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Inflammasome-associated pyroptosis and tumor angiogenesis in prostate cancer

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ABSTRACT

Tumor angiogenesis in prostate cancer is increasingly recognized as a dynamic process shaped by inflammatory signaling, endothelial adaptation, and microenvironmental stress. However, the mechanistic contribution of inflammasome-associated pyroptosis to vascular remodeling remains insufficiently integrated, particularly in relation to functional vascular endpoints such as perfusion, permeability, and therapeutic delivery. This review critically evaluates current evidence linking inflammasome activation and pyroptotic signaling to angiogenic remodeling within prostate tumor microenvironments. Current mechanistic and translational studies addressing inflammasome signaling, gasdermin-associated membrane permeabilization, endothelial activation, cytokine amplification, and vascular remodeling were synthesized with emphasis on spatial heterogeneity, hypoxia-associated stress, and methodological limitations. Available evidence suggests that inflammasome-associated pathways may influence angiogenic remodeling through interleukin-1-mediated endothelial activation, myeloid-cell inflammatory amplification, extracellular signaling, and context-dependent pyroptotic responses. Emerging findings further indicate that vascular consequences vary according to metabolic stress, compartment-specific signaling, and local inflammatory states. However, interpretation remains limited by reliance on static tissue measurements, bulk inflammatory analyses, and indirect vascular readouts that insufficiently distinguish inflammasome priming from terminal pyroptotic execution. Inflammasome-associated pyroptotic signaling may contribute to vascular remodeling in prostate cancer under defined biological conditions, although substantial mechanistic and translational uncertainties remain. Improved integration of spatial inflammatory profiling and functional vascular assessment may support more precise therapeutic targeting and clinically relevant vascular interpretation in heterogeneous prostate tumor microenvironments.

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Introduction

Angiogenic remodeling is an ongoing, adaptive process in prostate cancer that illustrates the co-evolution of tumor cells, stromal compartments (1), and vascular endothelium in response to varying oxygen tension, nutritional gradients, and therapy-induced selection pressures (2, 3). The resulting vasculature is not merely an increase in vessel number; rather, it represents a functional reorganization that may maintain perfusion in some areas while inducing leakiness, a propensity for microthrombosis (4), and variable flow in others, thereby influencing medication delivery and immune cell accessibility (5, 6). Inflammation in prostate tumors spans a spectrum from buffered to disruptive states (7). Buffered inflammatory signaling can help vessels adapt and partially normalize through coordinated cytokine cues, endothelial survival programs, and extracellular matrix (ECM) remodeling (8, 9). On the other hand, disruptive states emerge when the inflammatory load exceeds local regulatory capacity, leading to barrier breakdown, endothelial dysfunction, and necrotic or hemorrhagic microdomains that intensify hypoxia-driven angiogenic pressure (10, 11). Inflammasome activation represents one regulatory mechanism contributing to this transition (5). It links the perception of danger to the maturation of inflammatory mediators that rely on proteases and, in some cases, to the breakdown of membranes that cause pyroptosis (5, 12). These occurrences can affect angiogenesis through at least two non-exclusive mechanisms: indirect paracrine

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reprogramming of vascular cells by inflammatory mediators and lipid signals, and direct modification of tissue architecture and perfusion through pyroptosis-associated cellular loss, endothelial stress propagation, and the release of extracellular vesicles (EVs) or alarmins (12, 13). Nonetheless, the domain remains devoid of a functional integrative map that correlates distinct inflammasome and pyroptosis states with clinically significant vascular endpoints, including perfusion heterogeneity, permeability, endothelial activation phenotype, and therapy penetration, rather than predominantly depending on generic microvessel metrics (14, 15). Tumor sampling provides snapshots of spatially heterogeneous microenvironments. Conventional histological and transcriptomic analyses may obscure cell-type origin and fail to distinguish signaling activation from pyroptotic execution. Furthermore, vascular function is often inferred rather than directly measured, despite functional parameters being more closely associated with treatment response (13, 15). Consequently, mechanistic interpretations may be overgeneralized from restricted settings, and conceptual models may exceed the robustness of causal evidence (14, 15). This review synthesizes mechanisms linking inflammatory buffering to vascular outcomes. It further defines the transition from buffering to rupture, delineates quantifiable vascular endpoints that support mechanistic interpretation, and identifies testable connections aligned with translational relevance rather than conjecture (13, 16, 17).

Materials and Methods

Relevant studies addressing inflammasome signaling, pyroptosis, endothelial activation, angiogenic remodeling, and prostate tumor microenvironment biology were identified through systematic searches of PubMed, Scopus, and Web of Science databases. The literature search focused on experimental, mechanistic, translational, and review studies related to inflammasome-associated vascular remodeling in prostate cancer. Search terms included combinations of "inflammasome," "pyroptosis," "gasdermin," "IL-1," "angiogenesis," "endothelial activation," "vascular remodeling," "tumor microenvironment," and "prostate cancer." Additional relevant studies were identified through manual screening of the reference lists from selected articles and recently published reviews. Priority was given to studies with direct mechanistic or translational relevance to endothelial signaling, inflammatory amplification, vascular dysfunction, hypoxia-associated stress, spatial heterogeneity, and immune–vascular interactions within prostate tumor microenvironments. Both preclinical and clinically oriented studies were considered where relevant to angiogenic regulation and inflammasome-associated signaling pathways. Studies lacking clear relevance to prostate tumor angiogenesis or focused primarily on unrelated malignancies and non-inflammatory cell death mechanisms were excluded from detailed discussion. The collected literature was critically evaluated and integrated to provide a mechanistic and translational overview of inflammasome-associated pyroptotic signaling in prostate tumor angiogenesis, with particular emphasis on functional vascular endpoints, methodological limitations, and context-dependent inflammatory regulation.

Tumor angiogenesis in prostate cancer

Canonical angiogenic programs and endothelial activation states

Tumor angiogenesis in prostate cancer is best characterized as a regulated alteration in endothelial behavior (18), rather than a binary on–off mechanism. Endothelial-to-mesenchymal transition has been reported to induce endothelial phenotypic plasticity accompanied by loss of endothelial characteristics and increased permeability, with systematic evidence in solid tumors linking this process to tumor heterogeneity, metastatic potential, and context-dependent remodeling of the tumor microenvironment (19). Local perfusion demands, oxygen tension, and stromal signaling collectively determine whether vessels remain quiescent, become activated, or enter a state of continuous remodeling (2, 20); yet, the resultant vasculature often exhibits suboptimal maturation, characterized by inconsistent pericyte support and uneven flow (21), which may exacerbate localized hypoxia and promote further pro-angiogenic signaling (21). A crucial regulatory layer is the balance between pro-angiogenic signals and intrinsic inhibitory mechanisms that limit sprouting and maintain junctions (19), as well as microenvironmental checkpoints that modulate endothelial reactivity through extracellular matrix dynamics and inflammatory mediators (22). Integrative mapping is still limited in practice because "activation states" of endothelial cells are often guessed from static marker panels or bulk tissue measurements (22) that often fail to capture spatial gradients, transient phenotypes, or therapy-associated state transitions (23); even high-resolution profiling can misinterpret state labels when sampling is sparse or when dissociation biases affect cell recovery (24). The interpretative objective is to characterize endothelial activation as a limited, context-sensitive outcome of conflicting regulatory influences (24), thereby establishing a cautious foundation for subsequent sections that integrate inflammatory cell death signaling with vascular outcomes (20). As shown in Figure 1, converging DAMP signals and ionic perturbations position tumor-associated macrophages for NF-κB–dependent priming followed by NLRP3 assembly, caspase-1 activation, and gasdermin D–linked cytokine release, with several links presented as context-dependent rather than resolved.

Hypoxia-driven signaling and metabolic constraints on neovascularization

Hypoxia is a recurring microenvironmental characteristic of prostate cancers and a principal catalyst of compensatory neovascularization (25). Yet, it operates under stringent metabolic and spatial constraints that influence the quality, rather than just the quantity, of new vessel formation. Less oxygen availability stabilizes transcriptional programs that respond to hypoxia (26). These programs increase pro-angiogenic factor production, alter endothelial survival signaling, and shift stromal and tumor cell metabolism toward glycolytic flux, leading to lactate and proton accumulation (26). These modifications do not function independently. They cross paths with redox-sensitive checkpoints, competition for nutrients, and differences in local perfusion, which may lead to arteries that are leaky, poorly pericyted, or skewed toward high-demand niches rather than restoring uniform

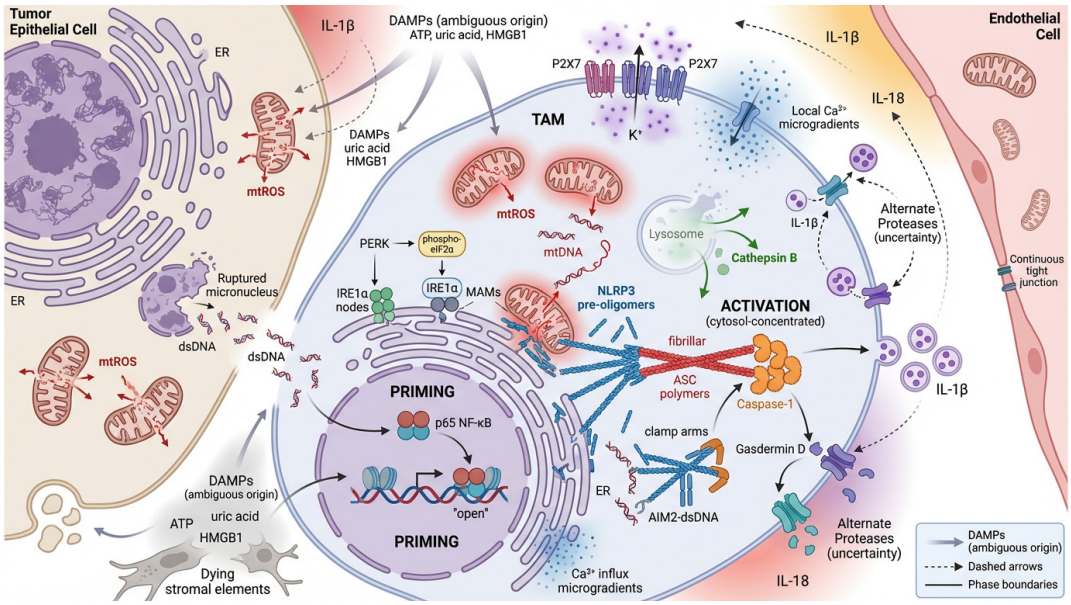

Figure 1. Inflammasome–damage-associated molecular pattern coupling in tumor-associated macrophage activation

Damage-associated molecular pattern signals derived from stressed tumor epithelial cells, including mitochondrial reactive oxygen species (ROS) and extracellular adenosine triphosphate (ATP), converge on tumor-associated macrophages to initiate a two-stage inflammasome response. Priming is mediated through nuclear factor kappa B (NF-κB)-dependent transcriptional opening downstream of endoplasmic reticulum (ER) stress sensors, including protein kinase R-like endoplasmic reticulum kinase (PERK) and inositol-requiring enzyme 1 alpha (IRE1α), enabling expression of nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) components and pro-interleukin-1 beta (pro-IL-1β). Subsequent activation integrates ionic fluxes via purinergic receptor P2X7 (P2X7), local calcium ion (Ca^{2+}) microgradients, and lysosomal destabilization with cathepsin B release, promoting NLRP3 oligomerization at mitochondria-associated membranes. Apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) polymerization scaffolds the recruitment of caspase-1, leading to gasdermin D cleavage and cytokine maturation. Dashed connections denote context-dependent protease contributions to IL-1β processing. These pathways are presented as mechanistic links within inflammatory microenvironments rather than direct evidence of vascular outcomes

DAMPs, damage-associated molecular patterns; ROS, reactive oxygen species; ATP, adenosine triphosphate; NF-κB, nuclear factor kappa B; ER, endoplasmic reticulum; PERK, protein kinase R-like endoplasmic reticulum kinase; IRE1α, inositol-requiring enzyme 1 alpha; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; IL-1β, interleukin-1 beta; P2X7, purinergic receptor P2X7; Ca^{2+}, calcium ion; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain

oxygenation (27). The connection between sensing low oxygen levels and reprogramming endothelial metabolism is an important regulatory layer (27). Endothelial cells rely on glycolysis to keep sprouting even when oxygen levels are low. Still, they become vulnerable to glucose shortages and acidosis-driven signaling distortions that slow down maturation and stabilize dysfunctional phenotypes (28). A practical limitation of integration is that many mechanistic models treat hypoxia as a uniform stimulus. In contrast, *in vivo* gradients fluctuate over minutes to days and are modified by therapy-induced vascular pruning, edema, and changes in cellular density (29). Methodologically, hypoxia indicators, perfusion imaging, and transcriptome readouts often span distinct time intervals and geographic scales (29, 30), thereby challenging the establishment of causal relationships between metabolic stress and vascular activity. The debate considers hypoxia as a conditioning factor influencing angiogenic outcomes when evidence is available; conversely, when inference remains theoretical, it is presented as a potential coordination issue among oxygen sensing, substrate availability, and endothelial energetics (26, 29). Hypoxia-associated metabolism influences vascular morphology and function in ways relevant to delivery feasibility and response variability, without assuming a single predominant pathway across tumor stages (31).

Vessel phenotype, perfusion quality, and therapy-relevant vascular dysfunction

The phenotype of blood vessels in prostate cancers is a balance between angiogenic drive, mural cell coverage, extracellular matrix restrictions, and local hemodynamic factors. In practice, dysfunction important to treatment typically presents as patchy spatial flow, higher-than-normal leakiness, and hypoxia that comes and goes (32). This may happen in areas that seem well vascularized on static imaging. The dynamic management of endothelial junctional integrity and tone is a major regulatory layer (32). Permeability programs and vasomotor signals work together to determine whether newly produced microvessels become functional conduits or stay structurally weak channels (33). These characteristics are significant since microregional perfusion states, which may fluctuate over brief time intervals, limit medication delivery, oxygen supply for radiotherapy, and the movement of immune cells (33, 34). A common problem with integration is that many datasets mix angiogenic indicators or microvessel density with perfusion competency, even though structural expansion and functional delivery are only partly linked (34). Methodologically, this is exacerbated by reliance on endpoint histology, limited temporal sampling, and inadequate surrogates for flow and oxygenation, complicating the differentiation between enduring vascular states and transient remodeling responses (34). Vascular dysfunction represents a measurable limitation to effective delivery, and causal inferences from correlational vascular data should be interpreted with caution in diverse clinical settings.

Inflammasome biology in the prostate tumor microenvironment

Inflammasome platforms and core components

Inflammasomes in the prostate tumor microenvironment act as modular innate immune platforms that turn different

danger signals into more uniform inflammatory responses (35). The effects depend on the type of cell, the stimulus context, and the way the response is linked to tissue remodeling. These platforms are generally composed of three core components (15, 16): A sensor that detects changes, an adapter that initiates assembly, and an effector that carries out cytokine maturation and, in some cases, the death of inflammatory cells. Sensors are divided into two groups: pattern-recognition sensors and stress-sensing sensors (15, 35). They differ in their activation logic: some respond to microbial patterns, whereas others are triggered by ionic flux, organelle stress, or cytosolic nucleic acids (36). All of these are possible in tumors that are experiencing hypoxia, necrosis, therapy pressure, or extracellular matrix disruption. The difference between priming and activation is an important part of regulation (37). Priming enhances the availability and preparedness of pathway components through transcriptional and post-translational modulation (37, 38). In contrast, activation is triggered by acute disturbances that facilitate oligomerization and proximity-induced effector cleavage (37, 38). This distinction is important in prostate cancers because androgen signaling, metabolic rewiring, and stromal cytokine fields may keep priming ongoing without triggering activation, and vice versa (39). Practical integration remains limited because people often infer platform identification from a small number of readouts, even when many sensors converge on the same effectors and cytokine outputs (40). Methodologically, bulk tissue profiling obscures compartment-specific assembly, and ex vivo stimulation may skew the trigger hierarchy relative to the *in situ* microenvironment (38-40). Inflammasome platforms are defined as operational concepts centered on key components and regulatory checkpoints. Causal claims are limited to contexts in which assembly, localization, and effector engagement are demonstrated in the corresponding cell types (40). Inflammasome platforms are organized across tumor, myeloid, and endothelial compartments, where priming establishes transcriptional readiness and activation integrates ionic flux, mitochondrial stress, and cytosolic sensing to drive caspase-1-dependent cytokine maturation and gasdermin D-mediated membrane permeabilization (Figure 2).

NLRP3 and non-NLRP3 inflammasomes in prostate tumors

Inflammasomes in prostate tumors can be conceptualized as context-sensitive stress sensors that convert microenvironmental disruption into cytokine maturation and, in certain contexts, lytic inflammatory cell death, with NLRP3 serving as a broadly responsive platform and non-NLRP3 complexes facilitating more stimulus-specific routing (15, 41). Several triggers are likely to be relevant in prostate cancer biology. These include potassium efflux associated with membrane damage or purinergic signaling, mitochondrial dysfunction with ROS amplification, lysosomal destabilization after particulate uptake (16, 42), and endoplasmic reticulum stress linked to proteostasis imbalance in rapidly adapting cells (42). These inputs

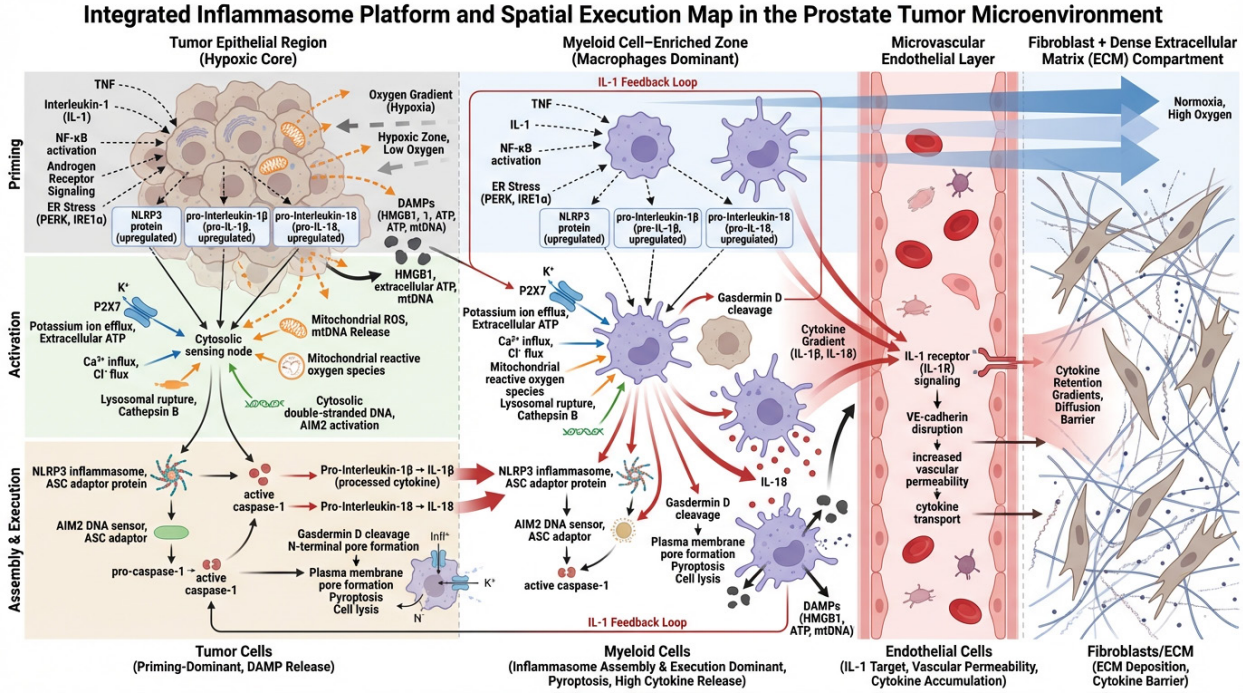

Figure 2. Spatially resolved inflammasome assembly across prostate tumor compartments

The figure maps inflammasome activity across tumor epithelial, myeloid, endothelial, and stromal regions under oxygen gradients. In hypoxic tumor cells, NF-κB-linked priming driven by cytokines, androgen signaling, and endoplasmic reticulum (ER) stress increases the availability of nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) and pro-interleukin-1β. At the same time, damage-associated molecular patterns (DAMPs) release and mitochondrial ROS provide upstream signals. In macrophage-enriched zones, adenosine triphosphate (ATP)–purinergic receptor P2X7 (P2X7)-mediated potassium ion (K^+) efflux, calcium ion (Ca^{2+}) influx, and lysosomal disruption converge to support NLRP3 assembly and caspase-1 activation. Gasdermin D cleavage enables cytokine release and membrane permeabilization, with interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) contributing to local feedback amplification. Endothelial cells respond via interleukin-1 (IL-1) receptor signaling, leading to junctional changes and increased permeability. Diffusion constraints within the extracellular matrix (ECM) are depicted as modulators of cytokine distribution rather than fixed determinants of vascular behavior

NF-κB, nuclear factor kappa B; ER, endoplasmic reticulum; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; DAMP, damage-associated molecular pattern; ROS, reactive oxygen species; ATP, adenosine triphosphate; P2X7, purinergic receptor P2X7; K^+, potassium ion; Ca^{2+}, calcium ion; IL-1β, interleukin-1 beta; IL-18, interleukin-18; IL-1, interleukin-1; ECM, extracellular matrix

come together to form licensing processes that control priming, complex assembly, and caspase engagement. The output depends on both transcriptional readiness and the strength of the acute danger signal (16, 43). At the same time, cytosolic double-stranded DNA arising from genomic instability, micronuclei rupture, or therapeutic damage may activate non-NLRP3 inflammasomes such as AIM2 (44). On the other hand, NLRC4-like responses are more likely to be linked to microbial or flagellin-associated patterns in inflamed tissue niches than to tumor-intrinsic programs. A significant challenge in practical integration is that several putative triggers are not exclusive to malignant epithelium (14, 44); they might also originate from stromal, endothelial, or myeloid compartments, hence confusing the attribution of inflammasome output to a single cellular source. Methodologically, dependence on bulk cytokine readouts and endpoint histology may mask whether signaling indicates inflammasome activation (37, 45), alternate protease processing, or mixed cell death pathways, and model systems often vary in androgen environment, immunological makeup, and baseline priming (37, 45). This part regards prostate-related triggers as a mechanistic framework for potential activation pathways, while reserving causal assertions for scenarios in which cell-specific activation and pathway specificity are empirically validated.

DAMPs, oxidative stress, and mitochondrial perturbation

When cells are stressed or injured, they lose compartmental control, exposing intracellular components that are typically immunologically quiet. Under these conditions, damage-associated molecular patterns (DAMPs) become exposed or released (46). Oxidative stress may amplify this signal in tumors and inflamed tissues by inducing protein oxidation, lipid peroxidation, and nucleic acid damage. These three things combined make it more likely that DAMP cargo will be released or displayed in a way that is easier to perceive (47). An important regulatory layer operates at the level of ionic flow, where potassium efflux, calcium influx, and chloride movement modulate membrane potential and organellar function (48). Mitochondria therefore operate as both targets and transmitters, in which membrane depolarization (48), permeability transition, and altered electron transport may enhance reactive species formation while concurrently modifying mitochondrial DNA and cardiolipin exposure patterns (49). The practical constraint is that these processes are closely linked in time and place, making it hard to determine which one caused the other when redox changes, ion-channel activity, and mitochondrial remodeling occur simultaneously (49). Methodologically, bulk measurements often overlook microdomain behavior and transitory events, whereas standard probes may disrupt the redox states they are designed to assess (50). The DAMP–redox–ion–mitochondria interface is examined, rather than downstream effector cascades, to delineate the boundary between plausible mechanistic integration and predominantly correlative inference (49-51).

Microbial signals and therapy-associated inflammatory cues

Microbial signals modulate the inflammatory tone in tumors through both direct pattern-recognition signaling and indirect immune priming mediated by barriers (52). Microbe-associated ligands may interact with innate sensors in myeloid and epithelial compartments, modulating cytokine setpoints that influence endothelial activation, antigen presentation, and local chemokine gradients (52). Therapy provides another depth. Radiation, cytotoxics, and other targeted treatments may cause damage signals, temporary changes in permeability, and episodic antigen release. These changes may cause the same innate mechanisms that respond to microbial products to function better or differently (53). A crucial regulatory factor is whether these inputs support resolution programs and regulated interferon-mediated surveillance, or perpetuate IL-1β and TNF-biased loops that facilitate recruitment without efficient clearance. Integration is still mostly restricted by context dependency (54). For example, microbial signatures vary with location, antibiotic exposure, nutrition, and sample depth. Also, the timing of therapy affects the direction and duration of inflammatory pulses (55). Methodologically, linking microbiome characteristics to tissue-level outcomes is limited by the low likelihood of contamination and by the imperfect mapping from stool to tumor-adjacent niches (56).

Cell-type localization across tumor compartments

Cell-type localization is not only a descriptive enhancement in prostate tumor angiogenesis; it is a mechanistic limitation that dictates the coupling of inflammasome signaling, pyroptotic outputs, and vascular responses (57). Tumor epithelium may give priming inputs and stress-derived ligands. Still, its major role is usually paracrine, meaning it filters into stromal programs rather than directly causing changes in endothelial cells (57). Myeloid cells occupy a more direct effector position within inflammatory signaling networks. They assemble inflammasome platforms and release cytokine and lipid mediators that can alter endothelial permeability, sprouting behavior, and compensatory immunosuppressive recruitment (58). Endothelial cells are both targets and players, but their response is limited by metabolic status, junctional integrity, and shear-dependent signaling, which may separate inflammatory activation from long-lasting vascular remodeling (59). Fibroblasts govern the space around them by depositing extracellular matrix, creating chemokine gradients, and presenting growth factors. This lets them either stabilize or trap abnormal microvessels (60). A practical constraint is that bulk measurements amalgamate various compartmental logics, making it unclear whether a specific signal is generated, detected, or merely aggregated in a given area. Spatial profiling and single-cell experiments are useful, but sample depth, dissociation bias, and marker ambiguity still make it hard to draw causal conclusions (60). Inflammasome activation in prostate tumors arises from integrated stress signals across compartments, with context-dependent engagement of NLRP3 and AIM2 pathways. Given limited pathway specificity in bulk measurements, key trigger–output relationships are summarized in Table 1.

Priming versus activation: Implications for target selection

Priming and activation are distinct biological states that often converge into a singular designation in therapeutic discourse; however, they correspond to discrete regulatory points in inflammatory signaling (68). Priming usually creates conditions that enable a quick response by altering the redox balance, membrane dynamics, and transcriptional upshifts in sensor and effector components (68). Activation

Table 1. Mechanistic mapping of inflammasome activation pathways in prostate tumor contexts

Mechanistic module	Signal origin	Signal class	Core molecular mediators	Target interface	Primary signaling pathway	Functional outcome (context-dependent)	Dominant activation niche	Biological implication	Challenges	Ref
Potassium efflux–NLRP3 activation	Membrane damage; extracellular ATP (P2X7)	Ionic flux	NLRP3, ASC, caspase-1, K^+ channels	Cytosolic inflammasome complex	Canonical NLRP3 inflammasome pathway	IL-1β maturation with variable pyroptosis	Necrotic tumor regions	Links membrane damage to inflammatory signaling	Ionic flux not directly measurable *in vivo*	(5)
Mitochondrial ROS–NLRP3 activation	Mitochondrial dysfunction; oxidative stress	Redox signaling	NLRP3, mtROS, mtDNA, cardiolipin	Mitochondria–cytosol interface	ROS-dependent NLRP3 activation	Cytokine release with context-dependent execution	Hypoxic tumor microenvironment	Couples metabolic stress to inflammasome activity	ROS causality difficult to isolate	(61)
Lysosomal rupture–NLRP3 activation	Particulate uptake; cellular debris	Organelle stress	NLRP3, cathepsin B, lysosomal enzymes	Lysosomal membrane–cytosol	Lysosome-mediated NLRP3 activation	Inflammasome assembly with variable cytokine output	Phagocytic myeloid cells	Connects debris sensing to inflammation	Lysosomal markers lack specificity	(62)
Cytosolic DNA–AIM2 activation	Genomic instability; micronuclei rupture	Nucleic acid sensing	AIM2, ASC, caspase-1, dsDNA	Cytosolic DNA-sensing complexes	AIM2 inflammasome pathway	IL-1β/IL-18 processing±pyroptosis	Therapy-exposed tumor cells	Detects endogenous DNA damage signals	DNA source attribution unclear	(63)
ER stress–NLRP3 priming	Proteostasis imbalance; unfolded protein response	Transcriptional priming	NF-κB, NLRP3, pro-IL-1β, PERK, IRE1α	Nuclear–cytosolic interface	NF-κB-mediated priming pathway	Increased inflammasome readiness without guaranteed activation	Rapidly proliferating tumor cells	Establishes activation threshold sensitivity	Priming does not predict execution	(64)
Microbial ligand–NLRC4-like signaling	Microbial products; barrier disruption	Pattern recognition	NLRC4, caspase-1, bacterial ligands	Cytosolic PRR complexes	NLRC4 inflammasome pathway	Cytokine maturation with limited tumor specificity	Inflamed tissue niches	Links microbiome signals to inflammation	Tumor relevance remains uncertain	(65)
Therapy-induced inflammasome activation	Radiation; chemotherapy; cell damage	DAMP-mediated stress	NLRP3, AIM2, caspase-1	Cytosolic stress interfaces	Mixed inflammasome activation pathways	Transient cytokine pulses with variable outcomes	Treated tumor regions	Integrates therapy with inflammatory signaling	Temporal variability complicates interpretation	(66)
DAMP–redox–ion integration module	Cellular damage; oxidative stress; ionic imbalance	Integrated stress signaling	NLRP3, ROS, ion channels, DAMPs	Cytosolic stress integration nodes	Multi-signal inflammasome activation	Nonlinear inflammatory responses	Heterogeneous tumor microdomains	Reflects combined stress sensing	Signal overlap prevents causal resolution	(67)

NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; ATP, adenosine triphosphate; P2X7, purinergic receptor P2X7; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; K^+, potassium ion; IL-1β, interleukin-1 beta; ROS, reactive oxygen species; mtROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial deoxyribonucleic acid; DNA, deoxyribonucleic acid; AIM2, absent in melanoma 2; dsDNA, double-stranded deoxyribonucleic acid; IL-18, interleukin-18; ER, endoplasmic reticulum; NF-κB, nuclear factor kappa B; PERK, protein kinase R-like endoplasmic reticulum kinase; IRE1α, inositol-requiring enzyme 1 alpha; NLRC4, nucleotide-binding oligomerization domain-like receptor family CARD domain-containing 4; PRR, pattern-recognition receptor; DAMPs, damage-associated molecular patterns

is the next phase that starts complex construction, catalytic conversion, and pore-forming execution. This leads to downstream vascular effects from mediator release, barrier stress, and localized coagulation cues (69). This division is important for choosing targets, since priming nodes may provide broader dampening but weaken protective monitoring (70). In contrast, activation nodes might seem more targeted but may be skipped by parallel triggers or duplicate execution paths (70). A practical constraint is that clinical samples often include heterogeneous states across cell types, rendering a "primed" signature ineffective in predicting the predominant activation inputs *in vivo* (69, 71). Methodologically, ex vivo stimulation and endpoint readouts might exaggerate route dominance by necessitating synchronous activation (72, 73). This discussion focuses on target-selection logic rather than ranking specific therapeutic classes.

Pyroptosis mechanism and context dependence

Gasdermin execution pathways and caspase routing

Pyroptosis is an inflammatory form of programmed cell death characterized by membrane pore formation and eventual cell lysis. Its main characteristic is that it breaks down membranes by forming gasdermin pores. However, its biological effects depend on how hole production is directed and controlled (74) and on how it is resolved within a specific tissue context. In most cases, the execution step is controlled by proteolytic activation of gasdermin family members, most notably gasdermin D (74). This occurs when cleavage separates an autoinhibitory C-terminus from an N-terminal pore-forming fragment that oligomerizes at the plasma membrane, allowing ions to flow rapidly and causing cells to swell and release soluble mediators (13). Caspase routing defines the upstream regulatory logic: canonical inflammasome signaling typically uses caspase-1 to process both IL-1 family cytokines and gasdermin D. On the other hand, alternative pathways use inflammatory caspases to cleave gasdermin D in response to microbial or danger signals within the cell (75, 76). The balance between cytokine maturation and immediate lysis depends on the strength of the stimulus and the compartmentalization of the cell (77). Regulatory control is not limited to caspase selection. Variations in pore density, membrane lipid composition, and membrane repair efficiency may shift outcomes from complete rupture to a 'hyperactive' state in which pores permit cytokine release without immediate cell death (76). One problem with practical integration is that many experimental readouts combine multiple states into a single label. This makes it harder to map mechanisms to vascular and stromal endpoints in tumors (76). In terms of methods, cleavage events and hole formation are often inferred from surrogate indicators rather than measured kinetics (74). Also, cell-line models may suggest that one route is more important than it is in a variety of clinical tissues. Gasdermin cleavage represents the conserved execution mechanism, with caspase routing and membrane repair capacity determining whether pyroptosis amplifies inflammation, alters microenvironmental signaling, or remains functionally buffered (13, 78).

IL-1 cytokine processing, release, and amplification

IL-1 family cytokines occupy a regulatory nexus where inflammatory detection is transformed into tissue-level amplification; nonetheless, their biology is characterized as much by processing and release mechanisms as by receptor signaling (79). In most cases, IL-1β and IL-18 are produced as inactive precursors that require proteolytic maturation (79). This usually occurs via inflammasome-

linked caspase-1 activity, but other cleavage pathways, such as neutrophil serine proteases, may also play a role when myeloid trafficking is the primary cause of the lesion (80). There is more than one release. During pyroptosis, mature cytokines can be released when the membrane breaks, but sublytic pathways also seem important. These pathways include secretion through gasdermin-formed pores with membrane repair, packaging into extracellular vesicles, or release within mixed death programs that combine apoptotic and necrotic features in stressed tumor and stromal compartments (81). These release modalities are important because they affect concentration gradients, timing, and how they connect to danger signals that are also produced. Together, these factors change endothelial activation, leukocyte recruitment, and secondary cytokine cascades that extend beyond the initial trigger (82). A practical integration issue is that many datasets infer "IL-1 activity" from bulk transcript markers or serum levels, which cannot determine where processing occurred, which cell type released the cytokine, or whether signaling reflects IL-1β vs IL-18 or IL-1α alarmin dynamics (83). Methodologically, tests often confuse precursor and mature forms, whereas tissue samples might spuriously activate proteases, so confounding causal interpretation (84). IL-1 processing and release are treated as context-dependent modules that can amplify inflammation without assuming a dominant inflammasome axis.

Sub-lytic gasdermin activity and membrane repair buffering

Sub-lytic gasdermin activity may be seen as a graded membrane stress state rather than a binary cell death switch, with tiny holes functioning as temporary conduits that alter ionic balance, metabolite flow, and local signaling without necessitating rupture. In this range, pore creation is balanced off by membrane repair processes that reseal, shed, or compartmentalize damaged membrane (85). This turns a potentially disastrous permeability event into a buffered perturbation. A useful regulatory hinge is the link between pore burden and repair capacity. When pore density and persistence stay within the kinetic bandwidth of repair, cells can stay alive while still sending out danger signals and soluble mediators (86). When repair capacity becomes insufficient, permeability progressively shifts toward lytic rupture and secondary inflammatory amplification. Integration is constrained by the practical challenges of defining sub-lytic states across models (87), since readouts often conflate early permeability with late loss of integrity and may be influenced by cell type, membrane composition, and baseline metabolic state (87). Methodologically, studies based on dye absorption, lactate dehydrogenase release, or endpoint viability exhibit inadequate temporal resolution, thereby overlooking transient repair cycles. At the same time, imaging techniques may insufficiently sample uncommon but significant high-pore subpopulations (88). In summary, the best way to understand this is to think of sub-lytic gasdermin activity as a tunable interface that can either stabilize inflammatory tone through repair-dominated buffering or become destructive when repair is outpaced. The boundary between these two states is likely to vary with tissue type and stress history (85, 87, 89). Figure 3 illustrates that gasdermin pores operate along a gradual stimulus scale: when pore numbers remain limited, repair pathways such as ESCRT and membrane shedding can preserve viability despite increased permeability. As pores accumulate and persist, this balance shifts toward a repair–lysis threshold, after which membrane integrity can no longer be maintained and rupture with DAMP release becomes more likely.

Adaptive versus pathological pyroptotic signaling in tumors

Pyroptotic signaling in tumors operates not as a

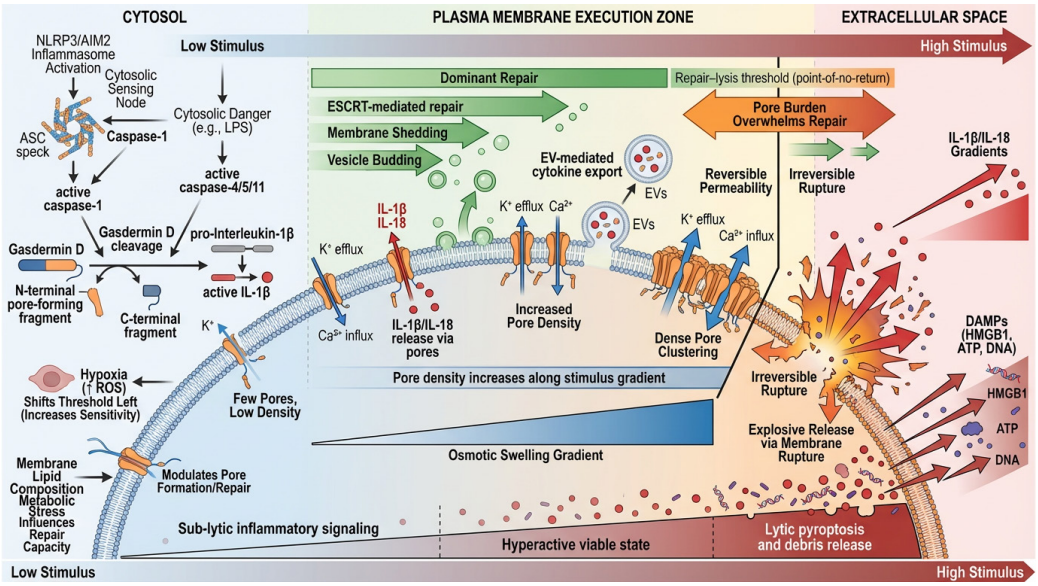

Figure 3. Gasdermin pore burden and membrane repair threshold dynamics
The figure depicts a stimulus-dependent transition from sub-lytic permeability to lytic rupture governed by pore density and repair capacity. Inflammasome activation leads to gasdermin D cleavage and insertion of pore-forming fragments, enabling potassium ion (K^+) efflux, calcium ion (Ca^{2+}) influx, and controlled release of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) at low pore numbers. In this range, endosomal sorting complexes required for transport (ESCRT)-mediated repair, membrane shedding, and vesicle budding counterbalance damage, supporting a viable but permeable state. Increasing pore clustering and persistence elevate osmotic stress and ion flux, progressively challenging repair mechanisms. A repair–lysis threshold is indicated where buffering becomes insufficient, after which irreversible membrane rupture and damage-associated molecular pattern (DAMP) release occur. Hypoxia and membrane composition are shown as modulators of this threshold rather than fixed determinants of outcome.
K^+, potassium ion; Ca^{2+}, calcium ion; IL-1β, interleukin-1 beta; IL-18, interleukin-18; ESCRT, endosomal sorting complexes required for transport; DAMP, damage-associated molecular pattern

standardized death program but as a context-dependent inflammatory switch that may either inhibit malignant proliferation or exacerbate microenvironmental dysfunction (90). In numerous contexts, the activation of the inflammasome and subsequent formation of gasdermin pores can eliminate stressed or infected cells, release danger signals, and temporarily enhance antigen availability (90, 91), potentially facilitating dendritic cell priming and the recruitment of cytotoxic effectors when vascular access and antigen presentation remain unaltered (91). This same membrane-rupture logic can become harmful when pyroptosis is only partial, occurs in certain areas, or recurs in compartments with little clearance (92). This is because cytokine release and alarmin flux can reinforce endothelial leak, coagulation bias, stromal activation, and myeloid skewing, all of which work together to keep the immune system from working properly (92). A crucial regulatory inflection point is whether upstream pattern sensing and caspase activity induce full lytic commitment or sub-lytic pore states that facilitate ion flux and cytokine maturation without effective cell elimination (93); these intermediate states can sustain inflammatory tone while ensuring tumor cell viability or allowing for rapid replacement. Practical integration remains limited by the difficulty of determining "where" and "in which cell type" pyroptotic machinery is active on clinically relevant time scales (94). Methodologically, several assays confuse pathway activation with terminal execution, while aggregate measures obscure microregional variability that presumably influences whether inflammation culminates in immune-mediated clearance or stabilizes into chronic, pro-tumor remodeling (94, 95). Pyroptosis operates as a thresholded circuit, with its overall impact contingent upon timing, cell identity, clearance capacity, and vascular context. The aim is to distinguish mechanistic feasibility from empirically validated outcome patterns, enabling prudent, schedule-conscious therapeutic modulation (90, 94, 95). A phase-resolved execution-repair framework clarifies how discrete gasdermin-caspase configurations map onto measurable inflammatory outputs and unresolved thresholds, as organized in Table 2.

Mechanistic coupling: Pyroptosis to angiogenic remodeling

Endothelial IL-1 signaling: Activation, permeability, sprouting bias

During inflammatory angiogenesis, endothelial function is often influenced more by the reconfiguration of barrier control, junctional mechanics, and chemotactic interpretation by cytokine tone than by a solitary growth factor signal (104). In this context, IL-1 signaling may function as a permissive amplifier, transforming the endothelium into an active state characterized by enhanced adhesion molecule expression, increased leukocyte-endothelial contacts, and a more permeable microvascular interface. In the canonical pathway (105), IL-1 receptor activation activates NF-κB and MAPK pathways, thereby increasing the transcription of chemokines, proteases, and junction-regulating mediators (105). This makes VE-cadherin–anchored contacts less stable, causes the cytoskeleton to contract, and opens paracellular routes in various ways, especially when hypoxia and oxidative stress coexist. Barrier relaxation does not inherently promote angiogenesis (106); rather, it modifies the local distribution of plasma proteins, fibrin, and myeloid cells, which subsequently provide VEGF-family ligands and facilitate matrix remodeling activity (106). IIL-1 may also influence sprouting decisions by increasing endothelial sensitivity to guidance cues and indirectly modulating Notch–DLL4 dynamics through inflammatory ligand availability and altered shear sensing (107). This results in more sprouts, but they are not always stable. A practical constraint to integration is that IL-1 effects are heavily influenced by vessel type, flow regime, and the competence of perivascular cells. This means that "activation" might refer to productive remodeling in certain areas but to leak-dominant malfunction in others (108). Methodologically, several *In vitro* experiments overstate the significance of sprouting by dissociating cytokine exposure from physiological shear and mural coverage (104, 109).

Table 2. Phase-resolved execution–repair topology with measurable instability nodes

Execution phase identity	Trigger intensity & origin context	Gasdermin–caspase configuration	Measurable output parameter	Evidence resolution level	Quantifiable gap	Ref
Primed non-executing state	Chronic cytokine exposure without an acute danger signal	Pro–IL-1 accumulation; no active GSDMD cleavage	Mature vs precursor IL-1 ratio (protein level)	Human tissue+bulk proteomics	Inability to define the activation threshold separating priming from execution	(14, 62)
Canonical lytic execution	High-intensity danger+inflammasome assembly	Caspase-1 → GSDMD full cleavage → high pore density	Membrane rupture kinetics (time-to-lysis, ion flux rate)	*In vitro* time-course+animal models	Lack of standardized kinetic benchmarks across models	(86, 96)
Non-canonical cytosolic sensing	Intracellular LPS / endogenous danger signals	Caspase-4/5/11 → direct GSDMD cleavage	Intracellular vs extracellular cytokine release ratio	Cell-based perturbation systems	Overreliance on non-tumor models limits tumor relevance	(97)
Sub-lytic signaling regime	Moderate, spatially restricted stress	Low-frequency GSDMD pore formation (non-lytic density)	Transient permeability (real-time dye flux, reversible)	Live-cell imaging (limited datasets)	Undefined pore-density threshold separating reversible vs irreversible damage	(98)
Repair-buffered equilibrium	Repetitive low-level activation with intact repair	Cyclic pore formation+ESCRT-like repair coupling	Membrane resealing rate vs pore persistence time	Indirect imaging+biochemical assays	No validated *in vivo* metric for repair capacity in tumor tissues	(99)
Mixed execution overlap state	Concurrent apoptosis/necrosis/pyroptosis inputs	Partial GSDMD activation + multi-protease cleavage	Co-detection of cleaved caspases with inconsistent lysis	Bulk tissue+multiplex staining	Pathway attribution failure due to overlapping markers	(100)
Vesicle-dominant cytokine export	Sub-lytic activation with intact membrane	GSDMD-independent or low-pore EV-mediated release	Cytokine concentration in EV fraction vs soluble pool	EV isolation+proteomics	Cargo origin ambiguity and co-isolation artifacts	(101)
Lytic transition boundary state	Escalating stress exceeding repair bandwidth	Rapid amplification of pore number beyond repair capacity	Critical transition point (nonlinear increase in permeability)	*In vitro* escalation models	Absence of defined quantitative "point-of-no-return" threshold	(102)
Immune-productive pyroptosis	Controlled execution with intact clearance	Coordinated GSDMD cleavage+effective cell removal	Antigen release+dendritic cell activation indices	Animal tumor models	Dependence on vascular access rarely quantified	(13)
Chronic pathological activation	Recurrent sub-lytic signaling across regions	Persistent low-level GSDMD activity without clearance	Sustained permeability+cytokine baseline elevation	Histology+longitudinal cytokine profiling	Spatial heterogeneity not captured by bulk measurements	(103)

GIL-1, interleukin-1; GSDMD, gasdermin D; LPS, lipopolysaccharide; ESCRT, endosomal sorting complexes required for transport; EV, extracellular vesicle

Still, *in vivo* imaging often fails to distinguish between endothelial-intrinsic IL-1 responses and macrophage-mediated relay (104, 109). This part characterizes IL-1 as a coupling signal that modifies endothelial permissiveness and sprout bias, while refraining from asserting that it alone dictates the enduring neovascular architecture.

Myeloid reprogramming under inflammasome tone

Myeloid cells play a crucial role in the interface between inflammatory signaling and vascular remodeling. They serve as sensors of danger-associated stimuli and as regulators of the local angiogenic environment through coordinated secretion, proteolytic processing, and metabolite handling (110). When inflammasomes remain active for extended periods, recruited monocytes and tissue-resident macrophages change their phenotype from programs that promote resolution of inflammation to states that help them cope with stress (110). These states are characterized by increased cytokine production, altered lipid metabolism, and improved ROS management (111). This change has a direct effect on the bioavailability of angiogenic factors because it changes how the extracellular matrix is remodeled, disrupts the presentation of heparan-sulfate-dependent ligands, and shifts the proteolytic balance toward fragment profiles with different pro- and anti-angiogenic properties (112, 113). Granule proteases from neutrophils and the formation of extracellular traps add to the intricacy, as these processes may trap growth factors within scaffold structures and cause microvascular blockage (114). Overall, increased myeloid recruitment does not necessarily translate into improved functional neovascularization. A significant integration difficulty arises from the context dependence of myeloid phenotype (113, 115), whereby surface marker profiles may insufficiently represent secretory or metabolic states across diverse conditions of hypoxia, iron availability, lactate buildup, or prior pharmaceutical treatment (115). At the methodological level, combining different types of myeloid cells across different time periods makes it harder to distinguish early endothelial-priming activity from later vessel-pruning or permeability-promoting effects, especially when sampling favors accessible compartments over perivascular niches (111, 114, 115). Myeloid reprogramming serves as a conditional, context-dependent modulator of angiogenic factor availability. Emphasis is placed on mechanistic plausibility rather than certainty (114).

Pyroptotic debris, EVs, and DAMP-driven vascular signaling

Pyroptosis in the tumor microenvironment may be seen as both a terminal death program and a source of organized extracellular information delivered to endothelial cells via debris fields (13), extracellular vesicles, and soluble warning signals (116). When a membrane breaks, it produces DAMPs and cytokine precursors, as well as oxidized lipids, nucleic acids, and cytoskeletal fragments (116). These alter the barrier tone and drive endothelial pattern-recognition and scavenger pathways toward activation (117). Simultaneously, vesicles released from stressed or dying tumor, myeloid, and stromal compartments may carry inflammasome-associated cargo, proteases, and regulatory RNAs that alter endothelial metabolism and junctional organization (12, 74, 118). These signals may shift the vascular environment from quiescent surveillance toward a more permissive remodeling state (119). A pertinent control layer is that a single ligand seldom governs vascular instruction; rather, it is influenced by concurrent signals converging on NF-κB, interferon-related pathways, and redox-sensitive checkpoints, in concert with shear stress and hypoxia (120). This creates a practical integration limitation: the same debris and vesicle signatures can support temporary vessel stabilization in one situation but cause leakiness, pericyte detachment, and disordered sprouting in another, depending on timing, clearance capacity, and baseline endothelial phenotype (120). Methodologically, it is challenging to distinguish vesicle-mediated effects from co-isolated protein aggregates, lipoproteins, or free nucleic acids, and functional tests often conflate multiple endothelial states into a single readout, such as tube formation or permeability (121). Consequently, the focus should be confined to localized endothelial signaling within prostate tumor microenvironments, avoiding extrapolation to systemic vasculitis-like conditions or to non-inflammasome-mediated cell-killing pathways (122). The key objective is to define the conditions under which pyroptotic byproducts act as local modulators of endothelial function (121, 122), as opposed to functioning primarily as nonspecific inflammatory signals that are associated with, but do not directly influence, angiogenic remodeling (119, 121, 122).

Spatial regulation within tumor vascular niches

Spatial heterogeneity is not a baseline characteristic of tumors; it is a regulatory state that influences the coupling of angiogenesis, cell death pathways, and inflammatory signals *in vivo* (123). Perivascular habitats provide temporary access to oxygen, nutrients, and survival signals from endothelial cells, and they usually favor phenotypes that are good at sticking to things, handling stress, and detecting cytokines in a regulated way (124). Hypoxic zones, on the other hand, limit metabolism, make protein folding harder, and create acidic microenvironments that may weaken certain immune effector functions while selectively boosting stress-responsive transcriptional programs (124, 125). Inflammatory gradients develop in regions due to unequal recruitment of myeloid cells, leaky blood vessels, and the removal of local debris. These gradients provide "set points" for inflammasome readiness and for the downstream risk of membrane rupture (126). A practical problem is that mechanistic connections derived from bulk tumor readouts sometimes amalgamate multiple compartments into a single averaged state, obscuring whether the observed signal reflects perivascular stability, hypoxia adaptation, or interface dynamics at their border (127). Spatial transcriptomics and multiplex imaging are better at detecting features. However, they still have problems with sample bias, low temporal resolution, and difficulty perfectly linking RNA, protein activity, and functional outcomes (127). This portion examines how compartment-specific limitations influence vascular behavior and inflammatory tone, while regarding cross-compartment causal assertions as conditional until substantiated by spatially defined functional disruption (128). This framework provides spatial structure as a verifiable source of variation that elucidates the contradictory relationships among inflammation, pyroptotic signaling, and angiogenic outcomes across different models (127-129). Figure 4 depicts spatially

distinct tumor niches where pyroptotic outputs, myeloid signaling, and endothelial responses couple unevenly, producing context-dependent permeability, sprouting bias, and patchy perfusion rather than a uniform angiogenic state. Mechanistic coupling between pyroptotic signaling and angiogenic remodeling can be more precisely interpreted by examining endothelial-, myeloid-, and debris-mediated pathways in relation to defined spatial niches and functional vascular constraints, as summarized in Table 3.

These mechanisms collectively suggest that pyroptosis-associated inflammatory signaling can influence angiogenic remodeling through context-dependent interactions involving endothelial activation, myeloid reprogramming, extracellular vesicle signaling, and spatial vascular heterogeneity. At the same time, the therapeutic relevance of these pathways depends on whether vascular dysfunction can be modulated without disrupting protective inflammatory buffering or broader host-defense balance. This mechanistic framework provides the basis for the following section, which discusses current therapeutic targeting strategies and their translational limitations within prostate tumor microenvironments.

Therapeutic targeting strategies and evidence boundaries

Targeting inflammasome signaling at sensor, adaptor, and downstream levels

Therapeutic targeting of inflammasome signaling is generally conceptualized as an endeavor to mitigate pathological inflammatory amplification while preserving baseline host-defense efficacy, which is significant in prostate tumors that already endure variable hypoxia, necrosis, and therapy-induced tissue stress (16, 142). Intervention may be structured into three operational tiers: sensor regulation to avert priming or activation, adaptor interference to obstruct complex formation, and downstream suppression to restrict effector execution and cytokine development (143). Sensor-directed strategies seek to mitigate the initial decision points; however, the regulatory landscape indicates that priming and activation are distributed across various danger signals and intersect with broader stress pathways (143). Consequently, selective blockade may be circumvented by concurrent inputs or may unintentionally redirect signaling towards alternative inflammatory pathways (144). Adaptor-level strategies promise a cleaner bottleneck, but they have a practical limit: adaptor function only works in small areas and can vary by cell type, which means that tissue delivery (144, 145), intracellular access, and compartmental pharmacodynamics are all major unknowns (145). Downstream inhibition is frequently the most manageable pharmacologically (146); however, it can obscure mechanisms, as decreases in cytokine production or lytic activity do not clearly indicate which upstream inflammasome configuration was implicated, particularly when other proteases and apoptotic pathways produce overlapping effects (146, 147). Methodologically, numerous preclinical studies deduce pathway suppression from a limited array of markers assessed at discrete time points. In contrast, the clinically pertinent criterion is whether

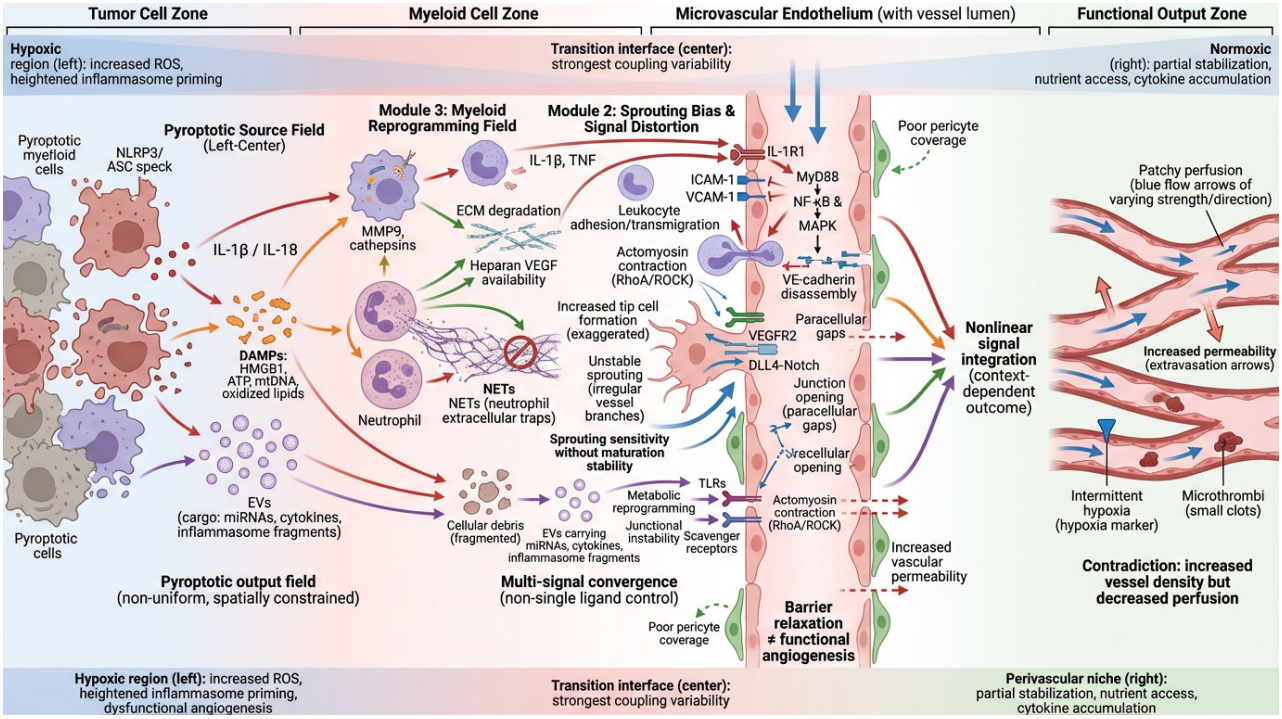

Figure 4. Spatial coupling of pyroptosis and endothelial heterogeneity

The figure illustrates compartment-specific signaling across tumor, myeloid, and vascular regions linked by cytokines, damage-associated molecular patterns (DAMPs), and extracellular vesicles. Pyroptotic activity within hypoxic tumor zones generates interleukin-1 beta (IL-1β), interleukin-18 (IL-18), and inflammatory debris that contribute to myeloid reprogramming and extracellular matrix (ECM)-associated signal redistribution. At the endothelial interface, interleukin-1 receptor (IL-1R)–myeloid differentiation primary response 88 (MyD88)–NF-κB signaling intersects with vascular endothelial growth factor receptor 2 (VEGFR2) and delta-like ligand 4 (DLL4)–Notch pathways to influence permeability and sprouting behavior. Convergence at this boundary is shown as variable rather than uniform, with dashed flows indicating context-dependent integration. Downstream vascular outcomes include uneven perfusion, intermittent hypoxia, and microthrombi, reflecting the non-linear translation of inflammatory inputs into angiogenic remodeling

DAMPs, damage-associated molecular patterns; IL-1β, interleukin-1 beta; IL-18, interleukin-18; ECM, extracellular matrix; IL-1R, interleukin-1 receptor; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; VEGFR2, vascular endothelial growth factor receptor 2; DLL4, delta-like ligand 4

Table 3. Mechanistic cross-compartment coupling in pyroptosis-associated angiogenic remodeling

Coupling axis	Dominant signal source	Core molecular mediators	Primary signaling pathway	Targeted vascular interface	Context-dependent functional outcome	Experimental basis	Key interpretive limitation	Ref
IL-1–endothelial activation module	IL-1β / IL-1α (myeloid+stromal release)	IL-1R1, MyD88, IRAK, TRAF6	NF-κB, MAPK (p38, ERK)	Endothelial junctions (VE-cadherin), adhesion molecules	Increased permeability, leukocyte adhesion, variable sprouting bias	*In vitro* endothelial assays; *in vivo* cytokine perturbation models	Cannot distinguish direct endothelial response vs macrophage-mediated relay	(130)
IL-1–sprouting sensitivity shift	Cytokine amplification under hypoxia+ROS	VEGFR2, DLL4, Notch1	VEGF–Notch signaling axis; NF-κB modulation	Tip–stalk selection machinery	Increased sprout initiation with unstable maturation	Animal angiogenesis models; indirect pathway inference	Sprouting readouts often dissociated from physiological shear and mural context	(131)
Barrier modulation–angiogenic relay	IL-1–induced barrier relaxation	VE-cadherin, RhoA, ROCK, MMPs, fibrin	RhoA/ROCK signaling; VEGF-mediated matrix remodeling	Plasma protein extravasation, fibrin deposition interface	Secondary VEGF availability, matrix remodeling support	Histology + permeability assays	Structural leak not equivalent to functional perfusion improvement	(132)
Myeloid cytokine–matrix remodeling axis	Inflammasome-activated macrophages/monocytes	IL-1β, TNF, MMP9, cathepsins, heparanase	NF-κB; protease-mediated ECM remodeling	ECM-bound growth factor reservoirs (heparan sulfate interface)	Altered ligand bioavailability, pro-/anti-angiogenic fragment balance	*In vivo* tumor models; proteolytic profiling (limited)	Surface markers poorly reflect secretory/metabolic phenotype states	(133)
Neutrophil protease–vascular obstruction interface	NETs+granule proteases	Neutrophil elastase, MPO, histones, extracellular DNA	ROS-dependent NETosis pathways	Microvascular lumen and perivascular matrix	Growth factor trapping, microthrombotic obstruction	Animal inflammation models; indirect vascular readouts	Difficult separation of obstruction vs angiogenic signaling contribution	(134)
Pyroptotic debris–endothelial sensing module	DAMPs, oxidized lipids, nucleic acids	HMGB1, ATP, oxidized lipids, mtDNA	NF-κB; pattern-recognition receptor signaling	Endothelial pattern-recognition receptors, scavenger systems	Barrier destabilization, inflammatory amplification	*In vitro* endothelial exposure models	Debris composition and concentration poorly controlled across studies	(135)
EV-mediated vascular instruction pathway	Tumor/myeloid-derived extracellular vesicles	EV-associated miRNAs, cytokines, proteins, GSDMD fragments	NF-κB, PI3K–Akt, redox-sensitive pathways	Endothelial metabolic and junctional regulatory nodes	Shift toward permissive remodeling or transient stabilization	EV isolation +proteomics; functional assays	Co-isolation artifacts and unclear cargo origin attribution	(136)
Multi-signal convergence node	Combined cytokine + DAMP+EV signaling	IL-1β, TNF, interferon-related mediators, ROS	NF-κB, interferon signaling, redox-sensitive pathways	NF-κB, interferon, redox-sensitive pathways in endothelium	Nonlinear vascular response (stabilization vs leak)	Multi-modal experimental inference	Signal contribution cannot be disentangled in most systems	(137, 138)
Perivascular niche stabilization regime	Local endothelial–stromal signaling+nutrient access	Angiopoietins, VEGF, integrins, ECM ligands	PI3K–Akt; integrin–FAK signaling	Perivascular endothelial interface	Controlled activation, survival-biased phenotype	Spatial transcriptomics; imaging (partial resolution)	Limited temporal resolution and causal linkage	(139)
Hypoxic niche stress-conditioning axis	Low oxygen, acidosis, metabolic restriction	HIF-1α, lactate, AMPK, ROS	HIF signaling; metabolic reprogramming pathways	Endothelial metabolic adaptation pathways	Dysfunctional angiogenesis, impaired maturation	Hypoxia models; metabolic profiling	Hypoxia gradients not captured dynamically *in vivo*	(28, 140)
Spatial gradient–inflammasome readiness coupling	Uneven myeloid recruitment + vascular leak	IL-1β, DAMPs, ROS gradients	NF-κB; inflammasome priming pathways	Regional inflammasome priming/activation thresholds	Heterogeneous inflammatory tone and rupture risk	Spatial omics; multiplex imaging	Bulk averaging masks compartment-specific dynamics	(141)

IL-1, interleukin-1; IL-1β, interleukin-1 beta; IL-1α, interleukin-1 alpha; IL-1R1, interleukin-1 receptor type 1; MyD88, myeloid differentiation primary response 88; IRAK, interleukin-1 receptor-associated kinase; TRAF6, tumor necrosis factor receptor-associated factor 6; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; VE-cadherin, vascular endothelial cadherin; ROS, reactive oxygen species; VEGFR2, vascular endothelial growth factor receptor 2; DLL4, delta-like ligand 4; VEGF, vascular endothelial growth factor; RhoA, Ras homolog family member A; ROCK, Rho-associated coiled-coil-containing protein kinase; MMPs, matrix metalloproteinases; TNF, tumor necrosis factor; ECM, extracellular matrix; NETs, neutrophil extracellular traps; MPO, myeloperoxidase; DNA, deoxyribonucleic acid; DAMPs, damage-associated molecular patterns; HMGB1, high-mobility group box 1; ATP, adenosine triphosphate; mtDNA, mitochondrial deoxyribonucleic acid; EV, extracellular vesicle; miRNAs, microRNAs; GSDMD, gasdermin D; PI3K–Akt, phosphoinositide 3-kinase–protein kinase B; FAK, focal adhesion kinase; HIF-1α, hypoxia-inducible factor 1 alpha; AMPK, adenosine monophosphate-activated protein kinase

vascular endpoints, perfusion heterogeneity, and therapeutic response exhibit a consistent trajectory under realistic dosing and tumor immune contexts (148). Inflammasome-directed inhibition can be viewed as a stratified therapeutic strategy with defined mechanistic targets. Its application remains constrained by evidentiary limitations, including cell-specific engagement, biomarker non-specificity, and limited integration with vascular endpoints (148).

Gasdermin and caspase targeting: Feasibility, selectivity, and safety risks

Targeting the gasdermin–caspase axis is appealing because it acts during the execution phase of pyroptosis, when pore formation and cytokine release can be modulated together. However, this same location renders practicality and safety interdependent on selectivity (149). In most cases, inflammatory caspases govern gasdermin cleavage as a licensing event. At the same time, death and stress pathways might come together to cause membrane damage or cytokine maturation (150). This creates regulatory redundancy, making it harder to forecast how single-node inhibition would work (150, 151). Inhibiting gasdermin pore formation may be a better strategy to reduce lytic inflammation than inhibiting signals higher up; however, tissue distribution, access to cells, and the need to maintain strong antimicrobial defense limit dosing and scheduling (151). Targeting caspases makes integration even harder because they are involved in many cell-fate programs and can change how immune cells develop and work. Blocking them may lower harmful inflammation, but it may also make surveillance or repair less effective, depending on the compartment and timing (152). A practical drawback is that tumor microenvironments comprise heterogeneous cell populations with varying activation thresholds, so "benefit" in one niche might translate into "risk" in another, especially when inflammatory stimuli co-regulate endothelial integrity and leukocyte trafficking (152). Methodologically, available readouts may conflate pyroptotic membrane rupture with secondary necrosis or apoptosis-to-pyroptosis transition. Also, bulk measurements might overlook pore activity that is only temporary and limited to a small area but is still physiologically important (153).

Cytokine pathway modulation (IL-1 axis) and vascular readouts

The interleukin-1 (IL-1) axis is a key point at which inflammatory sensing translates into endothelial activation. This makes it an interesting yet challenging way to link

cytokine modulation to vascular readouts in prostate cancer (154). IL-1α and IL-1β may amplify local stress signals, activate endothelial cells, and modify cell interactions around blood vessels by altering the expression of adhesion molecules, barrier tone, and paracrine crosstalk (155). These changes indirectly affect sprouting, leakiness, and leukocyte trafficking. A crucial regulatory checkpoint is the propagation of signals through the IL-1 receptor complex and subsequent transcriptional programs that intersect with hypoxia-responsive and growth-factor pathways (155, 156), resulting in non-linear outputs where minor cytokine variations may be mitigated in certain contexts but become significant in the presence of stromal priming, myeloid influx, or necrotic burden (157). The problem with practical integration is that the commonly used vascular endpoints can't be swapped out. For example, microvessel density can increase without improved perfusion, permeability can increase while oxygen delivery decreases, and "normalization-like" patterns might reflect temporary architecture rather than long-lasting function (158). Methodological limitations exacerbate this issue, since cytokine measurements often include compartment-mixed samples (tumor, plasma, and stromal fractions), and vascular tests exhibit variable spatial resolution and are influenced by medication timing and sampling (159). Consequently, the focus should remain on the pathway-to-readout logic rather than assuming a uniform direction of action (159). Additionally, any mechanistic model must distinguish experimental evidence for IL-1–induced endothelial state transitions from more general conclusions about clinical vascular advantages (157, 160). The aim is to identify vascular measures that best reflect IL-1–associated biology across tumor stages. This supports the selection of appropriate endpoints in translational studies.

Combination logic with standard prostate cancer therapies

Androgen receptor pathway inhibitors

Androgen receptor pathway inhibitors alter the ecology of prostate cancer by inhibiting transcriptional programs that promote proliferation, lineage plasticity, and stromal co-dependence, operating within a microenvironment that is already metabolically restricted and periodically hypoxic (161). At the signaling level, reducing androgen receptor output can decrease downstream growth factor crosstalk and alter oxidative and lipid-handling states. However, it may also favor stress-tolerant phenotypes that depend less on traditional androgen receptor pathways and more on compensatory survival mechanisms (162). This is important for combination logic because inflammatory signals linked to inflammasomes and membrane permeabilization near pyroptosis are not separate events; they interact with endothelial activation, myeloid recruitment, and barrier instability (162). All of these can be indirectly altered as tumor cells and stromal compartments adapt to androgen blockade. A practical constraint is timing: the introduction of an immune-inflammatory modulator into an androgen-suppressed system can yield ambiguous vascular outcomes (163), characterized by diminished tumor cell proliferation alongside therapy-induced cytokine release and endothelial priming, thereby making the overall trajectory of perfusion and permeability difficult to forecast without context-specific phenotyping (163, 164). Methodologically, several preclinical designs condense sequencing into brief intervals, use homogeneous cell-line models, or infer microvascular alterations from aggregate readouts, thereby exaggerating molecular interconnections and underrepresenting variation across metastatic locations (165). This is because dose, sequence, disease state, and previous exposure to androgen signaling suppression are the main factors that decide whether inflammatory cell death pathways increase antitumor pressure or create repair-adaptive niches (166). Combinations with androgen receptor pathway inhibitors are delineated to preserve cytostatic efficacy. At the same time, controlled endpoints are used to assess whether targeted inflammatory modulation improves vascular function and treatment infiltration without promoting escape states (165-167).

Radiotherapy and immunotherapy contexts

Radiotherapy and immunotherapy converge via their mutual reliance on the tumor's response to stress, injury, and antigen exposure within an immune-permissive milieu. Ionizing radiation may enhance the accessibility of tumor antigens and modify local cytokine gradients (168); however, it also initiates repair mechanisms and stromal responses that may reinstate immunological exclusion (168). A key regulatory axis is the balance between DNA damage sensing and interferon signaling. When nucleic acids accumulate in the cytosol and aren't cleared promptly, innate immune activation can enhance antigen presentation and facilitate T-cell recruitment (169). On the other hand, when damage is quickly repaired or redirected toward tolerogenic remodeling, the same exposure yields little immunologic gain (169). Timing and location make it hard to put practical integration into action. Dose, fractionation, and field design not only alter tumor-cell mortality patterns but also influence the risk of lymphocyte depletion and vascular integrity (170); these factors may significantly affect results, even when the immunotherapy agent is suitable (170, 171). Methodological constraints are significant: attributing responses is challenging because imaging alterations post-radiation may indicate inflammation, necrosis, or transient edema, and peripheral immune assessments may fail to accurately reflect intratumoral trafficking or states of functional fatigue (172). The scope should emphasize treatment-context biology rather than assuming that all histologies, lines of therapy, or checkpoint classes work together in the same way (173). The immediate objective is to define rational therapeutic pairing strategies that use radiation to provide a limited window of antigen exposure and permissive signaling, avoiding the saturation of lymphoid capacity or the enhancement of compensatory immunosuppression (173).

Translational constraints: Host defense and off-tumor effects

Translational targeting of inflammasome-linked pyroptotic signaling in prostate cancer angiogenesis occupies a precarious position between tumor control and the physiological imperative to maintain host defense (142, 174), as the same IL-1 family-centered circuits that enhance local vascular activation also regulate systemic antimicrobial preparedness and inflammation adjacent to barriers (15, 174). One important rule is that inflammasome activity is not a simple on/off switch. Instead, it is a stress-response module that is shaped by priming, ion flux, mitochondrial danger signals, and inhibitory checkpoints (35, 175). If you

change one of these nodes, it may send signals along parallel pathways that still activate endothelial cells or recruit leukocytes, making it harder to clear pathogens (103). The practical integration limitation is attribution: changes in perfusion, endothelial permeability, or microthrombotic tendency can arise from tumor-intrinsic modulation of pyroptosis (103, 176), altered myeloid cytokine tone, or therapy-induced systemic inflammation, making it challenging to delineate these components in patients with multimodal treatment exposures (176). Off-tumor vascular effects are significant due to the endothelium's conserved responsiveness to IL-1 axis mediators and to complement-coagulation crosstalk across organs (177). This raises potential risks of impaired wound healing, altered platelet-endothelial signaling, or exacerbated inflammatory responses in susceptible individuals, even when tumor angiogenic endpoints seem favorable (177). Preclinical models often condense time and comorbidity, whereas prevalent metrics such as bulk cytokines, static vessel density, or terminal histology inadequately capture dynamic vascular function and infection susceptibility (40, 178). Figure 5 positions therapeutic intervention across sensing, adaptor, execution, and cytokine layers, illustrating that modulation at any single node propagates through redundant, cell-type–dependent networks and yields vascular outcomes that remain non-linearly coupled to permeability, perfusion, and inflammatory readouts. Therapeutic targeting of inflammasome–pyroptosis pathways remains highly context-dependent, with vascular outcomes influenced by signaling specificity, endothelial responses, and translational constraints, as summarized in Table 4.

Measurement, biomarkers, and methodological vulnerabilities

Defining in vivo pyroptosis amid competing death programs

Pyroptosis *in vivo* is best understood as a patterned inflammatory response rather than a single, readily classified event, because tissue context requires overlapping morphologies, shared mediators, and heterogeneous cell states (189). Danger sensing may lead to the construction of inflammasomes, the activation of caspases, and the gasdermin-dependent permeabilization of membranes (189). This causes ionic collapse, swelling, rupture, and rapid release of intracellular contents, thereby increasing local cytokine and chemokine gradients (190). The specificity issue arises when readouts that are useful in tissue sections or bulk lysates are considered definitive: membrane permeability dyes, cleaved caspase signals, IL-1 family cytokines, and "speck-like" staining can also occur during necroptosis (191), secondary necrosis following apoptosis, or cytotoxic lymphocyte killing, particularly under conditions of hypoxia, acidosis, therapeutic stress, or elevated protease activity (191). Another problem is that regulatory cross-talk happens. Caspase-8 may inhibit or redirect necroptosis and can also facilitate inflammasome-adjacent processing (192). Meanwhile, mitochondrial damage, lysosomal rupture, and ROS-driven priming can exacerbate inflammatory phenotypes without ensuring gasdermin-driven execution

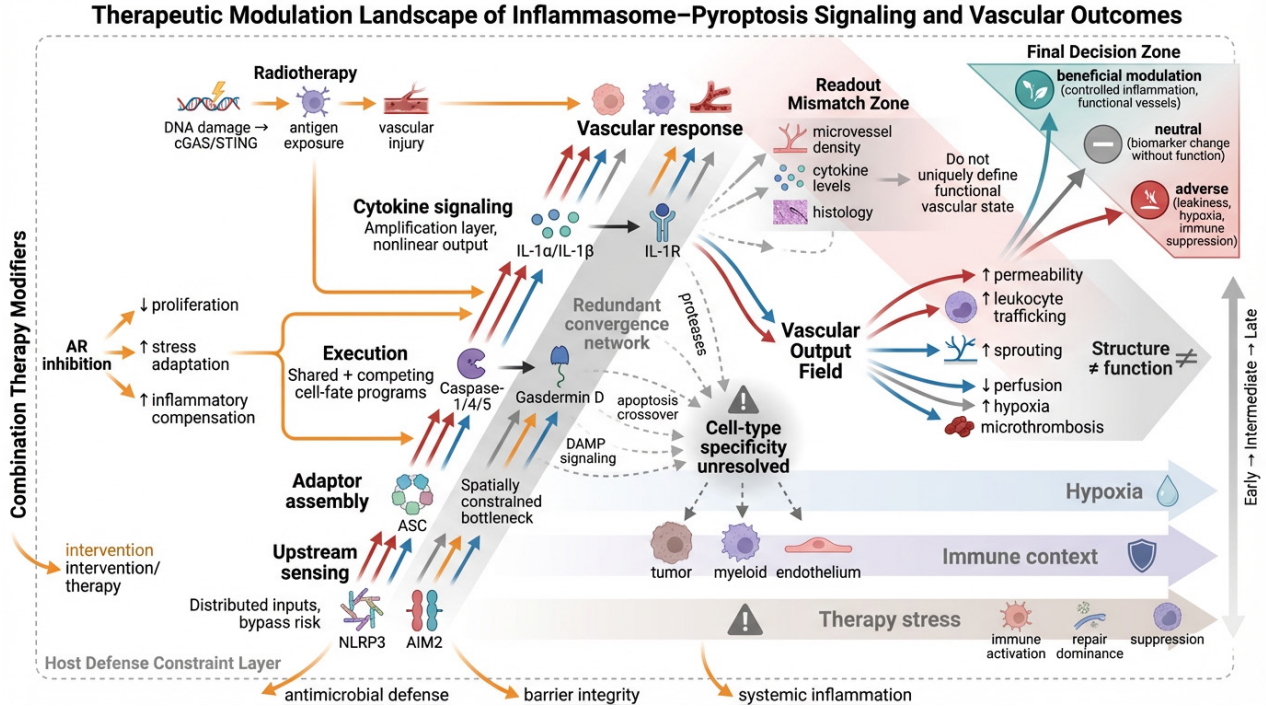

Figure 5. Therapeutic modulation nodes and vascular outcome divergence

The figure outlines intervention points across sensing, adaptor assembly, execution, and cytokine signaling layers within inflammasome–pyroptosis pathways. Upstream targeting of nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3), absent in melanoma 2 (AIM2), and apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) is depicted as a spatially constrained bottleneck. In contrast, downstream modulation of caspases and gasdermin D converges with parallel cell-death programs. Cytokine amplification through the interleukin-1 receptor (IL-1R) axis links these layers to endothelial responses, but signal propagation is shown to be redundant and cell-type-dependent. Combination therapies, including androgen receptor inhibition and radiotherapy, introduce additional stress inputs that reshape pathway engagement. Vascular outputs, such as permeability, leukocyte trafficking, sprouting, and perfusion, emerge as non-linearly coupled readouts rather than direct reflections of single-node modulation. The final decision space distinguishes beneficial, neutral, and adverse outcomes without implying uniform predictability

NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; IL-1R, interleukin-1 receptor

Table 4. Summary of inflammasome-targeting therapeutic strategies, vascular effects, and translational limitations in prostate cancer angiogenic remodeling

Therapeutic strategy	Main signaling target	Potential vascular effect	Major translational limitation	Ref
Sensor-level inflammasome modulation	Upstream danger sensing and inflammasome priming	May reduce cytokine-driven endothelial activation and inflammatory vascular stress	Redundant upstream triggers and limited pathway specificity *in vivo*	(179)
ASC adaptor blockade	Inflammasome scaffold assembly	Potential stabilization of endothelial inflammatory activation states	Intracellular delivery barriers and uncertain compartment-specific targeting	(180)
IL-1 axis suppression	IL-1 maturation and receptor signaling	Reduced endothelial permeability and leukocyte adhesion under controlled inflammatory conditions	Structural vascular changes may not correspond to functional perfusion improvement	(181)
Gasdermin pore inhibition	Gasdermin D–mediated membrane permeabilization	Reduced vascular leak, inflammatory rupture, and DAMP release	Risk of impairing antimicrobial defense and tissue-repair responses	(182)
Inflammatory caspase targeting	Caspase-dependent pyroptotic execution pathways	Modulation of endothelial activation and inflammatory amplification	Pathway redundancy and overlap with apoptosis-related signaling	(87)
IL-1 receptor pathway modulation	Endothelial IL-1R signaling and NF-κB activation	Context-dependent regulation of vascular permeability and sprouting behavior	Nonlinear vascular responses and limited spatial attribution of cytokine activity	(183)
Combination with androgen receptor inhibitors	Tumor metabolic and transcriptional adaptation pathways	Possible transient improvement in perfusion and therapeutic delivery	Adaptive resistance and therapy-induced inflammatory reprogramming	(184, 185)
Radiotherapy–immunotherapy combinations	DNA damage sensing and inflammatory antigen exposure	Increased vascular permeability and immune-cell infiltration under selected conditions	Difficulty distinguishing beneficial inflammation from edema or necrotic injury	(186)
Host-defense preservation strategies	Systemic inflammatory and endothelial homeostasis	Reduction of off-target vascular toxicity during inflammasome modulation	Potential impairment of protective inflammatory and antimicrobial responses	(187)
Biomarker-guided therapeutic monitoring	Integrated cytokine, imaging, and vascular profiling	Improved alignment between mechanistic activity and vascular response assessment	Lack of standardized multi-modal validation frameworks	(188)

ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; IL-1, interleukin-1; IL-1R, interleukin-1 receptor; NF-κB, nuclear factor kappa B; DAMP, damage-associated molecular pattern; DNA, deoxyribonucleic acid

inside the same cell (191, 192). Integration across platforms is constrained because single-marker immunohistochemistry, circulating cytokines, and transcriptional "pyroptosis signatures" fail to maintain cell identity, temporal dynamics, or the causal sequence of priming and execution (193). Methodologically, geographical sampling bias, post-ischemic artifacts, antibody cross-reactivity, and the short half-life of rupture-associated structures limit inference, and several experiments measure outcomes rather than mechanisms (194). This portion regards *in vivo* pyroptosis as a probabilistic categorization that requires convergent, cell-resolved data, while explicitly excluding assertions that cannot be distinguished from other death processes within the same lesion (192-194).

Inflammasome activity metrics: tissue, plasma, and single-cell considerations

Inflammasome activity is a multi-stage process that includes priming, assembly, protease activation, pore formation, and cytokine maturation. This means that the "measurement" relies on whatever phase a sample can accurately capture (195). In tissue, readouts may encompass transcriptional priming markers as well as protein-level indicators of inflammasome components and effector cleavage (195). However, spatial heterogeneity, variable necrosis, and disparities between tumor and stromal composition can alter perceived activity without indicating a genuine change in pathway flux (196). An important regulatory consideration is that priming via inflammatory signaling may remain elevated even as inflammasome assembly is constrained by ionic state, mitochondrial stress, or endogenous inhibitory tone (197). This can cause a mismatch between the amount of mRNA and the functional activation outputs. In plasma, convenience is counterbalanced by dilution, abbreviated half-lives, binding proteins (197), and systemic interference from infection, obesity, or therapy-induced inflammation, which constrains attribution to a prostate tumor microenvironment unless accompanied by meticulous clinical phenotyping (198). Single-cell methodologies enhance cellular attribution; nonetheless, they often infer activity from gene programs rather than accurately recording transient, protease-mediated events. Additionally, dissociation stress and ambient RNA may provide spurious inflammatory signals (199). Cross-platform integration is constrained by incompatible temporal frames, compartmental mixing, and non-equivalent endpoints, particularly when comparing cytokines, cleavage fragments, and transcriptional modules (199, 200). In practice, studies should avoid consolidating these readouts into a single 'inflammasome score' and instead treat them as complementary, stage-specific indicators (199, 200). A small set of assay-aware metrics is needed to preserve biological meaning while clearly indicating where inference remains indirect.

Angiogenesis endpoints: Perfusion, density, normalization, leak

Angiogenesis endpoints in prostate cancer are often treated as interchangeable; nevertheless, vessel density and tissue perfusion reflect distinct biological processes and may vary even with identical interventions (131, 201). Microvessel density reflects structural vessel abundance, whereas perfusion indicates whether those vessels carry blood under appropriate pressure gradients, hematocrit, and microvascular resistance (202, 203). A key regulatory hinge is the balance between pro-angiogenic signaling and stabilizing cues that recruit mural cells and maintain the integrity of endothelial junctions (204). When this balance changes, "normalization" can improve flow, oxygen delivery, and drug access without necessarily increasing vessel counts. On the other hand, "leak" can arise from junctional loosening and basement membrane disruption, even when density appears to remain the same (204). The practical difficulty is that several preclinical and clinical datasets conflate these endpoints, subsequently inferring functional benefits from structural measures or deducing diminished

aggressiveness from density decreases that may correlate with exacerbated hypoxia and elevated interstitial pressure (205). Perfusion assessments are influenced by imaging modality, temporal sampling, and region-of-interest bias, whereas density estimations are affected by sectioning method, marker selection, and geographical heterogeneity; neither serves as a direct proxy for oxygenation or effective drug exposure (206, 207). Perfusion, density, normalization, and leak are considered as distinct yet interconnected vascular endpoints. Interpretation should account for the specific properties of each assay, with endpoint selection aligned to the treatment mechanism under investigation (206, 207).

Model selection and interpretability across experimental systems

The model used in prostate cancer angiogenesis research has a significant effect on what can be said about vascular control, since each system maintains distinct layers of tumor-stroma-immune interactions. Standard cell lines enable manageable perturbations and provide distinct measurements of secreted angiogenic mediators (208); however, they diminish microenvironmental feedback and often fail to capture lineage plasticity adequately (208, 209). Organoids partially restore epithelial architecture and gradient formation, making them valuable for assessing alterations in hypoxia-responsive programs and junctional regulators throughout treatment (210). However, they often lack native vasculature and complete immune components unless specifically designed. Syngeneic models preserve a functional immune system and facilitate the examination of inflammatory regulation of endothelial activation and permeability (210); nevertheless, tumor genetics and growth kinetics may not accurately reflect the underlying pathology. Xenografts broaden the range of human tumors and facilitate the establishment of conventional vascular targets. However, immune insufficiency and stromal interactions between different species make it harder to understand cytokine signaling, myeloid recruitment, and matrix remodeling (211). Methodological diversity in implantation location, matrix use, and imaging method exacerbates the challenges of cross-study harmonization.

Reproducibility issues: Assay standardization and reporting gaps

In this discipline, reproducibility is limited more by the discrepancy between dynamic physiology and static measurement windows than by the lack of biological signal (212). For example, redox buffering, stress-sensing kinases, and inflammatory transcriptional programs change quickly as oxygen tension, substrate availability, and cell-state transitions change (212). As a result, assays that appear technically similar may actually evaluate distinct biological states. Variability in pre-analytical handling, stimulation settings, and sampling time relative to perturbation can substantially alter experimental outputs (213). One practical problem is that cross-study integration often treats assay labels as interchangeable, even though their operational definitions differ (213). For example, the choice of antibody clone, gating strategies, normalization anchors, and thresholding rules can turn a continuous distribution into inconsistent categorical calls (214, 215). Methodological restrictions exacerbate this issue: batch effects, restricted dynamic range, inadequate calibration, and undisclosed limits of detection are prevalent, but negative controls and duplicate structure are inconsistently defined (216). Priority should be given to standardization and transparent reporting rather than platform comparison, as platform performance depends on application context and sample quality (217). The main idea is that biological variability is getting mixed up with measurement variability. In experiments, the goal is to separate them by using standardized metadata, pre-defined analytic pipelines, and clear reporting of exclusions and uncertainty (217). The objective of interpretation is not to eliminate biological variability, but to improve cross-platform comparability so that mechanistic conclusions are supported by stable and reproducible data (217, 218). Figure 6 highlights that commonly used pyroptosis and inflammasome readouts intersect with multiple death programs and are further shaped by sampling, assay design, and temporal mismatch, such that individual signals do not uniquely resolve mechanisms without cell-resolved and context-matched interpretation. Interpreting pyroptosis–angiogenesis relationships requires aligning assay-derived signals with their true biological scope, as structured in Table 5.

Artificial intelligence and future perspectives

Multi-modal links between inflammasomes and vascular phenotypes

Inflammasome activity and vascular behavior are linked via tightly controlled endothelial integrity, leukocyte recruitment, and thrombogenic balance. However, these relationships are generally based on partial snapshots rather than on simultaneously observable phenotypes (195, 236). Multi-modal integration may be beneficial by correlating molecular readouts of inflammasome priming and activation with concurrent vascular characteristics, including perfusion heterogeneity (237), permeability indicators, and endothelial activation states within tumor and peritumoral compartments. The regulatory hinge is that cytokine processing and pore formation associated with pyroptosis may indirectly alter vascular tone and barrier function via paracrine signaling (237). This also changes the cellular makeup that controls the availability of angiogenic cues. One problem with practical integration is that datasets usually divide markers and phenotypes by platform, timepoint, and sampling location (238). This increases the possibility that observed associations may reflect study design characteristics rather than underlying biology (239). Some methodological problems include the cohorts being in different domains, label noise in imaging-derived endpoints, non-random missing values, and treatment exposures that affect both inflammasome markers and vascular readouts (238, 239). In theory, integrated models can rank candidate coupling patterns, find marker-phenotype pairs that don't match, and suggest where the same marker might map to different vascular regimes depending on the microenvironment (240). In practice, those outputs need to be anchored in the future with pre-specified acquisition windows and harmonized preprocessing (240). The broader translational goal is to improve patient stratification and identify clinically actionable vascular-inflammatory states that may support more precise therapeutic intervention strategies in prostate cancer.

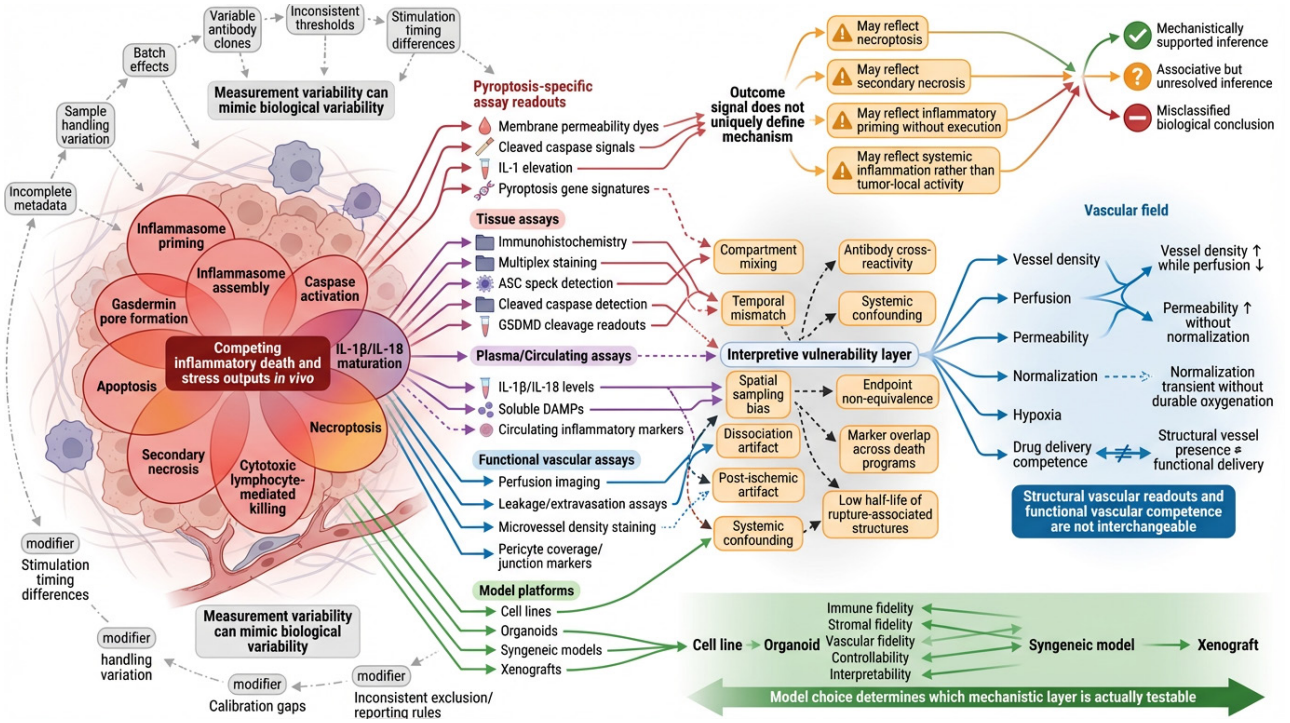

Figure 6. Interpretive limits in pyroptosis readouts and vascular endpoints
The figure integrates inflammasome priming, caspase activation, and gasdermin pore formation with overlapping death programs, emphasizing that in vivo outputs are not pathway-specific. Common assays, including membrane permeability dyes, cleaved caspases, cytokine levels, and detection of the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), are shown alongside tissue and plasma measurements that vary by compartment and time point. These readouts can reflect pyroptosis, necroptosis, or secondary necrosis, depending on context. An interpretive layer highlights confounders such as sampling bias, antibody cross-reactivity, and temporal mismatch, which complicate causal attribution. In the vascular field, density, perfusion, permeability, and normalization are depicted as non-equivalent endpoints. Model systems further constrain inference, as each preserves distinct aspects of immune, stromal, and vascular biology rather than a unified physiological state
ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain

Table 5. Assay vulnerability mapping across inflammatory and vascular measurement layers

Analytical layer (biological context)	Measurement platform/tool	Direct biological readout captured	Frequent interpretation error	Evidence context (model/system type)	Reproducibility and stability limitation	Ref
Cell death classification interface	Immunohistochemistry, permeability dyes	Membrane integrity loss, protease cleavage signals	Mislabeling mixed death programs as pyroptosis	Tissue sections, bulk assays	Marker overlap; indistinguishable morphology across pathways	(219)
Inflammatory output assessment layer	Cytokine quantification (plasma/tissue)	Released IL-1 family cytokine concentrations	Inferring execution events from downstream cytokine levels	Clinical samples+tumor lysates	Source ambiguity; systemic confounding signals	(220)
Priming-state detection layer	Bulk transcriptomics (RNA-seq)	Expression of inflammasome-related genes	Equating gene expression with functional activation	Bulk tissue sequencing	mRNA does not reflect protease activity or assembly	(5, 221)
Inflammasome assembly observation layer	ASC speck imaging, caspase cleavage assays	Presence of inflammasome complexes at fixed timepoints	Assuming temporal continuity from static detection	*In vitro* systems+fixed tissues	Transient events not captured; timing bias	(222)
Single-cell inflammatory mapping layer	Single-cell RNA sequencing	Cell-resolved inflammatory gene programs	Inferring enzymatic activity from transcriptional profiles	Human and model single-cell datasets	Dissociation artifacts; ambient RNA interference	(223)
Vascular structure quantification layer	Microvessel density staining (CD31/CD34)	Vessel counts per defined tissue area	Interpreting density as functional vascular competence	Histological studies	Spatial heterogeneity; no functional information	(224)
Perfusion characterization layer	Functional imaging (MRI, Doppler, contrast-based)	Blood flow distribution and velocity patterns	Assuming perfusion equals oxygenation or drug delivery	Clinical imaging+preclinical models	Modality variability; temporal instability	(225, 226)
Vessel stabilization assessment layer	Pericyte coverage, junctional integrity metrics	Structural features of vessel maturation	Interpreting transient normalization as sustained improvement	Preclinical+limited clinical inference	Lack of longitudinal validation	(227)
Barrier integrity evaluation layer	Leakage assays, contrast extravasation	Degree and dynamics of vascular permeability	Interpreting leak as improved delivery or angiogenesis	Imaging+experimental models	Leak does not correlate with effective delivery	(228)
Multi-signal integration layer	Composite inflammasome scoring systems	Aggregated signals across pathway stages	Treating composite indices as single biological states	Multi-omics integration studies	Temporal and compartmental mismatch	(229)
Experimental model dependency layer	Cell lines, organoids, xenografts, syngeneic models	Context-specific signaling under defined systems	Overgeneralizing findings across incompatible models	Experimental platforms (diverse)	Loss of immune/vascular fidelity; species differences	(230-232)
Cross-study comparability layer	Multi-lab datasets, replicated experiments	Variability across protocols and datasets	Assuming equivalence across assay conditions	Cross-study analyses	Batch effects; protocol inconsistency; detection limits	(233-235)

IL-1, interleukin-1; RNA-seq, RNA sequencing; mRNA, messenger ribonucleic acid; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; RNA, ribonucleic acid; CD31, cluster of differentiation 31; CD34, cluster of differentiation 34; MRI, magnetic resonance imaging

Imaging-assisted quantification of vascular function and inflammation

Imaging-based characterization of vessel function and inflammatory state has become crucial to integrating microvascular activity with tumor biology, since perfusion, permeability, and endothelial activation are not interchangeable readouts and frequently vary within the same lesion (241, 242). Functional vascular imaging typically measures parameters such as blood flow, transit time, oxygenation surrogates, and leakiness. Molecular or cellular imaging can also reveal leukocyte recruitment, macrophage burden, or endothelial adhesion signals (242). This enables a more integrated characterization of vascular competence relative to inflammatory pressure. One important idea in regulation is that inflammatory cytokine signaling and hypoxia-responsive programs alter the structure of endothelial junctions and the glycocalyx, shifting the balance between stable perfusion and pathologic permeability (241, 242). This can make structural imaging look like "high vascularity" even when convective delivery and oxygenation are poor and uneven. The practical integration limit is that many clinical pipelines treat these measurements as separate biomarkers rather than as linked states (243). This is because vessel diameter, flow heterogeneity, and immune cell margination are all linked in real time, and therapy can alter their relationships over short periods. There are some serious methodological problems (243): spatial resolution, motion artifacts, partial-volume effects, contrast-agent kinetics, and model assumptions can all affect estimates of perfusion and permeability. Inflammatory tracers may show cell density but not activation phenotype or compartmental localization (244). Imaging approaches are most useful when applied to identify stable vascular-inflammatory state markers that may support biologically informed stratification while avoiding causal claims that remain experimentally unverified.

Predictive support for target prioritization under validation constraints

Predictive support for target prioritization is becoming more common as a way to bridge the gap between mechanistic plausibility and clinical tractability (245). This is especially true when the candidate space includes endothelial programs, inflammatory mediators, and stromal regulators that interact in nonlinear ways and change with therapy (246). In this case, prediction is less about picking the "best" target and more about placing intervention sites in ways likely to change how vessels function without weakening the immune system or strengthening escape pathways (246, 247). One useful regulatory anchor is that feedback and redundancy often limit pathway activity. This means that suppressing a single proangiogenic or proinflammatory node can be undone by parallel ligands, receptor crosstalk, or metabolic rewiring that keeps endothelial cells alive while altering permeability and leukocyte motility (248). Validation and standardization limitations exacerbate the issue, as model performance may appear consistent within a single cohort but deteriorate with alterations in acquisition protocols, sample processing, or endpoint definitions (249). Furthermore, ground truth is frequently represented indirectly (e.g., survival, radiographic response) rather than as a direct assessment of the targeted vascular or inflammatory mechanism (249). It is hard to distinguish correlation-driven prioritization from causal plausibility without perturbational data or strong natural experiments (250). Also, uncertainty quantification is often underreported, even when it is very important for making safe decisions. It should also be clear that prediction ranking must be re-evaluated over time as validation improves. Ultimately, these predictive frameworks may help prioritize clinically relevant inflammasome-associated vascular targets and support the more rational integration of biomarker-guided therapeutic strategies in prostate cancer (249, 250).

Discussion

The available literature increasingly supports a link between inflammasome-associated pyroptotic signaling and vascular remodeling in prostate cancer; however, this interaction appears more context-dependent and spatially variable than many simplified inflammatory models suggest. Across experimental systems, endothelial activation, cytokine amplification, hypoxia-associated stress, and myeloid-cell recruitment often co-occur within the same tumor regions, making it difficult to determine whether inflammasome activity directly drives angiogenic remodeling or instead reflects broader microenvironmental adaptation to chronic tissue stress. This distinction is particularly important in prostate tumors with heterogeneous perfusion, intermittent hypoxia, and uneven inflammatory distribution. Another key issue is that inflammatory activation and pyroptotic execution are often conflated, despite representing biologically distinct processes. In many studies, elevated inflammasome-related markers are presented as evidence of active pyroptosis even when membrane rupture, pore persistence, or terminal lytic execution are not directly demonstrated. Similarly, vascular dysfunction is often inferred from structural or histological observations without parallel confirmation of functional perfusion or therapeutic delivery efficiency. These limitations may partially explain why reported vascular outcomes remain inconsistent across experimental models and translational settings. The present evidence also suggests that pyroptotic signaling cannot be interpreted exclusively as either protective or pathologic within tumor vascular niches. Depending on timing, metabolic state, local cytokine balance, and endothelial stability, inflammatory signaling may transiently support immune accessibility and adaptive remodeling in some regions while promoting leakiness, endothelial stress, and disorganized vascular behavior in others. As a result, angiogenic consequences likely arise from dynamic interactions among inflammatory amplification, tissue repair responses, stromal adaptation, and vascular compensation rather than from isolated pathway activation alone. Methodological variability further complicates mechanistic interpretation. Differences in tissue sampling, experimental timing, biomarker selection, and spatial resolution frequently limit direct comparisons between studies. In addition, bulk inflammatory measurements may obscure compartment-specific signaling across tumor, stromal, endothelial, and immune-cell populations. Greater integration of spatially resolved analysis, functional vascular assessment, and temporally coordinated inflammatory profiling may therefore be necessary to clarify how inflammasome-associated pathways influence clinically relevant vascular outcomes in prostate cancer.

Conclusion

Current evidence suggests that inflammasome-associated pyroptotic signaling contributes to angiogenic remodeling in prostate cancer through interconnected effects on endothelial activation, cytokine amplification, metabolic stress adaptation, and microenvironmental heterogeneity. Mechanistic findings increasingly support roles for IL-1–associated inflammatory signaling, gasdermin-mediated membrane permeabilization, and myeloid-cell reprogramming in shaping vascular permeability, endothelial behavior, and regional perfusion dynamics within prostate tumor microenvironments. At the same time, these pathways appear highly context-dependent, with vascular consequences varying with hypoxic burden, inflammatory intensity, spatial compartmentalization, and local tissue repair capacity. Despite growing mechanistic insight, several translational and methodological limitations remain unresolved. Many currently available studies rely on indirect vascular readouts, static tissue measurements, or bulk inflammatory analyses that insufficiently distinguish inflammasome priming from terminal pyroptotic execution and often fail to capture spatially heterogeneous vascular behavior *in vivo*. In addition, structural angiogenic endpoints do not consistently reflect functional perfusion quality, therapeutic delivery efficiency, or immune accessibility across heterogeneous tumor regions. These limitations continue to complicate mechanistic interpretation and cross-study reproducibility. Future progress in this field will likely depend on integrating spatial inflammatory profiling, functional vascular assessment, temporally resolved analysis, and cell-specific biomarker validation to improve mechanistic precision and translational interpretability. A more refined understanding of how inflammasome-associated pathways interact with endothelial adaptation, stromal remodeling, and immune accessibility may ultimately support the development of safer, more context-sensitive therapeutic strategies for prostate cancer.

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Ethics Approval and Consent to Participate

Not applicable. This article is a review based exclusively on previously published literature and does not involve human participants, human data, or animal subjects.

Authors' Contributions

HJA A conceptualized the study, designed the framework, and drafted the manuscript. RK J contributed to the literature review and interpretation. M N and R S contributed to literature curation and critical analysis. D P and MA A contributed to data organization and manuscript revision. NK T and R S provided methodological input and supervised the study. All authors reviewed and approved the final manuscript and are accountable for all aspects of the work.

Conflicts of Interest

The authors declare that they have no financial or non-financial conflicts of interest related to the preparation, authorship, or publication of this manuscript.

Declaration

The authors declare that they have not used any artificial intelligence tools or technologies to prepare this manuscript.

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