A (SAA) (after De Santo et al. [25]). SAA produced by cell of malignant tumor activates immunosuppressive granulocytes of $CD11b^+CD15^+$ phenotype through the FPR2 receptor. The latter release interleukin-10, which suppresses local T-cell immunity, providing competitive advantage to SAA-expressing tumor cells

Despite a clear connection between elevated level of SAA in blood plasma with development of malignant tumors of different organs and tissues, it is obvious that this protein is often likely to appear in blood in excess amounts under different conditions that are characterized by acute and chronic inflammation. Moreover, expression of acute phase SAA is known to occur predominantly in liver [1]. These facts suggest that in cancer the level of amyloid A is elevated as a part of the response of the organism to the inflammation connected with the tumor. That is why clinical value of this biomarker as well as its connection with tumor pathogenesis was thought to be limited [21].

Nevertheless, some tumor tissues were also shown to be characterized by an elevated expression of SAA. This applies at least to tissues of colorectal cancer [22], ovarian cancer [23], and different histological forms of uterine cancer [17, 18].

Messenger RNA of acute phase serum amyloid A and the protein itself are produced by tumor tissues in significant amounts and are detected in them in substantial concentrations. A question arises about the biological significance of this phenomenon. What advantages do cancer cells gain by expressing SAA?

The answer lies in the field of molecular immunology, in particular in data about the way SAA participates in regulation of immunity. For example, a short time ago a molecular SAA receptor was found that is expressed in many cells in hematopoietic lineages [24]. It is *N*-formyl peptide receptor 2 (FPR2, previously named "formyl peptide-like 1", FPRL1; UniProt accession number P25090).

An investigation important for understanding mechanisms of action of SAA on immune cells [25] showed that it is intensively expressed by malignant melanoma cells. The level of amyloid A correlates with the number of neutrophils with $CD11b^+CD15^+$ surface markers inside the tumor. As found earlier, these neutrophils possess immunosuppressive properties [26]. De Santo et al. [25] showed that SAA induces production of interleukin-10 (IL-10), which suppresses T-cell immunity by these neutrophils. The effect of amyloid A is expressed through the FPR2 receptor on neutrophils. Despite the fact that immunosuppression by these neutrophils is later regulated by SAA-activated T-cells, tumors apparently use such neutrophils for suppressing immunity.

The concept of "cancer genome" that is accepted today [27] assumes constant and significant genome modifications in dividing tumor cells, which allow particular clones to survive in the patient's body, resisting the immune system and competing for resources in the host tissues. Mutagenesis in cancer cell genomes leads to production of acute phase serum amyloid A in some of them as a result of increase in activity of one or several transcription factors that *trans*-activate SAA genes expression. Among them are NF-κB and STAT3 [28], C/EBP-

beta [29], and others. The ability of tumor cells to produce SAA probably increases their resistance to T-cells by activating immunosuppressive granulocytes (see figure). This proposed mechanism explains marker properties of SAA that were observed in many works cited above, and it lets us consider future projects connected with this protein for practical use. For example, SAA can be included in diagnostic and prognostic sets in some cases [10]. Moreover, the interaction of amyloid A with its receptor FPR2 is an interesting target for blocking by potential drugs for inducing antitumor immunity.

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