Published in final edited form as:

Curr Opin Pharmacol. 2011 August ; 11(4): 423–428. doi:10.1016/j.coph.2011.07.002.

NLRs in the immune privileged sites

Holly L. Rosenzweig^{1,2}, S.R. Planck^{1,3,4}, and J.T. Rosenbaum^{1,3,4}

¹Casey Eye Institute, Oregon Health & Science University, Portland, OR, USA

²Department of Molecular Microbiology & Immunology, Oregon Health & Science University, Portland, OR, USA

³Department of Cell & Developmental Biology, Oregon Health & Science University, Portland, OR, USA

⁴Department of Medicine, Oregon Health & Science University, Portland, OR, USA; Portland, OR, USA

Innate immunity serves as a critical first line of defense against invading microbial pathogens. In order to accomplish this task, germ-line encoded pattern recognition receptors (PRRs) have evolved to recognize conserved molecular structures derived from microbial pathogens [1]. Several distinct families have been identified with the two most studied being Toll-like receptor (TLRs) and nucleotide-binding domain, leucine-rich repeat-containing (NBD-LRR) receptors referred to as NLRs [2]. Activation of PRRs results in rapid initiation of signaling pathways that lead to production of cytokines and chemokines that amplify inflammation and subsequently shape adaptive immune responses for optimal host defense. In addition to their role in host defense against invading pathogens, many PRRs have been implicated in responding to endogenous, danger-associated molecular patterns (DAMPs) [3], which are host-derived proteins released from cells following tissue injury. The participation of NLRs in inflammatory responses during host defense is well recognized; however their contribution to inflammation in the immune privileged sites, such as brain and eye, is poorly understood and is a focus of this review.

Historically, immune privileged sites were defined as tissues within the body that are able to tolerate exposure to antigen without eliciting inflammatory immune responses. This is best exemplified by early studies demonstrating that tissue grafts into organs, such as brain or eye, survived without being rejected as would normally occur elsewhere in the body [4, 5]. The brain and eyes have many non-regenerating cell types that could suffer irreversible destruction in the face of inflammation. Therefore, it is thought that these organs have evolved to protect themselves against the potentially damaging effects of inflammation that could have profound effects on brain function or vision. The underlying mechanisms by which immune privilege is sustained is an active area of research and are thought to be multi-factorial involving increased presence of immunosuppressive factors, such as TGF- β or neuropeptides [6], and increased Fas ligand that promotes cellular death of possible invading leukocytes [7]. Increased anti-inflammatory factors are found in conjunction with diminished expression of MHC class I molecules and lack of lymphatic drainage [8, 9]. It is

© 2011 Elsevier Ltd. All rights reserved.

Please address correspondence to: Holly L. Rosenzweig, PhD, Oregon Health & Science University, Mail stop: L467 AD, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, Phone: 503-494-8157, Fax: 503-494-6875, rosenzwh@ohsu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

now understood that under some circumstances antigens can leave immune-privileged sites and elicit immune responses that induce immune effector cell infiltration of the brain or eyes.

The relatively recently identified NLR family is comprised of at least 21 cytosolic proteins that share conserved, structurally homologous domains and presumed function in host defense against bacterial and viral pathogens [2, 10]. NLRs are defined by three distinct domains that are believed to mediate protein-protein interactions. Akin to TLRs, a leucine-rich repeat domain (LRR), which is located at the C-terminus, is recognized to be essential for the responsiveness of NLRs to their respective agonists. NLRs also contain a centrally located nucleotide-binding domain (NBD), which is critical for self-oligomerization in the presence of ATP. The N-terminus varies in that it may be a pyrin domain (PYD), a caspase-recruitment domain (CARD), or a baculovirus-inhibitory repeat domain (BIR), all of which activate downstream signaling cascades. The NLRs are divided into two major subfamilies: the NODs (also referred to as NLRCs) and the NLRPs (previously called NALPs) [11].

The functions and agonists of the NLR family members are less understood than those of the TLR family. Even less is known of their involvement in the central nervous system (CNS) or eye. Direct binding between NLRs and their agonists has not been demonstrated. Moreover, given their cytosolic location in the cells, it is plausible that in some instances they may not directly recognize pathogens but instead serve as essential downstream modulators. Indeed, increasing evidence supports their having a regulatory role in dampening or amplifying TLR responses, thereby suggesting that NLRs may play a broad role in homeostasis of the innate immune system. Clearly there remains much to be understood regarding this family of PRRs.

The association of NLRs and inflammation however, is underscored by an increasing list of autoinflammatory diseases, some of which manifest in sites such as the brain and eye as neuroinflammation or uveitis, respectively. Uveitis is a clinical term used to describe intraocular inflammatory disease. Autoinflammatory disorders are diseases considered to result primarily from dysregulation of mediators of innate immunity and occur in the absence of adaptive immune responses such as antibody production or autoreactive T cell development. Examples of autoinflammatory diseases involving NLRs and the brain or eyes are discussed further below.

Initially, NLRs were considered only in the cellular function of myeloid, immune cells. Early work demonstrated constitutive expression of NLRs in secondary lymphoid tissues such as lymph nodes and spleen. Neutrophils, macrophages and dendritic cells were considered the predominant cell types to employ NLRs. A role for NLRs in other cell types that are not primarily immune cells, such as endothelial and epithelial cells, is now being realized. Furthermore, expression of NLRs such as NLRP1 is constitutively expressed in brain tissue and has been demonstrated within neurons, oligodendrocytes, astrocytes and microglia [12–14]. NLRP3 and NOD2 expression, for example, occurs within microglia and astrocytes [15, 16]. Tissue-specific expression of NLR family members has been found. Within the spleen, for example, there appears to be an organ-specific expression profile for the NLRs in that most are constitutively expressed but CITTA and NOD1 appear to be expressed to a greater extent than other NLRs such as NLRP1-3 and NLRP6 or 10 [12, 17, 18]. In contrast to the spleen, human brain tissue appears to express NLRP1-3 and NLRP6 and 12 and NOD1 and NOD2 at higher levels [17, 18]. However the greater expression of these particular NLRs did not necessarily correlate with NLR expression patterns in murine brain tissue. This suggests unique expression profiles of NLRs within immune-privileged sites and that that species differences may be observed as well. Few studies have investigated the extent to which NLRs may be differentially regulated in eye tissue; albeit

reports of NOD1, NOD2, NLRP3 expression in murine eye tissue [19–22] and human vascular endothelial cells from iris, choroid and retina express NOD2 [23] have been published. In general, studies to corroborate mRNA expression profiles at the protein level and to further distinguish cellular localization of NLRs within the CNS or eye are lacking. Despite the relatively low expression of NLRs in brain and eyes, they nonetheless appear to play important roles in these organs. The remainder of this review focuses on NLRP3 and NOD2, which are the most well-studied of the NLRs and have direct clinical relevance to diseases affecting the CNS and eyes.

NLRP3, which is encoded by the gene *CIAS1*, has been the studied to the greatest extent in part because of the discoveries of genetic aberrancies in NLRP3 that result in uncontrolled inflammation mediated by IL-1 β . NLRP3 is involved in responsiveness to viral, bacterial and fungal pathogens [2]; and in response to K⁺ efflux and ATP, NLRP3 activates the inflammasome. The inflammasome is a term used to describe a protein complex that includes caspase-1, the enzyme responsible for proteolytic cleavage of the pro-form of IL-1 β into its secreted and biologically active form. Cryopyrin-associated periodic syndrome (CAPS) is a rare, but treatable, hereditary autoinflammatory condition. Originally thought to be three distinct heritable diseases (familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile, neurologic, cutaneous, and articular syndrome (CINCA, also referred to as NOMID), it is now considered to represent a spectrum of severity of the same disease process involving NLRP3 [24–27]. Each involves episodic fevers that coincide with organ-specific inflammation involving the skin, joints, CNS and eyes. CINCA, which is considered to be a more severe phenotype of disease, involves neurologic complications including headache, migraine, aseptic meningitis, cerebral atrophy, hydrocephalus, sensorineural deafness, along with ocular complications such as conjunctivitis, optic disc swelling and uveitis that can result in vision loss [27, 28]. Patients are extremely responsive to treatment with anakinra (recombinant IL-1 receptor antagonist, IL-1RA), with near complete amelioration of clinical symptoms [27, 29]. The extent to which anakinra therapy is effective for treatment of CNS or ocular manifestations of disease are not always noted, but there have been reports of the resolution of deafness [30], uveitis [31], chorioretinitis and retinal dystrophy [27, 32].

Experimental evidence supports a role for NLRP3 in CNS inflammation. CNS autoimmunity against myelin proteins is known to be a contributory factor in the pathogenesis of multiple sclerosis and in the animal model of experimental autoimmune encephalomyelitis (EAE). NLRP3 and its adaptor protein, ASC, have been demonstrated to play roles in the progression of demyelination and neuroinflammation in EAE [33, 34]. NLRP3 deficiency delayed the onset of disease and reduced the severity of demyelination and oligodendrocyte loss. NLRP3 KO mice replicated the protective phenotype seen in caspase-1 KO mice and IL-18 KO mice but not in IL-1 β KO mice. These results indicate an NLRP3-dependent, but an IL-1 β -independent, mechanism of disease progression. NLRP3 has been demonstrated to regulate CNS inflammation in other scenarios as well. It promotes CNS inflammation in cerebral malaria [35]. Interestingly, NLRP3, but not caspase-1, was essential for progression of CNS inflammation and disease. Collectively, these studies demonstrating inflammatory roles for NLRP3 in CNS inflammation are particularly interesting as NLRP3 function in the CNS is not always linked with IL-1 β production, which is in contrast to the aforementioned CAPs diseases. NLRP3 has been implicated in reactivity to amyloid-beta, which is thought to be a pathogenic factor in Alzheimer's disease. The response of NLRP3 to amyloid-beta serves as an important initiating event in activation and recruitment of microglia and their production of cytokines and neurotoxic factors [15, 36]. We are unaware of any data supporting a genetic association with polymorphisms of *CIAS1* and Alzheimer's disease. Given that NLRP3 responds to K⁺ efflux and ATP, thereby activating caspase-1 and IL-1 β release, it seems reasonable that NLRP3 could participate in

ischemic injury as well. However, at the time of this review no functional studies using NLRP3 KO mice have tested this hypothesis.

Unfortunately, few studies have investigated functional roles for NLRP3 in experimental uveitis. NLRP3 is constitutively expressed at the mRNA level in murine eyes and is upregulated as a consequence of systemic LPS exposure [37]. Our own studies have confirmed expression of NLRP3 protein in murine eyes and have investigated its function in an established acute uveitis model, historically referred to as endotoxin-induced uveitis [38]. Mice are extremely sensitive to an administered intraocular injection of LPS, and a rapid inflammatory uveitis ensues. Using KO mice, we find that NLRP3 and caspase-1 are necessary for IL-1 β production within the eye, yet this pathway is not essential for endotoxin-induced uveitis because NLRP3 KO and caspase-1 KO mice developed a similar severity of inflammation as WT controls (unpublished observations).

NOD2 was one of the first NLRs to be characterized in terms of microbial recognition and its responsiveness to muramyl dipeptide (MDP), a breakdown product of the bacterial cell wall component, peptidoglycan (PGN). Its involvement in host defense has since been expanded beyond bacterial infections to include viral and parasitic infections [39, 40] and also responsiveness to fungal components [41]. Mutation of NOD2 is a genetic cause of a near complete penetrance form of uveitis, called Blau syndrome (or Jabs syndrome) [42, 43]. Blau syndrome is classified as an autoinflammatory disease characterized by multi-organ, granulomatous inflammation of the eye, skin and joint. The uveitis is usually bilateral, causes chorioretinal scarring, and results in severe visual loss. Missense mutations discovered in patients with Blau syndrome appear to be primarily localized to the NBD domain and nearby coding regions [44–47]. Interestingly, mutations of NOD2 within the LRR domain are associated with other types of granulomatous inflammation as it is one of the main genetic risk factors for Crohn's disease [48], a granulomatous inflammation of the intestine, wherein uveitis is a frequent manifestation. However, in contrast to the pathogenic mutations of Blau syndrome, the polymorphisms associated with Crohn's disease are thought result in a loss-of-function. Thus, despite *NOD2* being a common gene contributing to each disease, several differences are noted between Blau syndrome and Crohn's disease such as the location of mutations within *NOD2*, the functional consequences of the mutations, and the differences in tissues afflicted by inflammation. *NOD2* mutations have also been associated with Rasmussen syndrome, which is characterized by persistent focal seizures, and CNS granulomatous disease [49].

With respect to uveitis, little is known regarding the function of NOD2 within the eye. NOD2 is expressed in eye tissue [20] and by human vascular endothelial cells from iris, choroid and retina. It functions to amplify TLR2 or TLR4-triggered cytokine production [23]. NOD2 plays an important functional role in promoting cellular responses within the iris vasculature and tissue *in vivo*. Intraocular exposure to its agonist, MDP, elicits an acute inflammatory uveitis involving increased leukocyte-endothelial interactions within the iris, that are diminished in NOD2 KO mice [50]. IFN γ is an important downstream mediator of uveitis and serves to further amplify MDP-triggered ocular inflammation [51]. Intraocular stimulation of NOD2 activity generates IL-1 β and IL-18 by a caspase-1 dependent mechanism [52]. NOD2 deficiency prevented MDP-induced uveitis, yet somewhat surprisingly, caspase-1 and IL-1R1 deficiency had no impact on disease severity, suggesting an IL-1 β -independent mechanism of uveitis involving NOD2. Another complexity is that under some circumstances NOD2 functions to reduce inflammation. We have shown that NOD2 deficiency exacerbates peptidoglycan-induced uveitis [53], which interestingly replicates a similar phenomenon in the intestine, wherein NOD2 functions to negatively regulate PGN-triggered inflammation [54]. With regard to therapy, in contrast to the effectiveness of anakinra in treatment of the CAPS patients, anakinra does not appear to

have the same effectiveness in diminishing symptoms of patients with Blau syndrome; two case reports demonstrated that uveitis was not improved [55, 56].

NOD2 appears to exert a regulatory role elsewhere in CNS inflammation. In the experimental model EAE, NOD2 and NOD1 are essential for induction of disease by way of their common signaling intermediary, RIP2 [57], and NOD2 activation influences proliferation of spinal cord cells [58]. NOD2 present in microglia and astrocytes may play an important role in modulating inflammatory responses in the CNS to a variety of potential pathogens relevant to the brain such as *N. meningitides*, *B. burgdorferi*, *S. aureus*, or *S. pneumoniae* [16, 59–62]. Increased neuronal expression of NOD2 was noted in the context of oxygen-glucose deprivation *in vitro* [63], suggesting that NOD2 may play a role in ischemic brain injury. Akin to NLRP3, NOD2 has also been implicated in Alzheimer's disease and responsiveness to amyloid-beta [64].

Aside from the discussed studies pertaining to NLRP3 and NOD2, very little work has investigated other NLRs with respect to brain or eye inflammation. NLRP1 is constitutively expressed in brain tissue including neurons, astrocytes and microglia [13, 14, 17, 65], where it is thought to promote apoptosis and may be involved in ischemic brain injury. Interestingly, NLRP1 has been linked with the autoinflammatory disease vitiligo, which is an inflammatory condition involving the skin and can also afflict the mucous membranes of the mouth, nose and eyes. NLRP1 expression is minimally detectable in murine eye tissue [37] and the possible role of NLRP1 within the eye as it may relate to uveitis has not been explored. *NOD1* polymorphisms have been linked with sarcoidosis [66, 67], an inflammatory disease of the joints that also presents with uveitis. NOD1 protein is constitutively expressed in murine eyes [20, 21], and NOD1 functionally acts to promote uveitis upon exposure to its agonist in a mechanism mediated in part by IL-1 β [21].

In light of the rapidly emerging evidence supporting NLRs as regulators of inflammatory responses in a variety of capacities, it seems as though there is unrealized involvement of NLRs in inflammatory responses of the brain or eyes, either in the case of autoinflammatory diseases or in response to infection. NLRs may directly promote inflammation or modify responses in conjunction with TLRs. In this way NLRs could initiate and/or contribute to progression of CNS inflammation through a variety of possible mechanisms. Another level of complexity to our understanding NLR functions in immune privileged sites is that, while we might assume analogous functions to what has been reported elsewhere in the body, these might not necessarily be the same in the brain or eyes. Tissue-specific control of immune response within these sites is a phenomenon that is well established. As such, we have yet to fully realize the extent to which NLR function may be influenced by the unique immune-suppressive milieu of the brain or eyes. The lower expression of NLRs in brain, for example, might suggest that their induction is required, which would presumably result in a slower responsiveness. Or perhaps given the immunosuppressive environment, it may be that NLRs must overcome a certain threshold for their induction and/or activation before they are able to have any impact on inflammation. These could be viewed as possible protective mechanisms in immune privileged sites. How different cell types regulate NLR activity is also relevant. Our own studies have illustrated opposing effects of NOD2 in the eye versus the joint [53, 68], further exemplifying how NLRs may function uniquely within this tissue.

Although research on NLRs in the brain and eyes is in its beginning phase, it is becoming increasingly apparent that their capacity to regulate inflammatory response during host defense makes them likely to have an important influence on CNS or ocular inflammation and disease. Future investigation is necessary for our full understanding of CNS and ocular immune responses and inflammatory disease.

Acknowledgments

Funding support: This work was made possible by the support from National Eye Institute at NIH (grants EY019020 (HLR) and EY019604 (JTR)). Additional support was provided by the Stan and Madelle Rosenfeld Family Trust, the William and Mary Bauman Foundation, the William C. Kuzell Foundation, and Research to Prevent Blindness. HLR also receives support from the Research to Prevent Blindness and the American College of Rheumatology.

References

1. Janeway CA Jr, Medzhitov R. Innate immune recognition. *Annu Rev Immunol.* 2002; 20
2. Davis BK, Wen H, Ting JP. The inflammasome NLRs in immunity, inflammation, and associated diseases. *Annu Rev Immunol.* 2011; 29:707–735. [PubMed: 21219188]
3. Akira S. Toll-like receptor signaling. *Journal of Biological Chemistry.* 2003; 278:38105–38108. [PubMed: 12893815]
4. Barker CF, Billingham RE. Immunologically privileged sites. *Adv Immunol.* 1977; 25
5. Hong S, Van Kaer L. Immune privilege: keeping an eye on natural killer T cells. *Journal of Experimental Medicine.* 1999; 190:1197–1200. [PubMed: 10544192]
6. Streilein JW, Okamoto S, Sano Y, Taylor AW. Neural control of ocular immune privilege. *Ann NY Acad Sci.* 2000; 917:297–306. [PubMed: 11268357]
7. Brunner T, Yoo NJ, Griffith TS, Ferguson TA, Green DR. Regulation of CD95 ligand expression: a key element in immune regulation? *Behring Inst Mitt.* 1996; 97
8. Streilein JW, Stein-Streilein J. Does innate immune privilege exist? *Journal of Leukocyte Biology.* 2000; 67:479–489. [PubMed: 10770279]
9. Kaplan HJ, Niederkorn JY. Regional immunity and immune privilege. *Chem Immunol Allergy.* 2007; 92
10. Meylan E, Tschopp J, Karin M. Intracellular pattern recognition receptors in the host response. *Nature.* 2006; 442:39–44. [PubMed: 16823444]
11. Martinon F, Mayor A, Tschopp J. The Inflammasomes: Guardians of the Body. *Annual Review of Immunology.* 2009; 27:229–265.
12. Kummer JA, Broekhuizen R, Everett H, Agostini L, Kuijck L, Martinon F, et al. Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response. *J Histochem Cytochem.* 2007; 55:443–452. [PubMed: 17164409]
13. Liu F, Lo CF, Ning X, Kajikowski EM, Jin M, Chiriac C, et al. Expression of NALP1 in cerebellar granule neurons stimulates apoptosis. *Cell Signal.* 2004; 16:1013–1021. [PubMed: 15212762]
14. Abulafia DP, de Rivero Vaccari JP, Lozano JD, Lotocki G, Keane RW, Dietrich WD. Inhibition of the inflammasome complex reduces the inflammatory response after thromboembolic stroke in mice. *J Cereb Blood Flow Metab.* 2009; 29:534–544. [PubMed: 19066616]
15. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, et al. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. *Nature Immunology.* 2008; 9:857–865. [PubMed: 18604209]
16. Chauhan VS, Sterka DG Jr, Furr SR, Young AB, Marriott I. NOD2 plays an important role in the inflammatory responses of microglia and astrocytes to bacterial CNS pathogens. *Glia.* 2009; 57:414–423. [PubMed: 18803303]
17. Lech M, Avila-Ferrufino A, Skuginna V, Susanti HE, Anders HJ. Quantitative expression of RIG-like helicase, NOD-like receptor and inflammasome-related mRNAs in humans and mice. *International Immunology.* 2010; 22:717–728. [PubMed: 20584763]
18. Yin Y, Yan Y, Jiang X, Mai J, Chen NC, Wang H, et al. Inflammasomes are differentially expressed in cardiovascular and other tissues. *Int J Immunopathol Pharmacol.* 2009; 22:311–322. [PubMed: 19505385]
19. Scurrall E, Stanley R, Schoniger S. Immunohistochemical detection of NOD1 and NOD2 in the healthy murine and canine eye. *Vet Ophthalmol.* 2009; 12:269–275. [PubMed: 19604345]

20. Rodriguez-Martinez S, Cancino-Diaz ME, Jimenez-Zamudio L, Garcia-Latorre E, Cancino-Diaz JC. TLRs and NODs mRNA expression pattern in healthy mouse eye. *Br J Ophthalmol*. 2005; 89:904–910. [PubMed: 15965176]
21. Rosenzweig H, Galster K, Planck S, Rosenbaum J. NOD1 expression in the eye and functional contribution to IL-1{beta} dependent ocular inflammation in mice. *Invest Ophthalmol Vis Sci*. 2009; 50:1746–1753. [PubMed: 19074813]
22. Gonzalez-Benitez JF, Juarez-Verdayes MA, Rodriguez-Martinez S, Cancino-Diaz ME, Garcia-Vasquez F, Cancino-Diaz JC. The NALP3/Cryopyrin-inflammasome complex is expressed in LPS-induced ocular inflammation. *Mediators of Inflammation*. 2008; 2008
23. Davey MP, Martin TM, Planck SR, Lee J, Zamora D, Rosenbaum JT. Human endothelial cells express NOD2/CARD15 and increase IL-6 secretion in response to muramyl dipeptide. *Microvasc Res*. 2006; 71:103–107. [PubMed: 16414084]
24. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nature Genetics*. 2001; 29:301–305. [PubMed: 11687797]
25. Neven B, Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L, et al. Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood*. 2004; 103:2809–2815. [PubMed: 14630794]
26. Kilcline C, Shinkai K, Bree A, Modica R, Von Scheven E, I.J. F. Neonatal-onset multisystem inflammatory disorder: the emerging role of pyrin genes in autoinflammatory diseases. *Arch Dermatol*. 2005; 141:248–253. [PubMed: 15724022]
27. Goldbach-Mansky R. Current Status of Understanding the Pathogenesis and Management of Patients With NOMID/CINCA. *Curr Rheumatol Rep*. 2011; 13:123–131. [PubMed: 21538043]
28. Kitley JL, Lachmann HJ, Pinto A, Ginsberg L. Neurologic manifestations of the cryopyrin-associated periodic syndrome. *Neurology*. 2010; 74:1267–1270. [PubMed: 20404307]
29. Leslie KS, Lachmann HJ, Bruning E, McGrath JA, Bybee A, Gallimore JR, et al. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. *Arch Dermatol*. 2006; 142:1591–1597. [PubMed: 17178985]
30. Mirault T, Launay D, Cuisset L, Hachulle E, Lambert M, Queyrel V, et al. Recovery from deafness in a patient with Muckle-Wells syndrome treated with anakinra. *Arthritis and Rheumatism*. 2006; 54:1697–1700. [PubMed: 16646042]
31. Teoh SC, Sharma S, Hogan A, Lee R, Ramanan AV, Dick AD. Tailoring biological treatment: anakinra treatment of posterior uveitis associated with the CINCA syndrome. *Br J Ophthalmol*. 2007; 91:263–264. [PubMed: 17244662]
32. Rigante D, Stabile A, Minnella A, Avallone L, Ziccardi L, Bersani G, et al. Post-inflammatory retinal dystrophy in CINCA syndrome. *Rheumatol Int*. 2010; 30:389–393. [PubMed: 19424698]
33. Jha S, Srivastava SY, Brckey WJ, Iocca H, Toews A, Morrison JP, et al. The inflammasome sensor, NLRP3, regulates CNS inflammation and demyelination via caspase-1 and interleukin-18. *J Neurosci*. 2010; 30:15811–15820. [PubMed: 21106820]
34. Shaw PJ, Lukens JR, Burns SA, Chi H, McGargill MA, Kanneganti TD. Cutting edge: critical role for PYCARD/ASC in the development of experimental autoimmune encephalomyelitis. *Journal of Immunology*. 2010; 184:4610–4614.
35. Reimer T, Shaw MH, Franchi L, Coban C, Ishii KJ, Akira S, et al. Experimental cerebral malaria progresses independently of the Nlrp3 inflammasome. *Eur J Immunol*. 2010; 40:764–769. [PubMed: 19950187]
36. Salminen A, Ojala J, Suuronen T, Kaarniranta K, Kauppinen A. Amyloid-beta oligomers set fire to inflammasomes and induce Alzheimer's pathology. *J Cell Mol Med*. 2008; 12:2255–2262. [PubMed: 18793350]
37. Gonzalez-Benitez JF, Juarez-Verdayes MA, Rodriguez-Martinez S, Cancino-Diaz ME, Garcia-Vasquez F, Cancino-Diaz JC. The NALP3/Cryopyrin-inflammasome complex is expressed in LPS-induced ocular inflammation. *Mediators of Inflammation*. 2008; 2008:7.

38. Rosenbaum JT, McDevitt HO, Guss RB, Egbert PR. Endotoxin-induced uveitis in rats as a model for human disease. *Nature*. 1980; 286:611–613. [PubMed: 7402339]
39. Sabbah A, Chang TH, Harnack R, Froehlich V, Tominaga K, Dube PH, et al. Activation of innate immune antiviral responses by Nod2. *Nat Immunol*. 2009; 10:1053–1054. [PubMed: 19767725]
40. Shaw MH, Reimer T, Sanchez-Valdepenas C, Warner N, Kim YG, Fresno M, et al. T cell-intrinsic role of Nod2 in promoting type 1 immunity to *Toxoplasma gondii*. *Nat Immunol*. 2009; 2009:1267–1274. [PubMed: 19881508]
41. Rosenzweig HL, Clowers JS, Nunez G, Rosenbaum JT, Davey MP. Dectin-1 and NOD2 mediate cathepsin activation in zymosan-induced arthritis in mice. *Inflammation Research*. 2011 Mar 20. [Epub ahead of print].
42. Blau EB. Familial granulomatous arthritis, iritis, and rash. *The Journal of Pediatrics*. 1985; 107:689–693. [PubMed: 4056967]
43. Jabs DA, Houk JL, Bias WB, Arnett FC. Familial granulomatous synovitis, uveitis, and cranial neuropathies. *American Journal of Medicine*. 1985; 78:801–804. [PubMed: 3993660]
44. Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Hafner R, et al. CARD15 mutations in Blau syndrome. *Nature Genetics*. 2001; 29:19–20. [PubMed: 11528384]
45. Rose CD, Doyle TM, McIlvain-Simpson G, Coffman JE, Rosenbaum JT, Davey MP, et al. Blau syndrome mutation of CARD15/NOD2 in sporadic early onset granulomatous arthritis. *J Rheumatol*. 2005; 32:373–375. [PubMed: 15693102]
46. Wang X, Kuivaniemi H, Bonavita G, Mutkus L, Mau U, Blau E, et al. CARD15 mutations in familial granulomatosis syndromes: a study of the original Blau syndrome kindred and other families with large-vessel arteritis and cranial neuropathy. *Arthritis Rheum*. 2002; 46:3041–3045. [PubMed: 12428248]
47. van Duist MM, Albrecht M, Podswiadek M, Giachino D, Lengauer T, Punzi L, et al. A new CARD15 mutation in Blau syndrome. *Eur J Hum Genet*. 2005; 13:742–747. [PubMed: 15812565]
48. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature*. 2001; 411:599–603. [PubMed: 11385576]
49. Goyal M, Cohen ML, Bangert BA, Robinson S, Singer NG. Rasmussen syndrome and CNS granulomatous disease with NOD2/CARD15 mutations. *Neurobiology*. 2007; 69:640–643.
50. Rosenzweig HL, Martin TM, Jann MM, Planck SR, Davey MP, Kobayashi K, et al. NOD2, the gene responsible for familial granulomatous uveitis, is essential in a mouse model of muramyl dipeptide-induced uveitis. *Investigative Ophthalmology & Visual Science*. 2008; 49:1518–1524. [PubMed: 18385071]
51. Rosenzweig HL, Kawaguchi T, Martin TM, Planck SR, Davey MP, Rosenbaum JT. Nucleotide oligomerization domain-2 (NOD2)-induced uveitis: dependence on IFN-gamma. *Invest Ophthalmol Vis Sci*. 2009; 50:1739–1745. [PubMed: 19098321]
52. Rosenzweig HL, Martin TM, Planck SR, Galster K, Jann MM, Davey MP, et al. Activation of NOD2 in vivo induces IL-1 beta production in the eye via caspase-1 but results in ocular inflammation independently of IL-1 signaling. *Journal of Leukocyte Biology*. 2008; 84:529–536. [PubMed: 18495787]
53. Rosenzweig HL, Galster K, Vance EE, Ensign-Lewis J, Nunez G, Davey MP, et al. NOD2 Deficiency Results in Increased Susceptibility to Peptidoglycan-Induced Uveitis in Mice. *Invest Ophthalmol Vis Sci*. 2011 Feb 4. [Epub ahead of print].
54. Watanabe T, Kitani A, Murray PJ, Strober W. NOD2 is a negative regulator of Toll-like receptor 2-mediated T helper type 1 responses. *Nat Immunol*. 2004; 5:800–808. [PubMed: 15220916]
55. Arostegui J, Arnal C, Merino R, Modesto C, Antonia Caballo J, Moreno P, et al. NON2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. *Arthritis Rheum*. 2007; 56:3805–3813. [PubMed: 17968944]
56. Martin TM, Zhang Z, Kurz P, Rose CD, Chen H, Lu H, et al. The NOD2 defect in Blau syndrome does not result in excess interleukin-1 activity. *Arthritis Rheum*. 2009; 60:611–618. [PubMed: 19180500]

57. Shaw PJ, Barr MJ, Lukens JR, McGargill MA, Chi H, Mak TW, et al. Signaling via the RIP2 adaptor protein in central nervous system-infiltrating dendritic cells promotes inflammation and autoimmunity. *Immunity*. 2011; 34:75–84. [PubMed: 21236705]
58. Su Y, Zhang Z, Trautmann K, Xu S, Schluesener HJ. TLR and NOD2 ligands induce cell proliferation in the rat intact spinal cord. *J Neuropathol Exp Neurol*. 2005; 64:991–997. [PubMed: 16254493]
59. Liu X, Chauhan VS, Marriott I. NOD2 contributes to the inflammatory responses of primary murine microglia and astrocytes to *Staphylococcus aureus*. *Neurosci Lett*. 2010; 474:93–98. [PubMed: 20226841]
60. Liu X, Chauhan VS, Young AB, Marriott I. NOD2 mediates inflammatory responses of primary murine glia to *Streptococcus pneumoniae*. *Glia*. 2010; 58:839–847. [PubMed: 20091781]
61. Sterka DG Jr, Rati DM, Marriott I. Functional expression of NOD2, a novel pattern recognition receptor for bacterial motifs, in primary murine astrocytes. *Glia*. 2006; 53:322–330. [PubMed: 16265673]
62. Sterka DG Jr, Marriott I. Characterization of nucleotide-binding oligomerization domain (NOD) protein expression in primary murine microglia. *J Neuroimmunol*. 2006; 179:65–75. [PubMed: 16842862]
63. Li H, Hu J, Ma L, Yuan Z, Wang Y, Wang X, et al. Comprehensive study of baicalin down-regulating NOD2 receptor expression of neurons with oxygen-glucose deprivation in vitro and cerebral ischemia-reperfusion in vivo. *Eur J Pharmacol*. 2010; 649:92–99. [PubMed: 20863826]
64. Chen K, Zhang L, Huang J, Gong W, Dunlop NM, Wang JM. Cooperation between NOD2 and Toll-like receptor 2 ligands in the up-regulation of mouse mFPR2, a G-protein-coupled Abeta42 peptide receptor, in microglial cells. *Journal of Leukocyte Biology*. 2008; 83:1467–1475. [PubMed: 18299458]
65. Frederick Lo C, Ning X, Gonzales C, Ozenberger BA. Induced expression of death domain genes NALP1 and NALP5 following neuronal injury. *Biochem Biophys Res Commun*. 2008; 366:664–669. [PubMed: 18068672]
66. Tanabe T, Ishige I, Suzuki Y, Aita Y, Furukawa A, Ishige Y, et al. Sarcoidosis and NOD1 variation with impaired recognition of intracellular *Propionibacterium acnes*. *Biochim Biophys Acta*. 2006; 1762:794–801. [PubMed: 16935475]
67. Le Bourhis L, Benko S, Girardin SE. Nod1 and Nod2 in innate immunity and human inflammatory disorders. *Biochem Soc Trans*. 2007; 35:1479–1484. [PubMed: 18031249]
68. Rosenzweig HL, Jann MJ, Vance EE, Planck SR, Rosenbaum JT, Davey MP. Nucleotide-binding oligomerization domain 2 and Toll-like receptor 2 function independently in a murine model of arthritis triggered by intraarticular peptidoglycan. *Arthritis and Rheumatism*. 2010; 62:1051–1059. [PubMed: 20131263]