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The NLR gene family: An official nomenclature

Jenny P.-Y. Ting
Lineberger Comprehensive Cancer Center Department of Microbiology-Immunology University of North Carolina Chapel Hill, NC, 27599, USA jenny_ting@med.unc.edu

Ruth C. Lovering
HUGO Gene Nomenclature Committee The Galton Laboratory University College London, NW1 2HE, UK r.lovering@ucl.ac.uk

Emad S. Ph.D. Alnemri
Kimmel Cancer Institute Thomas Jefferson University Philadelphia, PA 19107, USA ealnemri@mail.jci.tju.edu

John Bertin
Synta Pharmaceuticals Lexington, MA 02421, USA jbertin@syntapharma.com

Jeremy M. Boss
Department of Microbiology and Immunology Emory University School of Medicine Atlanta, GA 30322, USA boss@microbio.emory.edu

Beckley Davis, Ph.D.
Lineberger Comprehensive Cancer Center, University of North Carolina Chapel Hill, NC, 27599, USA beckley_pdavis@med.unc.edu

Richard A. Flavell, Ph.D., FRS
Department of Immunobiology Howard Hughes Medical Institute Yale University School of Medicine New Haven, CT 06520-8011, USA

Stephen E. Girardin, PhD
Dept of Laboratory Medicine & Pathobiology University of Toronto Toronto, Ontario M5S 1A8, Canada stephen.girardin@utoronto.ca

Adam Godzik
The Burnham Institute La Jolla, CA 92037, USA adam@burnham.org

Jonathan A. Harton
Ctr for Immunology & Microbial Disease Albany Medical College Albany, NY 12208, USA hartonj@mail.amc.edu

Hal M Hoffman
University of California at San Diego Department of Pediatrics La Jolla, CA 92093-0635, USA hahoffman@ucsd.edu

Jean-Pierre Hugot
INSERM U843 Faculté de médecine Paris Diderot Hopital Robert Debré Paris, France. jean-pierre.hugot@rdb.aphp.fr

Naohiro Inohara
Department of Pathology, University of Michigan Medical School, Ann Arbor, MI 48109, USA

Department of Biochemistry II Interdisciplinary Graduate School of Medicine and Engineering University of Yamanashi Yamanashi 409-3898, Japan. ino@umich.edu

Alex MacKenzie

Children's Hospital of Eastern Ontario University of Ottawa Ottawa, Ontario Canada K1H 8L1 mackenzie@cheo.on.ca

Lois J. Maltais
Mouse Genomic Nomenclature Committee The Jackson Laboratory, Bar Harbor, ME 0460, USA ljm@informatics.jax.org

Gabriel Nunez
Department of Pathology The University of Michigan Med School Ann Arbor, MI 48109, USA bclx@umich.edu

Yasunori Ogura
Yale University School of Medicine Section of Immunobiology New Haven, CT 06520-8011, USA yasunori.ogura@yale.edu

Luc Otten
Département de Biochimie Faculté de biologie et médecine Université de Lausanne Suisse Luc.Otten@unil.ch

John C. Reed
Burnham Institute for Medical Research La Jolla, CA 92037, USA reedoffice@burnham.org

Walter Reith
Department of Pathology and Immunology University of Geneva Medical School Geneva 4, Switzerland Walter.Reith@medecine.unige.ch

Stefan Schreiber
Institute for Clinical Molecular Biology Christian-Albrechts-University Kiel, Germany s.schreiber@mucosa.de

Viktor Steimle
Departement de Biologie Universite de Sherbrooke Sherbrooke, Quebec, J1K 2R1 Canada Viktor.Steimle@usherbrooke.ca

Peter A. Ward
University of Michigan Department of Pathology Ann Arbor, MI 48109, USA pward@umich.edu

Summary

Iimmune regulatory proteins such as CIITA, NAIP, IPAF, NOD1, NOD2, NALP1, cryopyrin/NALP3 are members of a family characterized by the presence of a nucleotide-binding domain (NBD) and leucine-rich repeats (LRR). Members of this gene family encode a protein structure similar to the NB-LRR subgroup of disease-resistance genes in plants and are involved in the sensing of pathogenic products and the regulation of cell signaling and apoptosis. Several members of this family have been associated with immunologic disorders. *NOD2* for instance is associated with both Crohn's disease and Blau syndrome.

A variety of different names are currently used to describe this gene family, its subfamilies and individual genes, including CATERPILLER (CLR), NOD-LRR, NACHT-LRR, CARD, NALP, NOD, PAN and PYPAF, and this lack of consistency has led to a pressing need to unify the nomenclature. Consequently, we collectively propose the family designation NLR (nucleotide-binding domain and leucine-rich repeat containing) and provide unique and standardized gene designations for all family members.

The genomic mining of evolutionary conserved gene families with structural similarity and functional overlap has led to the discovery of important pathways in the immune system. This is highlighted by the discovery of a large gene family encoding proteins with a characteristic

arrangement of a nucleotide binding domain (NBD) and leucine rich repeat (LRR) in both plants and animals. Plants lack an adaptive immune system and rely on two major disease resistance genetic systems for combating pathogens. One encodes the transmembrane pattern recognition receptors (PRRs) and the second encodes the nucleotide-binding, leucine rich repeat proteins (NB-LRR (Jones and Dangl, 2006)). In addition to the NB-LRR domains plant NB-LRR genes also encode one of two possible N-terminal domains, either a coiled-coil or a TIR (TLR-IL1/18 receptor). Most plant NB-LRR proteins act primarily through an intracellular route and appear to recognize pathogens indirectly, although direct recognition is also possible. The consequence of pathogen sensing is a hypersensitive cell death response resulting in the restriction of pathogen spreading.

In the early 2000s, an NB-LRR-related gene family (NLR) and subfamilies were discovered in humans and named by various groups as CATERPILLER (Harton et al., 2002; Ting and Davis, 2005), NODs (Inohara et al., 2002), NOD-LRR (Inohara et al., 2005; Inohara and Nunez, 2003), NACHT-LRR, (Martinon and Tschopp, 2005) and NOD-like receptor (Fritz et al., 2006; Meylan et al., 2006) (Table 1). It is now recognized that NLR genes are found in animal species ranging from sea urchin to human and are thought to function mainly in the innate immune response.

The nucleotide binding domain of the NLR gene family has characteristic features which led to the alternative name of NACHT. The name NACHT is derived from the four plant and animal proteins which initially defined the unique features of this domain: the neuronal apoptosis inhibitory protein (**NA**IP), MHC class II transcription activator (**C**IITA), incompatibility locus protein from Podospora anserina (**H**ET-E), and telomerase-associated protein (**T**P1) (Koonin and Aravind, 2000) In both plants and animals, the NACHT domain has NTPase activity and exhibits preferential binding for GTP or ATP. The majority of family members also contain a domain comprised of two to ten conserved motifs and often referred to as the NACHT-associated domain (NAD).

The NLR family includes several subfamilies distinguishable by their N-terminal effector domains. There are 4 recognizable NLR N-terminal domains: acidic transactivation, pyrin, caspase recruitment domain (CARD), and baculoviral inhibitory repeat (BIR)-like domains (Table 1). These N-terminal domains have been used by several groups to subdivide the NLR gene family and there are now multiple names for each subfamily: the pyrin-containing subfamily has been named PAN, PYPAF, and NALP (Grenier et al., 2002; Pawlowski et al., 2001; Tschopp et al., 2003); members of the CARD-containing subfamily have been named CARD (Bertin et al., 1999) or NODs (Inohara et al., 2002); the BIR-containing subfamily has been named NAIP or BIRC (Roy et al., 1995). The inconsistent use of these names has resulted in further complexity and potential confusion.

In consultation with over 100 scientists and the human and mouse Gene Nomenclature Committees, a new nomenclature system has been agreed upon (Table 1). It was agreed that the family name “Nucleotide-binding domain and leucine-rich repeat containing” (NLR) should be used to highlight these two evolutionary conserved domains and to reflect the similarity of the NLR family to the plant NB-LRR proteins.

A subfamily derived nomenclature system is provided for the NLR family based on the N-terminal effector domains (e.g. CARD, PYD and BIR, Table 1) or reflecting the more commonly used names for the well-published proteins CIITA, NAIP, NOD1 and NOD2. Human genes are written in upper case, whereas murine orthologs are distinguished from the human genes by the use of upper case for the first letter only, followed by lower case. Although several human NLR genes have multiple murine paralogs, some human NLR genes do not

appear to have any murine counterparts, reflecting the dynamic evolutionary contraction and expansion of this family.

Existing data indicate several roles for these proteins in innate immunity. A prominent role is the recognition or “sensing” of pathogen products. The general strategy employed by most in the field is to demonstrate that the presence of a specific NLR protein is required for cellular responses to specific pathogen product(s). However the exact mechanism by which this recognition is achieved is not well understood and direct interaction between the NLR protein and microbial-derived product has not been demonstrated for any of these proteins. Nonetheless such an approach has been very useful in gauging the function of NLRs. NOD1 and NOD2 are revealed to mediate responses to the peptidoglycan-derived products meso-diamiopimelic acid and muramyl dipeptide respectively (Fritz et al., 2006). NLRP1 and NLRP3 mediate formation of the inflammasome complex required for caspase 1 maturation leading to the processing of pro-IL-1/IL-18 to mature IL-1/IL-18 in response to a host of pathogens and pathogen-derived products (Martinon and Tschopp, 2004, Ogura et al., 2006). These products include bacterial and viral-derived products as well as gout crystals and TLR3/7/8 agonists. NLRC4 and Naip5 are important for cellular responses to *Salmonella* and *Legionella* (Franchi et al., 2006; Mariathasan et al., 2004; Miao et al., 2006; Molofsky et al., 2006; Ren et al., 2006; Zamboni et al., 2006). Additionally, several of these proteins appear to mediate negative regulatory function in controlling pathologic inflammatory responses, including NLRC3, NLRP2, NLRP7 and NLRP12 (Bruey et al., 2004; Williams et al., 2005). More recent evidence indicates that NLRP1, NLRC4 and NLRP3 also intersect with cell death pathways (Bruey et al., 2007; Fernandes-Alnemri et al., 2007; Franchi et al., 2006; Fujisawa et al., 2007; Mariathasan et al., 2004; Suzuki et al., 2007; Willingham, 2007), which is reminiscent of the roles of NB-LRR proteins in causing a hypersensitive cell death response implants.

The importance of this family is further underscored by the genetic association of family members to a number of immunologic disorders. Genetic lesions in *CIITA* cause the immunodeficiency, Type II group A bare lymphocyte syndrome (BLS) due to a defect in the transcriptional activation of class II MHC genes (Reith and Mach, 2001; Steimle et al., 1993). Mutations in the gene encoding NLRP3 are associated with a spectrum of autoinflammatory syndromes with increasing severity: familial-cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and CINCA syndrome (Aganna et al., 2002; Dode et al., 2002; Hoffman et al., 2001)) . *NOD2* is associated with Crohn's disease, Blau syndrome (Hampe et al., 2001; Hugot et al., 2001; Miceli-Richard et al., 2001; Ogura et al., 2001) asthma and psoriatric arthritis (Schreiber et al., 2005). In addition to these diseases, *NLRP1* has been identified as a candidate gene for a large group of vitiligo-associated autoimmune disorders (Jin et al., 2007).

Since the discovery of this large NLR family in animals five years ago, numerous published reports support important roles in infectious diseases, autoimmune and autoinflammatory diseases. Additionally, they regulate critical cell signaling and cell death/survival pathways that act beyond the field of immunology. We anticipate the identification of both expected and unexpected functions of this family. The nomenclature described in this paper has been approved by the Human Genome Organisation (HUGO) Gene Nomenclature Committee and the Mouse Genomic Nomenclature Committee following extensive consultations with the scientific community. Concerted use of this unified nomenclature would reduce confusion and disparity, and promote the transparency of this important field. We urge all investigators to adopt the approved nomenclature in future publications and presentations.

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