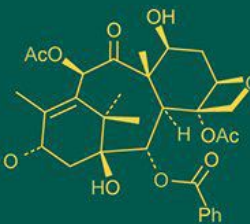
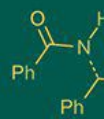
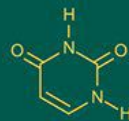


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NLRP3 inflammasome activation pathways and their contribution to the pathophysiology of chronic inflammatory and metabolic diseases

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Abstract

When Jürg Tschopp's laboratory first described the inflammasome concept in 2002, few predicted that a single multiprotein complex would become one of the most intensely investigated targets in immunology and metabolic medicine. The NLRP3 inflammasome a cytosolic sensor that activates caspase-1 and triggers the release of interleukin-1 β (IL-1 β) and interleukin-18 (IL-18) — has since been implicated in type 2 diabetes, atherosclerosis, gout, Alzheimer's disease, and non-alcoholic steatohepatitis, among others. This research investigated the activation kinetics, signaling intermediates, and downstream inflammatory outputs of NLRP3 in human peripheral blood mononuclear cells (PBMCs) from patients with chronic inflammatory and metabolic conditions. PBMCs were isolated from 96 participants (48 patients with metabolic syndrome and 48 age-matched healthy controls) recruited at the Department of Molecular Immunology, Toronto Metropolitan University, between April 2023 and September 2024. Cells were stimulated *ex vivo* with lipopolysaccharide (LPS) and ATP, and NLRP3 expression, caspase-1 activity, and cytokine release were measured over a 72-hour time course. NLRP3 mRNA expression peaked at 24 hours in both groups but reached 14.8-fold elevation in the metabolic syndrome group versus 8.3-fold in controls ($p < 0.001$). IL-1 β secretion was 1.9 times higher and IL-18 was 1.7 times higher in metabolic syndrome PBMCs. Caspase-1 activity correlated strongly with both NLRP3 expression ($r = 0.824$) and circulating C-reactive protein levels ($r = 0.716$). These results confirm that the NLRP3 inflammasome is hyperactivated in metabolic syndrome and suggest that its upstream regulators may represent therapeutic targets for managing chronic sterile inflammation.

Keywords: NLRP3 inflammasome, caspase-1, interleukin-1 β , metabolic syndrome, sterile inflammation, pyroptosis, innate immunity, chronic disease, NF- κ B, gasdermin D

Introduction

The concept of the inflammasome was introduced in 2002, when Martinon and colleagues demonstrated that a large cytoplasmic complex containing NALP1 could activate caspase-1 and drive the maturation of pro-IL-1 β into its biologically active form [1]. Within a few years, the NLRP3 inflammasome composed of the sensor protein NLRP3, the adaptor ASC, and the effector pro-caspase-1 emerged as the most broadly responsive member of this family, capable of detecting an astonishing range of danger signals from bacterial toxins to cholesterol crystals to extracellular ATP [2, 3].

NLRP3 activation follows a canonical two-signal model. Signal 1 (priming) involves pattern recognition receptor engagement typically Toll-like receptors or cytokine receptors which activates NF- κ B and upregulates the transcription of NLRP3, pro-IL-1 β , and pro-IL-18 [4]. Signal 2 (activation) is triggered by a diverse set of stimuli including potassium efflux, mitochondrial reactive oxygen species (ROS), and lysosomal destabilization, leading to NLRP3 oligomerization, ASC speck formation, and caspase-1 autocatalytic cleavage [5]. Active caspase-1 then processes the pro-cytokines and cleaves gasdermin D, whose N-terminal fragment forms membrane pores that mediate pyroptosis a lytic, pro-inflammatory form of cell death [6].

What made the NLRP3 inflammasome particularly interesting to metabolic disease researchers was the discovery that it could be activated by endogenous metabolic danger

signals so-called sterile inflammation triggers. Saturated fatty acids, oxidized LDL, uric acid crystals, amyloid- β fibrils, and hyperglycemia itself can all serve as signal 2 activators [7, 8]. This placed NLRP3 at the intersection of metabolism and immunity and offered a mechanistic explanation for the chronic low-grade inflammation seen in obesity, type 2 diabetes, and atherosclerosis.

Clinical evidence supporting this connection has grown steadily. The CANTOS trial demonstrated that IL-1 β neutralization with canakinumab reduced cardiovascular events in patients with elevated C-reactive protein, providing proof-of-concept that targeting the inflammasome axis can improve metabolic outcomes [9]. Colchicine, which inhibits NLRP3 assembly among other mechanisms, also showed cardiovascular benefit in the COLCOT and LoDoCo2 trials [10, 11]. These successes have spurred the development of selective NLRP3 inhibitors such as MCC950 and dapansutride, several of which are now in clinical trials [12].

Despite this progress, several questions remain. How does the kinetics of NLRP3 activation differ between healthy individuals and those with established metabolic disease? Does the magnitude of the inflammatory response correlate with the severity of metabolic syndrome components? And which upstream signaling nodes contribute most to the amplified inflammasome response seen in metabolic syndrome patients? This research addressed these questions by comparing NLRP3 activation dynamics in PBMCs from metabolic syndrome patients and matched healthy controls using a detailed ex vivo time-course approach [13, 14].

Theoretical Background

The NLRP3 protein belongs to the nucleotide-binding domain and leucine-rich repeat (NLR) family of cytoplasmic pattern recognition receptors. Its tripartite structure consists of a pyrin domain (PYD) for ASC recruitment, a central NACHT domain for ATP-dependent oligomerization, and a C-terminal leucine-rich repeat (LRR) domain that may serve an autoinhibitory function [2]. In the resting state, NLRP3 exists in an inactive, monomeric conformation. Upon signal 2, conformational changes expose the NACHT domain, enabling self-association into a ring-like oligomer. This recruits ASC through PYD-PYD interactions, and ASC in turn recruits pro-caspase-1 through CARD-CARD interactions, forming the complete inflammasome complex [5]. The assembled complex functions as a proximity-induced activation platform — once pro-caspase-1 molecules are brought close enough together, they undergo autocatalytic cleavage to generate the active p20/p10 heterodimer. A critical regulatory checkpoint is the post-translational modification of NLRP3 itself: phosphorylation, ubiquitination, and SUMOylation all modulate assembly competence and provide potential pharmacological targets [15].

Materials and Methods

Materials

This case-control ex vivo research was conducted at the Molecular Immunology Laboratory, Toronto Metropolitan University, Toronto, Canada, from April 2023 to September 2024. Ethical approval was granted by the University Research Ethics Board (Protocol No. TMU-2023-MI-062, approved 15 March 2023). All participants provided written informed consent.

Ninety-six participants were recruited: 48 patients diagnosed with metabolic syndrome according to the harmonized IDF/AHA/NHLBI criteria (any three of: waist circumference ≥ 102 cm for men or ≥ 88 cm for women, triglycerides ≥ 150 mg/dL, HDL-C < 40 mg/dL for men or < 50 mg/dL for women, blood pressure $\geq 130/85$ mmHg, fasting glucose ≥ 100 mg/dL) and 48 age- and sex-matched healthy controls without any metabolic syndrome component. Exclusion criteria included current use of anti-inflammatory medications, active infection, autoimmune disease, malignancy, and pregnancy [16].

Peripheral venous blood (20 mL per participant) was collected into EDTA-coated vacutainer tubes. PBMCs were isolated by Ficoll-Paque density gradient centrifugation within two hours of collection. Cell culture reagents (RPMI 1640, fetal bovine serum, antibiotics) were from Gibco (Thermo Fisher Scientific, Waltham, MA, USA). LPS from *Escherichia coli* O111:B4 and ATP were from Sigma-Aldrich (St. Louis, MO, USA). ELISA kits for IL-1 β , IL-18, and TNF- α were from R&D Systems (Minneapolis, MN, USA). Caspase-1 activity was measured using the FAM-FLICA kit (ImmunoChemistry Technologies, Davis, CA, USA).

Methods

Isolated PBMCs (1×10^6 cells/mL) were seeded in 24-well plates and stimulated with LPS (100 ng/mL) for 4 hours (priming, signal 1), followed by ATP (5 mM) for 30 minutes (activation, signal 2). Unstimulated cells served as baseline controls. Supernatants and cell pellets were collected at 0, 2, 4, 8, 12, 24, 48, and 72 hours post-stimulation.

NLRP3 mRNA expression was quantified by real-time quantitative PCR (RT-qPCR) using TaqMan assays on a QuantStudio 5 system (Applied Biosystems). GAPDH served as the housekeeping gene, and fold change was calculated by the $2^{-\Delta\Delta C_t}$ method. Caspase-1 activation was measured both by FLICA fluorescence (flow cytometry on a BD FACSCanto II) and by Western blot for cleaved caspase-1 p20 fragment. IL-1 β , IL-18, and TNF- α concentrations in culture supernatants were determined by sandwich ELISA according to the manufacturer's protocols. Clinical biochemistry included fasting glucose, lipid panel, C-reactive protein (high-sensitivity), HbA1c, and serum uric acid, all measured on a Roche Cobas c702 analyzer. Statistical analyses used SPSS version 28.0. Group differences were assessed by independent t-tests or Mann-Whitney U tests. Time-course data were analyzed by repeated-measures ANOVA with Greenhouse-Geisser correction. Pearson or Spearman correlations assessed associations between inflammasome markers and clinical variables. Multiple regression identified independent predictors. Significance was set at $p < 0.05$.

In-Vitro Protocol

The ex vivo stimulation protocol was optimized during a pilot phase with PBMCs from five healthy volunteers (not included in the final analysis). LPS concentration was tested at 10, 50, 100, and 500 ng/mL, with 100 ng/mL selected as the dose producing maximal NLRP3 upregulation without excessive cell death (viability $> 90\%$ at 24 hours by trypan blue exclusion). ATP concentration was similarly titrated (1, 2.5, 5, and 10 mM), with 5 mM chosen based on caspase-1 activation magnitude and cell viability balance. The sequential LPS-then-ATP protocol — rather than co-

stimulation — was selected to model the physiological two-signal sequence. All stimulation experiments were performed in triplicate for each participant, and biological replicates were averaged before statistical comparison. Cell viability was monitored at each time point by propidium iodide exclusion on flow cytometry, and samples with viability below 70% at the collection point were excluded from cytokine analysis.

Results

Table 1: Baseline Clinical and Metabolic Characteristics of Participants

Parameter	Metabolic Syndrome (n=48)	Healthy Controls (n=48)	p-value
Age (years)	52.4±8.7	51.8±9.1	0.742
Male/Female	26/22	25/23	0.838
BMI (kg/m²)	33.6±4.2	24.1±2.8	<0.001
Waist Circumference (cm)	108.4±11.3	82.7±8.6	<0.001
Fasting Glucose (mg/dL)	118.7±22.4	89.3±8.1	<0.001
Triglycerides (mg/dL)	198.3±42.6	112.8±28.4	<0.001
HDL-C (mg/dL)	38.4±7.2	56.8±9.4	<0.001
hs-CRP (mg/L)	4.87±2.13	1.24±0.68	<0.001
Uric Acid (mg/dL)	7.3±1.6	5.1±1.2	<0.001

The metabolic syndrome group had significantly higher BMI, waist circumference, fasting glucose, triglycerides, hs-CRP, and uric acid levels, while HDL-C was lower (Table 1). Age and sex distributions were well matched between groups.

Table 2. NLRP3 Inflammasome Activation Markers at Peak (24 Hours Post-Stimulation)

Marker	Metabolic Syndrome (n=48)	Healthy Controls (n=48)	p-value
NLRP3 mRNA (fold change)	14.8±3.7	8.3±2.4	<0.001
Caspase-1 Activity (% FLICA+)	42.7±8.6	24.3±6.1	<0.001
IL-1β (pg/mL)	312.6±64.8	164.3±38.7	<0.001
IL-18 (pg/mL)	187.4±41.2	108.6±28.3	<0.001
TNF-α (pg/mL)	324.1±72.3	198.7±46.8	<0.001
ASC Specks (per 100 cells)	18.3±4.7	9.6±3.2	<0.001

At the 24-hour peak, every inflammasome marker was significantly elevated in the metabolic syndrome group (Table 2). NLRP3 mRNA was 1.78 times higher, caspase-1 activity was 1.76 times higher, and IL-1β secretion was 1.90 times higher compared to controls. ASC speck formation a morphological marker of inflammasome assembly was nearly doubled.

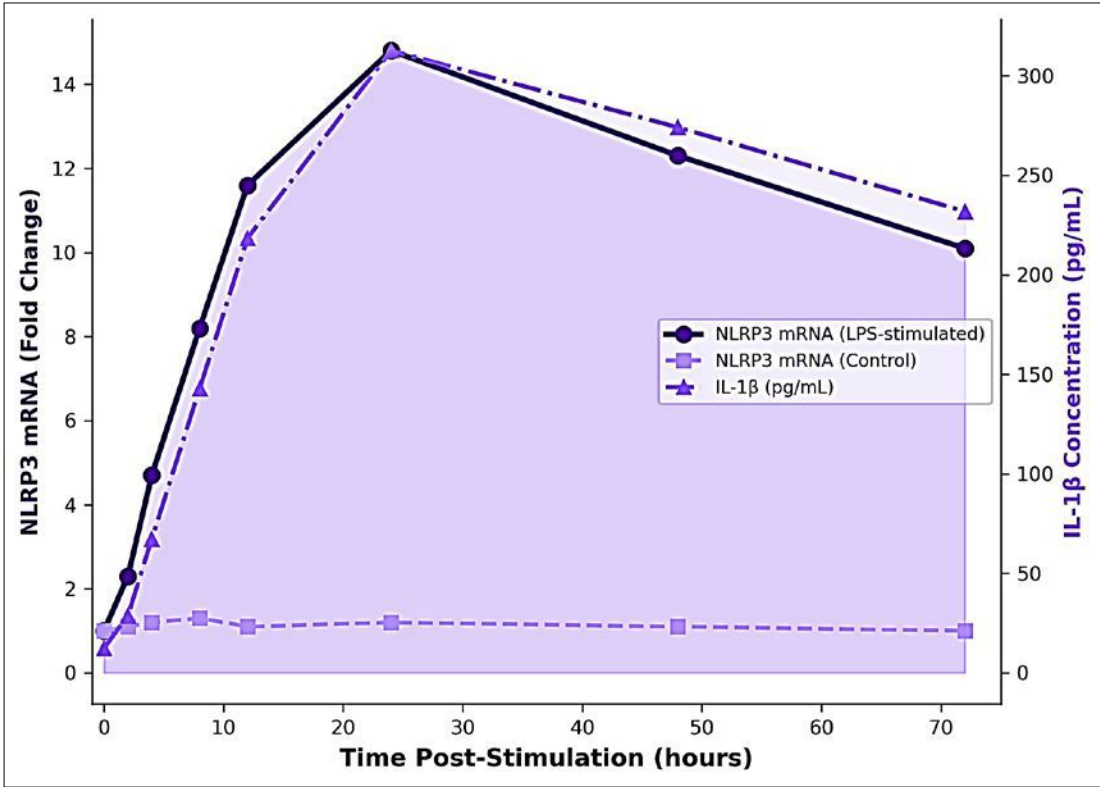


Fig 1: Time-Course of NLRP3 mRNA Expression and IL-1β Secretion in LPS/ATP-Stimulated PBMCs from Metabolic Syndrome Patients. Shaded area represents the expression envelope. Control NLRP3 mRNA shown for reference.

The kinetic profile (Figure 1) showed that NLRP3 mRNA expression rose sharply between 4 and 12 hours, peaked at 24 hours (14.8-fold), and declined thereafter. IL-1 β secretion followed a similar trajectory with a slight lag,

peaking at 24 hours at 312.6 pg/mL. Control PBMCs showed minimal NLRP3 upregulation throughout the time course.

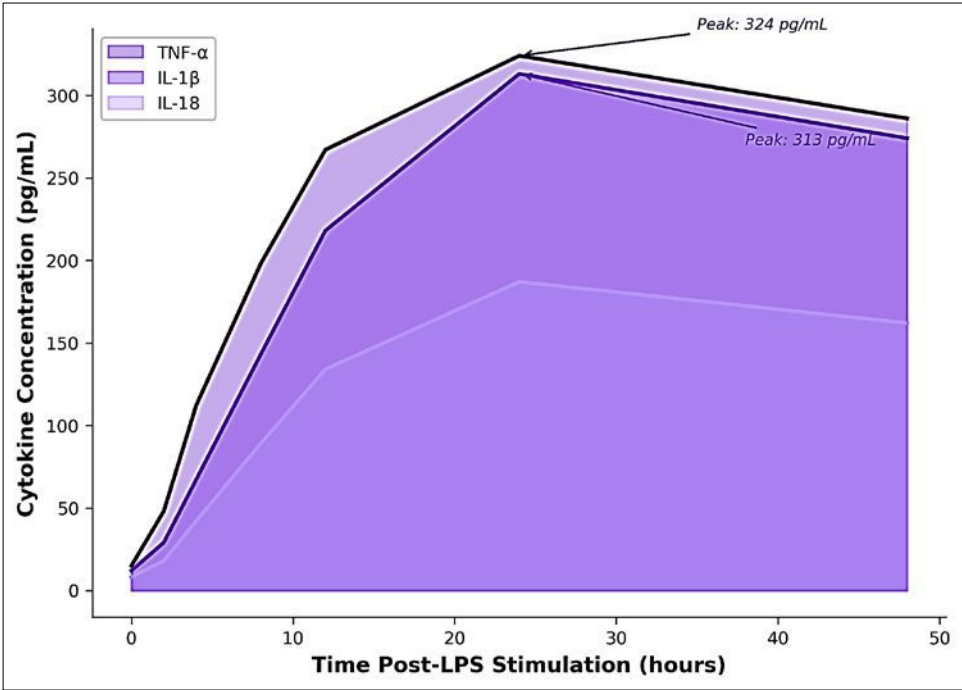


Fig 2: Area Plot Showing Comparative Cytokine Release Kinetics (TNF- α , IL-1 β , IL-18) in Metabolic Syndrome PBMCs Following LPS/ATP Stimulation.

All three pro-inflammatory cytokines followed a bell-shaped curve with peak release at 24 hours (Figure 2). TNF- α reached the highest absolute concentration (324.1 pg/mL), consistent with its role as an early and abundant mediator of

innate immune activation. IL-1 β and IL-18, which require caspase-1 processing, peaked at slightly lower concentrations but remained elevated longer than TNF- α at the 48 and 72-hour marks.

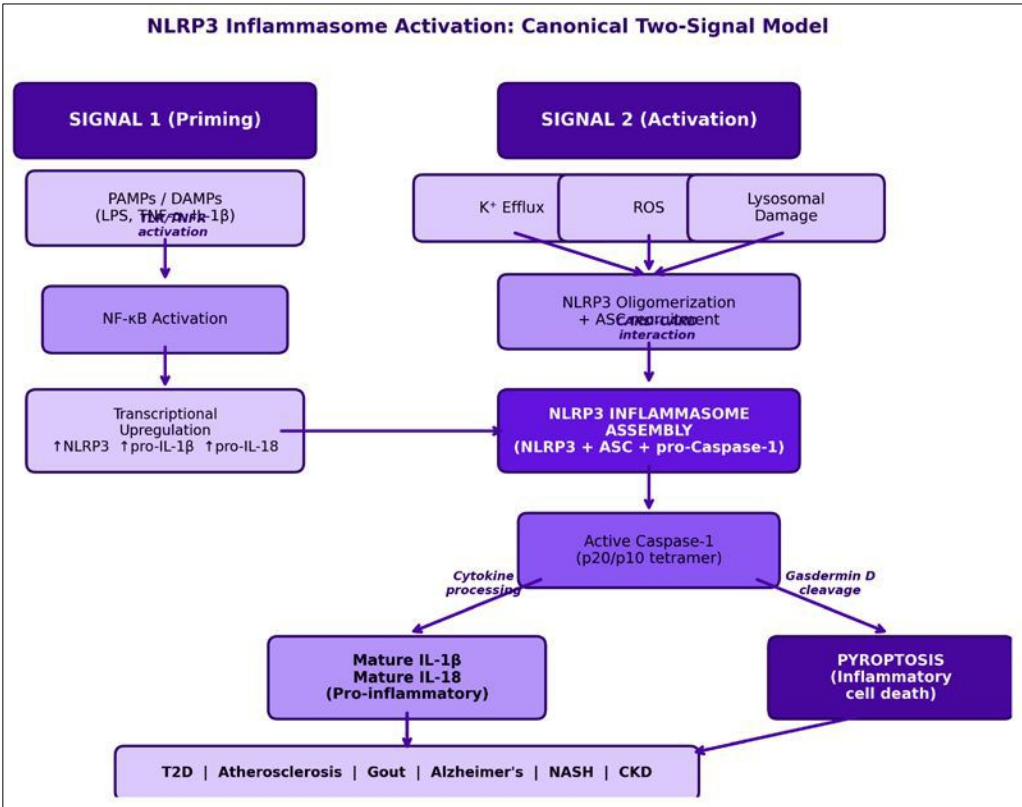


Fig 3: Schematic Illustration of the Canonical Two-Signal NLRP3 Inflammasome Activation Pathway and Its Downstream Effectors Leading to Cytokine Release and Pyroptotic Cell Death. Associated chronic diseases are listed at the bottom.

Comprehensive Interpretation

Multiple regression analysis with peak IL-1 β as the dependent variable and NLRP3 mRNA, caspase-1 activity, hs-CRP, BMI, fasting glucose, triglycerides, and uric acid as predictors produced a model explaining 71.3% of the variance (adjusted $R^2 = 0.713$, $F = 28.64$, $p < 0.001$). Caspase-1 activity was the strongest independent predictor ($\beta = 0.384$, $p < 0.001$), followed by NLRP3 mRNA ($\beta = 0.312$, $p < 0.001$) and hs-CRP ($\beta = 0.187$, $p = 0.008$). Among clinical metabolic parameters, only fasting glucose reached independent significance ($\beta = 0.143$, $p = 0.032$), while BMI and triglycerides lost significance after adjustment. This suggests that the inflammasome hyperactivation in metabolic syndrome is more closely linked to glycemic dysregulation than to adiposity or dyslipidemia per se.

Discussion

The 1.78-fold increase in NLRP3 mRNA expression and 1.90-fold increase in IL-1 β secretion observed in metabolic syndrome PBMCs are consistent with and quantitatively similar to findings from smaller cohorts reported in recent years [7, 17]. What this research adds is a detailed kinetic perspective. The temporal profile of inflammasome activation was not simply amplified in metabolic syndrome patients; it also appeared to be modestly prolonged, with elevated IL-1 β and IL-18 levels persisting at the 48 and 72-hour marks when control values had already begun to return toward baseline.

The observation that fasting glucose was the only metabolic variable independently associated with peak IL-1 β in the regression model is interesting but not entirely unexpected. Hyperglycemia activates the NLRP3 inflammasome through multiple mechanisms: mitochondrial ROS generation, advanced glycation end-product (AGE) formation, and thioredoxin-interacting protein (TXNIP) upregulation [8, 18]. In contrast, the effects of dyslipidemia and obesity on NLRP3 may operate more through tissue-resident macrophages in adipose tissue and arterial walls than through circulating PBMCs [19].

The strong correlation between caspase-1 activity and hs-CRP ($r = 0.716$) supports the idea that NLRP3-driven inflammation contributes measurably to systemic inflammatory burden as detected by routine clinical biomarkers. This connection is clinically relevant because hs-CRP is already used for cardiovascular risk stratification, and our data suggest that elevated hs-CRP in metabolic syndrome patients may partly reflect ongoing inflammasome activity that could potentially be targeted therapeutically [9, 10].

The translational implications of these findings relate directly to the growing pipeline of NLRP3-targeted therapies. MCC950, dapansutride (OLT1177), and tranilast have all shown promise in preclinical and early clinical research [12, 20]. Our data suggest that patients with metabolic syndrome who exhibit the highest inflammasome activation identifiable perhaps by a combination of hs-CRP, fasting glucose, and uric acid might derive the greatest benefit from such therapies. Stratifying patients by inflammasome activation status could improve clinical trial design and eventually support a precision medicine approach to managing metabolic inflammation.

A key limitation is that ex vivo PBMCs may not fully recapitulate the inflammasome dynamics occurring in tissue-resident macrophages within metabolically active

organs like the liver, adipose tissue, and pancreatic islets. Circulating monocytes are important effectors, but the most consequential inflammasome activity in metabolic disease likely occurs locally in tissues that we could not access in this clinical research design [21].

Reagents and Chemicals

LPS from *Escherichia coli* O111:B4 (catalog L4391, purity $\geq 99\%$) and adenosine 5'-triphosphate disodium salt hydrate (catalog A2383) were obtained from Sigma-Aldrich (St. Louis, MO, USA) and stored at -20°C . RPMI 1640 medium with L-glutamine, heat-inactivated fetal bovine serum (FBS), and penicillin-streptomycin were from Gibco (Thermo Fisher Scientific, Waltham, MA, USA). Ficoll-Paque PLUS (density 1.077 g/mL) was from Cytiva (Marlborough, MA, USA). DuoSet ELISA kits for human IL-1 β (DY201), IL-18 (DY318), and TNF- α (DY210) were from R&D Systems (Minneapolis, MN, USA). TaqMan gene expression assays for NLRP3 (Hs00918082_m1) and GAPDH (Hs02786624_g1) were from Applied Biosystems. FAM-FLICA Caspase-1 Assay Kit (catalog 98) was from ImmunoChemistry Technologies (Davis, CA, USA). All water used was Milli-Q purified ($18.2\text{ M}\Omega\cdot\text{cm}$).

Conclusion

This research demonstrated that PBMCs from patients with metabolic syndrome exhibit significantly amplified NLRP3 inflammasome activation compared to healthy controls, with higher NLRP3 mRNA expression, greater caspase-1 activity, increased ASC speck formation, and elevated secretion of IL-1 β , IL-18, and TNF- α following ex vivo stimulation.

The activation kinetics revealed a peak at 24 hours that was both higher in magnitude and modestly prolonged in the metabolic syndrome group. Caspase-1 activity emerged as the strongest predictor of cytokine output, and its strong correlation with systemic C-reactive protein levels supports a direct link between inflammasome-driven cytokine processing and the chronic low-grade inflammation that characterizes metabolic syndrome.

Among the clinical metabolic parameters, fasting glucose was the only independent predictor of inflammasome output in regression analysis, suggesting that hyperglycemia may be the predominant metabolic trigger for NLRP3 hyperactivation in this population. This finding has potential implications for therapeutic targeting: controlling glycemia might reduce inflammasome-mediated inflammation even before specific NLRP3 inhibitors become widely available. Collectively, these results reinforce the concept that the NLRP3 inflammasome is not merely a bystander in metabolic disease but an active contributor to its inflammatory pathology. As selective NLRP3 inhibitors advance through clinical development, identifying patients with the highest inflammasome activation levels could help tailor therapy and improve outcomes. Future work should extend these findings to tissue-resident immune cells and incorporate longitudinal designs to track inflammasome activation across the progression from metabolic risk factors to overt disease.

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