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REVIEW

Mechanistic and translational perspectives on the regulation of macrophage functional states by astragalus polysaccharides

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Abstract: Macrophage functional states are increasingly viewed as a dynamic spectrum rather than a fixed M1/M2 dichotomy. Astragalus polysaccharides (APS) are structurally heterogeneous natural polysaccharides with reported immunomodulatory, anti-inflammatory, antioxidant, antitumor and tissue-repair activities; however, their structure-activity relationships, receptor-recognition mechanisms and translational readiness remain incompletely defined. This review summarizes mechanistic and translational evidence for APS-mediated regulation of macrophage functional states, with emphasis on structural heterogeneity, innate immune recognition, pathway crosstalk, disease-context dependence and current barriers to clinical development. A narrative literature review was conducted using PubMed, Web of Science, Scopus, Google Scholar and selected publisher databases. The literature search focused on studies published between 2020 and 2026, with priority given to recent mechanistic, preclinical and translational studies addressing APS, macrophage activation, macrophage polarization, immunometabolism, oxidative stress and disease-specific immune remodeling. Predominantly preclinical evidence suggests that APS do not act as simple unidirectional inducers of M1- or M2-like polarization. Instead, APS appear to modulate macrophage functional states according to structural features, receptor engagement and disease context. TLR4/MyD88/NF-kappaB, MAPK, Notch, PI3K/Akt/Nrf2/HO-1, JAK/STAT, cGAS-STING, NLRP3 inflammasome and immunometabolic pathways form interconnected regulatory networks. Preclinical studies suggest that APS may promote antitumor inflammatory and antigen-presenting programs in tumors while attenuating excessive inflammatory activation and supporting reparative programs in diabetic vascular injury, acute kidney injury and chronic wounds. This review integrates APS structure-activity relationships with macrophage plasticity and translational limitations. Further progress toward clinical development would depend on high-purity fractionation, rigorous quality control, glycomics-based receptor mapping, single-cell and spatial validation, pharmacokinetic and safety studies and well-designed clinical investigations.

Keywords: Astragalus polysaccharides; cGAS-STING; Functional states; Immunomodulation; Macrophage plasticity; Nrf2/HO-1; Structure-activity relationship; TLR4/MyD88/NF-kappaB; Translational gaps

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INTRODUCTION

Macrophages are among the most plastic cell populations in innate immunity. They are distributed across the liver, lung, intestine, cardiovascular system, kidney, skin and tumor tissues, where they participate in phagocytosis, clearance of necrotic cells, initiation and resolution of inflammation, antigen presentation, tissue remodeling, angiogenesis, metabolic homeostasis and fibrotic responses. Single-cell RNA sequencing, spatial transcriptomics and lineage-tracing studies have shifted the field from a binary description of macrophages toward a tissue- and disease-stage-dependent model of functional states (Chen *et al*., 2023; Yan *et al*., 2024). Classically activated and alternatively activated macrophages are often described as M1-like and M2-like cells. Here, these terms are used only as convenient descriptors of functional tendencies. M1-like inflammatory states are usually associated with lipopolysaccharide (LPS), interferon-gamma, tumor necrosis factor-alpha (TNF-alpha), inducible nitric oxide synthase (iNOS), CD86, IL-1beta, IL-6 and IL-12. M2-like reparative states are usually associated with IL-4, IL-13, IL-10, transforming growth factor-beta (TGF-beta), arginase-1, CD206 and CD163. In vivo, macrophages often express mixed, transitional or disease-specific programs, including phagocytic, pro-angiogenic, lipid-metabolic, immunosuppressive and fibrosis-associated states (Kulakova *et al*., 2024).

Astragalus membranaceus is a traditional Chinese medicinal herb whose polysaccharide fractions are considered important contributors to its immunomodulatory actions. APS are not a single chemical entity but a family of polysaccharides with variable molecular weights, monosaccharide compositions, glycosidic linkages, branching patterns, conformations, purity levels and extraction histories. This structural diversity may explain why APS have been reported to enhance antitumor immunity in some models but to suppress excessive inflammation and promote

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tissue repair in others. Therefore, the central question is not whether APS induce M1 or M2 polarization, but how specific APS preparations reshape macrophage functional states in defined tissue and disease contexts (Zheng *et al*., 2020; Wang *et al*., 2025). Previous reviews have described the pharmacological actions of APS or the general biology of macrophage polarization. This narrative review integrates structure-activity relationships, innate immune receptor recognition, signaling crosstalk, oxidative stress, mitochondrial metabolism, cytokine networks, immune microenvironment remodeling and barriers to translation. The discussion is organized from macrophage plasticity and APS structural features to mechanistic evidence, disease-context implications and translational priorities (Chen *et al*., 2023; Wang *et al*., 2025; Yan *et al*., 2024).

Narrative review approach

A narrative review approach was used to provide a transparent, mechanism-oriented synthesis. Literature searches were performed in PubMed, Web of Science, Scopus, Google Scholar, ScienceDirect, SpringerLink, MDPI and Frontiers databases. Search terms included combinations of 'Astragalus polysaccharide', 'Astragalus membranaceus', 'macrophage polarization', 'macrophage plasticity', 'macrophage functional state', 'TLR4', 'NF-kappaB', 'MAPK', 'Notch', 'Nrf2', 'HO-1', 'JAK/STAT', 'cGAS-STING', 'NLRP3', 'immunometabolism', 'oxidative stress', 'tumor-associated macrophage', 'diabetic wound', 'acute kidney injury' and 'structure-activity relationship'.

The literature search focused on studies published between 2020 and 2026, with priority given to work from the most recent five years when directly relevant to APS, macrophage biology or translational immunomodulation. Foundational concepts were supported, where possible, by recent PubMed-indexed reviews and mechanistic studies. ***Literature selection***: Original research or high-quality reviews addressing APS, polysaccharide structure, receptor recognition, macrophage functional-state regulation, disease-relevant macrophage responses or translational barriers.

Literature not included: Duplicate publications, articles without mechanistic relevance, non-English articles whose essential information could not be verified and studies in which APS-related conclusions could not be separated from those of other active ingredients.

Evidence was synthesized narratively according to study type and mechanistic strength. Findings based only on RAW264.7 cells or animal models were classified as preclinical. Evidence supported by receptor blockade, genetic knockdown or knockout, rescue assays, or pathway-specific pharmacological intervention was considered mechanistically stronger, whereas findings lacking direct macrophage-specific validation were treated as proposed or associative rather than definitive causal mechanisms.

Conceptual framework: macrophage plasticity and functional states

Macrophage functional states reflect coordinated changes in transcription, metabolism and effector activity in response to local signals. Inflammatory programs support pathogen and debris clearance, whereas resolution-associated programs promote efferocytosis, angiogenesis and tissue repair. Prolonged activation at either end of this spectrum can contribute to chronic inflammation or fibrosis (Yan *et al*., 2024).

APS structural heterogeneity and innate immune recognition

APS are mainly composed of glucose, galactose, arabinose, rhamnose, mannose and xylose, but the exact monosaccharide ratio, molecular-weight distribution, glycosidic linkage type, branching degree, spatial conformation and purity differ substantially across preparations. Extraction solvent, temperature, alcohol precipitation, deproteinization, purification method and geographical source can influence the biological behavior of APS. Accordingly, studies using crude APS, purified APS, RAP, PG2 or other APS-containing preparations should not be interpreted as biologically equivalent (Zheng *et al*., 2020).

Molecular weight may affect cellular uptake, receptor clustering, tissue retention and viscosity. High-molecular-weight fractions may preferentially activate surface pattern-recognition receptors, whereas low-molecular-weight or chemically modified fragments may show altered solubility, permeability and receptor accessibility. Glycosidic linkages and branching patterns influence three-dimensional conformation and the presentation of glycan motifs to TLR4, C-type lectin receptors, scavenger receptors and complement-related recognition systems. Purity and contamination control are important interpretive considerations because trace lipopolysaccharide can mimic TLR4/NF-kappaB activation (Cai *et al*., 2023; Li *et al*., 2023; Wang *et al*., 2025).

At present, TLR4/MyD88-dependent signaling provides the most direct receptor-related evidence for APS-mediated macrophage activation, but TLR4 alone is unlikely to explain all reported activities. A combined approach incorporating glycomics, chromatographic fractionation, nuclear magnetic resonance analysis, methylation linkage analysis, receptor-binding assays, surface plasmon resonance, receptor-blocking antibodies, knockout macrophages and contamination controls would facilitate linkage of defined structural motifs with receptor recognition and macrophage-state remodeling (Fitzgerald and Kagan, 2020). The key structural and quality variables that may influence APS-macrophage interactions, together with their principal evidence gaps, are summarized in Table 1.

Table 1: Structure-activity considerations for APS-mediated macrophage regulation.

APS feature/preparation	Structural or quality parameter	Potential receptor/recognition implication	Biological interpretation	Evidence gap/limitation	References
Crude APS extracts	Mixed molecular weights, variable monosaccharide ratio and possible protein/polyphenol residues	May activate multiple pattern-recognition and glycan-recognition receptors	Broad immunomodulatory effects may reflect multi-component activity	Batch heterogeneity and impurity make mechanism attribution difficult	Zheng *et al*., 2020; Li *et al*., 2022; Wang *et al*., 2025
Purified or fractionated APS	Defined molecular-weight distribution and narrower composition	Improves testing of TLR4, CLRs, scavenger receptors and complement-related receptors	More suitable for structure-activity relationship analysis	Interpretation still depends on contamination control and receptor-validation assays	Cai *et al*., 2023; Wang *et al*., 2025
High-molecular-weight fractions	Greater chain length and possible multivalent receptor clustering	Potentially stronger surface receptor engagement	May promote cytokine production or antigen-presenting programs depending on context	Dose and viscosity effects may confound interpretation	Zheng *et al*., 2020; Wang *et al*., 2025
Low-molecular-weight or modified fractions	Improved solubility and altered conformation	May change uptake, bioavailability and receptor accessibility	Potentially useful for delivery systems or tissue penetration	Comparative pharmacokinetic data are limited	Cai *et al*., 2023; Wang *et al*., 2025
Branching and glycosidic linkages	Degree of branching and alpha/beta linkage patterns	Determine glycan motif exposure and receptor affinity	Likely central to macrophage recognition and functional outputs	Few studies directly link linkage analysis to macrophage responses	Cai *et al*., 2023; Wang *et al*., 2025
Endotoxin-controlled APS	Low endotoxin content verified by LAL assay and functional controls	Reduces false TLR4/NF-kappaB attribution	Strengthens confidence in macrophage mechanism studies	Not uniformly reported in current APS literature	Fitzgerald and Kagan, 2020; Li *et al*., 2023; Wang *et al*., 2025

Mechanistic evidence for APS-mediated macrophage regulation

Integrated signaling-network crosstalk

TLR4/MyD88/NF-kappaB and MAPK signaling can prime inflammatory cytokine production, iNOS expression and inflammasome activation. PI3K/Akt and Nrf2/HO-1 signaling can restrain oxidative stress, modify NF-kappaB tone and support reparative metabolic adaptation. JAK/STAT signaling translates the cytokine milieu into transcriptional programs, while cGAS-STING and NLRP3 inflammasome pathways amplify sterile inflammation when cytosolic DNA, mitochondrial damage or danger-associated molecular patterns are present (Fitzgerald and Kagan, 2020; Baird and Yamamoto, 2020; Decout *et al*., 2021).

These interacting pathways may account for the context-dependent effects reported across disease models. In tumor microenvironments dominated by immunosuppressive macrophages, APS-associated activation of inflammatory and antigen-presenting programs may be beneficial. In diabetic vascular injury, acute kidney injury and chronic wounds, APS may instead attenuate inflammatory amplification and support reparative functions, although the balance is likely to depend on disease stage and preparation-specific properties. An integrated overview of APS-related macrophage signaling and disease-context-dependent outcomes is presented in figure 1, while the principal signaling networks, their crosstalk and current evidence limitations are summarized in table 2.

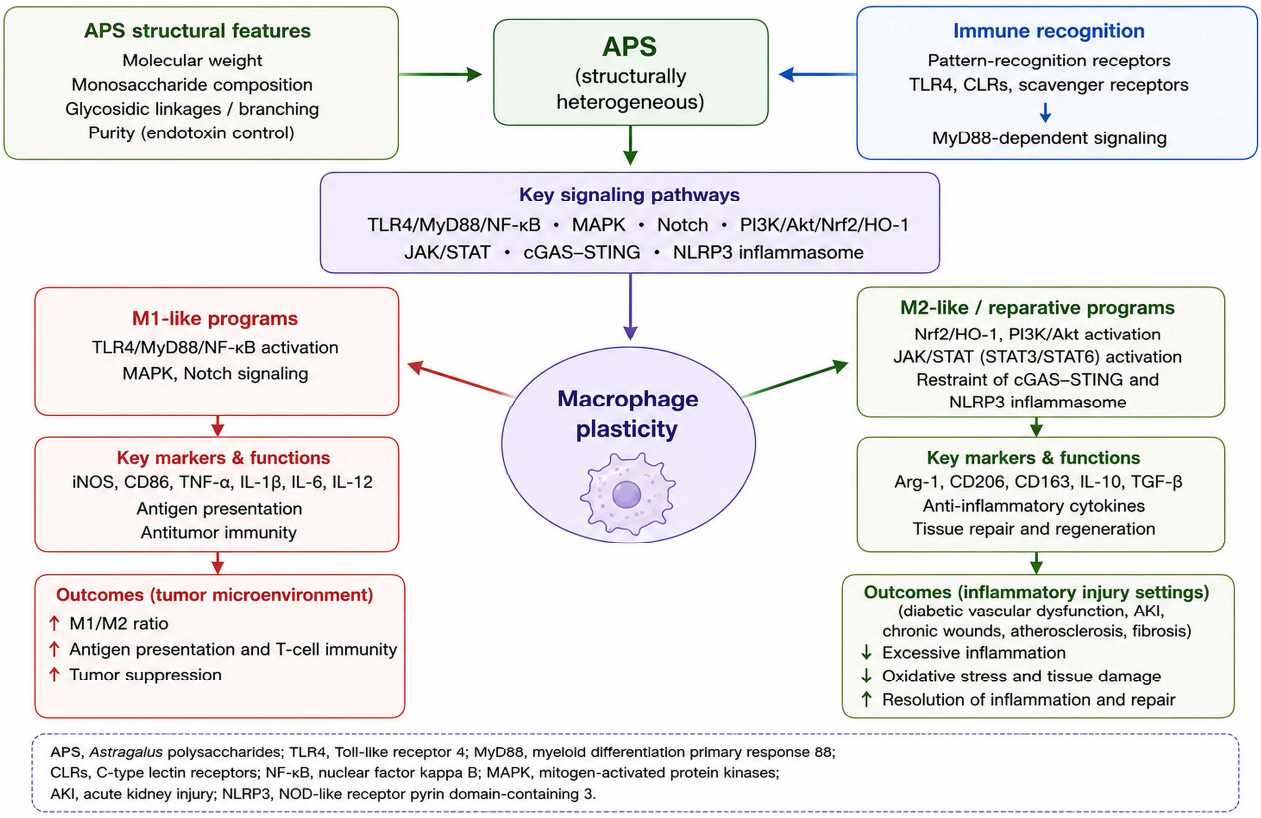

Fig. 1: Major molecular mechanisms and disease outcomes of APS-mediated macrophage functional-state regulation. The schematic summarizes APS structural features, innate immune recognition, signaling-network crosstalk and disease-context-dependent macrophage outcomes. High-resolution TIFF files are provided separately.

TLR4/MyD88/NF-kappaB and MAPK signaling

TLR4/MyD88/NF-kappaB and MAPK signaling is among the best-supported routes through which APS may influence macrophage activity. APS have been reported to stimulate macrophages through TLR4-mediated MyD88-dependent activation, leading to NF-kappaB and MAPK responses and downstream induction of TNF-alpha, IL-6, IL-1beta, iNOS and nitric oxide. In tumor or immune-hyporesponsive settings, such activation could increase antigen presentation, dendritic-cell maturation and T-cell-mediated antitumor immunity (Fitzgerald and Kagan, 2020).

However, TLR4 activation is not uniformly beneficial. In diabetes, acute kidney injury, atherosclerosis and chronic wounds, persistent NF-kappaB activity can intensify sterile inflammation, oxidative stress and tissue injury. The pathway is therefore best viewed as context dependent. Because contaminating LPS can produce a similar signal, contamination controls and macrophage-specific validation would be important before attributing TLR4/MyD88 activation directly to APS (Guo *et al*., 2023; Sun *et al*., 2024).

Notch signaling

Notch signaling regulates innate immune activation, cell-fate decisions and macrophage-tumor interactions. RAP, an APS fraction, has been associated with an M1-like macrophage phenotype characterized by increased iNOS, TNF-alpha, IL-6 and CXCL10, suggesting a possible link between selected APS fractions and antitumor macrophage activation. In tumor-associated macrophages (TAMs), Notch-related reprogramming may support antigen presentation, chemokine-driven T-cell recruitment and cooperation between macrophages and dendritic cells (Xu *et al*., 2023; Wang *et al*., 2025).

This effect should nevertheless be interpreted carefully. Notch signaling can generate different outcomes depending on tumor type, ligand availability, hypoxia, inflammatory tone and interactions with NF-kappaB, STAT3 and HIF-1alpha. APS-mediated Notch activation could be relevant in tumors dominated by immunosuppressive TAMs, but excessive or mistimed inflammatory activation may contribute to tumor-promoting inflammation. Macrophage-specific Notch inhibition, lineage tracing and single-cell profiling would help clarify causality (Duan and Luo, 2021; He *et al*., 2024; Zhang *et al*., 2025).

PI3K/Akt/Nrf2/HO-1 signaling

The PI3K/Akt/Nrf2/HO-1 axis may help explain the antioxidant and tissue-protective effects of APS in oxidative-stress-related diseases.

Table 2: Integrated signaling networks involved in APS-mediated regulation of macrophage functional states

Pathway/network	Major macrophage effect	Key markers or processes	Crosstalk	Current evidence and limitation	References
TLR4/MyD88/NF-kappaB/MAPK	Inflammatory activation, antigen presentation, or suppressed inflammatory tone depending on context	TNF-alpha, IL-6, IL-1beta, iNOS, NO, p65, ERK/JNK/p38	Primes NLRP3; intersects with Notch, PI3K/Akt and Nrf2	Direct APS evidence exists, but contamination control remains important	Fitzgerald and Kagan, 2020; Guo *et al*., 2023; Sun *et al*., 2024
Notch	Antitumor inflammatory and antigen-presenting programs	iNOS, TNF-alpha, IL-6, CXCL10, antigen presentation	Interacts with NF-kappaB, STAT3 and tumor cytokines	Evidence is strongest for selected APS fractions; macrophage-specific validation would strengthen interpretation	Duan and Luo, 2021; Xu *et al*., 2023; Wang *et al*., 2025
PI3K/Akt/ Nrf2/HO-1	Antioxidant and reparative macrophage programs	HO-1, NQO1, IL-10, reduced ROS, mitochondrial protection	Restrains NF-kappaB priming and ferroptosis-related injury	Supported in vascular and wound-related models; causal rescue remains limited	Baird and Yamamoto, 2020; Sha *et al*., 2023; Zhen *et al*., 2024
JAK/STAT	Cytokine-dependent inflammatory or reparative states	STAT1, STAT3, STAT6, IL-10, IL-4/IL-13 signals	Integrates cytokines induced by TLR4, Notch and Nrf2-regulated programs	Direct APS-STAT evidence remains limited	Chen *et al*., 2023; Yan *et al*., 2024; Kulakova *et al*., 2024
cGAS-STING/ NLRP3	Restriction of sterile inflammatory amplification	IFN-beta, IL-1beta, IL-18, caspase-1, GSDMD	Activated by mitochondrial damage; influenced by ROS and NF-kappaB priming	Emerging evidence in acute kidney injury; knockout and rescue assays would strengthen causality	Hopfner and Hornung, 2020; Decout *et al*., 2021; Paik *et al*., 2021; Sun *et al*., 2024
Immunometabolism	State transition through mitochondrial and nutrient-sensing pathways	Glycolysis, OXPHOS, fatty-acid oxidation, ROS, AMPK, mTOR, HIF-1alpha	Connects redox stress, cytokine tone and tissue microenvironment	Promising but preliminary; omics and flux analyses would improve mechanistic resolution	Wculek *et al*., 2022; Chen *et al*., 2023; Luo *et al*., 2022

Nrf2 induces HO-1, NQO1, GCLC and other cytoprotective genes, while PI3K/Akt signaling supports survival, metabolic adaptation and reparative programs. Preclinical studies have reported improved diabetic vascular endothelial function alongside Nrf2/HO-1-associated reparative macrophage responses after APS treatment (Baird and Yamamoto, 2020; Chen *et al*., 2021; Sha *et al*., 2023). Nrf2/HO-1 should not be viewed only as an antioxidant pathway. It intersects with AMPK, mitochondrial quality control, immunometabolism, ferroptosis-related defense and NF-kappaB regulation. In diabetic ulcers and chronic wounds, APS may converge on Nrf2/HO-1, beta-catenin/NF-kappaB and local inflammatory resolution. Mechanistic confidence would be improved by testing whether inhibition of Nrf2 or HO-1 attenuates APS-associated reparative macrophage functions (Wculek *et al*., 2022; Zhen *et al*., 2024).

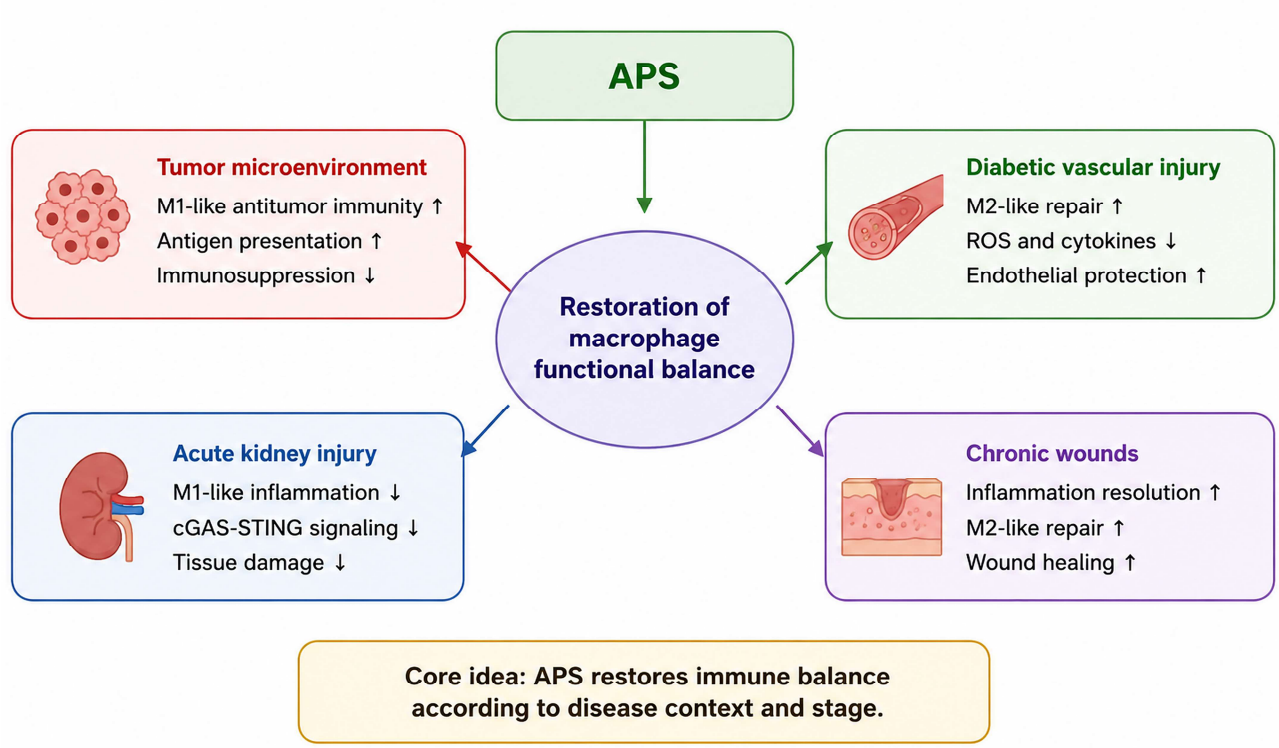

Fig. 2: Context-dependent model of APS-mediated regulation of macrophage function across diseases. The schematic emphasizes restoration of macrophage functional balance according to disease context and stage rather than one-directional polarization.

JAK/STAT signaling

The JAK/STAT pathway links cytokine networks to macrophage functional states. STAT1 is commonly associated with interferon-gamma-induced inflammatory responses, whereas STAT3 and STAT6 participate in IL-10-, IL-4- and IL-13-driven anti-inflammatory or reparative programs. APS have been reported to alter cytokine profiles, including TNF-alpha, IL-6, IL-10 and IL-12 and may therefore indirectly modify STAT-dependent macrophage states (Chen *et al*., 2023; Yan *et al*., 2024; Kulakova *et al*., 2024).

In tumors, persistent STAT3 activation is often associated with immunosuppressive TAM accumulation and impaired cytotoxic T-cell function, whereas STAT1-biased activation may support antitumor immunity. In tissue repair, moderate STAT3/STAT6 activity can support efferocytosis and extracellular matrix remodeling, but prolonged activation may contribute to fibrosis. Future APS studies would benefit from evaluating STAT1/STAT3/STAT6 balance, pathway timing, macrophage-specific knockout models and multiplex cytokine profiles rather than relying only on terminal markers (Duan and Luo, 2021; Chen *et al*., 2023; Yan *et al*., 2024).

cGAS-STING and NLRP3 inflammasome signaling

The cGAS-STING pathway senses cytosolic DNA derived from pathogens, damaged nuclei or injured mitochondria and triggers type I interferon and inflammatory cytokine responses. In sterile injury, mitochondrial DNA leakage can activate macrophage cGAS-STING signaling and amplify inflammatory tissue damage. In a rhabdomyolysis-induced acute kidney injury model, APS treatment was associated with reduced M1-like polarization and cGAS-STING activity, suggesting, but not establishing, this pathway as a potential mediator of the observed protective effects (Hopfner and Hornung, 2020; Decout *et al*., 2021; Sun *et al*., 2024). The broader disease-context-dependent implications of APS-mediated macrophage regulation are synthesized in figure 2, while the available evidence levels, proposed effects and principal limitations across disease settings are summarized in table 3.

The NLRP3 inflammasome is another inflammatory hub that is primed by NF-kappaB and activated by ROS, potassium efflux, lysosomal disruption and metabolic stress. Activated NLRP3 promotes caspase-1-dependent maturation of IL-1beta and IL-18 and can induce pyroptosis through gasdermin D. Direct evidence linking APS-mediated macrophage regulation to NLRP3 remains incomplete; APS could indirectly suppress this pathway by reducing oxidative stress, improving mitochondrial homeostasis, limiting TLR4/NF-kappaB priming or dampening cGAS-STING amplification.

Table 3: Disease contexts, evidence levels and limitations in APS-mediated macrophage regulation.

Disease/context	Study type and evidence level	Abnormal macrophage state	Potential APS effect	Principal findings and limitations	References
Tumor microenvironment	Mostly preclinical plus limited patient-associated immune observations	TAMs often immunosuppressive and pro-angiogenic	May promote antigen-presenting and antitumor inflammatory programs	May support immunotherapy, but tumor-specific context and combination safety require further validation	Duan and Luo, 2021; Xu *et al*., 2023; He *et al*., 2024; Zhang *et al*., 2025
Diabetic vascular injury	Animal and cell models	Persistent inflammatory activation and oxidative stress	May support Nrf2/HO-1-associated reparative functions	Promising for endothelial protection, but long-term vascular outcomes and dosing remain unclear	Sha *et al*., 2023; Liu *et al*., 2024; Luo *et al*., 2022
Acute kidney injury	Animal model evidence	Damage-associated M1-like inflammatory amplification	May restrain cGAS-STING and inflammatory macrophage activation	The relevance of intervention timing to early clearance and later repair remains to be clarified	Hopfner and Hornung, 2020; Decout *et al*., 2021; Sun *et al*., 2024
Chronic wounds/ tissue repair	Animal and biomaterial-oriented studies	Delayed inflammatory-to-reparative transition	May promote inflammation resolution and repair initiation	Local delivery, infection control and recurrence outcomes would benefit from further study	Wu *et al*., 2022; Zhen *et al*., 2024; Tang *et al*., 2025
Cardiovascular inflammation/ fibrosis	Mechanistic inference and limited APS-related data	Inflammatory clearance and reparative remodeling are both needed	May restrain excessive inflammation and oxidative stress	Fibrosis risk and disease-stage specificity require further evaluation	Hopfner and Hornung, 2020; Decout *et al*., 2021; Paik *et al*., 2021; Sun *et al*., 2024 Wculek *et al*., 2022; Chen *et al*., 2023; Luo *et al*., 2022

Mechanistic assessment would be strengthened by using STING- or NLRP3-deficient macrophages, mitochondrial DNA release assays, ASC speck formation, caspase-1 cleavage, gasdermin D cleavage and rescue experiments (Paik *et al*., 2021; Decout *et al*., 2021; Sun *et al*., 2024).

Immunometabolism, oxidative stress and immune microenvironment remodeling

Macrophage functional transitions are coupled to metabolic rewiring. Inflammatory states usually rely on glycolysis, pentose phosphate pathway activation, tricarboxylic-acid-cycle interruption, succinate accumulation and HIF-1alpha-mediated cytokine transcription. Reparative states more often depend on oxidative phosphorylation, fatty acid oxidation, mitochondrial integrity and amino acid metabolism. Because APS have been reported to influence oxidative stress, gut microbiota, short-chain fatty acids and systemic metabolism, immunometabolic regulation is a plausible but understudied mechanism (Wculek *et al*., 2022; Chen *et al*., 2023).

In chronic metabolic disease, APS may reduce ROS, improve mitochondrial homeostasis and support macrophage-endothelial communication. In tumors, however, hypoxia, lactate accumulation and metabolic competition may drive immunosuppressive macrophage states.

Future studies could combine Seahorse extracellular flux analysis, isotope tracing, targeted metabolomics, lipidomics, mitochondrial membrane potential assays and single-cell/spatial omics to distinguish primary APS-driven metabolic remodeling from secondary cytokine or redox effects (Luo *et al*., 2022).

Therapeutic potential of APS in disease microenvironments

Tumor microenvironment

Tumor-associated macrophages are abundant in many solid tumors and frequently acquire immunosuppressive, pro-angiogenic and tissue-remodeling functions that promote immune escape, invasion, metastasis and therapy resistance. Preclinical studies suggest that APS-containing preparations may increase the M1-like/M2-like ratio, enhance dendritic-cell maturation, improve antigen presentation and promote T-cell-mediated antitumor responses. Nevertheless, APS should not be regarded as a simple M1 inducer. Tumor type, hypoxia, lactate accumulation, stromal composition, baseline TAM states and concomitant chemotherapy or immune checkpoint blockade may influence whether macrophage activation is tumor-suppressive or tumor-promoting (Duan and Luo, 2021; Xu *et al*., 2023; He *et al*., 2024; Zhang *et al*., 2025).

Diabetic vascular injury

Diabetic vascular injury is characterized by hyperglycemia, advanced glycation end products, oxidative stress, endothelial dysfunction and chronic low-grade inflammation. Preclinical findings suggest that APS may improve macrophage-endothelial communication through Nrf2/HO-1-associated antioxidant and reparative responses. Because prolonged repair-associated programs could contribute to fibrosis or pathological remodeling, long-term studies would need to evaluate endothelial nitric oxide signaling, vascular permeability, oxidative stress, fibrotic markers and organ function (Liu *et al*., 2024; Sha *et al*., 2023; Luo *et al*., 2022).

Acute kidney injury

In acute kidney injury, damage-associated molecular patterns, mitochondrial stress and cytosolic DNA sensing can drive M1-like inflammatory amplification. In a preclinical rhabdomyolysis-induced acute kidney injury model, APS attenuated cGAS-STING signaling and inflammatory macrophage activation. The therapeutic window may be important because excessive early suppression could impair debris clearance, whereas delayed or balanced modulation may facilitate resolution and repair (Hopfner and Hornung, 2020; Decout *et al*., 2021; Sun *et al*., 2024).

Chronic wounds and tissue repair

Normal wound healing requires a timed transition from inflammatory macrophage functions to reparative programs that support efferocytosis, angiogenesis, extracellular matrix remodeling and re-epithelialization. Preclinical and biomaterial-oriented studies suggest that APS-containing wound platforms warrant further evaluation because local delivery could reduce systemic exposure and provide controlled macrophage-directed immunomodulation. Reporting APS structural characterization, release kinetics, contamination control, infection outcomes, angiogenesis, collagen organization and recurrence would facilitate comparison across studies (Wu *et al*., 2022; Zhen *et al*., 2024; Tang *et al*., 2025).

Disease-context evidence and therapeutic implications

Cardiovascular disease illustrates the need for balanced macrophage regulation. In myocardial injury, early inflammatory macrophages clear necrotic cardiomyocytes, while later reparative macrophages support angiogenesis and scar formation. In atherosclerosis, macrophages contribute to lipid uptake, foam-cell formation, defective efferocytosis and plaque remodeling. The translational steps needed to move from such disease-specific preclinical observations toward standardized clinical evaluation are outlined in figure 3. Limited preclinical evidence suggests that APS may restrain excessive inflammation and oxidative stress, whereas the potential for persistent reparative activation to favor fibrosis warrants evaluation in long-term disease models (Shaito *et al*., 2022; Liu *et al*., 2024; Yan *et al*., 2024).

Translational challenges and evidence limitations

Several translational challenges currently limit assessment of APS as clinically viable immunomodulatory candidates. First, reproducible development would require documented botanical source, extraction method, purification procedure, molecular-weight distribution, monosaccharide composition, glycosidic linkage profile, branching degree, purity and contamination testing. Without consistent reporting of these quality attributes, reproducibility across laboratories and prospects for clinical translation remain difficult to assess (Wang *et al*., 2025; Li *et al*., 2022; Zheng *et al*., 2020).

Pharmacokinetic and pharmacodynamic characterization is also limited. Because APS are macromolecular polysaccharides, their absorption, degradation, microbial fermentation, tissue distribution, immune-cell exposure and elimination may differ markedly from those of small molecules. Further studies would benefit from evaluating oral bioavailability, microbiota-dependent metabolism, local versus systemic exposure, dose-response relationships, treatment duration and tissue-specific macrophage engagement (Luo *et al*., 2022; Liang *et al*., 2024; Liu *et al*., 2024).

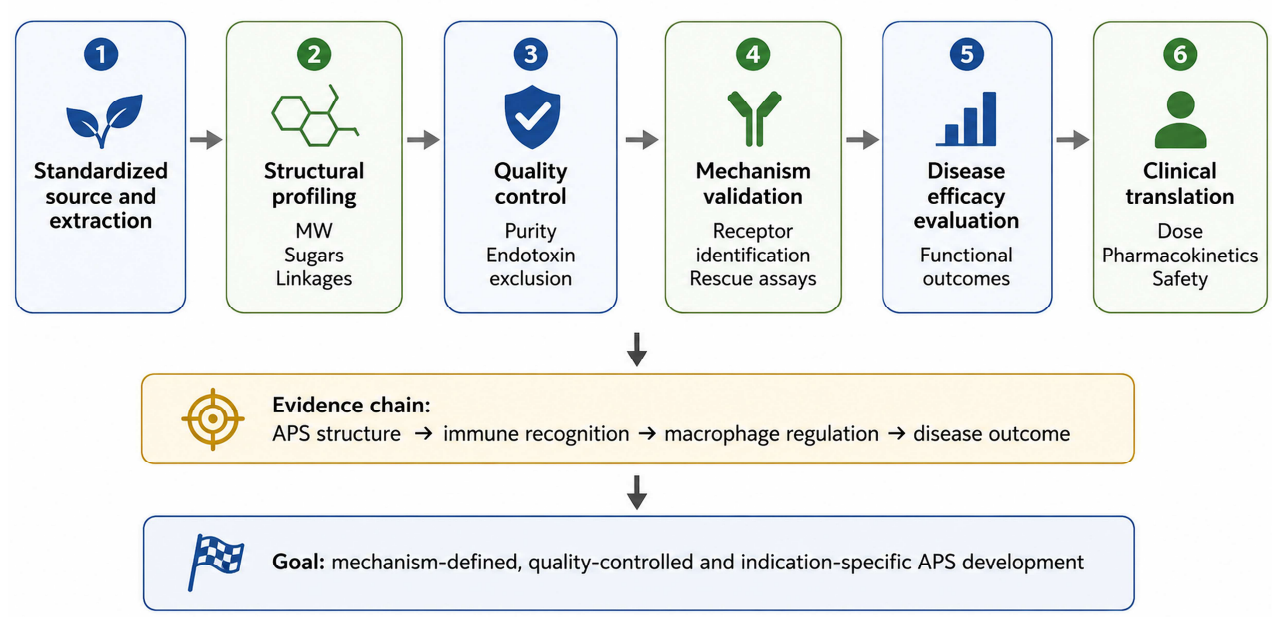

Fig. 3: Translational research roadmap for APS targeting macrophages. The figure summarizes source standardization, structural profiling, quality control, mechanism validation, disease efficacy evaluation and clinical translation. High-resolution TIFF files are provided separately.

Safety and toxicity require more systematic assessment. Although APS generally show favorable safety profiles in preclinical studies, immunomodulators may produce context-dependent risks, including excessive inflammatory activation, impaired host defense, interactions with cancer immunotherapy or chemotherapy and promotion of fibrosis in some reparative settings. Repeated-dose toxicity, immunotoxicity, reproductive toxicity and interaction studies would help define these risks (Li *et al*., 2022; Zhang *et al*., 2025; Wang *et al*., 2025).

Regulatory development would also depend on clear product definition. Crude extracts, purified fractions, modified APS and APS-loaded biomaterials may require different regulatory pathways. Clinical evaluation would be strengthened by using well-characterized preparations, predefined indications, standardized endpoints, biomarker-based macrophage readouts and appropriate safety monitoring.

Limitations of the current APS evidence base

Current APS research has several limitations. Much of the evidence is derived from RAW264.7 cells, murine macrophages or rodent disease models, which do not fully represent the heterogeneity of human tissue-resident macrophages. Many studies use limited marker panels, usually iNOS, CD86, Arg-1 or CD206, without functional assays of phagocytosis, antigen presentation, efferocytosis, migration, metabolic remodeling or tissue localization. Therefore, some conclusions about polarization should be regarded as phenotypic associations rather than validated macrophage-state transitions (Park *et al*., 2022; Chen *et al*., 2023; Yan *et al*., 2024).

Reproducibility is further limited by incomplete structural characterization, batch variability, possible contamination and non-standardized dosing. Some proposed pathways are inferred from expression changes without receptor blockade, genetic deletion or rescue assays. Clinical evidence remains sparse and current pharmacokinetic, pharmacodynamic, toxicity and regulatory data do not support definitive therapeutic claims.

Future directions and translational priorities

Future research could progress from descriptive polarization markers toward causal, quality-controlled and disease-stage-specific investigation. Glycomics-based receptor mapping, high-purity APS fractionation, surface-binding assays and macrophage-specific receptor knockout models would help define how structural motifs influence receptor recognition. Integrating single-cell RNA sequencing, spatial transcriptomics, proteomics and metabolomics could further distinguish mixed macrophage states within complex tissues.

APS may warrant evaluation as adjuvants in cancer immunotherapy, particularly where reprogramming of TAMs could improve antigen presentation and T-cell responses. APS-containing wound biomaterials, including hydrogels, microneedles, nanofibers and dressings, could also provide local macrophage-directed

immunoregulation. These applications require testing with standardized APS preparations, release-kinetic assays, tissue-specific immune readouts and long-term safety monitoring.

A coherent evidence chain could link APS structural characterization and quality control with receptor identification, pathway-specific causal validation, disease-relevant functional outcomes, pharmacokinetic and safety evaluation and eventual clinical confirmation. Establishing such a chain would help determine whether specific APS preparations can progress from empirical immunomodulators to quality-controlled, indication-specific therapeutic candidates.

CONCLUSIONS

Based predominantly on preclinical evidence, APS-mediated regulation of macrophages is better interpreted as context-dependent modulation via multiple receptors and pathways rather than as a simple induction of M1 or M2 polarization. Available studies suggest that APS may promote antitumor inflammatory and antigen-presenting macrophage programs in tumors while attenuating excessive inflammatory activation and supporting reparative programs in diabetic vascular injury, acute kidney injury and chronic wounds.

Translation of APS will depend on improved definition of structure-activity relationships, product quality, receptor recognition, causal pathway validation, dose standardization, pharmacokinetic behavior, safety and regulatory requirements. With rigorous quality control and modern immunological methods, well-characterized APS preparations could be evaluated as mechanism-informed, indication-oriented macrophage-targeted immunomodulators. However, robust clinical validation is still required before efficacy or therapeutic utility can be established.

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Author's contributions
Yao Tang: Conceived the review, designed the literature search strategy, collected and analyzed the literature, prepared the tables and figures, wrote and revised the manuscript and approved the final version for submission.

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No new datasets were generated or analyzed because this article is a narrative review.

Ethical approval
Not applicable. This article is a narrative review based exclusively on previously published literature and did not involve human participants, animals, or the collection of new experimental data.

Conflict of interest
The author declares no conflict of interest.

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