

REVIEWER'S REPORT

Manuscript No.: JNHM- 167

Title: The biochemical features, physiological aspects, and clinical applications of serum amyloid A : a review

Recommendation:

Accept after minor revision

Rating	Excel.	Good	Fair	Poor
Originality			✓	
Techn. Quality			✓	
Clarity		✓		
Significance	✓			

Reviewer's Name: Bilqees Hamza

Detailed Reviewer's Report

This review manuscript provides a comprehensive synthesis of the biochemical features, physiological mechanisms, and clinical applications of **Serum Amyloid A (SAA)**. SAA represents a highly conserved family of acute-phase apolipoproteins that play a central and multifaceted role in host defense, immune modulation, and lipid homeostasis during systemic inflammation. Under homeostatic conditions, circulating levels of SAA remain extremely low ($<10 \text{ mg/L}$). However, upon exposure to inflammatory stimuli, infection, trauma, or tissue injury, SAA production surges exponentially—rising over 1000-fold within 24 to 48 hours. This rapid hepatic synthesis is predominantly orchestrated by pro-inflammatory cytokines, including Interleukin-6 (IL-6), Interleukin-1 β (IL-1 β), and Tumor Necrosis Factor- α (TNF- α), through the activation of the JAK/STAT and NF- κ B signaling pathways. While hepatic synthesis accounts for the majority of circulating SAA during the acute-phase response, extrahepatic expression also occurs in adipocytes, endothelial cells, macrophages, and epithelial tissues, providing localized immune surveillance and amplifying regional inflammatory signals.

Biochemically, SAA is a small amphipathic protein of approximately 12 kDa (104 to 112 amino acids) characterized by an abundance of α -helices. These structural features facilitate its primary interaction with high-density lipoproteins (HDL) in plasma. During acute-phase reactions, SAA acts as the predominant apolipoprotein on HDL, effectively displacing apolipoprotein A-I (ApoA-I) and fundamentally altering the structural and functional profile of HDL particles. This remodeling diminishes HDL's normal cholesterol efflux capacity and antioxidant properties, transforming it into a pro-inflammatory or altered functional entity that directs lipids and bacterial products toward the liver for

REVIEWER'S REPORT

clearance. When dissociated from HDL or subjected to enzymatic cleavage, SAA exhibits remarkable conformational flexibility, transitioning from its native α -helical state into β -sheet-rich aggregates. N-terminal fragments derived from SAA1 and SAA2 are particularly prone to misfolding, acting as the primary pathogenic building blocks for insoluble fibril deposition in systemic AA amyloidosis.

Physiologically, SAA functions as an active immunomodulatory signaling molecule rather than a passive marker of tissue damage. It binds to a wide variety of cell-surface pattern recognition receptors, including Formyl Peptide Receptor 2 (FPR2), Toll-like Receptors (TLR2 and TLR4), Scavenger Receptor Class B Type I (SR-BI), and the Receptor for Advanced Glycation End Products (RAGE). Through these receptor pathways, SAA functions as a potent chemoattractant that directs the migration of neutrophils, monocytes, mast cells, and T lymphocytes to sites of injury. Furthermore, SAA stimulates the release of downstream cytokines, induces matrix metalloproteinases, activates MAPK and PI3K/Akt pathways, and participates in wound healing, tissue remodeling, and the regulation of adaptive immune responses.

Clinically, SAA's exceptionally rapid kinetics make it an extremely sensitive biomarker across several disease domains. In rheumatology and autoimmune conditions—such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease—SAA correlates tightly with clinical disease activity and flare states. It often outperforms traditional markers like C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), particularly in patients receiving IL-6 receptor antagonists where hepatic CRP production is selectively blunted. In infectious diseases, SAA aids in early detection and risk stratification for neonatal sepsis and pediatric infections. In cardiovascular medicine, elevated SAA levels independently predict atherogenesis, endothelial dysfunction, and adverse outcomes in coronary artery disease. In oncology, systemic SAA levels reflect tumor-associated inflammatory microenvironments and correlate with disease stage, metastasis, and poor survival across multiple malignancies. Finally, monitoring SAA levels to maintain concentrations below 10 mg/L is critical in managing AA amyloidosis to halt organ deterioration and induce regression of amyloid deposits.

Suggested Improvements

While the review provides a thorough narrative synthesis of SAA biology and clinical utility, several structural, factual, and analytical revisions are necessary to elevate the paper to a publishable standard:

1. Correction of Factually Inconsistent Textual Errors

- **Chromosomal Localization Conflict:** In the "Biochemical features of SAA" section, the text states that the human SAA gene cluster is located on **chromosome 11p15**, but two sentences later claims that "*all of them are close to each other on the chromosome 1*". The human SAA gene

REVIEWER'S REPORT

locus (*SAA1*, *SAA2*, *SAA3P*, *SAA4*) is located exclusively on chromosome 11p15.1. The reference to "chromosome 1" is an error and must be deleted.

- **Inappropriate Biomarker Substitution in Introduction:** In the Introduction, the text mentions that *"The central importance of CRP in systemic biology and its clinical significance as a biomarker... is evidenced by its dynamic synthesis pattern..."*. In an article entirely dedicated to Serum Amyloid A, substituting "CRP" into a foundational overview sentence appears to be an uncorrected manuscript drafting error. This must be corrected to "SAA".

2. Analytical Expansion of Structural Biology & Receptor Mechanisms

- **Clarify Receptor Isoform Specificity:** The manuscript discusses interactions with FPR2, TLR2, TLR4, SR-BI, and RAGE in broad terms. The review should clarify whether these receptor interactions are shared equally across acute-phase isoforms (*SAA1* vs. *SAA2*) or if recombinant vs. native native HDL-bound SAA exhibits differing receptor affinities.
- **Elaborate on AA Amyloidosis Mechanics:** The section on fibrillogenesis discusses β -sheet refolding. Expanding on the specific cleavage sites (e.g., matrix metalloproteinase or cathepsin cleavage generating 76-amino-acid N-terminal fragments) and specific *SAA1* allelic variants (*SAA1.1*, *SAA1.3*, *SAA1.5*) would provide crucial biochemical depth regarding individual susceptibility to reactive amyloidosis.

3. Critical Evaluation of Clinical Assays & Literature Selection

- **Addressing Assay Standardization Issues:** Although the abstract and conclusion state that assay standardization remains an ongoing clinical hurdle, the body text lacks a dedicated subsection analyzing this challenge. The manuscript should discuss variations between commercial immunoassay platforms (ELISA, turbidimetry, nephelometry), the lack of universal international standard calibrators, and how high-density lipoprotein binding interferes with antibody epitope recognition.
- **Refining Citation Appropriateness:** In the physiological discussion on host defense, the authors cite research performed on oysters (*Crassostrea gigas*) to support basic acute-phase SAA actions. Citing invertebrate model systems alongside human physiological pathways without explicit contextual framing disrupts narrative cohesion; this reference should be replaced with human or standard mammalian model literature.

4. Structural & Formatting Enhancements

- **Incorporate Visual Comparative Summary Tables:** To improve readability, the manuscript would benefit from a structured summary table comparing SAA with conventional inflammatory

Jana Nexus: Journal of Health and Medicine

Publisher's Name: Jana Publication and Research LLP

<https://www.jananexushm.com>

REVIEWER'S REPORT

biomarkers (CRP, ESR, Procalcitonin) across key parameters: baseline levels, half-life, fold-increase, regulatory cytokines, and primary clinical indications.

- **Standardize Section Subheading Formatting:** Capitalization in subheadings is inconsistent throughout the text (e.g., "*Biochemicalfeatures of SAA*" and "*Importance Clinical Importance of SAA*"). All subheadings must be corrected for spacing, grammar, and standardized title capitalization.

Final Acceptance Matrix

Decision: Accept Pending Minor Revisions