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Review

Role of NLR proteins in immunity

Hina Afroz[1]*, Zahid Hussain[1], Maria Azam[1], Maqsood Arif[1] and Rehan Rafique[2]

[1]Institute of Industrial Biotechnology, G. C. University, Lahore, Pakistan.
[2]Veterinary Research Institute, Lahore Cantt., Pakistan.

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The first line of defense in immune system is the innate immunity. Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) proteins are important for the innate immune response and they play a significant role in microbial sensing. These proteins are consisted of protein domains like Nucleotide Binding Domain (NBD), Nucleotide-binding oligomerization domain (NOD) centrally and a protein interaction domain; furthermore, Leucine Rich Repeats (LRRs) are present at the C terminal. NLR proteins are located in the cytoplasm and are able to recognize microbial antigens. Inflammatory responses occur as a result of activation of NLR protein via caspase-1 activation. Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor-kappa B (NF-κB) activation are also involved in the inflammatory reactions produced by NLR proteins. This review will cover mainly NOD like Receptor Protein 1 (NLRP1), NOD like Receptor Protein 3 (NLRP3), NOD like Receptor Card domain 4 (NLRC4) and especially their functions against pathogen attacks.

Key words: LRRs, PAMP, DAMP, inflammasomes, AIMS2.NALP1, NALP3, NALC4.

INTRODUCTION

The effectors molecules of Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) proteins of innate immunity play a key role in microbial sensing, leading to the initiation of the antimicrobial immune responses (Martinon et al., 2009; Janeway and Medzhitov 2002). NLR proteins are present in the cytoplasm and are able to recognize microbial products (Wilmanski et al., 2008). These proteins have an oligomerization domain and protein interaction domain known as Leucine Rich Repeats (LRRs) at the C terminal (Martinon et al., 2009; Wilmanski et al., 2008). When a bacterial cell enters the human body, all bacterial cell wall components are detected by Nucleotide-binding oligomerization domain 1 (NOD1) and Nucleotide-binding oligomerization domain 2 (NOD2) at first. Then the bacterial flagellum is detected by the Ice protease-activating factor (IPAF) and the Neuronal Apoptosis Inhibitory Protein (NAIP) (Kobayashi et al., 2005; Li et al., 2004). Lethal toxins of anthrax are detected by NACHT (named after the protein families NAIP, CIITA, HET-H and TP1) Domain, Leucine-Rich Repeat (LRR), and Pyrin domain-Containing Protein-1 (NALP-1). More than 20 NLR proteins are present in humans, which are specific to various pathogenic microorganisms (Wilmanski et al., 2008 ; Kobayashi et al., 2005; Li et al., 2004). When these proteins are activated, they mediate inflammatory response through Nuclear Factor-kappa B (NF-κB), Mitogen-Activated Protein Kinase (MAPK) or caspase-1 activation and secretion of various pro-inflammatory cytokines, such as TNF –α, IL-6 and IL-12 (Kobayashi et al., 2005; Li et al., 2004).

NLR PROTEIN FAMILY

NLR proteins have three domains in their structure: the C-terminal domains of NLR, which consisted of LRRs and which recognize microbial components, the NOD domains which induce self oligomerization and a complex is formed which induces the downstream signaling cascades. There are also some N-terminal domains like CARD (Caspase Recruitment Domain), PYD (Pyrin domain), DED (death effectors domain) and BIR (baculovirus inhibitor of apoptosis protein repeat) domains (Li et al., 2004; Moreira et al., 2012; Janeway and Medzhitov 2002), which are responsible for signal transduction. Any mutation in these domains can cause some chronic inflammatory diseases like Familial cold auto inflammatory syndromes, also known as familial cold

*Corresponding author. E-mail: anih_zorfa@hotmail.com.

urticaria, Muckle–Well and Crohn's disease urticaria, Muckle–Well and Crohn's disease. (Maeda et al., 2005 ; Hoffman et al., 2001).

NOD1 and NOD2

The immune system recognizes diverse pathogens or pathogens derived components with receptors present on innate immune cells. When a pathogen attacks a living body it starts producing infection, in that case these receptors play a vital role in providing first line of defense against that infectious particle (Moreira et al., 2012; Kumar et al., 2009). The initiation of this process involves sensation of pathogens within a cell by the cells of innate immune system (Moreira et al., 2012; Franchi et al., 2008). According to the latest research, in humans, 23 members related to NLR family are recognized and in mice they are more than 30. NLR family contains NOD1 and NOD2 whose major function is to recognize damage as well as molecular patterns associated with microbes (Moreira et al., 2012; Franchi et al., 2008; Akira et al., 2006). They abruptly recognize any invader, specifically pathogens, which have an additional property of multiplication inside a living body (Moreira et al., 2012; Franchi et al., 2008).
Now the functioning of NOD1 and NOD2 will be spotlighted in detection as well as their reaction towards the attacker pathogen like gram negative and gram positive bacteria, and their capability of response by signaling (Li et al., 2004; Moreira et al., 2012; Akira et al., 2006).

Position of NOD1 and NOD2

Among the NLRs family, two subgroups are well studied:

1. NLR-*P*
2. NLR-*C*

NLR-*P* subgroup of receptors contains a domain called "Pyrin" which is present in the amino-terminal section. The role of these receptors is their involvement in activating "Caspase-1" resulting in inflammasomes gathering.
NLR-*C* subgroup of receptors contains CARD (Caspase Recruitment Domain) domain which is also present in amino-terminal section. It includes two members, that is, NOD1 and NOD2 which are responsible for reorganization of foreign invader and ultimately is involved in activating innate immune response (Moreira et al., 2012).

Major functions

Many functions of NOD1 and NOD2 have been studied as activators, regulators and detectors. Some main functions are given below, after which their functions are discussed in detail:

- Peptidoglycan moieties recognition.
- Sensation of structure of microbes.
- Participation as signaling partner (Moreira et al., 2012).

NOD1 and NOD2 as activators of signaling pathway

Initiation of NF-κB pathway is responsible for activation of NOD1 and NOD2 dependent pathways. These pathways result in stimulation of c-Jun N-terminal kinase (JNK) and p38 MAPK. NOD pathways also activate other pathways including apoptosis via induction of caspases NOD protein's oligomerization and sensation of peptidoglycan that results in conscription of receptor-interacting protein 2 (RIP2). This process results in interaction of NOD with a complex called inhibitor of NF-κB (IκB) kinase (IKK) (Bourhis et al., 2007; Kumar et al., 2009). A loop of converged NF-κB-activating common pathway forms three signaling cascades which are TLR, IL-1 and TNF mediated. To alter this type of signaling, different proteins are also involved in the process as well as interaction of over expressed transforming growth factor (TGF)- β-activated kinase 1 (TAK1) and NOD2 plus interaction of NOD1 and NOD2 with suppressor of G2 allele of Skp1 (SGT1), which is also a co-chaperone of heat-shock protein 90 (HSP90) (Bourhis et al., 2007).

NOD1 and NOD2 as regulators of immune response

During earlier studies, we have studied that when NOD acts as transducer modifier, it regulates the innate immune response functions. NOD2 signaling could inhibit activation of TLR2 of NF-κ B subunit. For example in Crohn's disease, the presence or absence of NOD2 results in increasing responses of Th1 and in NF-κBc-Rel TLR2-mediated activation (Moreira et al., 2012). This results in increased Th1 response due to *Card15* mutations. An experiment was conducted with specimen mice. When bone marrow-derived macrophages (BMDMs) from NOD2 mice was stimulated with peptidoglycan (PGN) purified from *Streptococcus pneumonia,* it produced less IL-10 .(Moreira et al., 2008; Iwasaki and Medzhitov 2010; McDonaldet al., 2005). This cytokine is responsible to regulate inflammatory processes. The experiment suggested that NOD2 might have regulatory effect on production of IL-10 (Moreira et al., 2012; Moreira et al., 2008; Iwasaki and Medzhitov 2010). If IL-10 is produced in low quantities then IL-12 production will increase. This thing will help in excess inflammation in Crohn's disease victims. In humans, NOD2 mutation related Crohn's disease can suppress IL-10 transcription when it inhibits the action of ribonucleic protein hnRNP-A1. The mononuclear cells from peripheral blood of Crohn's patients showed the impair binding of hnRNP-A1 to the IL-10 locus when NOD2 3020insC mutation blocks p38 phosphorylation of

hnRNP-A1. It concludes that production of cytokine IL-10 may interfered by NOD2, which is responsible to regulate inflammatory response. In the second case, the experiment showed that NOD2 might increase inflammation of intestine of patients suffered with Crohn's disease. By doing this, NOD may act as positive regulator, as processed IL-1β and mutated NOD potentiated activity of NF-κB. Wild-type NOD-2 can reconcile autophagy so it results in clearing pathogens that get entry into the cytoplasm of host's cell (Moreira et al., 2012).

NOD1 and NOD2 as detectors of bacteria

In the foregoing, it was mentioned that NOD1 and NOD2 plays a role in peptidoglycan moieties recognition. They can also show response against live bacteria. For example NOD1 could recognize *Shigella flexneri*, *Escherichia coli*, *H. pylori*, *Pseudomonas aeruginosa*, *Chlamydia* species, *Campylobacter jejuni* and *Haemophilus influenza*, while NOD2 can identify *Salmonella enterica, Listeria monocytogenes* and *Streptococcus pneumonia*. NODs can sense persistent and non-persistent bacteria. In some cases, intracellular detection system of NODs by stimulation depends on the secretion system or pore forming toxin's presence (Bourhis et al., 2007).

NOD1 and NOD2 in human diseases

Crohn's disease is considered as an inflammatory bowel disease linked genetically to many types of NLRs mutations. The locus present at human chromosome has NOD2 on it plus several conditions of environment as well as several genes. Frame shift mutation is most commonly associated with NOD2 mutations affecting the LRR of molecule. This results in lessened antimicrobial activity in the gut as well as improved production of micro flora resulting in reduction of loss of tolerance towards abnormal inflammation and commensal flora (Fritz et al., 2004).

An autosomal dominant disease, Blau Syndrome, results from NOD2 mutation. This disorder is characterized by the appearance of rashes on skin, periodic arthritis and uveitis in children. Inflammatory lesions might also be observed which are related to granulomas. All of this occurs due to mutations in NOD2 resulting in triggering a molecule to be extra responsive when elicited by muramyl dipeptide (MDP) (Richard et al., 2011; Rosenzweig et al., 2009).

INFLAMMASOMES

The inflammasome is a protein complex formed and assembled by the stimulation of immune cells like macrophages and dandritic cells with microbial Pathogen-Associated Molecular Pattern (PAMPs). This inflammasome is made up of NLR members, on NLR proteins, AIM-2 (Interferon-inducible protein also seen to be absent in melanoma 2) and Apoptosis-associated speck-like protein (ASC).

This protein complex activates the inactivated caspase-1 which promotes the proteolysis of zymogens form of IL-1 family cytokines (Kumar et al., 2011).

NLRP1

The NLR proteins containing PYR domains are known as NLRP. NLRP1 was the first member of this family which was identified. Human beings have a single NLRP1 gene containing N-terminal PYR domain, a centrally located NOD domain, many LRRs, a function to find domain (FIIND) and a CARD domain which is located on C-terminal. In mice, three genes (Nlrp1a, Nlrp1b and Nlrp1c) of NLR proteins have been identified which are located at the same chromosomal regions with pyrin domains which are missing in these genes. NLRP1 in humans is expressed in thymus and spleen and is responsible for immune response. It is important in this regard that a locus containing NLRP1 is recognized for various autoimmune and auto inflammatory conditions like rheumatoid arthritis, hypothyroidism and familial vitiligo (a skin disorder occurring due to loss of pigmentation). NLRP1 inflammasomes have NLRP1, caspase-1, caspase-5 and ASC. In the presence of monosine diphosphate (MDP) and Adenosine triphosphate (ATP), NLRP1 oligomerizes and forms a multiprotein complex which activates caspase-1. In case of mouse, *Bacillus anthrax* is responsible for the activation of mouse Nlrp1b inflammasomes. It enhances the pathogenecity by various factors, for example, LT (lethal toxin), pore forming toxin and a protease like protective antigen (PA). Lethal toxin being a powerful toxin can cause cell death. While protective antigen is a receptor binding protein which creates a pore through which lethal factors are delivered into the cytosol of infected cell and will cause cell death. LT susceptibility is because of Nlrp1b and the susceptible macrophages induced with caspase-1 are also required for LT-induced cell death (Franchi et al., 2009).

NLRP1 is also associated with anti-apoptotic proteins B-cell lymphoma 2(Bcl-2) and B-cell lymphoma-extra-large (Bcl-X_L). It will suppress the caspase-1 activation so Bcl-2 protein can cause inhibition of cytotoxicity induced by lethal toxin (Faustina et al., 2009).

NLRP-3 inflammasomes

The most widely studied inflammasomes is NLRP3 associated which is activated by PAMPs, Damage-associated molecular pattern molecules (DAMPs), necrotic and traumatized host cell derived heat shock proteins and Bcl-2. Heat shock proteins and Bcl-2 are sensed by PRRs (Pattern recognition receptors) and are

responsible for induction of inflammatory cytokines (Kumar et al., 2011; Eisenbarth et al., 2008). According to previous reports, some environmental pollutants like silica and asbestos also activate NLRP3 inflammasomes (Franchi et al., 2009). The basic mechanism involved behind the NLRP3 sensing and biology is still unknown. So this inflammasome comprised NLRP3 –ASC complex and procaspase-1 (Franchi et al., 2009; Eisenbarth et al., 2008).

The oligomerization of NLRP 3 starts with the stimulation of cell via appropriate ligand which in turn promotes the joining of NLRP3 with ASC with the help of pyrin domain that is called PYD interaction (Kumar et al., 2011). Then the CARD domain of both ASC and procaspase-1 interacts with each other to make possible the catalysis of procaspase-1 to caspase-1. Caspase-1 consisted of P10/P20 tetramers which caused the proteolysis of inactive proIL-1 β (beta) to IL-1 β active form (Kumar et al., 2011; Franchi et al., 2008).

There are several theories and models present up till now for the activation of NLRP3. The examples are ATP-induced efflux of K^+ (potassium ions) with the help of P2X7 ion channels and pannexin-1 and also by the induction of Reactive Oxygen species (ROS) (Kumar et al., 2011; Franchi et al., 2009; Petrilli et al., 2007). There is another model presented by scientists for the activation of NLRP3 according to which lysosomal destabilization is proposed after phagocytosis of many different types of crystalline and insoluble ligand, for example, silica, amyloid-β, alum and antigen. All these ligands cause the disruption of lysosomal membrane and finally the NLRP3 is activated by the release of lysosomal hydrolytic enzymes and proteins (Kumar et al., 2011). Furthermore it is also noticed and studied that adaptive immunity is also regulated by the involvement of NLRP3 inflammasomes when the mice are challenged with antigen and alum (used as adjuvant in vaccines) (Kumar et al.,2011; Franchi et al., 2008; Eisenbarth et al., 2008). But the problem faced in this experiment was the inconsistency of the results which might be due to the difference in application of techniques and immunization procedure. So from this experiment, it was stated that if alum was used as adjuvant, the function of NLRP3 inflammasomes in adaptive immunity became complicated for understanding (Kumar et al., 2011). Regarding fungus and fungal infections, it has been seen from the latest research that two fungi named: *Candida* and *Saccharomyses* (commonly known as baker's yeast) activate NLRP3, ASC and caspase-1 and by the activation of these molecules IL-1 β was induced (Kumar et al.,2011; Franchi et al., 2008; Eisenbarth et al., 2008; Gross et al., 2009). Further research had revealed that the cause of activation of NLRP3 and the causative molecule for the NLRP3 inflammasomes activation was β-glucan, which is the major and essential component of the cell wall of the fungus. Moreover, the antibody responses produced by β-glucan are reliant of NLRP3 inflammasomes (Kumar et al., 2011; Gross et al., 2009; Hise et al.,2009).

Activation of NLRP3 by uric acid, asbestos and aluminium hydroxide

The activation of adaptive immune system by uric acid in the necrotic cells was discovered by Rock and his coworkers (Shi et al., 2003). Now it has also been demonstrated by Tschopp and coworkers that NLRP3 is required for the activation of caspase-1 when uric acid is involved Franchi et al., 2009; Eisenbarth et al., 2008; Martinon et al., 2006). Some other crystals like calcium pyrophosphate dehydrate (CPPD) (Franchi et al., 2009; Martinon et al., 2006; Hornung et al., 2008), silica and asbestos also have the ability to activate the NLRP3 inflammasome. While above mentioned uric acid and low cytosolic K^+ concentrations is needed for the activation of caspase-1 by uric acid and CPPD Caspase-1 activation by uric acid crystal, silica and asbestos also need pre-stimulation with LPS (lipopolysacchrides) and it suggests that inflammasome is activated by promoting PAMP internalization (Franchi et al., 2009; Martinon et al., 2006; Dostert et al., 2008; Hornung et al., 2008).

Alum has the ability to promote the secretion of IL-1 β in macrophages and dandritic cells. It has also been found that alum induced the innate and adaptive immune response by activating NLRP3 inflammasome (Franchi et al., 2009; Franchi et al., 2008; Hornung et al., 2008).

Bacterial activation of the NLRC4 inflammasome

Gram-negative bacteria, for example, *Salmonella, Legionella*, *Shigella*, *Pseudomonas* and *Yersinia pestis* bacterial type III secretion system (T3SS) or type IV secretion system (T4SS) activate NLRC4 (Chen et al., 2006; Broz et al., 2010; Franchi et al., 2007; Sutterwala 2007). The microbial molecule flagellin is required to induce NLRC4-mediated caspase-1 activation during *Legionella*, *Salmonella*, and low burden infection of *Pseudomonas* (Elinav et al., 2011; Miao et al., 2006).

ROLE OF NLR IN VIRAL INFECTION

In viral infection when DNA is induced into the cell, the production of IL-1 β starts with the help of AIM2 inflammasome (Kumar et al., 2011). For the inherent immunity to change into a DNA sensor, a PYD containing protein, an associate of HIN-200 family (hemopoietic expression, interferon-inducibility, nuclear localization) is newly identified, known as AIM2 (Kumar et al., 2011; Schroder et al., 2009). In septic macrophages, AIM2 elicits the association of inflammasome which results to inflammatory retorts mediated by caspase-1 via nonstop binding to external double stranded DNA which ultimately causes cell death (Burckstummer et al., 2009).

AIM2 functions both as tumor suppressor and tumor promoting factor. By reticence of NF-KB transcriptional

activity, AIM2 condenses human breast cancer and also overturn memory tumor growth in mouse (Chen et al., 2006). In human tumor bodies, AIM2 is often affected by genetic and epigenetic modifications. A coding 10-bp poly adenine region in Exon 6 of the AIM2 gene seems to be positively selected for frame shift mutations, in pre-neoplastic and neoplastic microsatellite unsatable lacerations (MSI) (Michel et al.,2010; Woerner et al., 2003; Woerner et al., 2005).

CONCLUSION

The recent progress in research has revealed the secrets behind the significance of NLRs in host pathogen interactions and immunological disorders. Research is ongoing on the outcomes of NLR activation. However its activation of NOD1, NOD2 in adaptive immunity is not fully understood. NLR signaling results in the activation of NF-κB, MAPK, and caspase-1 that result in the induction of proinflammatory cytokines, chemokines, and anti-microbial molecules. Several inflammatory diseases, such as Crohn's disease, Blau syndrome and Muckel-Wells syndrome, are caused by mutations in NLR proteins. Future studies are under progress about the mechanisms involved in microbial recognition with the help of NLRs, the exact role of NLRs in mucosal and systemic infection, and the mechanism by which genetic variants of NLRs increase the susceptibility to disease.

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