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Review Article

Dentistry Section

Role of Serum Amyloid A Protein in Various Diseases with Special Reference to Periodontal and Periapical Inflammation- A Review

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ABSTRACT

Serum Amyloid A (SAA) is an Acute-Phase Protein (APP) produced as an innate nonspecific response to any tissue damage. Hence, it plays a significant role in chronic inflammatory diseases. In particular, SAA levels increase dramatically in chronic periodontitis and chronic apical periodontitis. Recent studies suggest this role of SAA in the pathogenesis of various diseases, including chronic periodontitis and chronic apical periodontitis. Thus, the focus of this review is to sum up the current understanding of the role of SAA in health and disease and to elaborate on possible mechanisms by which SAA could play a role in the pathogenesis of chronic periodontitis and chronic apical periodontitis.

Keywords: Acute phase reactants, Chronic disease, Osteoimmunology, Pathogenesis, Periodontitis

INTRODUCTION

The first reaction of the body to immunological stress is the innate, nonspecific response preceding specific immune responses. The Acute Phase Response (APR) is a major early complex systemic defense mechanism of the organism which is triggered in response to either local or systemic disturbances caused by infection, inflammation or immunological disorders, neoplastic disorders, stress, tissue injury due to trauma or surgery [1,2].

The term "acute phase response" (APR) refers to a systematic nonspecific and complex reaction caused by an organism's innate body defense that is initiated immediately after any tissue damage, such as infection, trauma, neoplasia, inflammation, and stress [3]. This response is marked by the expression of certain blood proteins which are termed as APPs. These APPs are components of the nonspecific innate immune response pathway and their plasma concentration is proportional to the extent of tissue damage [3,4].

The serum concentrations of APP increase or decrease by at least 25% or more during inflammation. Such proteins are called either positive, which show an upregulated serum concentration, e.g., C-reactive proteins, Serum Amyloid A & Fibrinogen or negative APP, which show a downregulated serum concentration, e.g., Albumin, Transferrin in response to inflammation [5-7]. Positive APPs are categorised as major, moderate and minor or negative depending on the magnitude of increase: A 10-100 fold increase is seen with major APPs, while an increase of 2 to 10 fold is seen with moderate APPs and whereas a slight increase was seen with minor APPs [3,8].

Recently the measurement of APP serum levels is used as a laboratory; diagnostic and prognostic marker of the intensity of the inflammatory process in various diseases [5-7].

SERUM AMYLOID A PROTEIN

Serum Amyloid A (SAA) proteins are small APPs (104 amino acids) that are elevated under inflammatory conditions like trauma, infection, late-stage malignancy and severe stress as much as 1000-fold in 24 hours. Viral infections such as SARS2 can lead to inflammation and rapid viral replication. Thus, consequently leading to the release of an array of proinflammatory cytokines [9-12]. A recent study showed SAA to have the potential of being an independent predictive factor of COVID-19 [9]. It is also expressed in sterile inflammatory conditions and acts as a mediator of danger signal in inflammation [13,14]. SAA is an high-density apolipoprotein and is primarily formed in the liver in large quantities on induction by systemic infection and in the intestine by bacterial colonisation [15,16]. It is expressed by a variety of human cells including hepatocytes, adipocytes, macrophages, and fibroblast-like synoviocytes [17]. In addition, it is also associated with High-Density Lipoproteins (HDL) in plasma [18]. SAA proteins were first isolated and named five decades ago [12].

Functions of Serum Amyloid A Protein

SAA participates as an APP in lipid metabolism by influencing HDL-cholesterol transport [19]. In tissues, it attracts inflammatory cells and acts as an effector of neutrophil functions and modulates immune response [20]. Moreover, SAA induces synthesis of several cytokines and is chemotactic to neutrophils, monocytes and mast cells. It has also been recently shown to activate the inflammasome cascade and therefore, has a significant role in immunomodulation [21-24]. Summary of functions of Serum Amyloid A protein are listed in [Table/Fig-1].

Role of Serum Amyloid A Protein and its Association with Various Diseases

The biology of SAA since its first identification decades ago was not understood well. SAA, in cases of Amyloidosis, gets deposited extracellularly as insoluble amyloid fibrils that cause damage to the tissue structure and disrupt function. A 19th century pathologists who conducted light microscope postmortem examinations found amorphous infiltrative changes in organs such as kidney, liver and heart. They considered this material to be carbohydrate and of plant origin and the term 'amyloid' originated [12,31]. However, it is now well understood that SAA has a potent proinflammatory role. Its serum levels rise with many inflammatory and disease conditions and may have a role in pathogenesis of a number of diseases. Thus, SAA can serve to be a potential target in the treatment of diseases associated with chronic inflammation [21]. [Table/Fig-2] summarises the roles of Serum Amyloid A Protein in the pathogenesis of various diseases.

Author, Reference, Year	Role of Serum Amyloid A protein
Badolata R et al., [23]:1994, Su SB et al., [24]:1999	Phagocyte migration Neutrophil migration Monocyte migration.
Banka CL et al., [19]:1995	Is Lipophilic Participates in Lipid Metabolism Cholesterol efflux. Displace apo-A1.
Olsson N et al., [22]:1999	Induces Chemotaxis of Human Mast Cells
Hatanaka E et al., [20]:2003	Neutrophil priming.
Shah C et al., [25]:2006	Innate opsonin. Opsonizes gram-negative bacteria; Induced bacterial clearance
Su SB et al., [24]:1994, El Kebir D et al., [26]:2007	Promotes PMN adhesion to endothelial cells Extends the lifespan of PMN cells. Suppressing neutrophil apoptosis.
Sandri S et al., [27]:2008	Induces nitric oxide production through TLR4 in human macrophages
de Buck M et al., [28]: 2016	Inflammatory cytokine expression. Cytokine and chemokine-inducing capacity. Activates transcription factors.
Yan Q et al., [29]:2014, Li et al., [30]:2017	Epigenetic regulation of proinflammatory cytokine gene expression.
Sack Jr GH [12]:2018	Cytokine-like protein/Helps in cell to cell communication. Provides feedback in inflammatory, immunologic, neoplastic and protective pathways.

[Table/Fig-1]: Functions of Serum Amyloid A Protein [12,19,20,22-30].

Author, Reference, Year	Pathogenesis	Disease
Chambers RE et al., [32]:1987, Niederau C et al., [33]:1997	Acute phase marker	Crohn's disease
Liuzzo G et al., [34]:1994	Important inflammatory component in pathogenesis. Elevation of CRP and SAA predicts poor outcome.	Severe unstable angina
Ristori G et al., [35]:1998, Chung TF et al., [36]: 2000 Yokote H et al., [37]:2013	Elevated SAA levels. Peripheral inflammation. SAA plays a role in neuronal loss and white matter damage.	Multiple sclerosis.
Chung TF et al., [36]:2000	SAA can inhibit Lipid synthesis. SAA plays a role in neuronal loss and white matter damage.	Alzheimer disease
Niemi K et al., [38]:2006	Degradation of SAA and formation of Amyloidogenic SAA Fragment.	Amyloidosis
Engin-Ustün Y et al., [39]:2007, Ibrahim MI et al., [40]:2017 Swidan KH et al., [41]:2020,	Elevated levels of Acute phase proteins including SAA. May at least in part contribute to the pathogenesis of pre-eclampsia.	Pre-Eclampsia
Deguchi I et al., [42]:2010, Shridas P and Tannock LR [43]:2019, Fernández JA et al., [44]:2020.	Elevation of SAA is strongly linked to venous thromboembolic disease SAA itself is a potential enhancer of thrombin generation.	Thrombosis
Zhao Y et al., [45]:2010	Proinflammatory. Insulin resistance.	Obesity
Marzi C et al., [46]:2013, Klüppelholz B [47]:2015	Elevated SAA were associated with early deterioration of glycaemia. Strong prospective associations with type 2 diabetes. Proinflammatory.	Diabetes
Biaoxue R et al., [48]:2016	Higher levels of SAA are seen in patients with lung cancer and can be correlated with relatively high specificity with occurrence and development of lung cancer. SAA could be a new biomarker-diagnostic and prognostic indicator for some malignant tumors.	Neoplasia
Getz GS et al., [49]:2016, Shridas P and Tannock LR [43]: 2019	SAA participates in the early atherogenic process and pro-atherogenic activity. It is a plasma biomarker for future cardiovascular events	Atherosclerosis
Vitale A et al., [50]: 2014, Agilli M et al., [51]:2016, Lopalco G et al., [52]:2015	SAA levels may identify a thrombotic risk. Studies suggest the existence of a relationship between SAA and proinflammatory cytokines in the intricate scenario of BD pathogenesis.	Behçet's Disease
Morizane S et al., [53]:2016, Couderc E et al., [54]:2017	SAA contributes to pathogenesis.	Psoriasis
Lu W et al., [55]:2019	SAA is synthesised in the liver by activated monocytes and macrophages in response to pro-inflammatory cytokines.	Acute and Chronic Urticaria.
Yuan ZY et al., [56]:2019	Elevated serum SAA levels are seen in all patients with active liver diseases. Sensitive biomarker in pyogenic liver abscess.	Pyogenic liver abscess

[Table/Fig-2]: Role of Serum Amyloid A Protein in the pathogenesis of various diseases [32-56].

Circulating Serum Amyloid A Protein Concentrations

Previous studies have shown that physiological SAA serum levels vary substantially [57-60]. In healthy individuals, the serum concentration of SAA is about 1-2 µg/mL, that is, (100-200 ng/mL) [61]. However, some authors found relatively high physiological levels of SAA (15-40 µg/mL) [62]. This discrepancy may be the result of subclinical infection or inflammation [62].

The comparison between SAA levels in serum levels in health and disease showed an increase in SAA concentration during various diseases; inflammatory, autoimmune, neoplastic, trauma, surgery and other diseases. In disease, serum SAA levels vary between studies, ranging from about 10 µg/mL to about 500 µg/mL, up to even 1 mg/mL. In general, we can state that under pathological conditions, SAA concentrations raise more than 10 µg/mL and up to 1 mg/mL [63-66]. Therefore, serum SAA concentration is very sensitive but is generally a nonspecific marker in diagnosis, prognosis and monitoring of inflammatory, infectious diseases and cancer [67].

Serum Amyloid A in Periodontal Inflammation

Periodontitis is a chronic polymicrobial disease exaggerated by self-damaging host immune response elicited by bacterial colonisation as biofilms [68,69]. SAA concentrations in serum and gingival crevicular fluid in patients with chronic periodontitis is comparably elevated to periodontally healthy individuals [70,71]. It was found that high serum titers of antibodies to *P. gingivalis* and the presence of periodontal inflammation were independently related to high SAA and hs-CRP levels [70]. Vuletic S et al., in a study in 66 patients with advanced periodontal disease, showed that full-mouth tooth extraction significantly reduced SAA, a marker of inflammation [72]. Ardila CM et al., showed that pathological levels of SAA were associated with periodontal disease [70,73]. A recent study by Song LT et al., showed that inflammatory gingival tissues express SAA strongly. This can set in motion the secretion of inflammatory cytokines such as IL-6 and IL-8 by the TLR-2 pathway (Toll-like receptors) in human gingival fibroblasts. Thereby, the SAA participates in periodontal inflammation and the pathogenesis of chronic periodontitis [74].

Serum Amyloid A in Periapical Inflammation

The understanding of periapical inflammation in relation to bacterial infection has led to several studies on host-bacteria interactions [75-77]. Endodontic infection has shown to activate a series of inflammatory events which contributes to the containment and killing of pathogens. This systemic reaction to local disturbances in its homeostasis caused by infection is considered as APR. Thus, inflammation is primarily a protective mechanism in an individual. However, a chronic inflammatory state may result in failure of bacterial clearance, leading to periapical tissue destruction [1,78-80].

Currently, the factors which are considered crucial for induction of innate immune responses are bacterial infection, Pathogen-Associated Molecular Patterns (PAMPs) and Damage Associated Molecular Patterns (DAMPs) [75].

The host defence activation by pathogens depends on specific recognition of PAMPs which are detected through Pattern Recognition Receptors (PRRs) [81,82] These include TLR and Nucleotide Binding Site/Leucine Rich Repeat (NBS/LRR) [83,84]. The DAMPs are the endogenous molecules which are released by damaged or necrotic host cells [85,86]. Investigations have identified several DAMPs, and their number is still increasing [87,88]. The macrophages recognises DAMPs and inflammatory responses are triggered through different ways including inflammasomes and TLRs [88,89].

The DAMPs have shown to originate from various sources like plasma proteins (such as Serum Amyloid A), extracellular proteins (like Biglycan) and intracellular proteins (such as high mobility group box1) [13,88,90-92]. The plasma proteins including SAA have shown to extravasate from vessels to the sites of inflammation and act as DAMPs to produce inflammatory cytokines through TLR4 or TLR2 [13,90-92]. In situations, when DAMP's are persistently released, inflammation will fail to resolve which will lead to chronic inflammatory diseases, fibrosis or granulation tissue development [86].

A recent study revealed the expression of SAA (a DAMP) locally in the periapical lesions of humans and mice and also found the circulating SAA in mice to elevate in response to endodontic infection [75].

CONCLUSION(S)

SAA has been shown to regulate innate and adaptive immunity and plays a significant role in the pathogenesis of several diseases. It has also been found that SAA might have a closer role in the pathogenesis of periodontal diseases and chronic periapical inflammation. A thorough understanding of the regulatory mechanism of SAA in chronic periodontitis and chronic periapical inflammation will help to design better treatment modalities for these specific diseases.

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