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Immune inflammation revisited: cellular circuits, molecular switches, and translational opportunities

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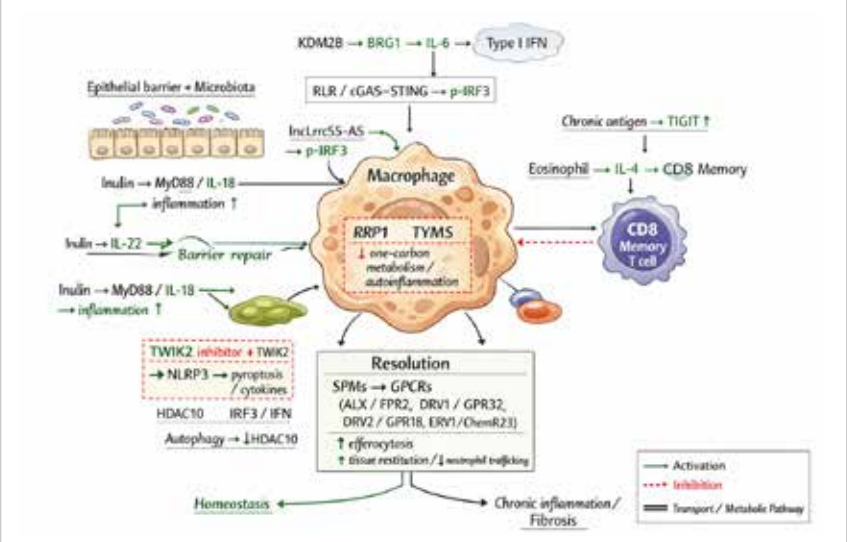

Integrated immune-inflammatory circuits centered on macrophages linking barrier cues, innate sensing, adaptive memory, and resolution.

The interaction between the epithelial barrier and the microbiome shapes the tone of the inflammatory response by enhancing MyD88/IL-18-driven inflammation while supporting IL-22-mediated barrier repair. Macrophages integrate nucleic-acid sensing pathways (RLR/cGAS-STING→p-IRF3) and epigenetic control (KDM2B→BRG1→IL-6)

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to modulate type I interferon programs, with additional regulation by lncLrrc55-AS. Inflammatory amplification is further coupled to metabolic and death pathways, including RRP1/TYMS-associated one-carbon metabolism/autoinflammation, TWIK2-NLRP3-pyroptosis, and an autophagy-HDAC10-IRF3/IFN regulatory loop. Adaptive immune outputs are shaped by chronic antigen–associated TIGIT signaling and eosinophil-derived IL-4, which supports CD8 memory T cell formation. Resolution is driven by specialized pro-resolving mediators (SPMs) acting through GPCRs (ALX/FPR2, DRV1/GPR32, DRV2/GPR18, ERV1/ChemR23) to enhance efferocytosis, promote tissue restitution, and limit neutrophil trafficking, thereby tipping the balance toward homeostasis rather than chronic inflammation/fibrosis. Green arrows denote activation, red dashed lines denote inhibition, and black lines indicate transport/metabolic pathways.

Abstract

Inflammation is the most visible operational mode of immunity in tissues, translating danger sensing into coordinated vascular, cellular, and metabolic responses that restrict injury and initiate repair. However, the same pathways that protect acutely can become pathogenic when amplification is mis-tuned, tolerance checkpoints fail, or resolution programs stall. This Review synthesizes a circuit-level view of immune inflammation, integrating tissue-encoded cellular networks with modular molecular switches that govern initiation, escalation, and termination. First, it outlines how barrier tissues and tissue-resident immune populations establish local inflammatory set points and explain context-dependent outcomes, exemplified by microbiota-diet interactions that can either support interleukin-22-dependent homeostasis or exacerbate colitis. Then, by describing myeloid circuits as the primary link between perception and systemic consequences, highlighting emerging control layers in RNA metabolism, chromatin remodeling, regulated cell death, and efferocytosis that shape persistence versus regression. Next, it elucidates specific and memory lymphocyte programs that can also lead to tissue damage through tolerance disruption, checkpoint remodeling, or an immunosuppressive microenvironment. Finally, the focus is on the active phase of inflammation resolution, regulated by phased leukocyte degradation, apoptotic cell clearance, and tissue repair, including specific pro-resolution mediators acting as lipid instructions. These mediators complement anti-inflammatory blockade therapies. Across infection, immunometabolic disease, neuroinflammation, fibrosis, and cancer, a unifying principle emerges: durable therapy requires combining selective suppression of maladaptive amplification with restoration of resolution capacity and preservation of protective immune competence.

KEYWORDS

Inflammatory response, Innate immunity, Adaptive immunity, Cytokines, Immunometabolism

Introduction

Inflammation is the most visible face of immunity in tissues. Classical descriptions—rubor, calor, tumor, and dolor—capture a conserved host program that increases vascular permeability, recruits leukocytes, restricts pathogen spread, and initiates repair(1). Modern immunology has expanded this view from a descriptive syndrome to a systems-level process governed by cell-cell communication, signal integration, metabolic adaptation, and regulated cell death. Within this framework, immunity can be defined as the host's integrated capacity to detect danger, deploy effectors, restore homeostasis, and retain protective experience(2, 3). It is commonly divided into innate immunity and adaptive

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immunity. Innate immunity provides rapid, pattern-based recognition through germline-encoded receptors, enabling immediate effector functions in barrier tissues and the myeloid compartment. Adaptive immunity confers antigen-specific recognition through clonally distributed receptors, yielding tailored effector responses with durable memory(4, 5). Inflammation represents a principal operational mode through which both arms of immunity act within tissues. It can be categorized as acute inflammation, typically self-limited and resolution-oriented, and chronic inflammation, marked by persistence, remodeling, and repeated cycles of injury and repair. Acute inflammation is initiated by pathogen-associated or damage-associated cues, amplified by cytokine and chemokine cascades, then actively terminated through suppression of recruitment, clearance of dying cells, and tissue restoration(6). Chronic inflammation arises when initiating triggers persist, when checkpoints fail to restrain amplification, or when resolution programs prove insufficient(7). Importantly, these categories reflect kinetics and tissue outcomes rather than a single molecular signature. The same pathway can be protective early yet pathogenic when sustained, which creates both conceptual and therapeutic challenges.

Inflammation is essential because immune protection requires controlled tissue disruption. Pathogen clearance depends on rapid sensing, coordinated leukocyte recruitment, and the deployment of antimicrobial mediators(8). Sterile threats—ischemia, trauma, metabolic stress—also demand inflammatory responses that remove damaged material and initiate repair. Problems arise when this protective logic is mis-tuned. Inflammatory dysregulation appears as a shared pathogenic substrate across heterogeneous clinical settings. In human spinal cord injury, acute inflammation transitions into a non-resolving state associated with oxidative injury, highlighting how persistent myeloid-driven programs can sustain tissue damage after the inciting even(9). In chronic HBV antigen contexts, perturbing tolerance control precipitates non-resolving inflammation and hepatocellular carcinoma, illustrating how adaptive immunity can become tissue-destructive when restraint mechanisms are disrupted (10). Immunometabolic amplification offers another route to chronicity: dyslipidemia-associated pathways elevate innate inflammatory tone and accelerate atherosclerotic pathology, reinforcing the concept that metabolic state rewires immune thresholds rather than merely reflecting disease burden(11). Barrier-microbiota circuits further demonstrate bidirectionality. Fiber-mediated support of IL-22-dependent colonic health protects against diet-induced metabolic dysfunction, whereas specific dietary substrates can exacerbate colitis through microbiota-dependent signaling, underscoring that “anti-inflammatory” inputs are context dependent(12). Viral disease provides an additional cautionary lesson: severe COVID-19 can couple inflammatory pathology with adaptive immune suppression, indicating that hyperinflammation may coexist with immunoparalysis, thereby complicating treatment selection(13). Collectively, these observations argue against a one-dimensional model of inflammation. Effective interpretation requires mapping inflammatory outputs onto immune state transitions, tissue context, and resolution capacity.

This review constructs immunity and inflammation as an integrative, phased program driven by tissue-encoded cellular circuits and modular molecular switches. It emphasizes the balance between initiation and expansion versus termination, regression, and repair, with failure to achieve these transitions leading to chronic inflammation, fibrosis, immunosuppression, or maladaptive immunity. By aligning mechanism with disease context, we aim to clarify actionable bottlenecks and to guide precision therapies that suppress harmful amplification, restore resolution, and preserve protective immune competence.

Cellular circuits of immune inflammation

Barrier and tissue-resident immunity

Barrier tissues do more than block pathogens; they define local inflammatory set points by controlling microbial proximity, tonic PRR stimulation, metabolite availability, and tissue oxygenation. Fermentable fiber provides a vivid example of context-dependent regulation. In a diet-induced obesity setting, fermentable inulin supported

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microbiota-dependent restoration of interleukin-22 (IL-22)-mediated colonic health, reducing metabolic syndrome features(12). Mechanistically, IL-22 is positioned as a barrier-repair cytokine that constrains microbial encroachment while shaping downstream systemic inflammation. Yet, helps in one context can harm in another. Dietary inulin aggravated colitis through microbiota modulation and MyD88/IL-18 signaling(14). This contrast cautions against "one-size-fits-all" barrier interventions: the same nutrient can promote homeostasis or exacerbate inflammation depending on baseline microbial ecology, epithelial integrity, and inflammasome tone.

Tissue-resident immune cells further encode local logic. Innate lymphoid cells (ILCs) can act as a trophic support system for regulatory networks. In the intestine, ILCs promoted regulatory T cell (Treg) biology through interleukin-2 (IL-2), linking innate tissue surveillance to adaptive suppression(15). This positions IL-2 not only as a systemic T cell growth factor but also as a locally provisioned metabolite-like signal that sustains immune restraint where antigen exposure is constant. A complementary theme is that "resident" does not mean static. Neonatal inflammation illustrates how developmental timing can install transient regulatory circuits. A neuropilin-1-high monocyte subset appeared as a protective population in early life, restraining inflammatory disorders in neonates and shaping outcomes such as necrotizing enterocolitis susceptibility(16). Therapeutically, this points toward age- and niche-specific cellular targets rather than uniform suppression.

The myeloid axis

Myeloid cells—monocytes, macrophages, dendritic cells, neutrophils—serve as the central "wiring harness" between sensing and systemic consequence. They produce cytokines, present antigen, shape coagulation and vascular responses, and decide whether inflammation resolves or becomes chronic. Atherosclerosis exemplifies myeloid amplification coupled to metabolic perturbation. Triggering receptor expressed on myeloid cells-1 (TREM-1) acted as an amplifier linking dyslipidemia to inflammation and lipid deposition, contributing to diet-induced monocytosis and pro-inflammatory programs(17). This is a useful archetype: metabolic inputs (lipids) do not simply "cause inflammation," they engage specific receptors that amplify myeloid output.

Recent work also elevates RNA biology as a myeloid control layer. The RNA-binding protein RRP1 suppressed autoinflammation by braking macrophage one-carbon metabolism; mechanistically, it bound thymidylate synthetase transcripts to lower TYMS expression and rewire inflammatory macrophage metabolism(18). Rather than targeting downstream cytokines, this strategy points to an upstream "metabolic permissiveness" checkpoint. Resolution similarly depends on myeloid competence, especially efferocytosis—the clearance of apoptotic cells. Stress granule assembly in macrophages impaired efferocytosis and aggravated allergic rhinitis, highlighting that translational arrest programs (stress granules) can directly sabotage resolution(19). This finding is conceptually important: defects in resolution are not merely due to "too much inflammation," but can arise from cellular stress architectures that prevent cleanup. Myeloid-driven inflammation is frequently coupled to chromatin remodeling. KDM2B promoted IL-6 production and inflammatory responses through BRG1-mediated chromatin remodeling in macrophages and dendritic cells(20). This reinforces that cytokine signatures are not only signaling outputs; they are epigenetically stabilized states that can persist, relapse, or resist therapy.

The lymphoid axis

Adaptive immunity contributes specificity and memory, but it can also drive pathology when tolerance breaks or when chronic antigen exposure induces exhaustion. CD8 T cell biology illustrates the duality. In a bacterial immunity context, eosinophils promoted CD8 T cell memory generation via eosinophil-derived IL-4, strengthening defense against Listeria monocytogenes(21). This reframes eosinophils: beyond type 2 effector roles, they can function as immunological "adjuvant cells" that sculpt cytotoxic memory. Conversely, persistent antigen exposure can lock CD8 T cells into dysfunctional tolerance-like states. In an HBV surface antigen transgenic model, age-associated expression of checkpoint receptor TIGIT increased on hepatic CD8 T cells, and disrupting immunotolerance dynamics drove nonresolving inflammation and hepatocellular carcinoma under specific immunological perturbations(22). This study underscores that "breaking tolerance" is not uniformly beneficial; it can accelerate tissue injury and carcinogenesis if resolution and tissue repair fail.

In cancer, lymphoid effectors face an immunosuppressive

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microenvironment. One translational strategy combined local innate activation with adoptive cell therapy: inhalable nanovesicles delivering a STING agonist enhanced CAR-T activity against lung solid tumors while reducing immunosuppressive populations such as myeloid-derived suppressor cells(23). The logic here is circuit-based: CAR-T efficacy depends on restoring a permissive innate cytokine milieu and reducing suppressive myeloid feedback. Adaptive immunity is both weapon and liability. Therapies that boost cytotoxicity must simultaneously secure resolution and prevent checkpoint-driven pathology.

Immune-stroma-neuroendocrine crosstalk

Inflammation changes tissue mechanics and vascular permeability, which in turn reshape immune cell trafficking and survival. Fibroblasts are not passive responders; they can enforce fibrotic "memory." An endoplasmic reticulum-anchored CRTH2 isoform antagonized collagen biosynthesis and organ fibrosis via binding LARP6; CRTH2 deficiency increased collagen production and worsened injury-induced fibrosis in mice(24). This provides a concrete molecular entry point for stromal control of chronic inflammation outcomes. Neuroimmune coupling is frequently invoked but less often mechanistically pinned. An unusually direct example shows that inflammation-induced splenic erythroblast-like Ter-cells inhibited acute lung injury progression via artemin, a neurotrophic factor(25). This suggests endocrine/neurotrophic mediators can serve as "remote controls" for inflammatory programs, operating outside conventional leukocyte lineages.

Molecular switches for the initiation and amplification of inflammation

Pattern recognition and alarm systems

Pattern recognition receptor (PRR) pathways translate microbial or damage cues into interferons and inflammatory cytokines. Several studies emphasize that host nucleic acids can become immunostimulatory substrates during infection or stress. RIG-I-like receptor (RLR) sensing extended beyond viral RNA to include host RNAs that facilitate cell-intrinsic immune responses against Kaposi's sarcoma-associated herpesvirus(26). This blurs the self/non-self boundary: antiviral immunity may depend on detecting altered self-RNA landscapes generated by infection.

Long noncoding RNAs also participate as inducible scaffolds. The interferon-inducible cytoplasmic lncRNA lncLrrc55-AS strengthened IRF3 phosphorylation to promote antiviral innate responses(27). Mechanistically, this implies that innate immunity is not only receptor–adapter wiring; it is supported by conditionally expressed RNA effectors that reinforce signaling throughput. DNA sensing via cGAS-STING further connects inflammation to cell cycle and cell death. A Cell study showed cGAS engagement during mitosis can promote mitotic cell death under specific conditions, illustrating how nuclear envelope dynamics can expose DNA to cytosolic sensors(28). While not a canonical inflammatory disease model, it highlights a general vulnerability: barrier breaches between compartments can turn "self DNA" into inflammatory fuel. Broader PRR involvement in autoimmune diseases is supported by a recent synthesis of Toll-like receptor roles in autoimmunity(29). The translational implication is not simply "TLRs are bad," but that receptor-specific and compartment-specific targeting may be needed to preserve antimicrobial defense.

Core transcription and signaling hubs

Inflammation is often described as cytokine-driven, yet cytokines are outputs of signal integration at hubs. Several studies underscore that hub modulation can be immunologically selective. Autophagy intersects antiviral signaling through IRF3. HDAC10 acted as an inhibitor of IRF3-mediated type I interferon responses; innate stimuli reduced HDAC10 abundance via autophagy, and PBMCs from systemic lupus erythematosus patients showed altered HDAC10 levels, suggesting disease relevance(30). This

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identifies a therapeutic axis—autophagy-HDAC10-IRF3—that could enhance antiviral defense while avoiding blanket interferon activation.

Negative regulation can also be encoded in atypical autophagy-like proteins. Beclin 2 negatively regulated innate inflammatory signaling and can protect against virus-driven pathologies, emphasizing that autophagy family members operate as signaling regulators, not only degradative machinery(31). The key point is architectural: controlling adaptor availability or trafficking may restrain cytokine cascades without shutting off recognition. Epigenetic remodeling, as noted earlier, sets the amplitude and persistence of cytokine programs. KDM2B-dependent chromatin remodeling promoted IL-6-dominated inflammatory output(20). This suggests that "anti-cytokine therapies" treat symptoms of a chromatin-stabilized state; upstream chromatin interventions may re-set inflammatory memory, albeit with safety challenges.

Inflammasomes and regulated cell death

Inflammasome activation and pyroptosis represent a decisive amplification point, converting sensing into cytokine release and barrier disruption. Non-canonical pyroptosis via caspase-11 was regulated by an ERK/Smurf1 axis: Smurf1 promoted caspase-11 ubiquitination, and macrophage-specific Smurf1 deficiency exacerbated sepsis mortality linked to hyperactivation of non-canonical inflammasome pathways(32). This is clinically relevant because it identifies ubiquitination control as a druggable layer upstream of terminal pore formation.

Ion channels also gate inflammasome activation. A TWIK2 channel inhibitor bound within the selectivity filter and protected against LPS-induced experimental endotoxemia in vivo while suppressing NLRP3 inflammasome activation in macrophages(33). Such data support a strategy of "biophysical gating" rather than direct cytokine blockade. Extracellular autophagy-related proteins can act as inflammatory mediators. Extracellular SQSTM1 was characterized as an inflammatory mediator, offering a bridge between intracellular stress responses and extracellular immune activation(34). This expands the catalog of DAMP-like signals beyond classical alarmins. Inflammasome biology is attractive therapeutically, yet systemic suppression risks impairing pathogen defense. Selective targeting of upstream regulators (ubiquitination, channel gating) may offer a better therapeutic index than blanket caspase inhibition.

Complement and coagulation-inflammation coupling

While research on direct complement mechanisms is limited, infection models and transcriptomic dynamics point to coordinated inflammatory programs that plausibly include complement and clotting cascades. Time-course transcriptional analysis after methicillin-resistant S. aureus lung challenge highlighted staged inflammatory initiation and balance, consistent with multi-system engagement beyond cytokines alone(35). COVID-19 provides a clinical anchor for immunothrombosis as an inflammation-vascular coupling process; curated evidence of adaptive suppression and cytokine dysregulation aligns with broader literature in which endothelial dysfunction, myeloid activation, and platelet-coagulation interactions create microthrombotic pathology(36). In practice, anti-inflammatory therapy in vascular-inflammatory syndromes often requires pairing immune modulation with antithrombotic strategies, guided by biomarker signatures.

Cytokine networks

Cytokines remain the most clinically validated inflammatory targets, yet mechanistic studies increasingly emphasize cytokine context rather than single-mediator dominance. IL-6 emerges repeatedly as a hub cytokine shaped by epigenetic machinery and likely reinforced by metabolic state(20). In cardiovascular inflammation, innate immune targeting has been proposed for acute cardioprotection, with the caveat that inflammation is necessary for debris clearance and repair, creating a narrow therapeutic window(37). Type I interferons occupy a similarly dual role. The HDAC10-autophagy-IRF3 axis and interferon-inducible lncRNA scaffolding illustrate how interferon programs can be boosted or restrained through non-cytokine targets, potentially improving safety relative to exogenous interferon therapy(27, 30).

Antigen presentation and co-stimulation/co-inhibition

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Inflammation shapes antigen presentation quality and T cell fate. A high-resolution view of dendritic cell lineage wiring shows DC2 lineages arise through a transcription factor relay involving TCF4 and KLF4(38). Such lineage architecture affects which antigens are presented, which co-stimulatory ligands dominate, and whether tolerance or effector priming ensues. Checkpoint pathways can protect tissues at the cost of antimicrobial or antitumor potency. TIGIT biology in HBV antigen tolerance models demonstrates that perturbing checkpoint balance can trigger nonresolving inflammation and cancer-promoting damage under specific conditions(22). In solid tumors, restoring effector function may require coordinated remodeling of suppressive circuits, as exemplified by local STING agonism to potentiate CAR-T activity(23).

Resolution and Repair

Stages of resolution

Resolution requires a sequence: remove the inciting stimulus, halt leukocyte recruitment, clear apoptotic cells, then rebuild tissue architecture. Failure at any step produces persistent DAMP generation, chronic cytokine production, and stromal remodeling. Efferocytosis sits at the center of this program. Stress granule assembly in macrophages impaired efferocytosis and worsened allergic inflammation, providing a direct mechanistic explanation for resolution failure(19). This suggests “resolution therapy” may need to restore macrophage translational capacity and phagocytic machinery, not merely suppress cytokines. In neuroinflammatory injury, human spinal cord injury exhibited acute and non-resolving inflammation associated with oxidative injury, illustrating how unresolved inflammation can become a chronic driver of tissue pathology rather than a transient response(9).

Specialized pro-resolving mediators (SPMs)

Resolution is not a passive decay of inflammatory signals; it is an actively orchestrated phase that requires termination of leukocyte recruitment, efficient clearance of dying cells, and rebuilding of tissue function. A central biochemical layer of this program is mediated by SPMs, a class of enzymatically generated lipid mediators derived from essential fatty acids. SPMs comprise four major families—lipoxins, E-series resolvins, D-series resolvins, protectins, and maresins—and function as “immunoresolvents” that promote catabasis while preserving host defense. Unlike conventional anti-inflammatory strategies that primarily blunt cytokine outputs, SPMs act through pro-resolving instructions: they can reduce further neutrophil trafficking, enhance macrophage efferocytosis, accelerate microbial clearance in certain settings, and support tissue restitution(39). These effects are mediated largely through G protein-coupled receptors (GPCRs), including examples ALX/FPR2, DRV1/GPR32, DRV2/GPR18, and ERV1/ChemR23(40). Importantly, receptor usage is ligand-and context-dependent. For instance, resolvin D1 (RvD1) engages DRV1/GPR32 and can also signal via ALX/FPR2, providing a molecular basis for cell-type-specific resolution circuits. In human traumatic spinal cord injury, acute inflammation transitions into a non-resolving state characterized by sustained pro-inflammatory microglial activation in the lesion rim and persistent oxidative axon–dendritic injury that remains elevated for months to years, supporting ongoing neurotoxicity beyond the initial insult(9).

From failed resolution to chronic inflammation

Chronic inflammation is often framed as “persistent cytokines.” A more mechanistic framing is persistent substrates (microbial dysbiosis, damaged ECM, altered self-RNAs), persistent state locks (chromatin remodeling, metabolic rewiring), and persistent resolution defects (impaired efferocytosis). The RRP1-one-carbon metabolism brake and stress granule-efferocytosis block provide concrete molecular handles for such state locks(18, 19).

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Translational Opportunities

Anti-cytokine or receptor blockade

Chromatin-driven IL-6 production suggests upstream transcriptional control as an alternative to downstream cytokine neutralization. Clinical inflammatory syndromes treated with IVIG illustrate that pleiotropic immunomodulators can succeed when pathology is multi-node and redundant(41). The translational challenge is identifying when a cytokine is causal versus compensatory—an issue sharpened by evidence of late-stage immunosuppression in severe COVID-19(42).

Signaling pathway inhibitors and host-directed therapy

Host-directed therapy can restrain inflammation while improving antimicrobial defense. Targeting the MEK1/2 pathway with ATR-002 was evaluated as a strategy to combat Staphylococcus aureus infection and inflammation in cystic fibrosis, including effects on TLR2-induced pro-inflammatory cytokine secretion in macrophages(43). This illustrates a useful paradigm: target host signaling nodes that pathogens exploit, while avoiding direct antimicrobial resistance pressure. In antiviral immunity, modulating autophagy-linked regulators can tune interferon programs. HDAC10 degradation by autophagy promoted IRF3-mediated antiviral responses and linked to systemic lupus erythematosus PBMC signatures(30). Such approaches may provide conditional enhancement—engaged only during innate stimulation.

Inflammasome and cell-death targeting

Non-canonical pyroptosis control via ERK/Smurf1-caspase-11 ubiquitination offers a druggable pathway-level lever(32). Membrane-proximal control via TWIK2 inhibition provides a complementary modality(44). Ferroptosis control in Kupffer cells suggests that organ-specific macrophage death programs can be therapeutically modulated to prevent systemic deterioration in sepsis(45).

Cellular therapies and immune modulation

In solid tumors, inhalable STING-agonist nanovesicles were reported to enhance CAR-T activity in the lung, representing a “local innate activation and adoptive cell” synergy that attempts to overcome stromal and innate suppression barriers(46). Vaccine approaches in cancer similarly aim to expand antigenic breadth and improve trafficking(47). Poly(I:C)-based HER2-targeted therapy illustrates that PRR agonism can modulate the tumor immune microenvironment while exerting anti-tumor effects(48).

Microbiome and barrier repair

Microbiome interventions require stratification. Fermentable fiber improved metabolic inflammation via IL-22-mediated barrier effects, yet inulin worsened colitis through MyD88/IL-18 pathways(12, 14). Translation therefore requires biomarkers of microbiota composition, inflammasome tone, and epithelial injury before recommending broad interventions. Microbiome effects extend into cancer immune ecosystems. Intratumor bacteria correlated with cytotoxic CD8 T cell infiltration and survival in cutaneous melanoma, supporting the notion that microbial niches can shape local immune setpoints even within tumors(49).

Precision stratification and biomarkers

System-level profiling is necessary to avoid over-suppression. Severe COVID-19 patients displayed profound adaptive immune suppression even after viral negativity, providing a cautionary template for post-infectious immunoparalysis and recovery monitoring(36). Obesity further associated with aberrant innate immune responses in hospitalized aged COVID-19 patients, underscoring metabolic context as a stratifier(50). Immunometabolic markers may be particularly actionable. NAD boosting (nicotinamide riboside) suppressed inflammatory activation of PBMCs in heart failure, linking systemic metabolism to immune tone(51). Such markers could guide “metabolic immunotherapy” adjuncts where conventional immunosuppression is risky.

Combination therapy strategy

IExisting research supports a three-step combined logic: inhibiting amplification, restoring regression, and correcting

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immune dysfunction. First, suppress harmful amplification at hubs such as MEK1/2, NLRP3, or TLR4-NF-κB when those programs dominate pathology(33, 43, 52). Second, restore resolution when efferocytosis or repair is impaired, a requirement emphasized by stress-granule-mediated efferocytosis blockade and by nonresolving inflammation states in spinal cord injury and hepatitis B-driven carcinogenesis(19, 22). Third, correct immune dysfunction by reinforcing protective memory through vaccines or by reprogramming tumor microenvironments to enable effective T cell function(23, 53). Supplementary work on SPM biology provides a mechanistic rationale for adding "resolution agonists" to anti-inflammatory regimens, while neuromodulation of the inflammatory reflex offers a circuit-level complement in selected chronic inflammatory diseases.

Conclusion

In summary, three mechanistic insights can be drawn from existing research on immunity and inflammation: First, immune-inflammatory responses are best understood as cellular circuits, not isolated mediators. Barrier tissues and resident immune cells define inflammatory thresholds and long-term bias through microbial and metabolic conditioning, explaining why identical triggers produce divergent outcomes across individuals. Second, myeloid programs sit at the junction of sensing, metabolism, and cell death. They can protect through antimicrobial pyroptosis and developmental immunosuppression, yet they can also drive lethal amplification through inflammasomes and ferroptosis. Third, chronic disease frequently reflects failed resolution—a state where inflammation persists because clearance and repair mechanisms are impaired, as concretely demonstrated by efferocytosis blockade and by nonresolving inflammation in human injury and tolerance breakdown.

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