

Forum

NOD-like receptors and human diseases

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Available online 27 January 2007

Abstract

NOD-like receptors are cytosolic proteins that contain a central nucleotide-binding oligomerization domain (NACHT), an N-terminal effector-binding domain and C-terminal leucine-rich repeats (LRRs). NOD-like receptors have been implicated as ancient cellular sentinels mediating protective immune responses against intracellular pathogens. Recent studies have described the genetic association of polymorphisms in NOD-like receptor genes with complex chronic inflammatory barrier diseases, such as Crohn's disease and asthma and with rare auto-inflammatory syndromes including familial cold urticaria, Muckle–Wells syndrome and Blau syndrome. Whereas genetic variability in NLRs may have been an important element to provide plasticity to antigen recognition and host defense in the past, recent changes in the lifestyle of industrialized societies (e.g. hygiene (“cold-chain-hypothesis”), nutrition, or antibiotics) may have turned ancient genetic variability into disease-causing mutations. The review focuses on NLR function in the molecular pathophysiology of human inflammatory disorders.

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Keywords: Inflammation; Human disease; Innate immunity**1. Introduction**

Unveiling the molecular pathophysiology of impaired pathogen recognition in human disease has become one of the major challenges of clinical research. In higher organisms, two distinct types of immune responses can be functionally defined. (i) A delayed adaptive immune response, which is mediated by clonal selection and expansion of T- and B-lymphocytes specific for an antigen. The adaptive immune response is capable of generating a high level of diversity and specificity and constitutes the individual immunological memory. The main limitation of the system is the time required for the expansion and differentiation of the immune effector cells, e.g. bacteria with fast acting toxins or short generation periods would cause irreversible damage to the organism before the immune system would have the chance to react. (ii) A fast innate response due to the recognition of invariant molecular patterns by a limited set of non-clonal, germline-encoded

receptors. These pattern recognition receptors (PRRs) may sense molecular structures present in pathogens (pathogen-associated molecular patterns, so-called PAMPs; e.g. lipopolysaccharides or unmethylated CpG DNA) or endogenous danger signals (e.g. extracellular heat shock proteins), which indicate profound cellular damage. The different sets of PRRs, which are often conserved among plants, insects and vertebrates, lie at the apex of the ancient process of innate immunity against microbial pathogens.

Various families of PRRs exist, which are either expressed on the cell surface, reside in intracellular compartments or may be released as secreted molecules in the extracellular space. Whereas the toll-like receptors (TLRs) represent the archetype of the transmembrane PRR with an extracellular ligand-binding domain [1], the intracellular NOD-like receptor (NLR) family seems to play a pivotal role in the recognition of intracellular PAMPs [2].

2. NOD-like receptors: modular domain structure and molecular links to disease

NLR genes encode for a growing family of regulatory proteins with a conserved tripartite domain structure,

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characterized by a central nucleotide-binding and oligomerization domain (NOD), C-terminal leucine-rich repeats (LRRs) and a N-terminal effector-binding domain, e.g. a Pyrin domain (PYD) or caspase recruitment domain (CARD) [2]. The activated proteins serve as molecular platforms by promoting the activation of downstream effector molecules through self-association and induced proximity of binding partners (Fig. 1). It is assumed that the LRRs of the NLRs form a horseshoe-like structure capable of interacting with specific protein, carbohydrate or lipid moieties of pathogenic or cellular origin. LRRs are protein motifs with a length of 20–29 amino acids and may serve as protein interaction platforms or regulatory modules of protein activation [3]. The LRRs of NLRs are homologous to those seen in plant disease resistance proteins (R proteins) and TLRs, which form the sensor module for the recognition of PAMPs. It is still a matter of controversy whether NOD-like receptor proteins directly recognize pathogenic components. Genetically, the LRRs of plant R proteins and TLRs are the determinants of their response specificity to certain PAMPs. Two models have been proposed to account for this specificity. The receptor–ligand model proposes a direct interaction between the LRR and its cognate ligand. A second model, the guard hypothesis [4] suggests that R proteins guard the targets of pathogen virulence factors (encoded by *avr* genes) and are activated by modifications to these targets.

The NOD domain, also designated as NACHT domain (domain present in neuronal apoptosis inhibitor protein (NAIP), the major histocompatibility complex (MHC) transactivator (CIITA), HET-E and TP1) [5] belongs to the recently defined STAND family of P-loop NTPases. It has a sequence homology with the nucleotide-binding motif of apoptotic protease activating factor-1 (APAF-1), which is responsible for the dATP/ATP dependent oligomerization of APAF-1 upon Cytochrome *c* sensing during intrinsic apoptotic processes. The oligomerized APAF-1 serves as a molecular platform inducing the recruitment and the activation of pro-caspase-9, a process called induced proximity signalling (reviewed in Ref. [6]). It is thus tempting to speculate that the NOD domain of the NLR proteins is pivotally involved in the initiation of a cellular signal upon binding of the respective ligand. An intramolecular complex formation between the LRR and NACHT domain has been proposed to inhibit autoactivation of NLRs [7]. Constructs encoding for forms of NOD2, IPAF and NAIP without LRRs or point mutations of putative interaction sites render the proteins constitutively active, whereas small truncations within the LRR of NOD1 and NOD2 that may interfere with the muropeptide recognition lead to inactive protein species. Disease-associated sequence variants in the central NACHT domain of NLRs are in close vicinity to conserved regions of that domain, e.g. certain NTPase motifs (Walker B-Box), which may interfere with the cycle of nucleotide-binding, -hydrolysis, and -release and/or conformational changes induced by NTP-hydrolysis [7].

Albeit the profound biological consequences of NLR autoactivation (sustained inflammation) or inactive NLRs (impaired recognition of pathogens), NLR protein function must be tightly controlled to provide a delicate balance between

the initiation and perpetuation of immune responses and anti-inflammatory mechanisms. Counter regulatory mechanisms may include negative feedback loops abolishing NF- κ B activation (NOD2) [8] or the induction of splice variants encoding for inhibitory “dominant-negative” protein isoforms (NOD1/NOD2) [9,10].

The pivotal role of NLRs in the physiological innate immune response is emphasized by the remarkable association of polymorphisms in *NLR* genes with human diseases (Fig. 2). Polygenic diseases associated with variations in NLRs include Crohn’s disease, atopic disease and asthma, which are characterized by chronic relapsing–remitting inflammation of barrier organs (intestine, lung, skin). Other rare auto-inflammatory diseases (Blau syndrome, CINCA, Muckle–Wells syndrome, familial cold urticaria, early-onset sarcoidosis) or immune defects (Bare lymphocyte syndrome) follow classical Mendelian modes of inheritance and are discussed below. Interestingly, the suggested association of certain forms of cancer (breast and colonic carcinoma, gastric MALT lymphoma) with germline mutations in *NOD2* further corroborates the hypothesis that chronic inflammation-induced by perturbed epithelial barrier function might constitute a crucial part of the etiology of malignant diseases.

A summary of the genes, polymorphisms and the associated diseases can be found in Table 1. In the following paragraphs, diseases linked to the archetypal NLR family members NOD2, NOD1 and NALP3 are discussed.

3. NOD2

The *NOD2/CARD15* gene encodes for a NLR with 2 adjacent N-terminal caspase recruitment domains and 10 C-terminal leucine-rich repeats [11]. Muramyl dipeptide (MurNAc-L-Ala-D-isoGln, MDP) derived from peptidoglycan was identified as the minimal structure of bacteria recognized by NOD2 [12,13]. Upon MDP-stimulation, NOD2 has been shown to recruit the receptor interacting protein kinase 2 (RIP2) [11]. The complexation leads to an activation of the I κ B-kinase/NF- κ B pathway via induced proximity signalling. NOD2 is constitutively expressed in monocytic cells, but has recently been shown to be upregulated by TNF- α /IFN- γ in via a NF- κ B-dependent mechanism [14]. Expression of NOD2 sensitizes intestinal epithelial cells to bacterial products and enhances the release of the chemotactic cytokine IL-8 and defensins [14,15]. NOD2 may itself serve as an anti-bacterial factor [16]. NOD2 deficient mice have an increased susceptibility to oral infection with cytoinvasive *Listeria monocytogenes* [15]. Thus, NOD2 has been implicated as a molecular sentinel in maintaining the integrity of the intestinal barrier against luminal pathogens [17].

3.1. Crohn’s disease

A frameshift mutation in the LRR of NOD2 (L1007fsinsC), which leads to a partial truncation of the LRR, and other single nucleotide polymorphisms (SNPs) within the LRR (R702W and G908R) are associated with the manifestation of Crohn’s

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