Latest Advances of human NLRP1

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Abstract

The human NLRP1 (hNLRP1) gene emerges as a pivotal player in a spectrum of human disorders, spanning from cancer to neurological ailments. Genetic variations within hNLRP1, particularly single nucleotide polymorphisms and several other point mutations, correlate strongly with these disorders, often residing in critical regulatory segments of the gene. These insights into genetic intricacies are instrumental in unravelling hNLRP1's involvement in various diseases and offer prospects for targeted therapeutic interventions. The human NLRP1 is infamous for its duality, providing subtle beneficiary roles in certain conditions when active in regulated levels and while being prominently higher and profound in most disease conditions that involve immune responses by inflammatory mediation, that can vary from autoimmune conditions to chronic disorders such as arthritis and cardiovascular ailments, ascertaining its nuanced nature when interacting with various types of stimuli and conditions. This review sheds light on the illustrative viewpoints of its mechanism of action, the multifaceted roles of NLRP1 in health and disease, and presenting avenues for future research and therapeutic development aimed at harnessing its potential for clinical benefit across diverse pathological contexts.

Keywords: NLRP1, inflammation, inflammasome, pyroptosis.

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1. Introduction

1.1. hNLRPS (human Nod-like receptors with pyrin domain)

The mammalian cell possesses a diverse array of molecular mechanisms specifically designed to promptly signal and alert neighbouring cells. One such mechanism involves the intricate functionality of an inflammasome complex—a sizable assembly of multiple proteins. This complex serves as a sensor, capable of detecting imminent threats that pose either immediate or potential lethality to the cell. Upon recognition, the inflammasome triggers a cascade of processes aimed at initiating inflammation.

Inflammasomes have been extensively investigated within myeloid cells, notably in macrophages and dendritic cells. However, recent studies have unveiled the presence and functionality of inflammasomes in epithelial cells, marking a novel discovery in the understanding of these innate immune signaling complexes. These studies have pinpointed the presence of inflammasomes in various epithelial sites, including the skin, gastrointestinal lining, and the alveoli, underscoring their distribution in diverse anatomical locations.

A typical inflammasome comprise of the basic components:

(i) A sensor protein within the inflammasome complex is tasked with detecting extracellular elements like pathogen-associated molecular patterns (PAMPs), which are foreign to the host cell and often include components from bacterial cell walls, double-stranded RNA, or single-stranded DNA. Additionally, it identifies damage-associated molecular patterns (DAMPs) like extracellular ATP, monosodium urate, cholesterol crystals, and amyloid beta, among others. These molecules, whether of host or external origin, serve as

potential threats and may or may not bind to specific receptors within the host cell's cytosol. Typically, the sensor is integrated into the inflammasome structure or resides within the recruited adaptor protein like ASC, facilitating the recognition and subsequent signaling cascade triggering the inflammatory response.

(ii) An adaptor protein such as apoptosis-associated speck-like protein containing a CARD, which is known as ASC consists of a pyrin domain linked to a caspase recruitment domain or CARD binds to the N-terminal of the NLRP, which acts as a mediator for the effector proteins such as caspases to locate their designated sensor protein and form a single monomer of an inflammasome.

(iii) Inflammatory caspases represent the active state of pro-caspases within cells. These caspases are categorised as 'zymogens' because their activation occurs solely following cleavage, rendering them functional only upon separation from their inhibitory domains. Notably, human caspases-1, 4, and 5 possess the capability to interact with their respective sensor proteins, thereby instigating a signaling cascade that triggers cellular responses.

A complete NLRP, together with its adaptor protein and effector protein, constitutes a single monomeric unit of an inflammasome. When multiple of these monomers assemble, they form a structural complex where the N-terminal regions are closely arranged inward, while the outermost part comprises the C-terminal regions, creating a micelle-like structure. This complex facilitates the proteolysis of procaspase-1, liberating activated caspase-1, a crucial initiator of the cascade leading to an inflammatory response. This response includes Gasdermin D-mediated cell death, known as pyroptosis, characterised by the formation of pore-like structures on the cell membrane (fig.1). This results in the disruption of the cytosolic

integrity, hence accelerating cell demise. Additionally, the activation of caspase-1 cleaves pro-inflammatory cytokines such as interleukins 1β and 18. These cytokines bind to the IL-1 receptor, initiating the transcription of the IL-16/TNF-α system, promoting vascular inflammatory signaling by upregulating cell adhesion proteins that are required to enable the immune cells such as leukocytes to form a firm adhesive bond with the endothelial cells and 'roll' along the endothelium lining of the vascular tissues, thereby making an easier pathway towards the targeted site of inflammation. Moreover, the caspase's downstream pathway recruits interferon-γ which is also known as IFN-γ, a vital cytokine that induces the synthesis of small signalling antiviral proteins, alerting neighbouring cellular structures to an incoming viral invasion [1,2].

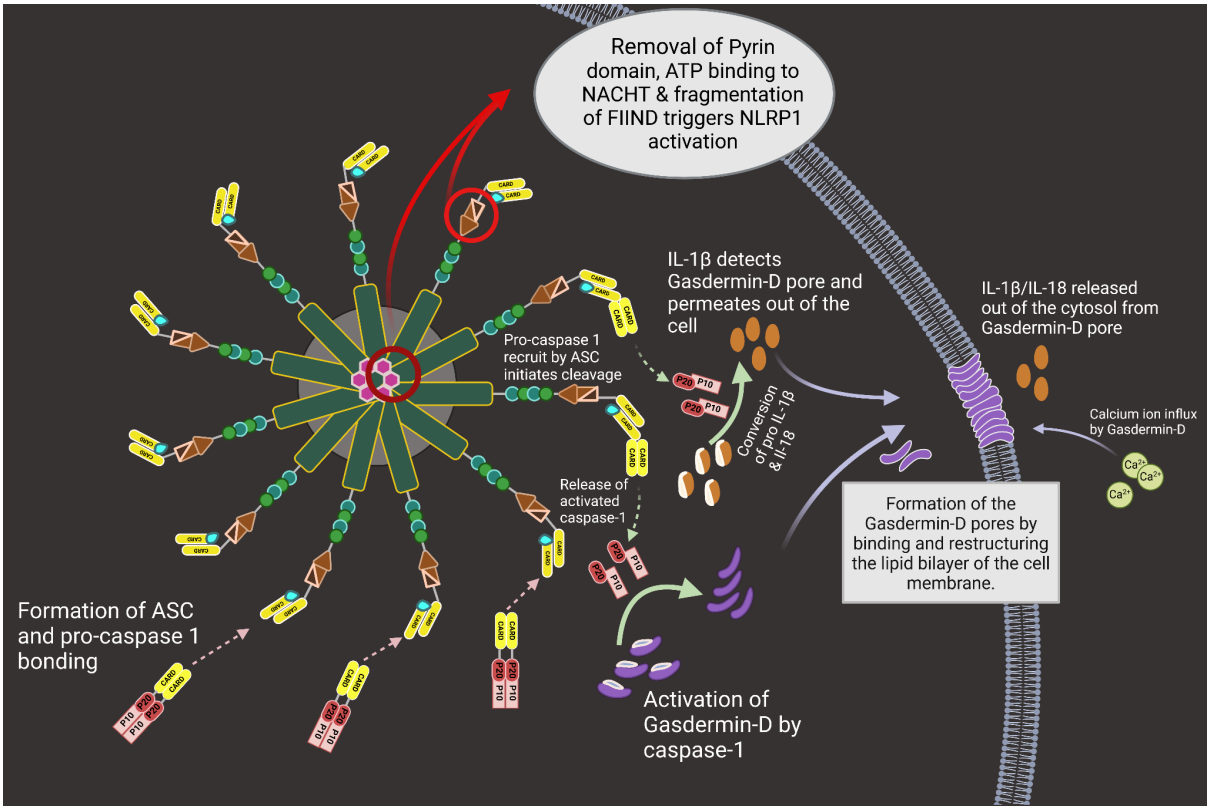

Fig.1. *A typical structure of an inflammasome complex belonging to the NLRP subunit and the associated processes present after post assembly.* By the removal of pyrin domain from the N-terminal of the protein, the molecule de-stabilises which makes it prone to additives that can bind to various oligomerising parts such as ATP, untangling the protein and eventually leading to separation of a section of FIIND domain to release the C-terminal that initiates the summoning of pro-caspase, the inactivated form of caspase by the ASC. This leads to a cascade of events that form the spiral structure which is able to deactivate various dormant mediators such as interleukins and Gasdermin-D that form the sequels of occurrences which determines the mortality of the cell.

Nucleotide-binding oligomerization domain-like receptors (NLRs), a subset of Pattern Recognition Receptors (PRRs), are ubiquitously present within the cytoplasm of nearly all cells. The NLRP1 gene exhibits widespread expression of its receptor across various tissues, with prominent presence in the skin, spleen, lymph nodes, appendix, lungs, bone marrow, and

urinary bladder. Additionally, it shows minor expression in approximately 20 other tissues [3]. These receptors are regarded as among the earliest evolved structures for detecting pathogens. They feature leucine-rich repeats (LRRs) that form a distinctive horseshoe-shaped structure. This specific configuration allows NLRs to engage in interactions with other protein structures through their CARD domain, acting as binding or docking sites with proteins possessing their own CARD subset. Upon recognition of its target at the LRR binding site, a critical cellular signalling protein called Receptor-Interacting Serine/Threonine-Protein Kinase 2 (RIPK2) engages with the CARD domain of the NLR. This interaction which is termed as oligomerization, triggers the activation of specific immune-inflammatory kinases and protein complexes that include TAK-1, IKK, and NF-κB. Through this mechanism, they recognize extracellular proteins originating from diverse sources, thereby initiating a cascade of NLR-protein interactions. These interactions stimulate downstream pathways, summoning signalling molecules pivotal in alerting the innate immune system. These events mark the crucial and initial steps that are necessary in the subsequent decision-making processes within the innate immunology.

The NACHT domain which is an abbreviation from the initials of proteins such as NAIP, CIITA, HET-E, and TP1 is found within the NOD-like receptors (NLRs). It constitutes a crucial part of NLR protein structure and is integral in the formation of larger NLR complexes by promoting their assembly or oligomerization. The NACHT domain actively participates in binding to nucleotides and exhibits ATPase activity that helps in regulating the NLR activity. This engagement contributes significantly to the activation and functional signalling of NLRs. Upon encountering specific triggers or stimuli, NLRs undergo structural alterations such as dimerization which is facilitated by the NACHT domain. These alterations result in the

creation of multi-protein complexes that initiate downstream pathways, triggering immune responses, inflammation, and various cellular activities.

The human genome encodes 23 distinct types of NOD-like receptors (NLRs). Among these, two main subfamilies are prominent: NLRP, characterised by the presence of a ‘pyrin’ domain, and NLRC, which contains a ‘caspase’ recruitment domain. Among these, extensive research primarily focuses on NLRP due to its pivotal role within the immune system. NLRP plays a central role in forming a specialised and significant structure known as the inflammasome. This inflammasome formation is unique and holds significant importance in various autoimmune and inflammatory conditions affecting the human body. Studying the mechanisms governing NLRP's function and its related inflammasome has emerged as a critical pursuit in unravelling diverse disease pathways associated with inflammation and the dysregulation of the immune system.

1.2. The hNLRP1 (human Nod-like receptor with pyrin domain-1)

The structure of hNLRP1 distinguishes itself from the other NLRPs due to the presence of a unique subunit featuring additional domains known as FIIND (function-to-find) and CARD (caspase activation and recruitment domain) situated at the C-terminal of the protein (fig.2). Additionally, NLRP1 includes its own ASC (adaptor associated speck-like protein containing CARD), which eliminates the need for an ASC recruitment step. This unique feature simplifies the process, facilitating a direct interaction between the inactivated stage of caspase-1 known as pro caspase-1 and subsequent cleavage during the proteolytic phase. This interaction triggers the assembly of a circular convoluted complex known as the

inflammasome. Activation of pro-caspase-1 within the inflammasome leads to the conversion of inactive cytokines which are critical components detected in inflammatory pathways.

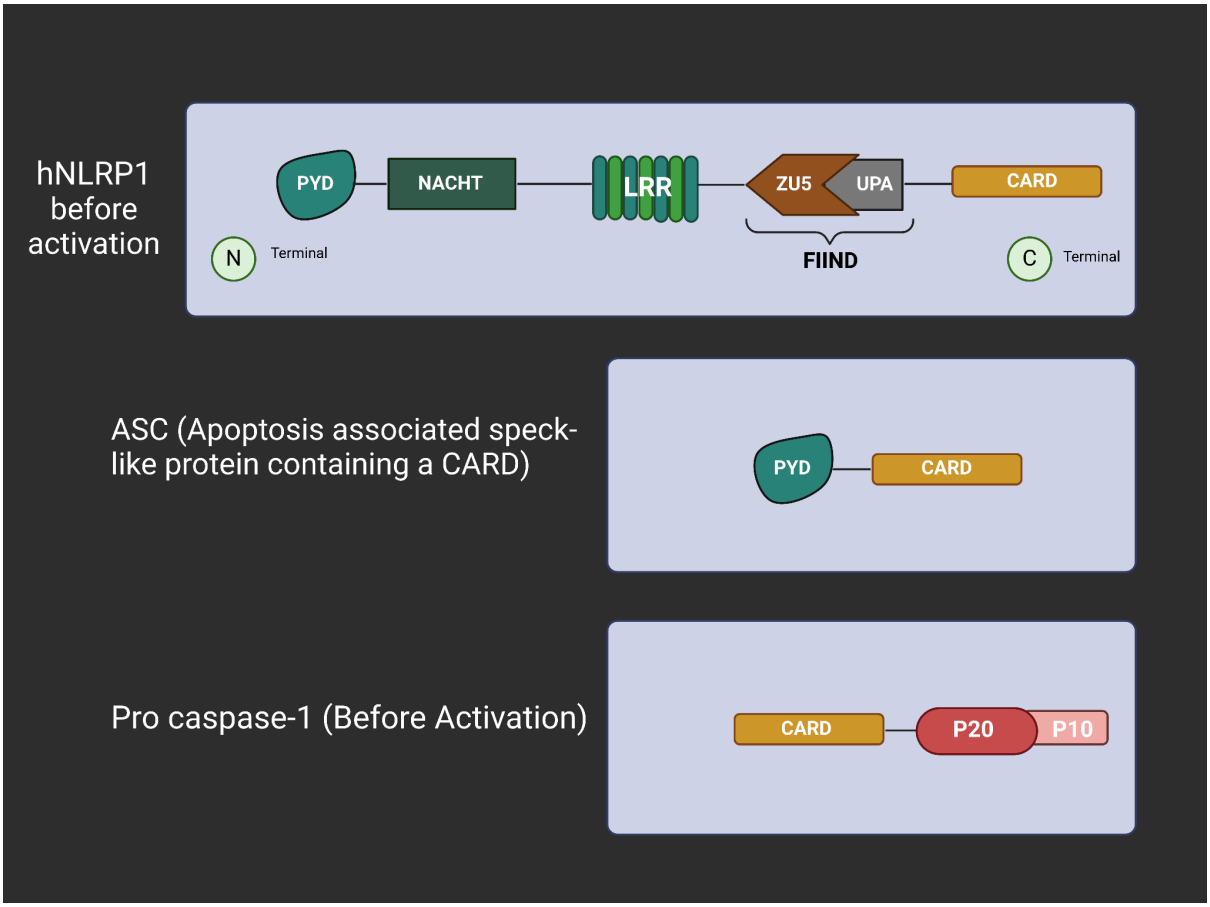

Fig.2. *Illustration of the various essential parts of an inflammasome*. hNLRP1 (human Nod-like receptor with pyrin-1), ASC (Apoptosis associated speck-like protein containing CARD) and inactivated caspase or Pro caspase-1 which is kept dormant by the attachment of a CARD domain.

NLRP1 falls within the family of Pattern Recognition Receptors (PRRs), crucial components of the innate immune system. PRRs play a fundamental role in identifying distinctive patterns from external sources that could potentially disrupt the normal functioning of the host cell. These patterns include foreign genetic material or proteins from microorganisms and unrecognised extracellular components within the cytosol. The human NLRP1 gene encodes a multifaceted protein comprising several structural domains including NACHT, LRR, FIIND, CARD, and PYD. The NACHT domain spans approximately 300 to 400 amino acid residues, representing a nucleoside triphosphatase (NTPase) domain present in proteins across diverse organisms like animals and microorganisms. It draws its nomenclature from proteins such as NAIP, CIITA, HET-E, and TP1 [4]. The LRR (leucine-rich-repeats) units which can be referred to as essential amino acid repeating sequences, constitute a fundamental component within the structure of the NLRP1 protein. FIIND stands for function-to-find domain, while CARD denotes the caspase activation and recruitment domain which is crucial for detecting apoptosis signals. Finally, the PYD (pyrin domain) is situated in the N-terminal region of the protein which completes the structural elements of NLRP1.

This protein was the original one identified to assemble an inflammasome and hence the naming constitutes the number. The expression of NLRP1 is widespread across diverse cell types, primarily within hematopoietic and epithelial cells of the small intestine, gastrointestinal tract, and respiratory tract. Genetic variations in NLRP1 have been associated with various auto-immune conditions such as skin-related manifestations in Crohn's disease (CD), psoriasis and vitiligo. Furthermore, specific polymorphisms in NLRP1 have been linked to autoimmune disorders such as lupus erythematosus (LR) and type 1 diabetes

(DM-1). THE NLRP1 gene translates a protein belonging to the Ced-4 family, known for its involvement in apoptosis (programmed cell death) which is known as caspase recruitment domain (CARD) and serves as crucial regulators in programmed cell death processes. The protein encoded by this gene comprises a distinct N-terminal pyrin-like motif which facilitates the interactions between various proteins with the same CARD component. Particularly, the NLRP1 protein exhibits strong interactions with caspase 1 and 2, with weaker interactions observed with caspase 9. Experimental studies have shown that the overexpression of this gene leads to the induction of pyroptosis, which is known to be a specific form of cell death without DNA disintegration characterised by heightened inflammatory communication in cells [5].

The human NLRP1 (hNLRP1) gene is positioned on the seventh chromosome and harbors a multitude of SNPs (single nucleotide polymorphisms) and mutations. These genetic variations have been strongly correlated with a wide spectrum of human disorders, including but not limited to cancer, immune-related and inflammatory conditions, infectious diseases, as well as neurological disorders. Moreover, these variations often occur within crucial regions of the gene, particularly in transcriptional and regulatory segments of a gene. The exact chromosomal locations housing the extensively researched alterations linked to the hNLRP1 gene have sparked ongoing debates, necessitating the utilisation of bioinformatics for precise identification. These polymorphisms which lead to point mutations have the potential to significantly impact the function of the NLRP1 gene along with alteration of its role within cellular defense mechanisms or contributing to abnormal responses against internal or external threats. Understanding these genetic intricacies is essential for clarifying the gene's role in various diseases and could pave the way for targeted therapies or interventions [9].

The polymorphic variant M1184V of NLRP1 arises from a point mutation where the amino acid Methionine (MET) is replaced by Valine (VAL) at position 1184 within the amino acid sequence. This particular polymorphism has been notably implicated in the progression of asthmatic diseases. The alteration caused by this polymorphic variant renders the NLRP1 protein more susceptible to N-terminal dissociation. This susceptibility arises from the increased vulnerability of the FIIND (function-to-find) domain to cleavage, primarily due to the inhibition of DPP9 (dipeptidyl peptidase 9). DPP9 serves as a crucial regulator for NLRP1, primarily aiding in maintaining the unique folded structure of the NLRP1 protein, which represents its inactive state. This regulation occurs through DPP9's interaction with the FIIND (function-to-find) domain of NLRP1 since the FIIND domain is known for its auto-proteolytic activity. DPP9's interaction with the FIIND domain ensures the gene remains in a folded state which prevents it from unfolding into a linear chain and self-cleaving in response to external stimuli (fig.3). Consequently, this regulation suppresses the downstream signaling cascades that would otherwise initiate upon the activation of the NLRP1 protein. Such modifications or alterations in the structure and function of the NLRP1 protein can significantly influence its role in inflammatory pathways, potentially contributing to the development or exacerbation of asthma and related conditions [10,11].

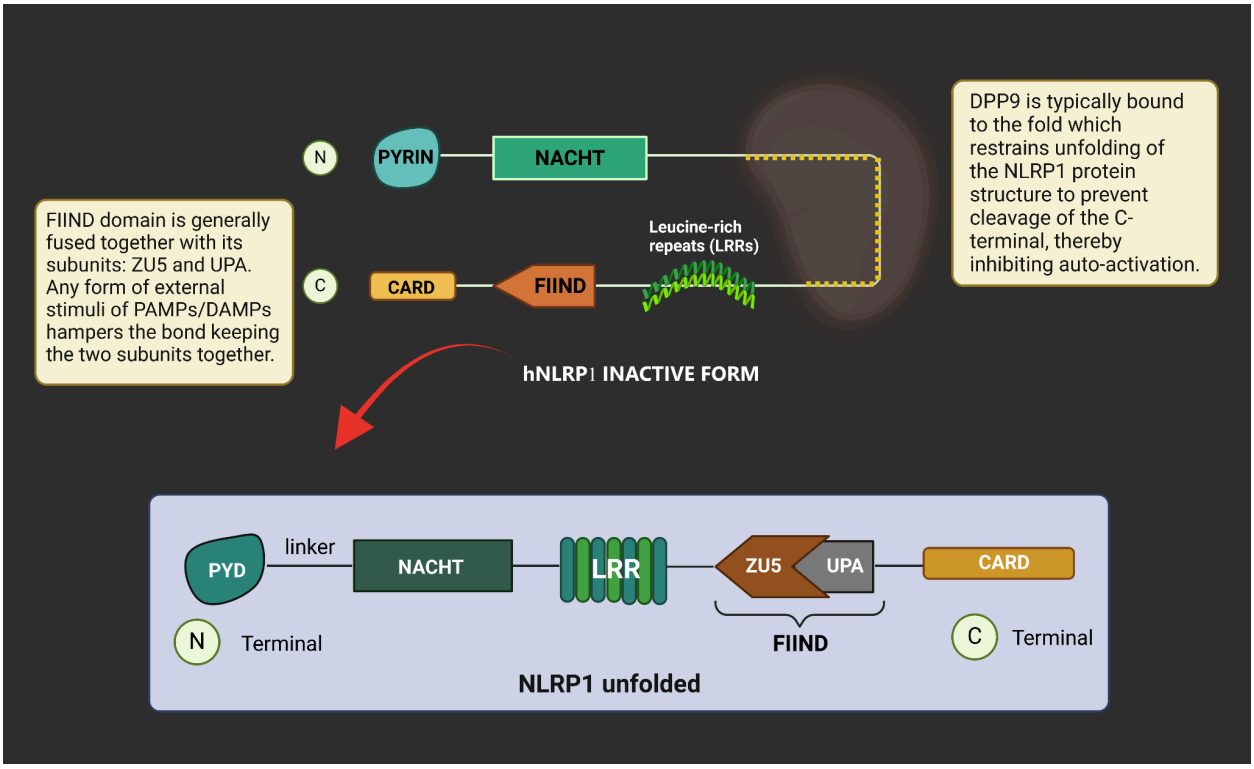

Fig.3. *A diagram displaying the natural conformation of the human NLRP1 (hNLRP1) when held by DPP9 (Dipeptidyl peptidase 9).* The protein responsible for preventing any form of disarray by the unweaving of NLRP1. Upon unfolding by various triggering structures such as PAMPs (Pathogen -associated molecular pattern molecules) or DAMPs (Damage-associated molecular pattern molecules), the pyrin domain protein undergoes a segregation within its FIIND domain into ZU5 and UPA which is accentuated by enhancement of instability of the N-terminal portion of the protein.

Thioredoxin, a vital protein involved in various physiological redox processes and signalling, has been revealed in studies by Zhang, Z., Shibata, T.,Fujimura, A. et al. (2023) to interact with NLRP1 in the NACHT region, preventing the cleavage necessary for the activation of the inflammatory pathway which can be induced by mutagenesis or DAMPS activation [12]. Specifically, TRX1, a component of Thioredoxin within its redox composition which interacts with NLRP1 by oxidising itself through the available reactive oxygen species

in the cytosol, forming disulphide bonds at the NACHT-LRR position of NLRP1 by the utilisation of ATP as the source of energy [13,14].

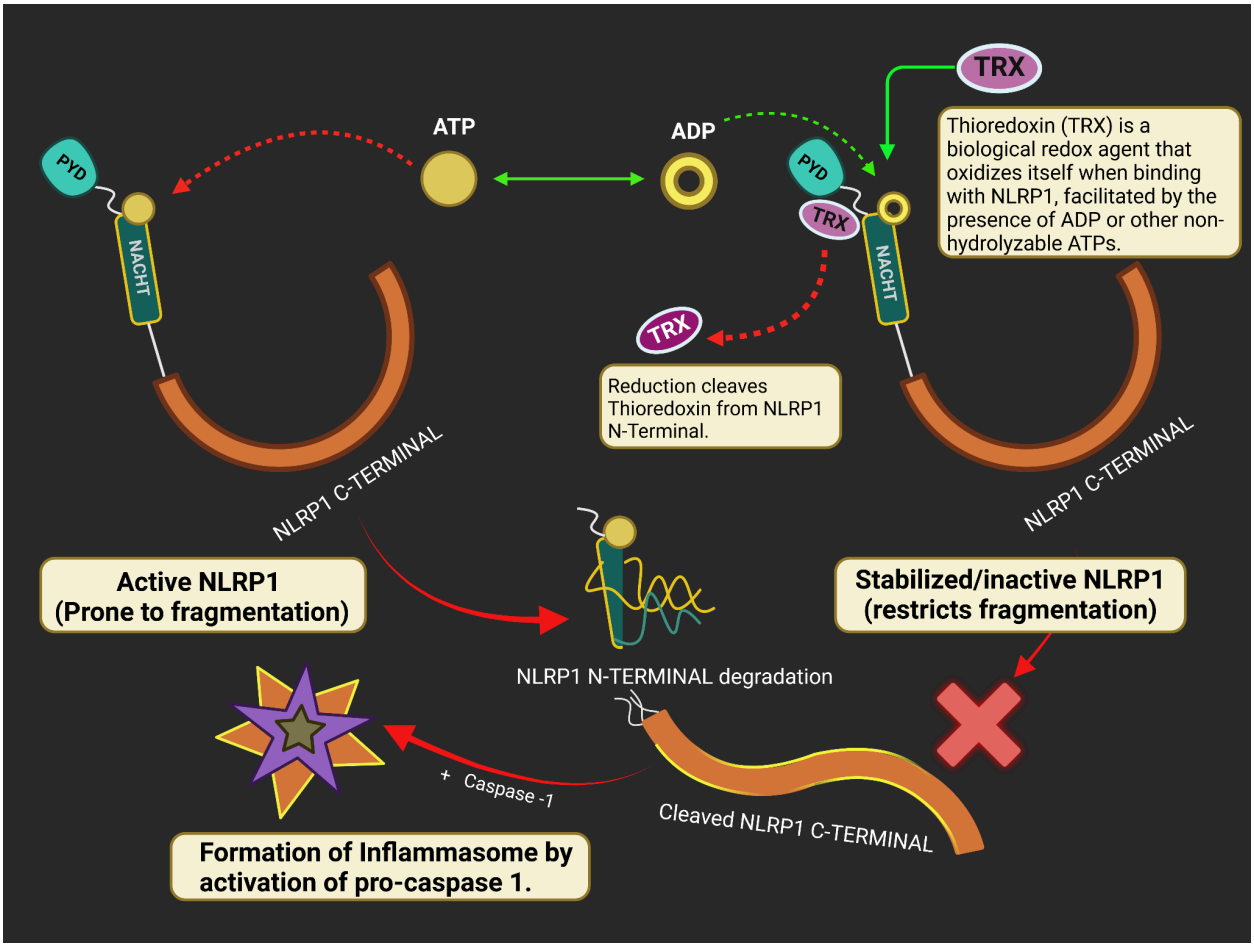

Fig.4. *Diagrammatic description of the importance of the biological redox agent, Thioredoxin, also known as TRX1.* The absence of of ADP (adenosine diphosphate) or other non-hydrolysable ATPs promotes the addition of an oxidised Thioredoxin to the N-terminal of the NLRP1 protein chain which enhances stability of the molecule from any external factors that can destabilise the receptor integrity. When Thioredoxin is reduced by the presence of reducing agents within the cell, it easily segregates from the receptor which paves way for ADP to undergo phosphorylation, making the receptor active and vulnerable to manipulation by the trigger of PAMPs/DAMPs (Pathogen -associated molecular pattern molecules/Damage-associated molecular pattern molecules) that leads to the cleavage of the C-terminal of the receptor and eventual polymerisation to assemble an inflammasome.

However, under conditions with high reductive agents in the cell or excess amounts of antioxidants, the stable interaction between NLRP1 and TRX1 could be disrupted due to the reduction of TXR1 (fig.4). NLRP1 is predominantly expressed in epithelial cells which acts as the primary barrier for the deeper layers of the skin. Any hyper-inflammation in these cells indicates a disruption in the strict controlling patrol mechanism of the natural barrier. Understanding the chemical properties of the bond between these two structures could illuminate future drug development prospects aimed at controlling NLRP1 hyperactivity or inducing an underactive NLRP1 protein for targeted inflammasome activation [14,15]. Thioredoxin's ability to inhibit downstream activities associated with NLRP1 stimulation suggests a potential therapeutic pathway for suppressing the NLRP1 gene.

Although the FIIND domain is composed of two subunits, experimental analysis indicates its existence as a single unit or monomer. Within the FIIND domain, the ZU5 fragment is essential in hindering the potential separation of UPA, as it has a tendency to form oligomers with CARD. The ZU5 domain plays a pivotal role in inhibiting NLRP1 by directly or indirectly binding to DPP9. When DAMPs cleave the N-terminal segments, this disrupts the auto-regulatory function of ZU5, leading to the proteolytic separation of UPA from the remainder of the chain (fig.5). Consequently, this accelerates the liberation of the UPA-CARD dimer, a crucial contributor to the inflammatory pathway. It is widely accepted that inhibiting active domains of NLRP1, such as the UPA from the FIIND monomer with its C-terminal CARD molecule, through the sequestration formation process, serves as a common mechanism for modulating the initiation of the inflammasome [11,16,17].

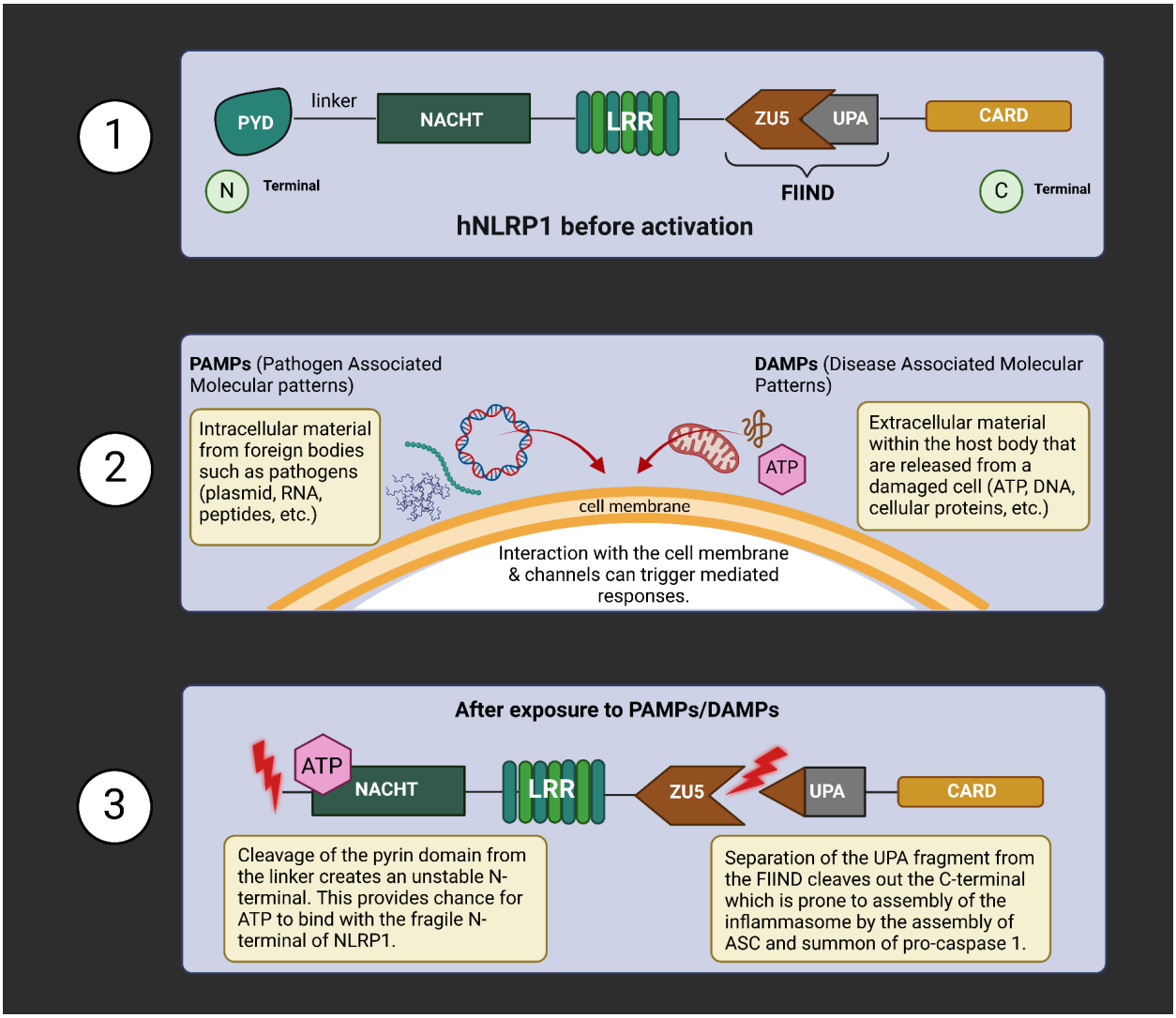

Fig.5. *A schematic diagram of how external factors place an effect on the activation of hNLRP1 (human NOD-like receptor with pyrin domain-1).* The response is corresponded by PAMPs (Pathogen -associated molecular pattern molecules) or DAMPs (Damage-associated molecular pattern molecules) interacting with the cell membranes and triggering successive responses that unlock various protective segments of the inflammasome receptor which leads to its activation and further mobilisation or other components that stage pyroptosis through sequel of events. (1) Displays the shape and form of an inactivated NLRP1 at rest without the interaction of any external trigger. (2) Describes the different types of PAMPs and DAMPs that can interact with the cell membrane and initiate a chain of signal mediation that can stimulate the activation of the receptor. (3) Elaborates the key mechanisms that lead to the activation of the NL-receptor pyrin domain-1 by the digestion of the N-terminal and the cleavage of the FIIND domain that make the structure unstable, leading to the segregates C-terminal prone to capture pro-caspase 1 and initiate the propagative reaction that form the inflammasome.

1.3. Noteworthy characteristics of NLRP1

●Identification of external matter: NLRP1 demonstrates the capability to identify double-stranded RNA (or dsRNA), a characteristic trait often associated with viral protease activity that serves as a sensor for nucleic acids derived from viruses. Research conducted by Stefan Bauernfried et al. (2021) through cellular studies unveiled that only long double-stranded RNA had the ability to activate the downstream pathway of the NLRP1 inflammasome. One proposed explanation for this phenomenon lies in the hydrolytic activity of ATP along with magnesium ion as a co-factor induces significant conformational changes within NLRP1 that leads to structural changes within the NLRP1 receptor protein when it detects the presence of a PAMP like dsRNA which consequently promotes its oligomerization that facilitates the formation of the inflammasome complex [18,19].

●Indication of infection: Infections initiated by *Pseudomonas aeruginosa* in human corneal and airway epithelial cells trigger the NLRP1 pathway which thereby, stimulates the release of IL-1β/IL-18 and that ultimately leads to pyroptosis. This was affirmed through immunoblotting techniques that detected various proteins that assist in the formation of inflammasome structure within the epithelial cells under study. When NLRP1-deficient cells were cultured with *P. aeruginosa*, they exhibited a deficiency in cell death, as measured by incorporating propidium iodide (PI) and releasing lactate dehydrogenase (LDH), along with reduced IL-1β/IL-18 cytokine release. Additionally, research showed that the activation of human NLRP1 inflammasome by *P. aeruginosa* in the concerned epithelial cells occurs

through a proteolytic activity. This process involves the inhibition of ubiquitination and subsequent proteasome-driven functional degradation of the receptor protein which leads to the separation of the active NLRP1 C-terminal fragment and, ultimately, the formation of the inflammasome complex [20].

●Pyroptosis and its significance: The infiltration into human cells by *C. diphtheria*, utilising the DT exotoxin, triggers kinase ZAKα-driven auto-phosphorylation as a result of Ribosomal protein inhibition Stress Response (RSR). This activation, coupled with the involvement of the inflammasome sensor NLRP1 leads to inflammatory cell death known as pyroptosis which is evident through observable indicators such as increased cell turgidity, absorption of propidium iodide (PI), release of IL-1β, p17, and Gasdermin D. Gasdermin D is a specific chemical that serves as the causative agent triggering pyroptosis by the enhancement of perforation in a swelled cell membrane, a distinct form of cell death characterised by an inflammatory response [21].

●Activation by antibiotics and K+ ion abnormality: An intriguing aspect of NLRP1 activation involves its induction by certain antibiotics through a process mediated by potassium ion outflow, exemplified by Nigericin in primary cell lines. This antibiotic not only triggers NLRP1 activation but also disrupts ribosome-related mechanisms by inhibiting the mRNA elongation step. This inhibition occurs due to the sudden loss of cytosolic potassium ions, leading to the phosphorylation of the stress sensor against ribosomes, ZAK-α, particularly in epithelial cell lines. Interestingly, while Nigericin exhibits agonistic activity in

hematogenic cells where NLRP3 is more prevalent, its effects on NLRP1 are noteworthy in epithelial cells. The rise in intracellular electronegativity resulting from potassium ion outflow hampers protein formation in ribosomal units, leading to incomplete translational steps. An interesting point to note is that not all co-transporters can induce NLRP1-mediated Gasdermin cleavage leading to pyroptosis. Only compounds with an effective counter-transport system capable of extracting more than twenty percent of cytosolic potassium ions have higher chances of triggering NLRP1 inflammasome activation. This intricate interplay sheds light on the diverse mechanisms underlying NLRP1 activation and its implications for cellular responses to antibiotics and potassium ion dynamics [22].

2. Methodology

The purpose of this literature review is to organise data collected over the past four years from various scholarly journals accessible through online databases. This review spans from 2020 to the latest clinical findings and statistical correlations available in 2024, the year this article has been written. Although this literature may not be as extensive as research accumulated over decades, it offers a recent snapshot of pharmacological evidence that has been effective in mitigating NLRP1-mediated symptoms, which play a role in exacerbating certain diseases. Additionally, the review includes instances where the receptor can be beneficial in regulating certain chronic conditions, based on careful observations.

2.1. Latest evidences of hNLRP1 in various clinical conditions

2.1.1. NLRP1 in Diabetes Mellitus

The involvement of NLRP1 in endothelial cells during Gestational Diabetes Mellitus (GDM) is a common occurrence. Studies involving samples from umbilical cords and plasma obtained from GDM patients, alongside high-glucose-cultured human umbilical vein endothelial cells (HUVECs) aimed to elaborate the pathogenesis associated with the onset of type 2 diabetes mellitus and cardiovascular complications. The trigger of endothelial injury by the thrombin pathway or PAR-1 (protease-activated receptor-1) activation induces inflammatory responses which includes the formation of the NLRP1 inflammasome. Adhesion of glycated macromolecular stages of proteins and lipids have higher tendencies to localise themselves and build deposition, which can in turn exemplify into vasculature stiffness, an evident manifestation in degenerative vascular ailments. Knockdown or deletion of PAR-1 resulted in decreased NLRP1 expression and interleukin-18 levels in cultured cells which is one of the cytokines activated by NLRP1 mediation. Additionally, sarsasapogenin (SAR), a natural steroidal compound from the timosaponins family, displayed protective effects by inhibiting the thrombin/PAR-1 pathway which was able to preserve the vascular endothelium. In conclusion, these findings emphasise the significant role of inflammation in gestational DM. This highlights the importance for heightened vigilance and preventive measures among medical practitioners and researchers to comprehend and address the inflammatory aspects underlying gestational diabetes which can mitigate associated health risks [23].

Human Periodontal Ligament Cells (HPDLCs) of the gingival cavity are particularly susceptible to inflammation in individuals with diabetes, often leading to periodontitis. In a study, these cells were exposed to Advanced Glycation End products (AGEs) and subsequently stimulated with muramyl dipeptide (MDP). Within a day of this treatment, there was a noticeable increase in inflammatory cytokines like IL-6 and IL-1β, alongside elevated expression levels of NLRP1, NLRP3, and apoptosis-associated speck-like protein containing a CARD (ASC). When the NF-κB pathway was silenced, there was a subsequent reduction in the expression of Nod-like receptor proteins of the pyrin domain (NLRPs). These findings strongly suggest the involvement of NLRs, including NLRP1, in AGEs-mediated inflammatory responses observed within the cells of individuals affected by diabetes [24].

2.1.2. NLRP1 in Gastrointestinal tract (GIT) related conditions

Inflammatory Bowel Disease (IBD) is a prevalent inflammatory disorder known to significantly heighten the risk of colorectal malignancies which includes cancer. Secoisolariciresinol diglucoside (SDG), a plant compound derived from flaxseed, has exhibited promising capabilities in impeding various processes contributing to chronic epithelial inflammation, notably the regulation of NLRP1 expression. In experimental mouse cells, the mRNA levels of NLRP1, ASC, and caspase-1 notably escalated in the non-control group in comparison to the control group. The elevation in the expression of IL-1β and IL-18, the key inflammatory cytokines associated with NLRP1 inflammasome activation, was observed in non-control group cells which were effectively suppressed by SDG. SDG

down-regulated NF-κB, a crucial signalling mediator known to stimulate NLRP1 activation, consequently reducing active ASC and caspase-1 p20 expression. This intervention by SDG significantly improved the deactivation of the NLRP1 inflammasome, offering promising implications for inflammatory modulation [25,26]. Research conducted by Wang H. and Ma Y.C. in 2020 presented further evidence supporting the involvement of NLRP1 in inflammatory bowel disease (IBD), particularly in children affected by conditions like Crohn's disease and ulcerative colitis. The study analysed the gene expression of key factors—NLRP1, NLRP3, activated Caspase-1, and interleukin 1β—among the study participants which revealed a significant association between IBD and these NLR-related elements. This revealed the striking dependence of diseased cells in IBD on the levels of these specific factors. The activation of the inflammasome pathway contributes to the exacerbation of various inflammatory deteriorations, particularly the increased serum levels of immunoglobulins M and G. Given the chronic nature of IBD, the sustained pathogenicity is linked to the continuous conversion of caspase-1 by the expression of NLRP1 and NLRP3, leading to pyroptosis in immune cells like macrophages and monocytes. This prolongs cellular damage via ROS, rendering the intestinal mucosal cells highly susceptible to the adverse effects of inflammatory bowel-related syndromes [27].

2.1.3. NLRP1 in pregnancy

Preeclampsia, an inflammatory syndrome arising in pregnancy which manifests with an elevated blood pressure, edema, and various other pathological symptoms after 20 weeks of gestation which greatly poses risks to the health of both the foetus and the mother [28]. This condition emerges due to inadequate trophoblast-induced changes in uterine arteries, resulting

in insufficient oxygen supply and subsequent production of reactive oxygen species (ROS). These ROS contribute to intensified inflammation and disruption of the normal balance in the endothelium layer of cells within the uterine wall. In this altered uterine cellular environment, various endogenous components that include foetal genetic material, ROS, and hyaluronan, interact with receptors like NLRs (NOD-like receptors) which likely initiate an increased inflammatory reaction through the activation of NF-κB-mediated cytokine responses. Analysis of monocytes from preeclampsia patients as well as monocytes stimulated by DAMPs (damage-associated molecular patterns) that mature into macrophages revealed the activation of NF-κB phosphorylation, cleavage of pro-caspase-1, and cytokine mediators such as IL-1β and IL-18, predominantly dependent on the presence of NLRP1 expression in the cytoplasm which were the vital reasons for the aggravation of the condition. Interestingly, interventions involving progesterone or progesterone-like compounds, such as cholecalciferol (vitamin D3), which are naturally abundant in non-preeclampsia patients, showcased significant modulation of these factors. These compounds exhibited a natural anti-inflammatory activity, providing insights into potential therapeutic avenues for managing preeclampsia [29,30].

Moreover, the protective role of vitamin D3, previously identified in its association with preeclampsia and NLRP1 involvement, has been observed in regulating stimulated inflammasomes in human skin keratinocytes. A controlled study by Nakajo T., Katayoshi T., Kitajima N., and Tsuji-Naito K. (2021) elucidated how vitamin D3 augments the antioxidant protein transcription factor, NRF2 (Nuclear Factor Erythroid Related Factor-2). This augmentation assists in attenuating oxidative stress provoked by activated inflammasome fragments and downregulating interleukin levels associated with infections or autoimmune

conditions. The findings highlight vitamin D3's anti-inflammatory benefits through NRF2-mediated mechanisms [31].

Intrauterine growth restriction (IUGR), a known disorder that culminates before birth of an infant is marked by limited foetal growth in the womb has been frequently associated with cognitive impairment, consisting of a marked insufficient cognitive function which is attributed to inadequate brain development during foetal growth. A thorough investigation led by Wan L., He X., et al. (2023) sought to establish a potential link between cognitive impairment in rats with IUGR and observable neuronal damage within the hippocampus caused by inflammatory pyroptosis. Additionally, the study aimed to assess the preventive efficacy of early intervention with docosahexaenoic acid (DHA). Docosahexaenoic acid, though not exhibiting overpowering potency, is able to manifest a noteworthy anti-inflammatory intervention. Its impact extends to the reduction of pyroptosis by intervening in the expression of Gasdermin. Moreover, DHA plays a proactive role in impeding the translation and activation of NLRP1, spliced caspase-1, and the modification of interleukins, particularly IL-18 and IL-1β. This multifaceted influence is crucial, especially considering that NLRP1 is expressed in neurons in the hippocampus. The release of these cytokines can set off inflammatory orchestral events within neuronal environments, culminating in the swelling and degeneration of neurons. Such consequences contribute significantly to diminished cognitive abilities, a characteristic prominently observed in offspring with intrauterine growth restriction (IUGR) conditions. The potential of DHA to mitigate these inflammatory responses at various molecular levels presents a promising avenue for exploring preventive measures and therapeutic mediation to ameliorate the cognitive impacts associated with IUGR [57,62].

2.1.4. NLRP1 in the neurological and psychological conditions

The onset of depression has been linked to a deficiency in the autophagic elimination of cellular organelles and metabolites that have lost functionality and are no longer required by the cell. This deficiency is exacerbated by the role of mTOR, which promotes the synthesis of inflammatory signals while inhibiting autophagy, as evidenced by the involvement of NLRP1 inflammasome complex units such as caspase-1, ASC, and circulating interleukins that is observed in studies by Zhu Y.J., Huang J., Chen R. et al. (2024). The accumulation of cellular debris and inflammatory pyroptosis contributes to depression-like symptoms in experimental trials, including decreased enthusiasm in completing tasks such as forced swimming tests, reduced mobility, and decreased interaction with others. Genetic manipulation of the NLRP1 gene, through gene silencing or elimination, has been shown to restore autophagy, thereby alleviating depressive symptoms. Additionally, administration of Rapamycin, a known mTOR inhibitor, has been found to diminish depressive symptoms in experimental subjects. This effect is accompanied by the reactivation of halted auto-phagocytic pathways and a significant reduction in the levels of activated interleukins. These findings underscore the co-dependency of NLRP1 and the mTOR pathway and their significant role in depressive behaviours [32,33].

The ageing process is marked by a slowing of waste disposal, increased deposition of undetected cell metabolites, accumulation of ineffective proteins, and heightened cellular inflammation, both mentally and physically. These observations are significant due the critical role of NLRP1 and its association with cell cycle regulators such as mTOR, which ultimately leads to the cessation of cell growth and division. To counteract these neurodegenerative processes associated with ageing, researchers have turned to rapamycin, a bacterial-derived drug that is used for its immunosuppression as well as the notably known effect of slowing

down cellular ageing. Rapamycin works to restore the regular homeostatic functions of cells by enhancing the detoxification of neurons and promoting the activation of cell division. This intervention offers promising prospects for mitigating the effects of ageing and maintaining cellular health and functionality over time [34,35].

Accumulation of Aβ (β-amyloid) and tau proteins triggers an excessive activation of macrophages in the cerebral microenvironment. This disrupts the normal balance of immune cells in the hippocampus, leading to inflammatory invasion and neuronal degeneration, the primary hallmarks of Alzheimer's disease. In a study involving Alzheimer's patients with a disease progression that exceeds a period of three years, specific components associated with the NLRP1 pathway were examined. Elevated levels of cleaved caspase-6 were identified in areas where tau proteins accumulated, such as neurofibrillary tangles (NFTs) and neural plaques, key chronic cerebral deformities linked to Alzheimer's disease. Activation of caspase-1 was observed to activate caspase-6 [36,37,38]. NLRP1 expression was region-specific, primarily visible in certain areas of the hippocampus, correlating with the overall quantification of NFTs. To explore therapeutic approaches, genetically modified (GM) mice carrying human APP mutations were utilised. These mice displayed short-term memory loss, impaired visual memory and learning, and increased Aβ plaque generation and deposition over an average period of half a year. The experimental mice were divided into groups: one group expressed NLRP1 and its components, while the other had these genes silenced or knocked out. Alzheimer's-specific experimental assessments were conducted, showing promising outcomes with increased spatial navigation, improved visual memory and recognition. Biopsy analysis indicated elevated levels of the synaptic glycoprotein synaptophysin and the restoration of dendritic branches in the spinal cord. Additionally, the

neuroprotective chemokine CXCL1 showed immunomodulating effects in the cerebrospinal region. Suppression of NLRP1, Caspase-1, and Caspase-6 led to the stabilisation of CXCL1, TNF-α, and IFN-γ, exhibiting potential benefits in enhancing cognitive health, decision-making, and memory retention. Notably, a significant reduction in Aβ deposition in the hippocampus, a common clinical finding in Alzheimer's patients, was observed as a remarkable outcome of the comprehensive study [39].

In a recent study, transgenic mice models expressing conditions akin to the early signs of Alzheimer's disease were utilised to investigate the potential anti-inflammatory benefits of Ginsenoside or Rg1, a potent steroidal compound derived from ginseng. Alzheimer's disease is marked by autophagy inhibition of cell death, and disrupting or preventing this autoregulation is considered crucial in delaying neurodegenerative manifestations and improving cognitive memory capacity. The involvement of NLRP1 which is a member of the NLR family, in cellular processes within the neuronal cytoplasm has already been established, providing a plausible explanation for the persistence of neuroinflammation as a pathway leading to disease deterioration. The study focused on evaluating sensory recognition, particularly through smell, and other cognitive impairments, including observation leading to memory stimulation and learning from new experiences. The Morris water maze (MWM) test, a widely recognized experiment, was employed for these assessments. Immunoblotting techniques, quantitative PCR, and reverse transcription PCR were utilised to observe the expression of NLRP1 and its subsidiary components, such as interleukins, in the tissue of the experimental mice nurtured for nine months. The results revealed the presence of the inflammasome complex in an active state within the experimental mice. Furthermore, the study investigated the deposition and subsequent deterioration of neurons due to β-amyloid

plaques. Administration of Ginsenoside demonstrated a notable improvement, showing fewer instances of inflammatory lesions and spontaneous neuronal cell death. Additionally, the study highlighted the antagonist effects of Ginsenoside, accentuated by the use of the plant-derived antioxidant Apocynin. This dual approach aimed at mitigating the stimulatory communication between cytosols associated with NLR and the inflammatory conditions observed in autoimmune or auto-inflammatory conditions. By employing one of various techniques to silence NLRP1 mRNA, a more in-depth exploration into its connection with neuronal disintegrative conditions was conducted. The results showed a significant reduction in disorientation in locomotion and overall movement of limbs. A key pathway associated with controlled cell death is the AMPK/mTOR mediation, and the study revealed that silencing NLRP1 mRNA effectively halted this prominent pathway. This finding suggests a direct interrelation between the AMPK/mTOR pathway and the expression of NLRP1 mRNA, shedding light on the regulatory role of NLRP1 in these crucial cellular processes [40,41,42].

Various addictive substances impact the neurological and physiological aspects of a normally functioning human body such as alteration of the cognitive abilities to concentrate at one particular topic in hand, comprehension, memorization along with control of voluntary muscles and social intelligence. One of the known laboratory prepared stimulants that has been known to be an alternative prescription drug for attention deficit hyperactivity disorder as well as obesity has been misused for recreational purposes such as METH or methamphetamine. This drug is in key attention due to the visible damage it can cause to the hippocampal cells that lead to impairment of normal cognitive abilities upon excessive usage of this particular compound which is by cell degeneration that leads to necrosis and release of various inflammatory cytokines after cell death. This led to the connection of inflammatory

signal manifestos being involved with METH-related cerebral damage that can prolong to cause irreversible adversities. Much to the suspicions, the level of NOD-like receptor with pyrin domain-1 (NLRP1), activated caspase-1 and cytokines that mediate inflammatory responses such as interleukin-1β and tumour necrosis factor-α have been observed in prominent proportions than the control group which consisted of only feeding saline in case of administration of METH to several groups of experimental rats that have undergone a NOR test which is known to assess the short and long lived memory retention capacity of experimental models. Moreover, Gasdermin-mediated cell death or pyroptosis has been recorded which directly links the role of NLRP1 with its role in METH-induced pro-inflammatory stimulation and progression (Fan et al., 2022) [75].

2.1.5. NLRP1 in skin-related conditions

Despite Temozolomide's status as an anticancer treatment, it has exhibited limited success in advancing the progression-free status of melanoma patients. This lack of efficacy has been attributed in part to the action of an enzyme known as MGMT or O6-methylguanine-DNA methyltransferase, which significantly undermines the effectiveness of Temozolomide. However, it's essential to note that the action of MGMT alone doesn't entirely account for Temozolomide resistance. Recent research conducted by Zhai Z., Samson J.M. et al. in 2020 has uncovered intriguing insights into the role of NLRP1 in cancer-associated drug resistance. In a study involving human melanoma cells expressing low levels of MGMT, as well as TMZ-sensitive cells, exposure to Temozolomide over a 48-hour period led to a noteworthy increase in caspase-1 activity and IL-1β secretion in both cell lines. Surprisingly, these resistant cells exhibited minimal response to TMZ, showing little impact on the expression of

significant NLR pyrin domain subtypes and caspase-1 cleavage. These findings strongly suggest that Temozolomide augments the expression of NLRP1 and NLRP3, thereby activating the inflammasomal complex and triggering factors that require IL-1β release, potentially inducing apoptosis in melanoma cells. Delving deeper, the study revealed a compelling correlation between the expression of NLRP1 in melanoma cells and Notch-1, a signalling pathway that has been associated with promoting tumour growth factors and conferring increased tolerance to MAPK antagonists and TMZ. Notch signalling plays a pivotal role in modulating cancer stem cell regeneration, viability, and pathways related to cell death, cell cycle progression, and cellular longevity, thereby impacting tumour establishment and chemo-resistance. Therefore, the activation of Notch or the correlative induction of NLRP1 might contribute significantly to the development of tolerance to various medications or cross-resistance to alternative therapies with differing modes of action. This intricate interplay between NLRP1 and Notch pathways sheds light on potential avenues for therapeutic interventions aimed at mitigating drug resistance in cancer treatments [43].

The multifaceted role of NLRP1 in disease pathogenesis extends to small non-melanoma skin cancers, introducing a paradoxical dimension to its involvement in cancer progression. A recent study examining this protein's influence in cutaneous cancers found intriguing insights into its potentially beneficial role. Among the patients diagnosed with this condition, approximately 11% had succumbed to their illness. Notably, patients displaying lymphatic metastasis or myometrium penetration demonstrated markedly lower levels of expressed NLRP1 genes compared to both the surviving patients and a non-cancer control group. Similarly, patients experiencing recurring cases also exhibited lower degrees of NLRP1 expression. However, the precise protective mechanism or the specific role of NLRP1 in these

scenarios was not explicitly clarified in the study. This enigmatic behaviour of NLRP1 in non-melanoma skin cancer patients adds complexity to its characterization, presenting a dualistic nature wherein it seemingly acts as a protective factor in certain disease progressions while potentially remaining ambiguous in its exact protective mechanism. The intricate and paradoxical role of NLRP1 in disease progression warrants further comprehensive research to decipher its exact mechanism and ascertain whether it could be harnessed as a therapeutic agent or necessitates downregulation for targeted interventions. The potential of NLRP1 as a biomarker was highlighted in a study by Tan J., Li J., Zeng Y. (2023), demonstrating its significance in non-melanoma cancer patient survival through serum evaluation. The study revealed marked differences in serum levels of NLRP1 between diseased and non-diseased groups, suggesting its relevance as a prognostic indicator. Metastatic biomarkers like CEA and CYFRA21-1 exhibited higher levels in the 11% mortality rate among the control group, inversely correlating with the decreased levels of NLRP1 in the same patients, with an average sensitivity of 80% [44].

A study investigating the efficacy of antioxidants on keratinocytes exposed to direct UV radiation unveiled the involvement of the inflammasome in the inflammatory cascade triggered by laboratory condition based exposure-induced protein degradation. UV rays are known to excite electrons to higher energy states, stimulating melanocytes in the skin cells, particularly in individuals with darker skin tones, and in severe cases, contributing to skin cancer or melanoma. Recreating typical daytime environmental conditions, the study exposed keratinocytes to particulate matter and ozone, common sources of air pollutants known to exacerbate skin damage and respiratory issues. The experimental conditions were maintained for 56 hours to enable a comparative analysis of skin damage levels and intracellular cytokine

levels indicative of dysfunction. Observations revealed a notable increase in NFκB levels, escalating every 24 hours. Further investigation uncovered heightened transcription of inflammasome components such as caspase-1 and ASC, alongside the detection of interleukin 1β and 18, confirming the involvement of NLR, particularly the pyrin domain-1, in activating cascading pathways. Ozone emerged as a critical inducer, elevating reactive oxygen species (ROS) levels that interacted with essential cellular proteins, triggering an influx of inflammatory mediators. Hydroxyaldenal, a highly reactive unsaturated aldehyde produced via lipid degradation, was identified as a major damage-associated molecular pattern (DAMP) capable of cleaving NLRP1's N-terminal, inducing its disassembly and subsequent ubiquitination, leading to ASC oligomerization and inflammasome complex formation which is responsible for the culmination in pyroptosis or heightened inflammation. Application of an antioxidant mixture containing l-ascorbic acid, alpha-tocopherol, and ferulic acid to affected cultured tissue significantly reduced ROS levels, thereby preventing skin impairment and inhibiting the cyclooxygenase-2 pathway for further inflammatory summon. This comprehensive study sheds light on the skin-directed defence mechanisms against further damage when the primary barrier fails, cautioning against the counterproductive effects of an overstimulated immune system [45,46,47,48].

2.1.6. NLRP1 in cellular ageing

Cellular senescence, characterised by decreased viability and cessation of cell division, is a fundamental aspect of ageing in multicellular organisms. However, environmental factors and external stressors can accelerate this process. In particular, chronic exposure to pro-aging agents such as reactive oxygen species (ROS) and environmental pollutants can hasten cellular senescence. Reorganisation of the cell structure and the functioning is prevalent in cells entering the senescence phase which restrict growth, repair and recovery by arresting cell cycle. Senescence-associated secretory phenotype (SASP) is a term used to describe the state in which cells begin to assemble various compounds to maintain this particular stage. In an experimental study utilising irradiation with x-rays on animals, tissue samples were extracted after a month for evaluation to assess the inflammatory levels of senescence. The results reveal a peak in NLRP1 activity which resulted in a Gasdermin mediated cGAS activated pathway. cGAS is an intracellular detection mechanistic pathway that detects cytosolic genetic materials which are generally found only in the nucleus. Irradiation induces DNA arrangement and modification that accentuates the cGAS pathway and a trigger channel for NLRP1 assembly for further activation of other downstream signalling molecules that are relevant in cell arrest. Suppressing cGAS has been able to subdue the elevation of NLRP1 and its inflammatory components such as interleukins; in addition the the levels of signalling proteins such as p16 and p21, which are known to be tumour recognising factors are also detected when cell cycle is reduced or halted; a clear denotation of the cell reaching a halt in cellular activities. The findings were consistent with conditions observed in hepatocytes of liver inhabiting cirrhosis, highlighting the comparable effects of both internal ailments and external inducers on organ health [49,50].

Although early senescence has been described to be mediated via NLRP1 inflammasome arrangement, normal biological ageing of the body has been closely associated with cognitive diminishment that results in depressive-like symptoms and eventually develops into chronic stress induced depression. Experimental models undergoing stress level assessments such as open field test, tail suspension test, forced swimming and sucrose preference test indicate extended dormancy, delayed reactions and disinterest in exploration and interaction with other members in the assessment. These results direct towards a clear indication revealing emotional and mental melancholy which is evident in human depression as well. Moreover, the relative dependency of the level of expression of the pyrin domain-1 subunit of NLR has been directly proportional to the increasing age of the mice. The level of cytokine expression such as TNF and ILs follow the same pattern which indicates the major role of NLRP1 in the age progressive decline in the overall wellbeing of the diseased organism. To verify the role of NLRP1 in the age-related inflammatory pathway towards depression, the gene was selectively targeted and knocked out, which resulted in nullification of the pronounced inflammatory mediators as well as distressed behavioural symptoms when compared to previous readings, proving the conspicuous intervention of the inflammasome regarding senescence [51,52].

2.1.7. NLRP1 in cardiovascular conditions

In another study focusing on the regulation of diet and its impact on NLRP1, the effects of Phosphatidylethanolamine, a crucial phospholipid present in cell membranes, were investigated. The oxidised form of LDL, commonly known as low-density lipoprotein, significantly contributes to cardiovascular ailments like coronary artery disease and atherosclerosis [53]. The supply of exogenous Phosphatidylethanolamine repaired the inflammatory and autophagy-disrupting effects induced by oxidised-LDL in mammalian cells. Phosphatidylethanolamine's role in promoting autophagic vesicle maturation and its anti-inflammatory properties showcase its potential therapeutic significance during elevated and abnormal activation of the NLRP system [54].

A small group of Ischemic patients under 200 with a history of stroke have been under supervision for the levels of NLRP1 related cytokine relevancy in their system in comparison to carotid artery atherosclerosis as control. Surprisingly, the immense level of prominent values in the interleukins activated by caspase-6 were evident in blood works through ELISA of ischemic patients in comparison to control. The role of NLRP1 as a suitable prognostic marker for atherosclerosis is able to build foundation through this observatory study, with the limitation in the unclear relationship of the ischemia and NLRP1 [55]. It is hypothesised that the exacerbation of condition is mainly due to the lack of sufficient supply of oxygen along with the localization of triglycerides that initiate a chain of reaction creating free radicals and clogging of vessels that may signal an inflammatory upregulation confined area [46,55].

Omega-3 fatty acids, specifically docosahexaenoic acid (DHA), are abundant in fatty fish such as salmon, tuna, and sardines, as well as in certain edible seeds and seaweeds. Additionally, these fatty acids are produced by various algae and micro-level organisms within the sea, contributing to the high DHA levels in certain fish. DHA is a polyunsaturated

fatty acid crucial for the health of cell membranes, forming an integral part of the phospholipid backbone that constitutes the double-layered cell membrane. This membrane houses essential transporters and receptors, enabling semi-permeability. While DHA is naturally present in the cellular structure of the human brain, the body lacks the mechanism to synthesise it on its own. Therefore, a dietary supply of DHA is necessary to meet this nutritional requirement. As a response to this need, various cooking oils and salad dressings have been reformulated to be rich in omega-3 and omega-6 essential fatty acids. This adjustment aims to compensate for the body's inability to produce its own DHA and ensure a sufficient supply of these crucial fatty acids [56,57]. An intriguing observation has been made in the lack of correlation between healthy dietary fatty acids, including EPA, DHA, and other forms of omega-3 and omega-6 fatty acids, with the regulation of interleukin-18 (IL-18). Despite this, dietary fatty acids seem to exert an anti-inflammatory role by elevating HDL-C levels. Remarkably, they do not contribute to inflammation or play a role in contributing to LDL-C or triglyceride levels, highlighting their potential benefits in promoting cardiovascular health [58].

Various non-coding RNAs which are involved in the regulatory function of gene expression are being surfaced by scientists due to their role as a suitable biological marker in response to a growing inhabiting ailment within the body. One such RNA is lncRNA (long non-coding RNA) of the subtype 00346 has an unique sequestration mechanism against miR-148a3p (a micro non-coding RNA) to inhibit its role in binding to its corresponding mRNA. Hence, they have an inversely proportional relationship. The 00346 subtype has been found to be escalated during high inflammatory responses, especially during vascular damage such as in coronary artery disease (CAD) due to oxidised form of lipoproteins, which

common in cardiovascular patients, when compared against a control group composed of non-CAD patients. In such a high systemic immune condition, the rise in NLRP1 expression has been noted to become evident which was directly correlated to the levels of LINC00346 (lncRNA 00346). Suppression of this non-coding subtype eventually accentuates the levels of miR-148a3p which aids in diminishing the inflammatory mediation by halting the advancing levels of LINC00346/NLRP1 crosstalk, paving a pathway to a potential anti-inflammatory and anti-necrosis therapeutic target [59,60].

Intriguingly, recent research sheds light on the impact of sodium chloride influx within the nasal passage, leading to hyper-stimulation of NLRP1 activation. This surge in activity correlates with the increased presence of specks of apoptosis-associated speck-like protein containing CARD (ASC), a pivotal building block of inflammasome complexes. Existing studies have already established the adverse effects of diets high in sodium intake, particularly fast foods, contributing to various inflammatory-induced illnesses such as acne vulgaris, hypertension, cardiovascular interventions, and arthritis, often exacerbated by prolonged edema. Gene silencing experiments targeting NLRP1 have demonstrated a reduction in inflammatory components, including mediating cytokines. Notably, the induction of apoptosis by NaCl shows a significant increase when compared to unstimulated cells, with matured macrophages expressing prominence in the amount of interleukins IL-1, IL-1β, and IL-18. This research underscores the intricate interplay between dietary factors, NLRP1 activation, and inflammatory responses, offering valuable insights into potential preventive measures against sodium-induced health issues [61].

2.1.8. NLRP1 in trauma and transplantation

Brain strokes induced by local ischemia in arterial vessels lead to significant aftereffects and increased mortality. However, a more alarming concern is an observable tissue injury and progression towards atrophy resulting from the restoration of blood circulation within the affected area, a condition known as cerebral ischemia-reperfusion injury (CIRI). Post-vascularization often exacerbates deterioration rather than improvement, and the primary causes remain elusive. In a study conducted by Huang Y., Han M., et al. (2024), autonomous cell death emerged as a major contributor to CIRI, with the NL-receptor of pyrin domain-1 pathway playing a crucial role. Cell death in this context triggers inflammatory symptoms, including an increase in reactive oxygen species (ROS), mobilisation of cytokines, and permeation of clot-generating components such as platelets and macrophages. These anomalies result in edema, haemorrhage, neuron disintegration, and a higher likelihood of causing another ischemic stroke. Given that NLRP1 is evident in the neuronal cytoplasm, further investigation into its related interleukins indicates high activation during and after the reintroduction of the vascular framework. A thromboxane synthetase inhibitor, 4-(2-(1H-imidazol-1-yl) ethoxy)-3-methoxybenzoate or HY-021068, developed by a pharmaceutical company in China, shows potential in preventing the recurrence of stroke and exhibits defensive properties against neuroinflammation [63,64]. Further investigation, involving the silencing of the NLRP1 gene in this context to pinpoint the causal relationship, has unveiled the inhibition of its subsidiary components in the inflammasome activation pathways. This includes the downregulation of caspase-1, interleukins, and reinstates the functionality of various regulatory mechanistic pathways, including mTOR and sequestosome 1/p-62 protein which proves with tested theory and evidence that this apoptosis gene of the ced-4 family is indeed involved in CIRI, following the effective course of protective effects

from the emerging platelet aggregation inhibitor on the developing vasculature inflammation [65].

Purine activating cell surface receptors called purinergic receptors were found in almost all the major involuntary cells of the body such as macrophages, neurons, smooth and cardiac muscles. The subtype 2X within these receptors mainly plays a role by the influx of sodium and calcium ions which promote depolarisation of the cell for contraction and cellular signalling propagation. Over-expression of one of the types within the purinergic 2X subtype known as P2X4 is a major instance that has been observed in neurological disease or caused by trauma, reversing its natural neuroprotective effects to begin causing damage to the cells due to the abnormality caused by a systemic inflammation. As discussed earlier, the role of inflammation is crucial in exacerbating the micro environment within the delicately intertwined neuronal pathways within the CNS. Intracerebral haemorrhage (ICH) has been deduced to be involved in such vasculopathy. By the initiative taken by Wu Y., et. al. (2023), the role of P2X4 and its connection with NLRP1 has been verified in ICH laboratory models. Silencing of the 2X4 subtype receptor by the delivery of shRNA via a recombinant adenovirus attenuates the elevation of neurological discomfort such as mobility and cognitive impairment. The research further reveals the role of 2X4 subtype silencing also ameliorates the micro-environment of the CNS by hampering the prevalence of post-inflammatory cytokines. This information traces back to the case of CIRI which opens up the possibility of the involvement of NLRP1. The study concludes with addressing the existence of NLRP1/caspase pathway being codependent with over-activation of P2X4 in the neurons; as such, the vector RNA silencing aids in inhibiting the expression of NLRP1 which correlated to the improvement of the cerebral health of the affected laboratory models [66].

Bone marrow transplantation is one of the most extensively used procedures to restore healthy hematopoietic cells by replacing the defective cells. Such technique requires the pre-treatment of the transplantation graft which can cause rejection by the host tissue as well as deformation of the natural microflora within the bone marrow tissue by the invasion of the immune cells from the graft. Further realisation of the host and graft relationship, it has come to an understanding that the mesenchymal stem cells (MSCs) and endothelial cells (ECs) of the hematopoietic tissue are greatly affected by the emergence of an overactive immune response that is directly dependent upon the reasons of graft rejections and accommodation. A comprehensive study conducted by Hong F., Chen Y. et. al, 2021, foreshadows the presence of IL-1β and IL-18 during a post-surgery analysis which clearly correlates the activity of NLRP1 within the bone marrow environment. Such inflammatory mediators attracted the invasion of neutrophils which increased in levels in the span of two weeks. Expectedly, the levels of neutrophils, the immune cell responsible for the first line of defence had reduced in the course of two to three weeks within NLRP1 knockout stem cells which is directly proportional to the levels of surfacing chemical mediators such as TNF-α, IFN-γ, IL-6, IL-18, and IL-1β in post-transplantation surgery through ELISA. A reduced amount of haemoglobin content, increase in the output of progenitor hematopoietic cells that include the maturing as well as circulating platelets and leukocytes had a significant amount of elevation in post-surgical NLRP1 depleted stem cells, suggesting the inhibitory effects of NLRP1 on the success in the differentiation, maturation and viable health of the bone marrow. Through various staining examinations of knockout cells and regular stem cells, the astonishing decrease in the formation of lipids by adipocytes and demineralization of osteoblasts in NLRP1 knockout cells corresponded the relation of these process to the inhibitory mechanism of

megakaryocytic development. Additionally, the transfer as well as the diminishing conversion of pro-caspase-1 to accentuate the activities of NF-κB was one of the key factors in improving the chances of graft and host acceptance by the increasing ability of the graft to merge with the original niche of the bone marrow and stimulate the production of healthy stem cells. Such positive results were relatively observed within a time span of three weeks after treatment procedures via transplantation [69].

2.2. Regulation of over-stimulated NLRP1

In this section, the literature compiles evidence of various therapeutic agents that have been successful in regulating the levels of excessively activated NLRP1 protein as well as instances where the deficiency of an adequate basal level of this receptor has led to the development of conditions that can be downregulated by the introduction of mechanisms through which the receptor protein is activated in the living organism.

2.2.1. Hyperoside

The genus Hypericum stands out as a prominent source of phytomedicine, renowned for its efficacy in addressing diverse bodily distresses, including psychological, cardiac, and skin-related conditions. Its pharmacologically active principal compound, Hyperoside, is a potent antioxidant flavonoid which is a galactoside derivative of quercetin. Although quercetin itself is a powerful antioxidative agent, its underwhelming short half-life due to phase I metabolism limits its effectiveness. Derivatives of quercetin, such as Hyperoside, offer an alternative with similar efficacy and longer bioavailability, ensuring a prolonged exposure to targeted receptors. These flavonoids, known for their antioxidant properties, are particularly valuable for modulating inflammatory pathways; a pivotal factor in the pathogenesis of numerous chronic disorders. Hyperoside has demonstrated significant potential in enhancing the physiological states of myocardial tissues in experimental models of cardiac disorders. It effectively suppresses intercellular inflammatory mediation and mitigates the accumulation of clot-forming components which can result in programmed cell death, all connected to the prevalence of NLRP1 in these sectors. These findings emphasise

the emerging significance of Hyperoside in alleviating symptoms and preventing the progression of inflammatory-based disorders, including manifestations such as organ enlargement, elevated arterial blood pressure, and localised lesions [67,68].

2.2.2. Valproic acid and Furosemide

Over-firing caused by uncontrollable neuronal depolarization is one of the leading causes of epilepsy consisting of seizures that affect the normal day to day life as it interrupts daily life of diagnosed patients due to insufficient control over their own body with unpredictable timings and frequency of seizures that is able to make a person unconscious abruptly without prior warning to the body. Certain drugs and their combinations that were not administered for epileptic symptoms have been used with successful progression in recovery that include Valproic acid and Furosemide. Through in-vivo tests conducted in male Wister rats that have been subjugated to epilepsy by pharmacological agent for a period over two weeks, presence of compounds in the control group such as NLRP1 and other pyrin related gene without any form of treatment medication were recorded along with the elevation in the levels of ASC domain that is crucial in recruiting caspase subtypes in inflammasome assembly as well as the expression of AIM2 levels, a double stranded DNA structured sensor that plays a crucial role in warning the immune system of any cellular stress requiring attention and necessary action for control. With the addition of Valproic acid or/and Furosemide in the treatment groups, the levels of these stats were significantly lowered to manageable conditions which confirms the role and cause of inflammatory prognosis in epilepsy. In addition, neuronal cell death caused by chronic exposure to seizures can be led by inflammatory pyroptosis which has been significantly lowered in the treatment groups despite being a neurological disorder, prevailing

no signs of inflammation in the disease pathology when the causal property was assumed to be the disturbance in the neuronal transmitters [77].

2.2.3. Anakinra and ruxolitinib

One of the rare autoimmune arthritis cases involves mutagenic NLRP1, manifesting as NLRP1 associated auto-inflammation with arthritis and dyskeratosis (NAIAD). Treatments for such uncommon disorders are limited, with progression leading to poor vision and potential metastasis. Traditional therapies, including steroids and monoclonal antibodies, have shown minimal progress. Due to the rarity of this condition, clinical trials are constrained by participant availability. Burlakov (2024) introduces a novel combined innovation using the IL-1 receptor inhibitor anakinra and a potent kinase inhibitor ruxolitinib. This combination significantly reduces inflammatory markers to near-baseline levels observed in non-NAIAD patients over a period of thirty six months, with negligible adverse effects. Despite persistent corneal damage and hyperkeratotic skin lesions, the therapy effectively decreases systemic inflammation and improves blood parameters related to arthritis, gingivitis, and anaemia.

2.2.4. Regulation in Autoimmune Diabetes Mellitus Type-1

An astounding revelation of the critical role of NOD-like receptor pyrin rich domain-1 gene in the protective regulatory mechanism against the development and deterioration of the autoimmune type of diabetes mellitus, Type-1 DM has been demonstrated by Costa F.R.C., Leite J.A., et al. (2021). Their study aimed to investigate a similar behaviour of the absence of NLRP1 gene in both murine and human β-pancreatic cells that has been elusively correlated

with the increase in levels of IL-17 and Th-17 cells, both being part of the innate immune response and hence proving the claim of Type-1 diabetes being a dysfunction of the natural response of the body. After promising results of negative feedback mechanism by NLRP1 related genes against the elevation or mobilisation of helper-T17 cells that produce IL-17 were exhibited in regular mice and NLRP1 knockout mice, the experiment was safely incorporated among a group of type-1 DM patients with a pathological duration of minimum one and half decade with a specific polymorphic NLRP1 genotype - rs12150220 that does not show any significant difference during translation. Unrelated to helper-T1 cells, the small figure in the levels of helper-T17 cells was noticed. Additionally, the presumption of an elevated level of memory Th-17 cells due to the duration the disorder was nullified, including the T-lymphocyte related to cytokine IL-17, suggesting the role of abeyance of an inflammasome complex in keeping the pancreatic cells from the invasion of Th-17 related cellular differentiations [70].

2.2.5. Regulation in other metabolic disorders

The proper regulation of NLRP1 appears to play a pivotal role in addressing the root causes of certain major metabolic disorders. Research indicates a promising correlation between the effective functioning of adipocytes and enhanced glucose utilisation, leading to potential improvements in obesity-related conditions. Notably, NLRP1, in contrast to NLRP3, demonstrates a protective role in its own cells when its homeostatic functions are appropriately controlled [71]. Through the regulated activation of interleukin-18 and its levels, NLRP1 contributes to stimulating adipocytes, encouraging more efficient utilisation of stored energy, such as glycogen. This mechanism promotes the reduction of circulating levels

of glucose in the blood, facilitating its storage within the liver and adipocytes. Consequently, this process lowers the risk of obesity while simultaneously enhancing cellular sensitivity to insulin acceptance. Improved insulin sensitivity is essential for facilitating the entry of glucose into cells through transporters, further supporting overall metabolic health [72,73].

2.2.6. Regulation in lung carcinoma

A biostatical analysis of clinical trials of the level of NLRP1 in correspondence to lung-related metastasis, particularly lung adenocarcinoma or LUAD suggested the role of NLRP1 in prolonging the survival of patients compared to patients lacking in NLRP1 expression. Due to the immune-inflammatory role of NLRP1 in cases of over activation that is one of the reliable source of pathogenicity in inflammatory based ailments, the levels were surprisingly suppressed in a few cases of cancer involving LUAD where the accelerated metastasis makes it unable for extended duration of survival. The levels of CD4-T cells, CD8-T cells, dendritic cells, macrophages, neutrophils and B-lymphocyte cells, and the immune cells responsible for invasion in the colony of tumour cells were significantly elevated in patients harbouring active NLRP1 expression that was directly proportional to their decreased mortality. The study could be a reliable source of further research into the therapeutic approach of NLRP1 towards latent stages of multi-tissue cancer prognosis since the data analysis comprised of more than 400 reliable clinical trial patients of various geographical areas with varying stages of LUAD, including non-cancerous patients adjacent to the study to compare the levels of the targeted gene in discussion [74].

2.2.7. Regulation in viral infections

The human NLRP1 was made to be expressed in modified epithelial cell lines of the alveoli named $A549^{ACE2}$ which readily expresses the various components of its inflammasome creating components. With the use of a fluorescent marker, the activation of NLRP1 to form an inflammasome, induced by Val-boro, a pharmacological agent was localised and incubated with the premise that the cell lines were susceptible to SARS-CoV-2 infection. The results include the revelation of the direct dependency of the expression of NLRP1 inflammasome with the increasing level of the viral invasion which were evident in the cells that were modified to transcribe the NLRP1 gene. Additionally, a promising backing to the study includes the observation of NLRP1 being expressed against each and every variant of the virus without any obstacle which further proves the efficacy of NLRP1 being a suitable biological marker against most viral infections. The effect of the SARS-CoV-2 inhibitors on the function of NLRP1 was also observed by exposing the cell lines to market approved drug, Remdesivir. The level of cell mortality as well as the limitation in the availability of ASC-bound entities proved the above conclusion that NLRP1 activation is inconspicuous in case of inhibition of the viral invasion. Moreover, the inhibitor did not place any alteration in the functional pathways of NLRP1 when it was actively expressed due to stimulation by Val-boro. Another interesting factor to be discussed is the critical rise of caspases in the levels of severity of the viral invasion is threatened by the use of a caspase inhibitor known as Z-VAD which abruptly halts the cell pyroptosis that is mediated by the elevation of NLRP1 mediated inflammatory pathway against the detection of the SARS-CoV-2 virulence. The study was also successfully established in normal human bronchial epithelial cells (NHBEs) with the evidence of the same results as mentioned. The role of inflammasome activation

leading to pyroptosis was investigated by monitoring virulent particles in cell lines under observation, with results pertaining to the cells devoid of NLRP1 gene being more susceptible to the viral infection, theorising that pyroptosis can aid in the representation of an effective strategy to limit the development of competent and transmissible viruses but lacks enough evidence for prohibitive mechanisms by an immediate approach [76].

Porcine deltacoronavirus, also known as PDCoV, is an enveloped, single-stranded positive-sense RNA virus with a genome length of approximately 25.4 kb which belongs to the family Coronaviridae, genus Deltacoronavirus. Initially detected in wild Asian leopard cats and Chinese ferret badgers, PDCoV gained prominence following its identification in pigs in the early 21st century, primarily linked to severe diarrhoea outbreaks in piglets across the United States. Its global spread has since raised concerns, especially due to being an interspecies communicable disease noted in various animals, including calves, chickens, and even human plasma samples from children in Haiti. Recent investigations highlight the pivotal role of NOD-like receptor family pyrin domain-containing 1 (NLRP1) in combating PDCoV infection showcasing its antagonistic activity. While its direct antiviral role remains unclear, previous studies revealed its potential as an interferon-stimulating gene (ISG) against transmissible gastroenteritis virus (TGEV). Additionally, interleukin-11 (IL-11), a cytokine pivotal in tissue repair and immunity, emerges as a key player in inhibiting PDCoV replication, mediated by NLRP1. Mechanistic insights revealed that NLRP1 suppresses PDCoV replication by upregulating IL-11 expression, consequently inhibiting the phosphorylation of the ERK signalling pathway, a known intracellular signalling pathway. Moreover, the inhibition of ERK phosphorylation by administration of an ERK pathway inhibitor effectively impedes PDCoV replication in swine herds [78]. These findings indicate

the presence of a novel antiviral signalling axis of NLRP1-IL-11-ERK, but also sheds new light on potential treatments for coronaviruses and the development of corresponding pharmaceuticals.

Conclusion

The discovery of human NLRP1 (hNLRP1) marked a significant milestone in immunology, yet its functional pathways remain underexplored compared to other NLRs like NLRP3. Recent research has highlighted hNLRP1's dual role in the immune system, acting both as a protector and a contributor to various inflammatory and autoimmune disorders. Its involvement spans numerous tissues and organs, including the brain, cornea, lungs, skin, uterus, cardiac arteries, bowel system, and certain cancers and viral infections. The hNLRP1 activation leads to the release and elevation of key inflammatory mediators such as interleukins 1β and 18, and up-regulates NF-κB, TNF, and proteins associated with tumour suppression and DNA damage, indicating its pivotal role in disease pathogenesis and progression.

Genetic variations in the hNLRP1 gene, such as SNPs and mutations [9], are strongly linked to various disorders, necessitating targeted gene therapy. Understanding these genetic intricacies is crucial for uncovering the gene's role in disease pathogenesis and holds potential for targeted therapeutic interventions. Additionally, proteins like Thioredoxin, which acts as a natural antioxidant, interact with NLRP1 and provide insights into potential therapeutic targets for modulating NLRP1 activity [15].

The involvement of hNLRP1 in diseases such as Alzheimer's, diabetes, Crohn's disease, arthritis, and various skin disorders is concerning. However, its protective roles are also noteworthy. hNLRP1 helps prevent autoimmune diseases like Type-1 Diabetes Mellitus [70], regulates glucose utilisation in adipocytes to mitigate obesity [71,72], and reduces mortality from lung-related carcinoma by activating dormant levels of NLRP1 [74]. Furthermore, NLRP1 serves

as a potential biomarker and antiviral receptor, reducing viral replication in certain infections [44,76].

Over the past decade, extensive research has revealed the complex and diverse roles of hNLRP1 in numerous pathological conditions and biological processes. Its multifaceted nature underscores its importance in modulating inflammatory and immune responses, making it a promising therapeutic target. Regulating hNLRP1 activity—activating it during crises and down-regulating it when excessive—could improve patient outcomes and reduce disease recurrence. This approach offers new avenues for drug development aimed at alleviating symptoms and addressing the root causes of diseases that have long eluded effective treatments.

In conclusion, while hNLRP1 is indeed a double-edged sword, its careful regulation holds significant therapeutic potential. Balancing its protective and harmful effects could lead to improved management and treatment of various complex biological disorders.

Summarization of the above literature has been organised into three tables: Table 1, Table 2, and Table 3. Table 1 condenses the texts where NLRP1 has been a catalyst and/or deeply involved in the progression of a diseased condition. Table 2 comprises the role of NLRP1 in regulating abnormal cell activity when it is under supervision of not being activated excessively. Table 3 outlines various agents which have been able to control the elevated levels of NLRP1 successfully and show promising results in reducing the symptomatic signs and pathways for improvement in patient condition.

3.1. Table 1

Involvement of NLRP1 in the mediation and exacerbation of various diseases.

Serial No.	Targeted tissue and the resultant effect.	Genetic inclination	External source of trigger	Responsible Researchers/Authors
1.	Lungs : Inflammation by ROS.	No	Benzo α-pyrene or BaP in air.	Kohno R, Nagata Y, et. al. (2023) (79)
2.	Skin: Vitiligo	Yes, polymorphism	Ultraviolet rays and heat	Męcińska-Jundziłł, K., Tadrowski, T., et. al. (2023) (80)
3.	Respiratory system: Asthma	Yes, polymorphism	Antigens (viral particles) and allergens (dust, mite, pollen)	Moecking, J., Laohamonthonkul, P., et. al. (2021) (10)
4.	Barrier disruption: Corneal and airway epithelial cells	No	*P. aeruginosa*	Pinilla, M., Mazars, R., et. al. (2023) (20)
5.	Keratinocytes: cytotoxicity and cell pyroptosis	No	DT toxin by *C. diphtheria*	Robinson, K.S., Toh, G.A., et. al. (2023) (21)
6.	Non-haematopoietic cells: pyroptosis by reducing more than 20% of intracellular K+ ions.	No	Nigericin: blocking influx of K+ ions	Rozario, P., Pinilla, M., et al. (2024) (22)
7.	Uterus: endothelial cell disruption	No	Gestational Diabetes, Thrombin pathway	Liu, Y., Tang, Z., et al. (2020) (23)
8.	Gingiva: periodontal ligament cell inflammation	No	Periodontitis and AGEs due to Diabetes Mellitus	Yi, X., Song, Y., et al. (2024) (24)
9.	Colon: Inflammatory Bowel Disease (IBD),	Yes, polymorphism	Congenital, and autoimmune disease	Ji, Y., Yang, Y., et al. (2022) (26)

	Crohn's disease.	and other genetic mutations		and Hong, W., Yan-Chun, M. (2020) (27)
10.	Preeclampsia: inflammatory hypertension in pregnancy	No	Lack of oxygen supply to trophoblast, heightened monocytic response	Matias, M. L., Romão-Veiga, M. et. al. (2021) (28)
11.	Neurological: depression	No	mTOR activation and deposition of cellular debris.	Zhu, Y., Huang, J., et al. (2024) (32)
12.	CNS: Alzheimer's disease	No	Inflammatory exacerbation by caspase-1 and caspase-6	Španić, E., Horvat, L., et. al. (2022) (37) and Flores, J., Noël, A., et al. (2021) (39)
13.	Melanocytes: resistance to Temozolomide (anti-cancer drug)	No	Acquired drug resistance with hyperactive NLRP1	Zhai, Z., Samson, J. M., et. al. (2020) (43)
14.	Melanocytes: trigger of melanin	No	UV radiation	Ferrara, F., et. al. (2020, 2022, 2024) (45) (46) (47) (48)
15.	Early cellular ageing	No	Irradiation and other forms of chronic stress that create ROS	Muela-Zarzuela, I., Suarez-Rivero, J.M., et. al.
16.	Cardiovascular tissue: plaque formation	No	Hypoxia, elevated oxidised LDLs and abundance of triglycerides	Zong, J., Wang, Y., et. al . (2023) (54) and Tao, C., Wang, Y., & Xiao, S. (2023) (49) (2023) (55)
17.	Nasopharyngeal cavity: Edema	No	Sodium ion influx (Na+)	Sposito, F., Northey, S., ey. Al. (2023) (61)
18.	Brain tissue: cerebral ischemia-reperfusion	No	Re-vascularisation permeates the entry of	Li, P., Huang, J., et. al. (2020) (64)

	injury (CIRI)		inflammatory mediators	and Wu, L., Xiong, X., et. al. (2020) (65)
19.	Bone marrow: post surgery graft rejection	No	Foreign graft: Diminishing megakaryocytic division and maturation, insurge of inflammatory response	Fu, H., Chen, Y., et. al. (2021) (69)
20.	CNS: cognitive and locomotive degradation	No	Methamphetamine	Fan, R., Shen, Y., et. al. (2022) (75)

3.2. Table 2

Activation of dormant levels of NLRP1 to regulate cell activity and prevent disease exacerbation.

Serial No.	Target tissue.	Protective Effect displayed by NLRP1	External source of trigger	Responsible Researchers/ Authors
1.	Non-melanoma cells	Lower levels of NLRP1 act as a biomarker	Non-melanoma skin cancer	Tan J, Li J, Zeng Y. (2024) (44)
2.	□-cells of pancreas	Diminishing effects of autoimmune degradation	Helper T-17 cells (Th17) invasion into pancreas in auto-immune conditions	Costa, F. R. C., Leite, J. A., et. al. (2021) (70)
3.	Glycolysis	Improved glucose intake	Weight loss, Replenished gut microbiota	Lacerda, R. R. E., Fang, H., et. al. (2023) (71) and Antonioli, L., Moriconi, D., et al. (2020) (72)
4.	Adipocytes	From obesity	Weight loss,	Lacerda, R. R.

			Replenished gut microbiota	E., Fang, H., et. al. (2023) (71) and Antonioli, L., Moriconi, D., et al. (2020) (72)
5.	Pulmonary tissue	From Carcinoma	Activation of dormant NLRP1 genes	Shen, E., Han, Y., et. al. (2021) (74)
6.	Pulmonary tissue/cells	From exaggeration of infection	SARS-CoV 2 (Severe acute respiratory syndrome coronavirus 2)	Planès, R., Pinilla, M., et. al. (2022) (76)

3.3. Table 3

Successful inhibition of NLRP1 and related disease symptoms by various pharmacological agents.

Serial No.	Ailment	Target symptoms	Therapeutic agent	Reference
1.	Pyroptosis	Inflammatory chain reaction	Thioredoxin	Yap, J. K., Emming, S., & Schroder, K.. (2024) (15)
2.	Preeclampsia	Inflammation, hypertension	Vitamin D3	Nunes, P. R., Romão-Veiga, M., et. al. (2022) (30)
3.	Alzheimer's disease	Neurodegeneration, cognitive and locomotive functions	Ginsenoside	Li, X., Huang, L., et. al. (2022) (40)
4.	Cardiovascular diseases	Plaque formation, oxidative damage, inflammatory corrosion of vascular epithelium	Phosphatidylethanolamine	Hao, T., Fang, W., et. al. (2023) (53)

5.	Intrauterine growth restriction (IUGR)	Cognitive impairment of foetus	Docosahexaenoic acid (DHA)	Wan, L., He, X., ET. AL. (2023) (57)
6.	Myocardial Infarction (MI)	Suppression of autophagy, cardiac remodelling, inflammatory plaque formation	Hyperoside (a quercetin derivative)	Yang, Y., Li, J., et. al. (2021) (67)
7.	Epilepsy	Neuronal relapsing symptoms of seizures.	Valproic acid and Furosemide.	Samadianzakaria, A., Abdolmaleki, Z., et. al. (2022) (77)
8.	Sepsis	Abnormal organ dysfunction towards infection.	miR-122-3p microRNA	Li, M., Hu, L., et. al. (2023) (81)
9.	NLRP1 associated auto-inflammation with arthritis and dyskeratosis (NAIAD)	Loss of corneal function, skin irregularities, and arthritis.	Anakinra and ruxolitinib	Burlakov, V., Kozlova, A., et. al. (2024) (82)

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