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CLINICAL AND PROGNOSTIC SIGNIFICANCE OF PYROPTOSIS MARKERS IN THE PROGRESSION OF AXIAL SPONDYLOARTHRITIS

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Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease predominantly affecting the axial skeleton, including the spine and sacroiliac joints. Pyroptosis — a caspase-dependent pro-inflammatory form of programmed cell death — plays a significant role in the pathogenesis of axSpA. Recent evidence suggests that activation of the NLRP3 inflammasome, elevated levels of IL-1β and IL-18, and cleavage of gasdermin D may correlate with disease progression and inflammatory activity. This review discusses the relationship between pyroptosis markers and clinical parameters, radiological progression, and inflammatory activity in axSpA. Investigation of pyroptosis markers may have considerable value for early diagnosis and the development of targeted therapeutic strategies.

Keywords

axial spondyloarthritis, pyroptosis, NLRP3 inflammasome, gasdermin D, IL-1β, IL-18, clinical prognosis, biomarkers

Axial spondyloarthritis (axSpA) sits at an uncomfortable intersection of immunology and orthopedics: a disease that quietly erodes the spine and sacroiliac joints over years, often long before conventional imaging catches up with the clinical picture. Affecting roughly 0.1–1.4% of the global population, axSpA shows a particular predilection for HLA-B27 carriers, though the antigen alone is far from the whole story. Clinically, the disease spans a spectrum — from non-radiographic axSpA (nr-axSpA), where structural damage is not yet visible on plain X-ray, to full-blown ankylosing spondylitis (AS), defined by unambiguous sacroiliitis on conventional radiography [1].

The arrival of biologic therapies — particularly TNF inhibitors and IL-17 inhibitors — transformed clinical outcomes for many axSpA patients. Yet a disquieting reality remains: a meaningful proportion of patients still progress structurally despite treatment, and we lack reliable tools to identify them early. Crucially, this gap has driven growing interest in novel biomarkers that can go

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beyond CRP and ESR to predict disease trajectory, guide therapeutic decisions, and, ultimately, improve long-term functional outcomes [2].

Pyroptosis occupies an intriguing niche in cell biology — it is neither the quiet, orderly exit of apoptosis nor the chaotic rupture of necrosis, but something in between: an inflammatory form of programmed death that deliberately broadcasts a danger signal to the surrounding tissue. At its core, the pathway hinges on pattern recognition receptor activation, inflammasome assembly, and the caspase-mediated cleavage of gasdermin D (GSDMD). The resulting GSDMD pores punch holes in the plasma membrane, triggering cell swelling and the release of IL-1β (IL-1ββ and IL-18 into the extracellular space [3]. Growing evidence implicates pyroptotic pathways in the perpetuation of inflammation in various autoimmune and musculoskeletal disorders.

In axSpA specifically, the NLRP3 inflammasome and its downstream effectors appear to be far more than innocent bystanders in the inflamed synovium and enthesis. This review brings together current evidence on the clinical and prognostic significance of pyroptosis-related markers in axSpA, examining what they tell us about disease activity and structural progression, and why they may deserve a place in future diagnostic and therapeutic strategies [4].

Untangling the pathogenesis of axSpA is a bit like trying to solve a puzzle where several pieces look identical but belong in different places. The genetic architecture is dominated by HLA-B27 — present in 85–95% of AS patients — yet this antigen alone is clearly insufficient to cause disease. Why? Because most HLA-B27-positive individuals never develop axSpA. Current hypotheses implicate aberrant peptide presentation, intracellular protein misfolding, and activation of the unfolded protein response (UPR) as potential bridges between genetic susceptibility and actual disease onset [5].

Immunologically, axSpA is a disease that has lost its internal brakes on both the innate and adaptive sides. Macrophages, dendritic cells, and innate lymphoid cells converge on the sacroiliac joints and entheses, where toll-like receptors and NOD-like receptors continuously sample the environment for danger signals — microbial or otherwise. When those signals arrive, the downstream inflammatory cascade follows with remarkable efficiency, and in axSpA, it seems to never quite shut off [6].

At the cytokine level, the IL-23/IL-17 axis commands much of the narrative in axSpA, but TNF-α, IL-1β, and IL-6. Th17 cells and innate lymphoid cell type 3 (ILC3s) are major sources of IL-17A and IL-22, which promote entheseal inflammation and new bone formation. IL-1β, — unleashed primarily through inflammasome-dependent cleavage — amplifies local damage, drives

osteoclastogenesis, and encourages fibrosis. It is this intricate cytokine choreography, rather than any single mediator, that determines how aggressively the joints remodel [7].

Adding another dimension to this picture, recent transcriptomic and proteomic work has detected consistent inflammasome-related gene signatures in both synovial tissue and circulating blood cells of axSpA patients. These molecular fingerprints are not incidental noise — they point toward pyroptotic pathways as active participants in the inflammatory milieu, not merely downstream consequences, and have prompted a focused investigation into their prognostic value [4].

When pyroptosis was first observed in macrophages dying from intracellular bacterial infections, it looked like a curiosity — an unusual form of cell death that happened to be messy and inflammatory. The name itself was chosen deliberately to signal this: unlike the silent cleanup of apoptosis, pyroptosis is designed to make noise, to alert the immune system that something dangerous is happening. Two main molecular routes lead to this endpoint: the canonical caspase-1 pathway and the non-canonical caspase-4/5 pathway in humans (caspase-11 in mice) [3].

In the canonical route, the NLRP3 inflammasome assembles in resp — a multiprotein complex consisting of the NLRP3 sensor, the ASC adaptor protein, and pro-caspase-1 — is triggered by danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs). Upon assembly, auto-cleavage of pro-caspase-1 generates active caspase-1, which then cleaves pro-IL-1β and pro-IL-18 into their mature inflammatory forms and cuts GSDMD at a critical linker domain. The liberated N-terminal fragment of GSDMD migrates to the plasma membrane and punches a ring of pores — allowing cytokines to pour out and ions to flood in, generating the osmotic imbalance that ultimately tears the cell apart [8].

What makes NLRP3 particularly troublesome in joint diseases is its remarkably catholic taste in activating stimuli: uric acid crystals, extracellular ATP, reactive oxygen species, fatty acids, hypoxia — all of which accumulate naturally in an inflamed joint. In axSpA, there is the additional possibility that mechanical stress at entheseal attachment sites may itself trigger NLRP3 activation, forging a direct link between the biomechanical loading characteristic of the disease and innate immune amplification [9].

NLRP3 does not operate alone. Emerging evidence points to contributions from NLRC4, AIM2, and PYRIN inflammasomes in inflammatory arthritis tissues, suggesting that the pyroptotic landscape in axSpA may be more diversified than initially appreciated. The non-canonical caspase-4/5 pathway is also worth noting

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here: activated by cytosolic LPS, it becomes particularly relevant in axSpA given the well-documented evidence of increased intestinal permeability in this population — a leaky gut that may be continuously feeding pro-pyroptotic signals into the systemic circulation [10].

The clinical evidence linking NLRP3 to axSpA disease activity is accumulating steadily. Multiple studies have now documented that NLRP3 protein levels and ASC speck formation — a microscopic signature of inflammasome assembly — are significantly elevated in axSpA patients compared to healthy individuals, and, importantly, that these elevations track with how patients are actually feeling: higher BASDAI and ASDAS scores go hand in hand with greater inflammasome activation [11].

Looking directly at the tissue tells a compelling story. Immunohistochemical analysis of synovial and entheseal biopsies from axSpA patients shows NLRP3, ASC, and activated caspase-1 clustering together — particularly in the macrophages and mast cells that have taken up residence at sites of inflammation. This co-localization is not simply a static snapshot; it reflects an ongoing pyroptotic program that is likely feeding the very inflammation it was meant to resolve [12].

Genetic data add a causative dimension to this picture. Polymorphisms in NLRP3 itself, and in CARD8 — an inhibitory partner within the inflammasome complex — have been linked to differences in disease severity and radiological progression across axSpA cohorts. These are not random associations; they suggest that heritable variation in inflammasome regulation shapes how aggressively axSpA unfolds in individual patients [13].

Controlled in vitro experiments round out the picture. Monocyte-derived macrophages isolated from axSpA patients show a noticeably heightened readiness to release IL-1β via NLRP3-dependent pathways when challenged with LPS and ATP — as though the cells are already primed and waiting for the trigger. This inflammasome hair-trigger may help explain something clinicians have long observed: the tendency of axSpA to fluctuate between relative calm and acute flares, sometimes without obvious external cause [4].

If the NLRP3 inflammasome is the trigger of pyroptosis, gasdermin D is the gun. Cleavage of GSDMD by caspase-1 generates the N-terminal domain (GSDMD-NT) — the fragment that actually punches holes in the plasma membrane and drives cell lysis. From a biomarker perspective, this makes GSDMD-NT particularly attractive: measuring it in blood or tissue provides a direct, rather than surrogate, readout of active pyroptosis, something that most other inflammatory markers simply cannot offer [8].

In practice, axSpA patients consistently show elevated plasma GSDMD-NT levels relative to both healthy controls and patients with non-inflammatory back pain — an important distinction that suggests the elevation is not merely a pain response. What is more, GSDMD-NT tracks with established inflammatory markers (CRP, ESR) and clinical activity scores (BASDAI, ASDAS-CRP), implying that it captures disease burden across both the blood and the joint [14].

Perhaps the most clinically consequential finding from longitudinal work is the emerging link between baseline GSDMD-NT and subsequent structural damage. Patients with higher GSDMD-NT at the start of follow-up appear more prone to radiographic sacroiliitis advancement and new syndesmophyte formation over a two-year window — a pattern that, if confirmed in larger prospective cohorts, would position GSDMD-NT as a genuine predictive biomarker rather than just a disease activity correlate [15].

There is also a practical therapeutic angle: among axSpA patients treated with TNF inhibitors, those who respond clinically show a meaningful fall in circulating GSDMD-NT over 24 weeks, while non-responders do not. This on-treatment behaviour suggests GSDMD-NT could serve a dual purpose — not only flagging high-risk patients before treatment begins, but also providing real-time feedback on whether the chosen therapy is actually doing what it is supposed to [14].

Interleukin-1β (IL-1β) is one of the principal downstream effectors of NLRP3 inflammasome activation and caspase-1 cleavage, and represents a pivotal mediator of inflammation in axSpA. Elevated serum and synovial fluid concentrations of IL-1β have been consistently reported in axSpA patients with active disease, and correlate with indices of systemic inflammation and structural damage [16].

IL-1β promotes multiple pathological processes relevant to axSpA, including upregulation of adhesion molecules on endothelial cells, stimulation of prostaglandin synthesis, induction of matrix metalloproteinase activity, and direct activation of osteoclasts. Importantly, IL-1β also stimulates the IL-23/IL-17 axis by promoting Th17 cell differentiation, thereby linking pyroptotic innate immune signals to adaptive immune dysregulation characteristic of axSpA [17].

Clinical trial data on anakinra — recombinant IL-1 receptor antagonist — in AS patients offer modest but genuine evidence of benefit, particularly in patients selected on the basis of elevated baseline IL-1β levels. These results are not dramatic, but they matter because they demonstrate that IL-1β in a subset of axSpA patients and highlight the need for biomarker-guided patient selection in future trials [18].

IL-18 does not receive the same attention as IL-1β, but its role in axSpA should not be underestimated. As another caspase-1 substrate, IL-18 stimulates IFN-γ production in T cells and NK cells, amplifying the Th1 arm of the immune response in a manner that complements — and compounds — the Th17-driven inflammation already present. Elevated serum IL-18 in axSpA patients correlates with disease activity and tracks particularly closely with extra-articular manifestations such as uveitis and inflammatory bowel disease. Whether IL-18 independently predicts structural progression remains to be settled in properly designed longitudinal studies [19].

Measuring caspase-1 activity directly — rather than inferring it from downstream products — provides perhaps the most mechanistically pure readout of canonical inflammasome engagement. Studies doing exactly this in axSpA peripheral blood monocytes find reliably elevated enzymatic activity versus healthy donors, activity that tracks with both serum IL-1β and clinical disease scores. In other words, the inflammasome is not just genetically predisposed to fire more readily in axSpA — it is actually firing [20]. Zooming out beyond caspase-1, the gut-joint axis in axSpA invites scrutiny of the non-canonical caspase-4/5 pathway. Subclinical gut inflammation is present in up to 60% of axSpA patients — a striking prevalence that has long puzzled rheumatologists. Given that caspase-4/5 is activated by cytosolic LPS from translocating gut bacteria, this pathway may represent a mechanistic bridge between intestinal dysbiosis and joint inflammation, turning a leaky gut into a persistent source of pro-pyroptotic stimuli [10].

Caspase-3, long regarded as the quintessential apoptotic executor, has recently been found to drive a secondary pyroptotic pathway via gasdermin E (GSDME) — adding yet another layer to the cell death landscape in inflammatory disease. In axSpA, this pathway is still being mapped, but early transcriptomic signals from inflamed entheseal tissue show upregulated GSDME expression, hinting that secondary pyroptosis may contribute to tissue damage in ways that have not yet been systematically studied [21].

Few challenges in rheumatology are as clinically frustrating as predicting which axSpA patient will progress structurally. Syndesmophyte growth and sacroiliac joint fusion are irreversible changes that chip away at functional independence, often silently, over years. The existing predictors — elevated CRP, elevated ESR, baseline syndesmophyte burden, smoking — capture some of this risk, but their sensitivity and specificity leave a great deal to be desired, and too many high-risk patients slip through unrecognized [22].

This is where pyroptosis markers begin to look genuinely promising. In cross-sectional analyses of established AS, GSDMD-NT and IL-18 levels correlate

significantly with mSASSS — the modified Stoke Ankylosing Spondylitis Spine Score — and these associations survive adjustment for CRP and ESR. Independence from traditional markers is the critical qualifier: it means pyroptosis biomarkers are capturing something about structural risk that routine blood tests are missing [15].

Longitudinal data reinforce this impression. Patients whose inflammasome activation markers remain persistently elevated over 12–24 months accumulate significantly more radiological damage than those with normalized or low levels — a finding consistent with the idea that sustained pyroptotic activity sculpts a pro-osteogenic local environment via IL-1β-mediated signaling cascades that ultimately promote pathological new bone formation [23].

There is, of course, a well-known paradox lurking here: TNF inhibitors can dramatically suppress inflammation yet fail to halt syndesmophyte growth in many patients. This dissociation implies that some osteogenic drivers — Wnt pathway activation and BMP signaling among them — operate independently of conventional inflammation. Whether pyroptosis markers capture radiological risk via these inflammation-independent routes, or whether they only track the inflammatory component, remains an open and important question [24].

The reach of axSpA extends well beyond the spine. Acute anterior uveitis, psoriasis, and inflammatory bowel disease appear in a significant minority of patients, reflecting shared pathogenic circuitry rather than coincidence. The fact that inflammasome-related mechanisms have been implicated across all these conditions raises an intriguing possibility: pyroptosis may function as a unifying thread connecting what are otherwise treated as separate organ-specific manifestations, and understanding this connection could meaningfully reshape how clinicians approach systemic disease management [25].

Uveitis, affecting 25–40% of axSpA patients at some point during their disease course, provides a window into ocular pyroptosis. Retinal pigment epithelial cells and uveal stromal cells show evidence of inflammasome-driven pyroptotic death during acute episodes, and elevated NLRP3 expression alongside raised IL-1β in ocular tissue and aqueous humor correlate meaningfully with disease severity and recurrence risk. Notably, systemic IL-18 is consistently higher in axSpA patients who experience recurrent uveitis versus those who do not — a distinction that may eventually help identify patients needing more aggressive preventive therapy [19].

The gut dimension is equally compelling. In both IBD and the subclinical gut inflammation characteristic of axSpA, pyroptosis of colonocytes — driven by caspase-4/5 in response to luminal LPS — appears to compromise epithelial integrity, effectively opening a door for microbial antigens to enter the systemic circulation. Once there, these antigens may act as persistent immunological sparks,

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reigniting or sustaining the joint inflammation that clinicians are trying to extinguish [10].

Recognizing pyroptosis as a driver — not merely a consequence — of axSpA inflammation immediately raises the question of whether it can be targeted therapeutically. The early answer from preclinical work is encouraging. MCC950 (CP-456773), a small-molecule inhibitor that selectively blocks NLRP3 ATPase activity and thereby prevents inflammasome assembly, has shown impressive anti-inflammatory potency in murine arthritis models. Whether this translates to human disease remains to be seen, but the mechanistic rationale is solid [26].

The GSDMD pore itself is also a viable target. Disulfiram — a drug already approved for alcohol dependence and therefore with an established safety profile — has been shown to block GSDMD pore formation and dampen pyroptotic inflammation in experimental models. The prospect of repurposing a well-characterized, inexpensive drug for a chronic inflammatory disease is genuinely appealing, though it will need proper clinical validation before it can be recommended [27].

It is worth noting that clinicians may already be modulating pyroptosis without knowing it. TNF inhibitors reduce NLRP3 expression and caspase-1 activity in monocytes from treated axSpA patients — a finding that suggests part of their benefit may flow through inflammasome suppression rather than direct TNF neutralization alone. IL-17 inhibitors, by depleting the cytokine milieu that keeps NLRP3 primed, may similarly exert indirect anti-pyroptotic effects. This raises an interesting question: could the variable clinical responses to these agents be partly explained by differences in baseline pyroptotic tone [2]?

Looking ahead, the most rational therapeutic architecture in axSpA may involve dual targeting: suppressing the adaptive IL-23/IL-17 arm while simultaneously dampening NLRP3-driven innate amplification. This combination approach, if validated, could address the disease more completely than any single-axis intervention. Pyroptosis markers — GSDMD-NT, IL-1β, caspase-1 activity — would naturally fit into this framework as tools for stratifying patients before therapy and monitoring their biological response throughout [28].

The evidence reviewed here is genuinely exciting, but it deserves a measured reading. The majority of studies are cross-sectional, meaning that causality remains an open question: we can observe that pyroptosis markers are elevated in active disease, but we cannot yet say with confidence that they drive the outcomes we are trying to predict. Sample sizes are generally modest, populations are heterogeneous in terms of disease duration, HLA-B27 status, and treatment history, and this heterogeneity complicates interpretation [29].

There is also a technical gap that must be addressed before pyroptosis biomarkers can be adopted clinically. Assay methods for GSDMD cleavage products, circulating caspase-1 activity, and ASC specks vary considerably between laboratories, and this pre-analytical and analytical variability makes it genuinely difficult to compare findings across studies. Standardized, validated assays — ideally ones that can be run on routine clinical analyzers — are a prerequisite for any realistic translation into practice [30].

The most pressing research priority is straightforward to articulate, if not to execute: large-scale prospective cohorts with long-term follow-up, designed specifically to test whether pyroptosis markers independently predict radiological progression, loss of spinal mobility, and sustained treatment response. Embedding pyroptosis readouts within multiomics frameworks — integrating genomics, metabolomics, and microbiome data — could both sharpen their prognostic precision and shed light on the mechanistic questions that current studies can only gesture toward [31].

On the therapeutic side, early-phase clinical trials of NLRP3 inhibitors and GSDMD-targeting agents in treatment-refractory axSpA patients would be genuinely valuable — not only for their obvious therapeutic implications, but because they would generate the kind of human mechanistic data that preclinical models simply cannot provide. Pharmacodynamic readouts from such trials could resolve lingering questions about patient selection and help define the populations most likely to benefit from pyroptosis-targeted treatment [28].

Pyroptosis has moved from an immunological curiosity to a mechanistically credible contributor to axSpA pathogenesis in a relatively short period of time. The accumulated evidence is coherent: NLRP3 inflammasome components, GSDMD cleavage products, IL-1β, IL-18, and caspase-1 activity are all elevated in axSpA, track with clinical disease activity, and — in early data — predict structural progression. This convergence across multiple markers and multiple study designs is reassuring and suggests that the pyroptotic signal in axSpA is real, not artifactual.

The therapeutic implications are equally encouraging: existing biologics appear to partially dampen pyroptotic activity as a secondary effect, and dedicated NLRP3 inhibitors and GSDMD-targeting drugs are queuing up for clinical evaluation. The path forward requires rigorous longitudinal studies, standardized assays, and properly powered trials — none of which are trivial undertakings, but all of which are achievable. If pyroptosis biomarkers deliver on their early promise, they could finally give clinicians something this disease has long lacked: a reliable window into structural risk, early enough to change the outcome.

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