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Role of inflammasomes NLRC4 in pathogenesis of leprosy

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Abstract

Mycobacterium leprae is the organism responsible for causing leprosy, a persistent contagious illness. The inflammasome is a complex of cytosolic proteins that mediates the inflammatory response in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the latter of which is responsible for the maturation of caspase 1, secretion of IL-1 and IL-18, and a type of cell death known as pyroptosis. One protein, interleukin-1 conversion enzyme (ICE)-protease activating factor, was found to be responsible for initiating caspase-1. (IPAF). The amino-terminal CARD domain and its surrounding amino acids confirmed its membership in the NLR protein family, prompting the nomenclature change to NLRC4. In reaction to bacterial infections that target the cytoplasm of host cells, like *M. tuberculosis* and *M. leprae*, new data indicates that the NLRP3 inflammasome is involved in the inflammatory response caused by caspase-11. Activation of the NLRP3 inflammasome follows a classical pathway that begins with the recognition of PAMPs or DAMPs by TLRs, which then activates nuclear factor kappa B (NF- κ B)-mediated signaling and up-regulates transcription of inactive NLRP3, pro-IL-1, and pro-IL-18. Oligomerization of NLRP3 is the second stage, which is then followed by the formation of a complex containing NLRP3, ASC, and pro-caspase-1. This results in the synthesis and release of mature IL-1 and IL-18, as well as the self-activation of pro-caspase-1 into the enzymatically active form by proteolytic cleavage. The clinical course of an infection depends on the result of this first interaction, and it now appears that NLRP1, NLRP3, caspase 1, IL-1, and IL-18 collaborate in a concerted effort to trigger this early reaction.

Keywords: Leprosy, inflammasomes, caspase, NLRC4, inflammation

Introduction

Mycobacterium leprae is the organism responsible for causing leprosy, a persistent contagious illness. Granulomatous lesions are the hallmark of this illness and typically first appear on the epidermis and peripheral nerves [1]. T helper 1 (Th1) cytokine profile (mainly IL-2 and IL-12) is associated with the tuberculoid (TT) leprosy form, while the lepromatous (LL) leprosy form is associated with the Th2 cytokine profile (mainly IL-4) [2]. The clinical and histopathological characteristics of the disease span a spectrum depending on the pattern of the host immune response.

Macrophages and emerging cytokine profiles are two examples of natural immune variables that have recently been linked to leprosy's immunopathogenesis. Th9, Th17, Th22, and Th25 are all involved in the pathogenesis of reactive states and contribute to the development of leprosy's various clinical manifestations [3].

The inflammasome is a complex of cytosolic proteins that mediates the inflammatory response in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the latter of which is responsible for the maturation of caspase 1, secretion of IL-1 and IL-18, and a type of cell death known as pyroptosis [4-6]. Pattern recognition receptors (PRRs), an adaptor protein, and an effector enzyme combine to create inflammasomes (caspase). Classical (or canonical) signaling pathways involve activation of caspase 1, while noncanonical signaling pathways involve activation of other caspases to induce inflammation [4].

The nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) is a prominent type of pattern recognition receptor (PRR) involved in inflammasome development. The mammalian NLR PRR family has 22 different members.

A variable N-terminal effector domain, a central NACHT domain, and a C-terminal section abundant in leucine repeats make up their fundamental structure. Depending on the sequence of their N termini, NLRs can be divided into one of four subfamilies: NLRA (containing the acid activation domain), NLRB (containing the BIR-type domain), NLRC (containing the activation domain and caspase recruitment), or NLRP (pyrin domain) [7, 8].

NLRC4

[NOD-like receptor (NLR) containing a caspase activating and recruitment domain (CARD) 4]

Poyet *et al.* [9] were the first to characterize NLRC4 and its role in apoptosis. One protein, interleukin-1 conversion enzyme (ICE)-protease activating factor, was found to be responsible for initiating caspase-1. (IPAF). The amino-terminal CARD domain and its surrounding amino acids confirmed its membership in the NLR protein family, prompting the nomenclature change to NLRC4 [10].

Structural features of NLRC4

NLRC4 has the same three-domain organization as the rest of the NLR family, including a CARD domain at its N terminus, an NBD domain in the middle, and a set of LRRs at its C terminus. (Figure 1). The first 94 amino acids of NLRC4 make up the homotypic interaction region and are expected to fold into a common structural pattern called the CARD. Commonly, the CARD will coil into a structure consisting of six anti-parallel α -helices surrounding a hydrophobic center. The NBD contains a core RNA nucleoside triphosphatases (NTPase) domain and two helical domains (HD1 and HD2) that are separated by a region called a winged helical domain (WHD), all of which are structural characteristics shared with other NLR proteins. (Figure 2). The 440 amino acids at NLRC4's carboxy-terminus are organized into 15 repetitive structural units, or LRRs. These units are composed of a leucine-rich β strand connected to a short α helix containing 8-15 amino acids [10].

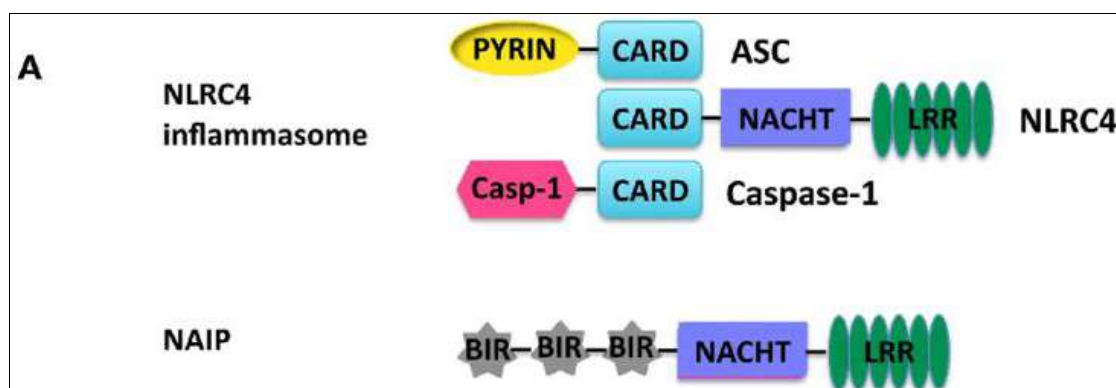


Fig 1: Structure of the NLRC4 inflammasome and NAIP proteins [11].

CARD (caspase activation and recruitment domain), ASC (Apoptosis associated speck-like protein containing CARD), NACHT (NOD) (nucleotide-binding oligomerization domain), LRR (leucine rich repeat), NLRC4 (NOD-like receptor containing CARD), BIR (baculo virus inhibitor of apoptosis protein Repeat).



Fig 2: Schematic representation of domain organization of NLRC4 [12].

CARD (caspase activation and recruitment domain), NBD (nucleotide-binding domain), HD (helical domain), WHD (Winged helical domain), LRR (Leucine rich repeat). HD1, WHD and HD2 form an adenosine diphosphate (ADP) binding pocket that stabilizes NLRC4 in its inactive conformation. Upon LRR detection of ligand-bound NAIP, the NOD undergoes a conformational change that promotes ADP for ATP exchange, NLRC4 oligomerization and inflammasome assembly [13].

Activation of NLRC4 inflammasome

The NLRC4 inflammasome is typically activated by flagellin or structural components of facultative intracellular

bacteria (e.g., bacteria including *Salmonella typhimurium*, *Shigella flexneri*, *Burkholderia thailandensis*, *Pseudomonas aeruginosa*, and *Legionella pneumophila* [14]. NLRC4 does not directly interact with its ligands. Instead, NLRC4 is activated via contact with the sensor protein NAIP which physically binds either flagellin [13]. NAIPs are NLR proteins that lack death fold domains, but instead contain baculoviral inhibitor of apoptosis protein repeat (BIR) domains at their N-termini [12]. (figure 1)

Two EM investigations reported NLRC4 oligomerization after ligand binding to NAIP. During activation, ligand-bound NAIP first interacts with an inactive NLRC4 molecule, causing the molecule to undergo structural remodeling by rotating the WHD-HD2-LRR regions around the hinge region. This, in turn, causes the basic amino acids in the NBD to interact with an acidic surface on the next monomer added to the structure, in a domino-like reaction, forming the well-known disk-shaped complex [15] (figure 3). NLRC4's auto-inhibited state requires continuous supply of ADP. The significance of ADP in NLRC4 regulation and the need to keep inflammasome activation in check have been proven by showing that mutation of residues in the ADP binding pocket can result in constitutively active NLRC4 and sickness in individuals [16].

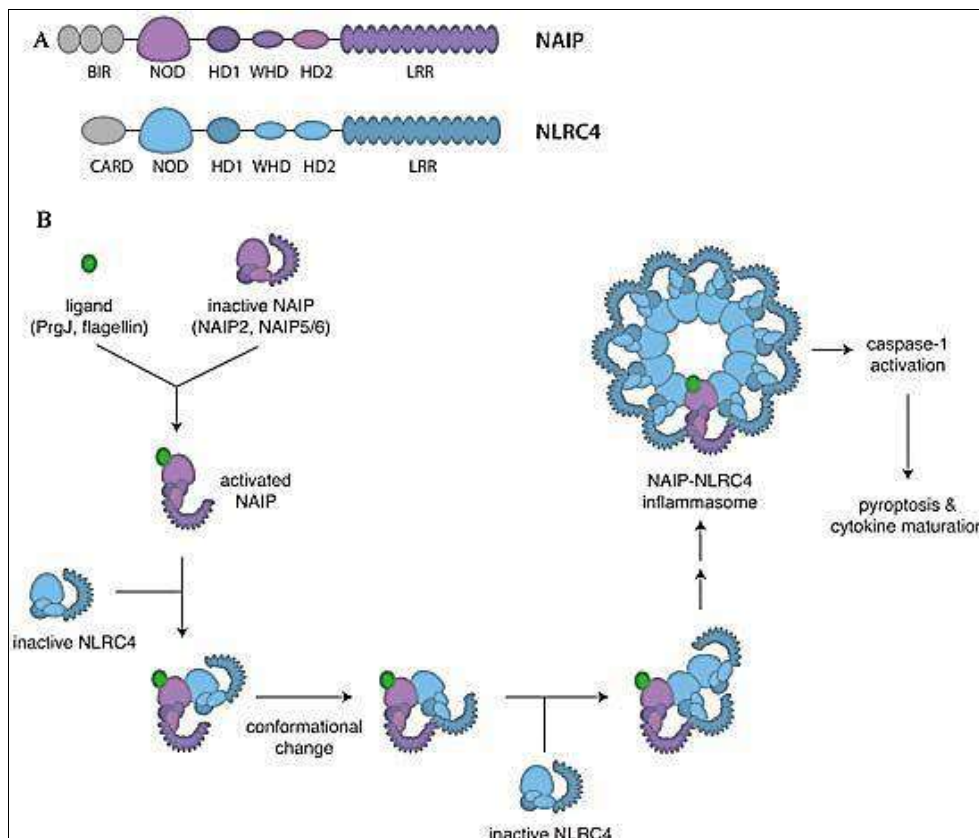


Fig 3: (A) Domain organization of NAIPs and NLRC4 in mice. (B) Assembly mechanism of NAIP-NLRC4 inflammasomes ^[17].

NLRC4 (NOD-like receptor containing CARD), NAIP (NLR family of apoptosis inhibitory protein), BIR (Baculoviral inhibitor of apoptosis protein repeat), NOD (nucleotide-binding domain), HD (Hinge region), WHD (winged hinge region), CARD (Caspase activation and recruitment domain), LRR (Leucine rich repeat).

NLRC4 effector mechanism

Several host signaling events, including caspase-1, the main protease responsible for transforming proIL-1 to active, secreted IL-1, appear to be activated upon NLRC4 inflammasome activation. As with IL-12, IL-18 undergoes enzymatic processing via caspase. (125).

Gasdermin-D is an inactive cytosolic protein that is activated by caspase-1 proteolysis; the resulting amino-terminal segment assembles into cytoplasmic membrane holes ^[18]. Gasdermin stimulation is known to cause a breakdown in cell membranes, which leads to pyroptosis (programmed cell death). (Figure 4). In contrast to apoptosis (classical planned cell death), pyroptosis results in the leakage of proinflammatory intracellular components like the protein high mobility group box 1 (HMGB1), which in turn causes further inflammatory signaling in adjacent host cells. This process may be how macrophages produce

cytokines after being triggered. Pyroptosis aids host defense by disrupting the intracellular milieu favorable to the pathogens that trigger NLRC4 ^[19], in addition to causing inflammatory reactions in the host.

Caspase-1 activation downstream of NLRC4 leads to fast synthesis of pro-inflammatory prostaglandin (PG) and leukotriene (LT) including PGE2 and LTB4, as well as processing pro-cytokines and causing pyroptosis. The activation of NLRC4 is also exceptional because of its capacity to directly engage with caspase-1. By interacting with the CARD domain of procaspase-1, NLRC4 is able to directly trigger the protease. However, the presence of ASC increases NLRC4-induced caspase-1 activation in cells. (Figure 5). Both a pyrin domain and a CARD domain make up the ASC. (Figures 1&4). Condensation of the cytoplasmic ASC into a potentially large insoluble oligomer known as the apoptotic speck can occur in response to inflammasome activation or the start of apoptosis ^[20]. It has been discovered that NLRC4 brings procaspase-8 into the inflammasome complex. It takes both NLRC4 and ASC for caspase-8 to be recruited and activated in reaction to a *Salmonella* infection. It indicates that stimulation of caspase-8 can replace caspase-1 in the processing of pro-IL-1 ^[21].

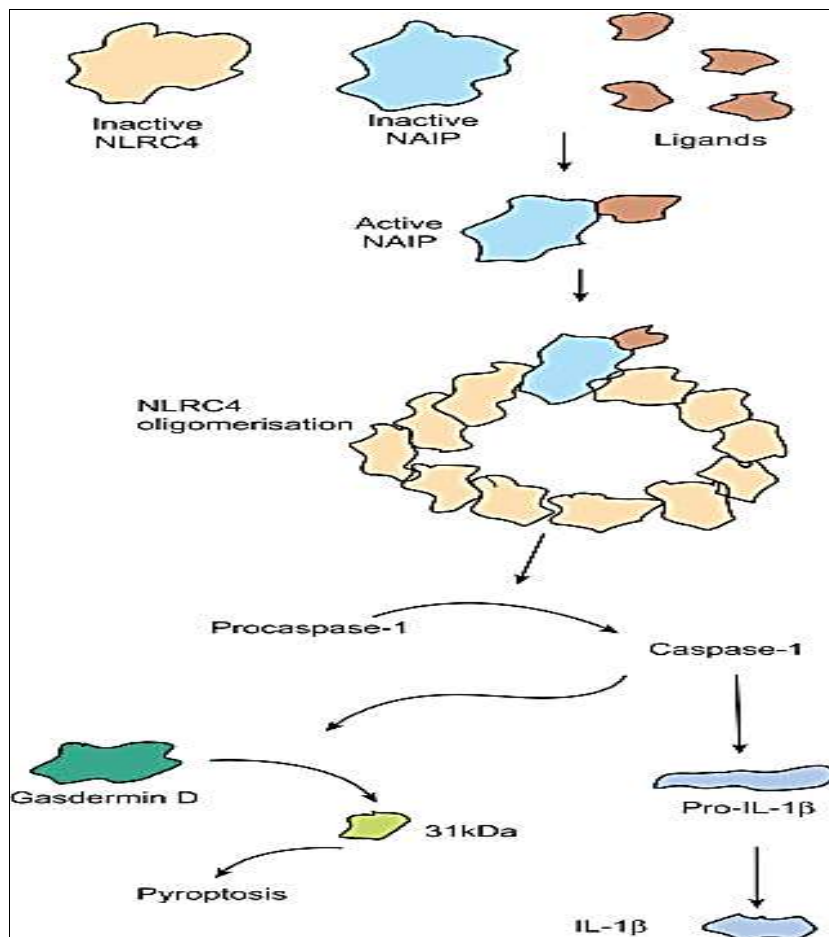


Fig 4: Activation and signaling by the NAIP/NLRC4 inflammasome ^[22]

NLRC4 (NOD-like receptor containing CARD), NAIP (NLR family of apoptosis inhibitory protein).

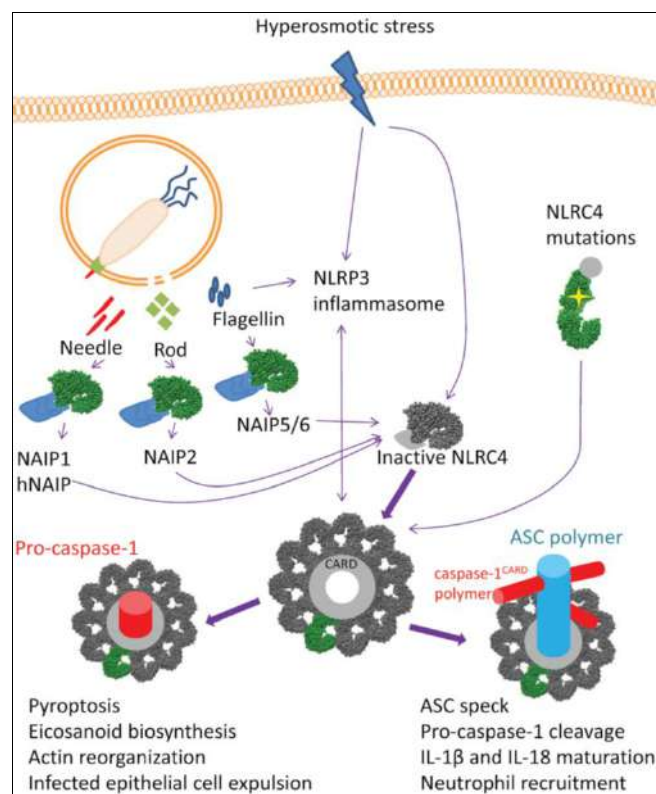


Fig 5: NLRC4 can directly interact with procaspase-1 but maximal NLRC4 inflammasome activation might require ASC ^[23]

NLRC4 in host defense

NLRC4 is a critical component of defense against enteric pathogens

1. Upon *Salmonella* infection, NLRC4 triggers procaspase-1 via its CARD domain, leading to cell demise. Activation of NLRC4 effects other parts of cell biology that are crucial in host defense ^[24], including elimination of infected cells via pyroptosis and perpetuation of inflammation via IL-1 and IL-18 release.
2. When *Salmonella* invades macrophages, NLRC4 triggers a reaction characterized by an increase in actin polymerization and a subsequent decrease in bacterial uptake, as well as an increase in intracellular reactive oxygen species (ROS) generation, with the latter effect boosting intracellular killing and the latter reducing bacterial spread ^[25]. In order to limit the spread of *Salmonella* infection, stimulation of NLRC4 in epithelium cells is essential. Thus, removing inflammasome components (NAIP 1-6, NLRC4, and caspase-1/caspase-11) from the epithelium leads to an increase in bacterial burden and spread outside the intestines ^[26].
3. One unexpected aspect of NLRC4 activation is the fast host mortality seen in a rodent model where flagellin is delivered intraperitoneally. (within 30 min). This remarkable inflammasome-dependent reaction does not require either interleukin-1 or interleukin-18, but rather depends on the generation of eicosanoids to cause rapid vascular fluid loss and mortality ^[24].
4. It is presently unknown how the NLRC4 inflammasome triggers biosynthesis of eicosanoids or if this role of

eicosanoid production can be generalized to all inflammasomes.

NLRC4 is a critical component of defense against systemic pathogens

A number of non enteric bacteria require NLRC4 for full recognition and clearance such as *Listeria monocytogenes* [27], *Pseudomonas aeruginosa* [28], and non-flagellated bacteria such as *Klebsiella pneumoniae* [29]. Pulmonary pathogens like *Burkholderia pseudomallei* can trigger both the NLRC4 and NLRP3 inflammasomes and both are required for full protection [30].

Similar to the conventional NLRC4 triggering enteric pathogens like *Salmonella* and *Shigella*, these non-enteric pathogens activate NLRC4 through the detection of flagellin or parts of bacteria by NAIP proteins. However, the intracellular rickettsial pathogen *Anaplasma phagocytophilum* may trigger NLRC4 activation via a process reliant on cyclo-oxygenase 2 (COX2)-mediated prostaglandin synthesis, even in the absence of the production of these PAMPs [31, 32].

Mutations in NLRC4 cause auto-inflammation

In recent years, three missense variants in NLRC4-H443P, V341A, and T337S have been associated with autoinflammatory disorders. One Japanese family was found to carry the H443P heterozygous variant after members began reporting symptoms like arthralgia, urticaria, and fever when exposed to chilly weather. Mice bearing the H443P NLRC4 mutation showed symptoms of autoinflammatory syndrome, including eczema, joint swelling, and splenomegaly. This was due to the mutant's propensity for oligomerization in the cellular system. Cold weather induced an autoimmune response that was reliant on interleukin-1 beta and neutrophil interleukin-17a [33].

Neonatal-onset enterocolitis is one of the serious inflammatory phenotypes caused by the V341A mutation in people, while the T337S mutant produces recurrent fever flares and macrophage activation syndrome in young children. (MAS). These mutated forms of NLRC4 can function independently of any known activators. When compared to serum IL-18 levels in healthy individuals [34, 35], those of V341A and T337S patients were extremely elevated.

The NOD module is the site of all three pathogenic missense variants in NLRC4. HD1 contains T337 and V341, and their changes may weaken HD1/NBD contacts or ADP binding. The ADP makes straight hydrogen bonds with H443 in WHD. The H443P variant is predicted to impair ADP binding and, by extension, the primary contacts in the NOD module [12].

More than a hundred NLRP3 or NOD2 variants have been linked to autoimmune inflammation. Somatic mosaicism of the NLRC4 locus was also found in a patient with neonatal onset multisystem inflammatory illness in a recent investigation. (NOMID). Disruption of the mutated NLRC4 in patient macrophages derived from induced pluripotent stem cells verified that the inflammatory phenotype was due to an NLRC4 T177A mutation [36]. The patient did not contain gain of function mutations in the NLRP3 gene or somatic mosaicism in NLRP3, and these findings ruled out other potential causes of the inflammatory phenotype.

Next-generation sequencing and transcriptomics have made it more probable that NLRC4's involvement in other

inflammatory diseases will be determined in the near future. Patients with active systemic-onset juvenile idiopathic arthritis had higher amounts of NLRC4 mRNA [37]. Patients with MAS often have elevated blood levels of IL-18, suggesting that therapies directed at this cytokine may be helpful. In reality, recombinant human IL-18 binding protein (rhIL-18BP), which binds IL-18 and blocks its signaling, was associated with rapid improvement in a case analysis of a patient with NLRC4(V341A)-MAS [38].

NLRC4 involvement in stroke and cancer

Emerging evidence points to NLRC4 as a key player in several diseases fueled by sterile inflammation. Substantial proof for caspase-1 activation and the function of IL-1 in neurodegeneration existed long before inflammasomes were discovered. In the past decade, it has become clear that NLRP3, NLRP1, and missing in melanoma 2 (AIM2) are key mediators of neuroinflammation in a range of neurological disorders [39]. It has been shown that the NLRP3 inflammasome is activated in response to ischemic brain damage by a number of different mechanisms, including reactive oxygen species (ROS) generation, acidosis, potassium efflux, and others [40].

Initial evidence suggested that NLRP3 mediates ischemic brain damage in a rodent model [41], but this was refuted subsequently. In chemically caused cerebral ischemia, mice lacking AIM2, NLRC4, or ASC had reduced infarct size, better neurological scores, and diminished activation of microglia and leukocyte recruitment [42]. In contrast, NLRP3 deficient mice fared no differently than wild-type controls. Since NLRP3 is thought to be the primary sensor of sterile damage and NLRC4 activation is activated by known PAMPs, these findings come as a surprise. However, this work hints that NLRC4 is crucial in sterile conditions, though more research into the mechanisms of NLRC4 activity in sterile inflammation is required. Denes *et al.* [42] hypothesized that the observed impact is mediated by systemic NLRC4 activation due to host microbiota or that NLRC4 is able to detect an as-yet-unidentified DAMP, given that there are signs that both systemic and central IL-1 signaling contribute to brain injury [43].

NLRC4's multifaceted functions in the development of cancer have been studied. The protective impact of NLRC4 against azoxymethane-dextran sodium sulfate-induced colitis-associated colon cancer was shown by Hu *et al.* [44]. This result was observed in both NLRC4-deficient and wild-type animals, and did not rely on the presence of inflammation. Specifically, they hypothesized that p53 stimulation by epithelium NLRC4 signaling controls apoptosis [45]. However, Allen *et al.* [46] used the same mouse model of colitis-associated colon cancer and discovered no variations in tumorigenesis between NLRC4-deficient and wild-type animals, while attributing protective benefits to NLRP3 [12].

Obese individuals with breast cancer were found to have an activated NLRC4, but not an NLRP3, inflammasome [47]. In the tumor microenvironment, NLRC4-activated macrophages produce IL-1, which stimulates adipocyte synthesis of Vascular Endothelial Growth Factor A (VEGFA) and angiogenesis. It has been shown that metformin or blocking IL-1 can reduce the development of tumors brought on by fat. The trigger NLRC4 is still shrouded in mystery. The authors speculate that NLRC4 activation could result from changes in microbiota brought

on by obesity or from a rise in endotoxemia brought on by a high-fat diet. The same researchers demonstrated that, in addition to NLRP3, the NLRC4 inflammasome adds to diabetic nephropathy by secreting IL-1^[48].

NLRC4 and skin diseases

NLRC4 and psoriasis

Psoriatic sores are caused by a series of inflammatory substances that may have their origins in both the environment and genetics. Pro-inflammatory cytokines like interleukin (IL)-1, tumor necrosis factor (TNF)-, chemokines, and antibacterial peptides are secreted from keratinocytes by the T-cell-derived mediators IL-17A and IL-22. One of the main cytokines in the pathogenesis of

psoriasis is interleukin-1 (IL-1), a mediator of the inflammatory response that is primarily generated by keratinocytes in lesional psoriatic skin and adds to the development of T-cell-dependent inflammation in psoriasis-like skin disorders. Recent research into the process of IL-1 stimulation in psoriasis has pointed to inflammasomes^[49]. Among the possibilities found in the psoriatic scale samples, NLRC4 stood out. Upregulation of NLRC4 was observed by immunohistochemistry in the lesional epidermis of some psoriatic patients, while modest expression of NLRC4 was identified in the normal and non-lesional epidermis. These results raise the possibility that NLRC4 contributes to the worsening or alteration of psoriatic lesions, as depicted in figure (6)^[49].

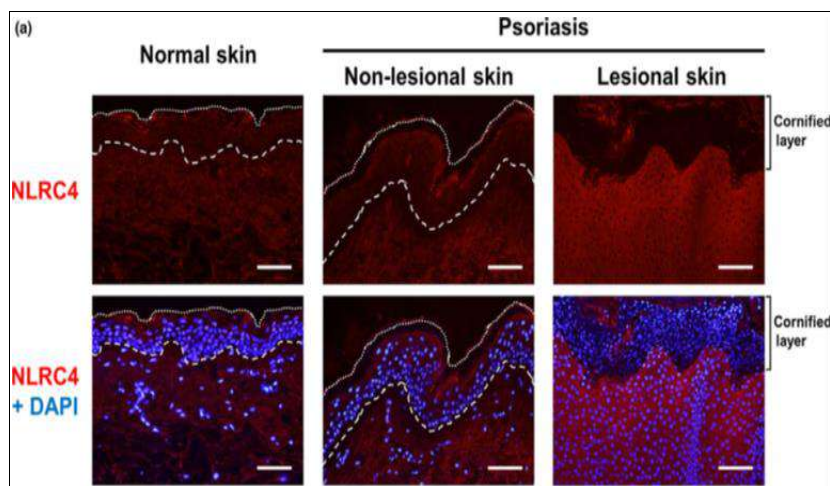


Fig 6: Immunohistochemical analysis of the expression of NLRC4^[49].

NLRC4 and candidal infection

In a 2011 investigation, researchers found that *Candida* infection up-regulates mucosal expression of NLRP3 and NLRC4, and that rodents lacking these genes had trouble with this process. The study also found evidence that the NLRC4 inflammasome participates in protection against fungi. Important for mucosal *Candida* infection management, NLRC4 influences inflammatory cell recruitment to affected regions and provides protection against systemic infection spread. Both pro-inflammatory and antibacterial peptide reactions in the mouth were significantly dampened in NLRC4- and NLRP3-deficient mice. As a result, NLRC4 is crucial in controlling oral candidiasis^[50].

NLRC4 and skin cancer

Independent of the inflammasome components caspase-1 and ASC, NLRC4 has been shown to inhibit tumor development in melanoma and Lewis lung cancer^[51]. The inflammasome-independent function of NLRC4 is now well-established. It was hypothesized by the authors that an unidentified DAMP induces NLRC4 signaling in macrophages, which then suppresses melanoma growth^[22]. Lower levels of IL-6 and subsequent reduced stimulation of Signal Transducer and Activator of Transcription 3 (STAT3) are observed in NLRC4-deficient monocytes. They also found that NLRC4-deficient mice showed increased tumor development because tumor effector CD4+ CD8+ T cells generated fewer IFN-. Additionally, in human individuals with advanced melanoma, fewer NLRC4+ tumor-associated macrophages were found. (Compared to

primary melanoma). Further research are required to elucidate the processes of NLRC4- dependent tumor development suppression^[12].

Inflammasomes in leprosy

In reaction to bacterial infections that target the cytoplasm of host cells, like *M. tuberculosis* and *M. leprae*, new data indicates that the NLRP3 inflammasome is involved in the inflammatory response caused by caspase-11. But the innate stimuli that initiate these pathways are still a mystery, and our findings, which corroborate those of a prior research, indicate that this protein complex is likely ineffectual in regulating infection in lepromatous lesions^[52, 53].

Mechanism of inflammasomes in Leprosy

Activation of the NLRP3 inflammasome follows a classical pathway that begins with the recognition of PAMPs or DAMPs by TLRs, which then activates nuclear factor kappa B (NF- κ B)-mediated signaling and up-regulates transcription of inactive NLRP3, pro-IL-1, and pro-IL-18. Oligomerization of NLRP3 is the second stage, which is then followed by the formation of a complex containing NLRP3, ASC, and pro-caspase-1. This results in the synthesis and release of mature IL-1 and IL-18, as well as the self-activation of pro-caspase-1 into the enzymatically active form by proteolytic cleavage. The majority of research on the alternative activation mechanism of the NLRP3 inflammasome has been conducted on Gram-negative bacteria. Microbial products or particulates, such as LPS, must first activate caspase-11 and human caspases-4/5^[53, 54].

ASC having a CARD. It aids in the creation of the inflammasome complex by bridging the gap between the NLR and pro-caspase [55]. Its development is the result of the interaction of two protein domains, the N-terminal pyrin (PYD) and the C-terminal caspase recruitment domain (CARD).

There are two major classes of caspases, the inflammation (which includes caspases 1, 4, and 5) and the apoptosis. (Initiators: caspases 2, 8, 9, and 10; executors: caspases 3, 6, and 7). As the primary inflammation caspase, caspase-1 is responsible for the activation of IL-1 and IL-18 as well as the activation of gasdermin D, a facilitator of pyroptosis [56]. In addition to cleaving cytokines, other caspases may be responsible for causing pyroptosis. Pyroptosis may be aided by caspases 4 and 5, which are triggered by Gram-negative microbes and may degrade gasdermin D. By helping to create the inflammasome and triggering IL-1, IL-18, and gasdermin D, caspase 8 serves as a mediator of inflammation and death. Furthermore, caspase 8 initiates the noncanonical pathway that triggers IL-1 separately of caspase 1 via the dectin-1 receptor (a lectin type C receptor) [57, 58].

It is possible that the non-canonical pathway NLRP3 is activated in the multibacillary form of leprosy in a manner analogous to that found in reaction to Gram-negative bacteria like *Escherichia coli*, *Citrobacter rodentium*, and *Vibrio cholerae*. LPS molecules, found primarily in the outer membrane of these bacteria, bind to and immediately trigger caspase-11, the human orthologue of caspases-4/5. However, the *M. leprae* component(s) that could activate this route remain unidentified. This observation for the tuberculoid pole is consistent with the interesting discovery that *M. tuberculosis* inhibits NLRP3 inflammasome activation to prevent the processing of caspase-1 and IL-1 [53, 59].

Recognition of an intracellular PAMPs or DAMPs by an NLR causes recruitment of ASC into a PYD-PYD binding complex and subsequent stimulation of the normal inflammasome activation pathway. A CARD-CARD interaction then occurs between pro-caspase 1 and ASC. This triggers IL-1 and IL-18 production as well as pyroptosis via normal stimulation of the inflammasome [60, 62].

There are two possible mechanisms for action of the noncanonical inflammasome activation pathway. Pyroptosis is triggered by the activation of caspases 4 and 5 in response to Gram-negative bacterial lipopolysaccharide (LPS). In addition to activating caspase 1, which in turn triggers the generation of IL-1, LPS activates the nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 (NLRP3) inflammasome. Caspase 8 activation via lectin type C receptors is an additional noncanonical route. This process causes IL-1 to be made without the involvement of caspase 1 [61–63].

IL-1, IL-18, and caspase 1 have all been studied for their roles in the inflammatory response in leprosy [64], [65]. Patients receiving treatment have been shown to express higher levels of IL-1 in their blood than those who were only exposed to the virus but not infected, suggesting a role for this IL in the immunopathogenesis of the illness (Costa *et al.*) [65]. In their research on *M. leprae*-exposed peripheral blood monocytes, Sinsimer *et al.* [66] found a significant reduction in IL-1 levels alongside an increase in IL-1Ra, a natural regulator of IL-1. Delay in caspase 1 activation has

also been linked to lower amounts of IL-18, as documented by these authors. In a study on guinea pigs with a defect in the synthesis of NAIP5, a protein of the NLR family, Kang *et al.* [67] confirmed the reduced activation of caspase 1 and IL-1 secretion, indicating participation of NLR proteins in the immunological response associated with leprosy. Pontillo *et al.* have chosen five nucleotide-binding oligomerization domain-like receptor containing pyrin domain 1 (NLRP1) SNPs and two NLRP3 SNPs to investigate their potential effects on leprosy susceptibility. These authors hypothesized that two different NLRP1 haplotypes joined together might be linked to a disease result, particularly in paucibacillary forms. NLRP3 mutations were not associated with any diseases [68].

Conclusion

Our results demonstrate the important role that an inflammasome-mediated reaction plays in the development of leprosy's clinical course. This involvement starts at the very first encounter with the bacillus in the earliest phases of the illness. The clinical course of an infection depends on the result of this first interaction, and it now appears that NLRP1, NLRP3, caspase 1, IL-1, and IL-18 collaborate in a concerted effort to trigger this early reaction.

Conflict of Interest

Not available

Financial Support

Not available

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