Short Communication

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Molecular Signaling and Ocular Inflammation: An Update on the NOD-Like Receptors (NLRs)

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Uveitis (i.e. intra-ocular inflammatory disease) is a leading cause of blindness worldwide in that in years of vision morbidity, it accounts for approximately the same amount of visual loss as macular degeneration or diabetes because it affects children as well as young adults [1-7]. Clinically, uveitis is classified by its phenotype and anatomical locality of inflammation within discrete ocular tissues [8]. Uveitis encompasses a heterogeneous group of inflammatory disorders whose etiology may be infectious, non-infectious (i.e. autoimmune), drug-induced, or trauma-related. In all cases, uveitis is believed to be immune-mediated and results from aberrant control of the immune system [9-12]. Consistent with the autoimmune or autoinflammatory basis for uveitis, it is one of the most clinically important manifestations in a number of systemic immunological disorders including ankylosing spondylitis, Behçet's disease, sarcoidosis, and inflammatory bowel disease [5]. Despite its prevalence, however, very little is understood of the cellular and molecular underpinnings of uveitis. Even less is known of how early innate responses may participate in orchestration of ocular inflammatory disease.

Our innate immune system functions as an important initial barrier of host defense. It relies on a gamut of germ-line encoded families of innate immune receptors that elicit inflammation in response to pathogenic or endogenous insults. The discovery of the first such family, the toll-like receptors, or TLRs [13,14], has revolutionized our understanding of host-microbial interactions and for which numerous reviews have been written. Within the past decade other families and signaling pathways such as the NLRs (NOD-like receptors) have come to be recognized as an important aspect of defense against intracellular challenges including bacterial, viral, parasitic, fungal, as well as endogenous danger signals [15-17]. The NLRs are cytosolic proteins comprised of 3 structural domains: the C-terminal leucine-rich repeat (LRR) domain, which is essential for their agonist-sensing ability; a central NOD (nuclear oligomerization domain), which is important for ATP-dependent self-oligomerization; and varying N-terminal domains including caspase recruitment domains (CARD) or pyrin domains (PYD) both of which are considered important for protein-protein interactions and formation of signaling platforms. Activation of NLRs results in rapid initiation of signaling pathways that leads to cytokine and chemokine production, which then amplify inflammation and subsequently shape adaptive immune responses for optimal host defense. Whilst there are over 22 NLR family members that have been identified, the specific functions and agonists of many NLR family members remain unknown. Even less is known of how

NLRs are involved within immune privileged organs such as the eye. The role of NLRs (particularly NOD2 and NLRP3, the best-studied of NLRs to date) within the eye has been previously reviewed [11,18]; here, we expand upon our understanding of NLRs in the research arena of uveitis.

NLRP3 is encoded by the gene *CIAS1*, mutation of which is associated with cryopyrin-associated periodic syndrome (CAPS) a spectrum of autoinflamatory diseases with ocular manifestations [19-24]. In this disease, uncontrolled inflammation ensues and is mediated by IL-1β [21,22,25-27]. Unfortunately, the role for NLRP3 in uveitis is not well-studied. NLRP3 may be involved in ocular Behçet's in human patients [28,29], but little is known about its functional role in experimental models of uveitis. Constitutive expression of NLRP3 occurs at the transcriptional and translational level in healthy murine ocular tissue and is upregulated as a consequence of LPS exposure [30,31]. Studies have investigated its function in an established acute uveitis model adapted in mice, historically referred to as endotoxin-induced uveitis (EIU) [32]. Mice are extremely sensitive to an intraocular injection of the TLR4 agonist LPS, which results in a rapid inflammatory uveitis. However, studies using gene-deficient mice show that NLRP3 is not essential for endotoxin-induced uveitis [31]. NLRP3 and caspase-1 were demonstrated to be critical for IL-1β production (considered an integral aspect of inflammatory diseases such as CAPS, Blau Syndrome and ocular Behcet's disease) within the eye; yet caspase-1 KO mice develop similar severity of uveitis as NLRP3 KO and WT controls. Their lack of functionality in this particular murine model of uveitis is consistent with the report that mice deficient for the IL-1 receptor (IL-1R) do not show reduced ocular inflammation [33]. The role for IL-1β in this context seems somewhat paradoxical since the eye is in fact responsive to IL-1β and IL-1R antagonist (IL-1Ra) plays an important role in suppressing local ocular responses [33]. Collectively, these data suggest that even though NLRP3 is dispensable for EIU it is likely that IL-1β is still an important aspect of uveitic diseases. Moreover, the context in which NLRP3 may participate in uveitis is more complicated beyond what is modeled by direct activation of TLR4. NLRP3 has been reported to be involved in other types of eye diseases such as ischemic retinopathy [34] and age-related macular degeneration [35], an ocular disease whose association with inflammatory processes is increasingly being elucidated. Thus, it seems entirely likely that NLRP3 participates in other aspects of uveitis, especially since this pathway is known to play a role in shaping pathogenic Th17 effector responses. IL-1 signaling in fact necessary for the prototypical T cell-mediated model of uveitis, autoimmune experimental uveitis (EAU) [36], underscoring the importance of future studies that examine how NLRP3 and other NLRs are involved in orchestration of autoimmune T cell responses that target the eye.

NOD2 was one of the first NLR family members to be characterized in terms of its structure and function. NOD2 is unequivocally linked with human uveitis, as mutations in NOD2 result in the autosomal dominant multi-organ disease, Blau syndrome, which is characterized by uveitis, arthritis, and dermatitis [37-40] NOD2 senses the bacterial cell wall component peptidoglycan, or PGN, of which the minimal moiety required for NOD2 activation is muramyl dipeptide (MDP)) [41-43], and thus is critical for host defense against intracellular bacterial infection [44]. NOD2 has more recently been shown to participate in MDP-independent responses such as viral infection [45], thereby indicating a more complex role for NOD2 than may have been originally appreciated. Moreover, most of the described inflammatory actions of NOD2 have been attributed to its interaction with the signaling kinase RIP2, yet NOD2 is capable of directly interacting with many other proteins [46-50] thereby suggesting its involvement in alternate signaling pathways. Polymorphisms in NOD2 are associated with susceptibility to a number of other granulomatous inflammatory diseases such as Crohn's disease and sarcoidosis [51-54] that are also linked to ocular inflammation, but little work has focused on NOD2 biology and function within the eye itself. NOD2 is expressed in ocular tissue and specifically by human vascular endothelial cells from iris, choroid, and retinal blood vessels where its activation by MDP amplifies TLR2 or TLR4-triggered cytokine production [55]. NOD2 may also play an important functional role in promoting cellular responses within the iris *in vivo* in that intraocular injection of MDP results in acute inflammatory uveitis (i.e. manifested as increased leukocyte-endothelial interactions within the iris) that is abrogated in NOD2 KO mice [56].

Surprisingly, and in contrast to MDP-triggered ocular responses, NOD2 attenuates ocular inflammation induced by PGN [57], which triggers complex signaling responses that involve TLR2, NOD2, and PGRPs (peptidoglycan recognition proteins) amongst other proteins [58-61]. NOD2 KO mice demonstrate exacerbated cell trafficking responses into the iris, cell infiltration into the vitreous, and cytokine production. This observation suggests that NOD2 may serve differential roles in the eye to either promote or temper inflammation, which would be akin to the intestine wherein NOD2 exerts a role in suppressing inflammation triggered by PGN and other TLRs in the context of colitis [62-64]. Studies conducted in our own lab have found an involvement of the NOD2-RIP2 pathway in the protection of the eye to PGN (Figure 1). Such a capacity of NOD2 to mitigate inflammation of the eye may be intrinsic to cells within the retina, as organotypic retina cultures derived from naïve NOD2 KO mice produce greater amounts of IL-12p40 in response to PGN (personal communication). Studies to further dissect the molecular pathways through which NOD2 affects ocular inflammatory responses would be of interest.
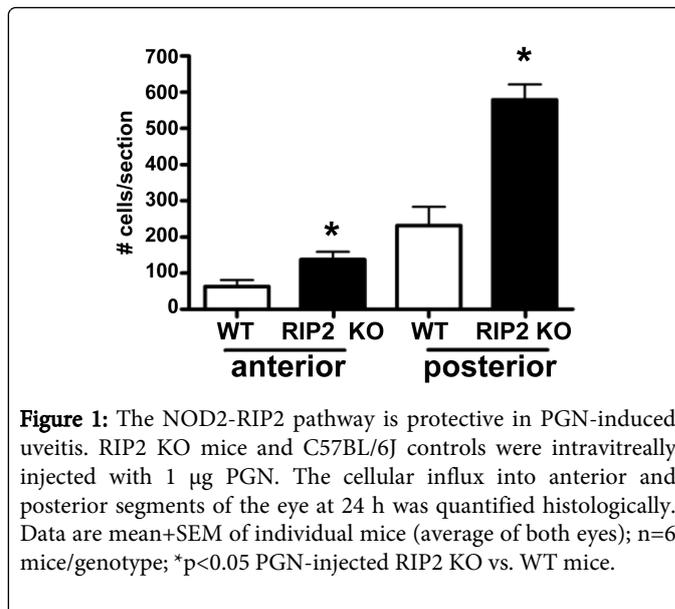

Figure 1: The NOD2-RIP2 pathway is protective in PGN-induced uveitis. RIP2 KO mice and C57BL/6J controls were intravitreally injected with 1 μg PGN. The cellular influx into anterior and posterior segments of the eye at 24 h was quantified histologically. Data are mean+SEM of individual mice (average of both eyes); n=6 mice/genotype; *p<0.05 PGN-injected RIP2 KO vs. WT mice.

The relevance of the above described experimental models for understanding uveitis in human patients could be disputed since the uveitis manifested is not sustained and is independent of adaptive immune components. In contrast, experimental autoimmune uveitis (EAU) in rodents shares many similarities with clinical uveitis in that it is a chronic and T cell-dependent disease [6,65,66]. EAU can be considered the prototypical T cell-dependent disease wherein animals peripherally immunized with retinal antigens develop organ-specific autoimmune disease. Using the EAU model, Jiang et al. [67] have examined the influence of direct activation of NOD2 by MDP in cultured retinal astrocytes. Their studies support the inflammatory actions of MDP and its potential to amplify TLR2-initiated priming of uveitogenic T cell responses and EAU disease severity. Retinal astrocytes have the potential to act as antigen-presenting cells (APCs). They may play a critical role in host defense by priming immune responses and contribute to adaptive immunity, thereby placing NOD2 at the interface between innate and adaptive immunity in the eye. However, once again the biological functions of NOD2 seem to deviate in more complex situations wherein NOD2 is not directly activated by MDP in the eye. Studies conducted in our own lab using the EAU model have uncovered a protective role for endogenous NOD2 in mitigation of ocular inflammation in that NOD2 deficiency markedly exacerbates EAU [68]. Collectively, such experimental observations may help better inform us as to the underlying pathogenesis of uveitis as occurs in Blau syndrome; especially in light of paradoxical clinical observations. Due to its inheritance pattern and the excessive inflammation that occurs in Blau syndrome, it has been presumed that disease results from gain-of-function mutation in NOD2. However, recent clinical studies that examined cellular responses of peripheral blood mononuclear cells in patients with Blau syndrome did not necessarily support such a paradigm since excessive cytokine production was not observed, and if anything it was diminished [39,69,70].

In conclusion, very little work has investigated the contribution of NLRs with respect to ocular inflammation. The above mentioned studies indicate that NLRs such as NOD2 or NLRP3 may serve as important early sentinels contributing to ocular inflammation but it is quite possible. They also mediate endogenous protective mechanisms.

Given that current uveitis therapies generally target later events (e.g. adaptive T cell functions) which occur after tissue damage has likely already occurred, NLR pathways that operate within the eye may be ideal targets on which to capitalize for development of novel therapies for uveitis. It is important to keep in mind, however, that studies have demonstrated differential effects of NLRs in the eye versus other organ systems, exemplifying how NLRs may function uniquely within individual organs, especially the eye wherein the immune-privileged microenvironment is controlled differently from other areas of the body [18]. Future studies are warranted to understand the complexity of NLRs and how they may use different molecular pathways in immune privileged organs such as the eye.

Acknowledgements

References

1. Chang JH, Wakefield D (2002) Uveitis: a global perspective. Ocul Immunol Inflamm 10: 263-279.

2. Gritz DC, Wong IG (2004) Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. Ophthalmology 111: 491-500.

3. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, et al. (2004) Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol 88: 1159-1162.

4. Lee RW, Dick AD (2012) Current concepts and future directions in the pathogenesis and treatment of non-infectious intraocular inflammation. Eye (Lond) 26: 17-28.

5. Nussenblatt RB (1990) The natural history of uveitis. Int Ophthalmol 14: 303-308.

6. Caspi RR (2010) A look at autoimmunity and inflammation in the eye. J Clin Invest 120: 3073-3083.

7. Wakefield D, Chang JH (2005) Epidemiology of uveitis. Int Ophthalmol Clin 45: 1-13.

8. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 140: 509-516.

9. Guly CM, Forrester JV (2010) Investigation and management of uveitis. BMJ 341: c4976.

10. Rothova A, Buitenhuis HJ, Meenken C, Brinkman CJ, Linssen A, et al. (1992) Uveitis and systemic disease. Br J Ophthalmol 76: 137-141.

11. Willermain F, Rosenbaum JT, Bodaghi B, Rosenzweig HL, Childers S, et al. (2012) Interplay between innate and adaptive immunity in the development of non-infectious uveitis. Prog Retin Eye Res 31: 182-194.

12. Pennesi G, Caspi RR (2002) Genetic control of susceptibility in clinical and experimental uveitis. Int Rev Immunol 21: 67-88.

13. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr (1997) A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature 388: 394-397.

14. Parham P (2009) The immune system. (3rdedn), Garland Science, Taylor & Francis Group, LLC, New York.

15. Davis BK, Wen H, Ting JP (2011) The inflammasome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol 29: 707-735.

16. Magalhaes JG, Sorbara MT, Girardin SE, Philpott DJ (2011) What is new with Nods? Curr Opin Immunol 23: 29-34.

17. Philpott DJ, Sorbara MT, Robertson SJ, Croitoru K, Girardin SE (2014) NOD proteins: regulators of inflammation in health and disease. Nat Rev Immunol 14: 9-23.

18. Rosenzweig HL, Planck SR, Rosenbaum JT (2011) NLRs in immune privileged sites. Curr Opin Pharmacol 11: 423-428.

19. Dollfus H, Hafner R, Hofmann HM, Russo RA, Denda L, et al. (2000) Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease syndrome: ocular manifestations in a recently recognized chronic inflammatory disease of childhood. Arc Ophthalmol 118: 1386-1392.

20. Shakeel A, Gouws P (2007) Muckle-Wells syndrome: another cause of acute anterior uveitis. Eye (Lond) 21: 849-850.

21. Kawai M, Yoshikawa T, Nishikomori R, Heike T, Takahashi K (2013) Obvious optic disc swelling in a patient with cryopyrin-associated periodic syndrome. Clin Ophthalmol 7: 1581-1585.

22. Kuemmerle-Deschner JB, Haug I (2013) Canakinumab in patients with cryopyrin-associated periodic syndrome: an update for clinicians. Ther Adv Musculoskelet Dis 5: 315-329.

23. Masters SL (2013) Specific inflammasomes in complex diseases. Clin Immunol 147: 223-228.

24. Terrada C, Neven B, Boddaert N, Souied EH, Prieur AM, et al. (2011) Ocular modifications in a young girl with cryopyrin-associated periodic syndromes responding to interleukin-1 receptor antagonist anakinra. J Ophthalmic Inflamm Infect 1: 133-136.

25. Goldbach-Mansky R, Kastner DL (2009) Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. J Allergy Clin Immunol 124: 1141-1149.

26. Goldbach-Mansky R (2011) Current status of understanding the pathogenesis and management of patients with NOMID/CINCA. Curr Rheumatol Rep 13: 123-131.

27. Goldbach-Mansky R (2012) Immunology in clinic review series; focus on autoinflammatory diseases: update on monogenic autoinflammatory diseases: the role of interleukin (IL)-1 and an emerging role for cytokines beyond IL-1. Clin Exp Immunol 167: 391-404.

28. Yuksel S, Eren E, Hatemi G, Sahillioglu AC, Gultekin Y, et al. (2014) Novel NLRP3/cryopyrin mutations and pro-inflammatory cytokine profiles in Behçet's syndrome patients. Int Immunol 26: 71-81.

29. Liang L, Tan X, Zhou Q, Zhu Y, Tian Y, et al. (2013) IL-1beta triggered by peptidoglycan and lipopolysaccharide through TLR2/4 and ROS-NLRP3 inflammasome-dependent pathways is involved in ocular Behcet's disease. Invest Ophthalmol Vis Sci 54: 402-414.

30. González-Benítez JF, Juárez-Verdayes MA, Rodríguez-Martínez S, Cancino-Diaz ME, García-Vázquez F, et al. (2008) The NALP3/Cryopyrin-inflammasome complex is expressed in LPS-induced ocular inflammation. Mediators Inflamm 2008: 614345.

31. Rosenzweig HL, Woods A, Clowers JS, Planck SR, Rosenbaum JT (2012) The NLRP3 inflammasome is active but not essential in endotoxin-induced uveitis. Inflamm Res 61: 225-231.

32. Rosenbaum JT, McDevitt HO, Guss RB, Egbert PR (1980) Endotoxin-induced uveitis in rats as a model for human disease. Nature 286: 611-613.

33. Planck SR, Woods A, Clowers JS, Nicklin MJ, Rosenbaum JT, et al. (2012) Impact of IL-1 signalling on experimental uveitis and arthritis. Ann Rheum Dis 71: 753-760.

34. Rivera JC, Sitaras N, Noueihed B, Hamel D, Madaan A, et al. (2013) Microglia and interleukin-1beta in ischemic retinopathy elicit microvascular degeneration through neuronal semaphorin-3A. Arterioscler Thromb Vasc Biol 33: 1881-1891.

35. Doyle SL, Campbell M, Ozaki E, Salomon RG, Mori A, et al. (2012) NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components. Nature Medicine 18: 791-798.

36. Su SB, Silver PB, Grajewski RS, Agarwal RK, Tang J, et al. (2005) Essential role of the MyD88 pathway, but nonessential roles of TLRs 2, 4, and 9, in the adjuvant effect promoting Th1-mediated autoimmunity. J Immunol 175: 6303-6310.

37. Jabs DA, Houk JL, Bias WB, Arnett FC (1985) Familial granulomatous synovitis, uveitis, and cranial neuropathies. Am J Med 78: 801-804.

38. Blau EB (1985) Familial granulomatous arthritis, iritis, and rash. J Pediatr 107: 689-693.

39. Rose CD, Martin TM, Wouters CH (2011) Blau syndrome revisited. Curr Opin Rheumatol 23: 411-418.

40. Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, et al. (2001) CARD15 mutations in Blau syndrome. Nat Genet 29: 19-20.

41. Girardin SE, Travassos LH, Hervé M, Blanot D, Boneca IG, et al. (2003) Peptidoglycan molecular requirements allowing detection by Nod1 and Nod2. J Biol Chem 278: 41702-41708.

42. Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, et al. (2003) Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. J Biol Chem 278: 5509-5512.

43. Kim YG, Park JH, Shaw MH, Franchi L, Inohara N, et al. (2008) The cytosolic sensors Nod1 and Nod2 are critical for bacterial recognition and host defense after exposure to Toll-like receptor ligands. Immunity 28: 246-257.

44. Franchi L, Warner N, Viani K, Nuñez G (2009) Function of Nod-like receptors in microbial recognition and host defense. Immunol Rev 227: 106-128.

45. Sabbah A, Chang TH, Harnack R, Frohlich V, Tominaga K, et al. (2009) Activation of innate immune antiviral responses by Nod2. Nat Immunol 10: 1073-1080.

46. McDonald C, Chen FF, Ollendorff V, Ogura Y, Marchetto S, et al. (2005) A role for Erbin in the regulation of Nod2-dependent NF-kappaB signaling. J Biol Chem 280: 40301-40309.

47. Kufer TA, Kremmer E, Banks DJ, Philpott DJ (2006) Role for erbin in bacterial activation of Nod2. Infect Immun 74: 3115-3124.

48. Yamamoto-Furusho JK, Barnich N, Xavier R, Hisamatsu T, Podolsky DK (2006) Centaurin beta1 down-regulates nucleotide-binding oligomerization domains 1- and 2-dependent NF-kappaB activation. J Biol Chem 281: 36060-36070.

49. Zurek B, Schoultz I, Neerincx A, Napolitano LM, Birkner K, et al. (2012) TRIM27 negatively regulates NOD2 by ubiquitination and proteasomal degradation. PLoS One 7: e41255.

50. Lee KH, Biswas A, Liu YJ, Kobayashi KS (2012) Proteasomal degradation of Nod2 protein mediates tolerance to bacterial cell wall components. J Biol Chem 287: 39800-39811.

51. Le Bourhis L, Benko S, Girardin SE (2007) Nod1 and Nod2 in innate immunity and human inflammatory disorders. Biochem Soc Trans 35: 1479-1484.

52. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, et al. (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 411: 599-603.

53. Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, et al. (2005) Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. Blood 105: 1195-1197.

54. Zhang FR, Huang W, Chen SM, Sun LD, Liu H, et al. (2009) Genomewide association study of leprosy. N Engl J Med 361: 2609-2618.

55. Davey MP, Martin TM, Planck SR, Lee J, Zamora D, et al. (2006) Human endothelial cells express NOD2/CARD15 and increase IL-6 secretion in response to muramyl dipeptide. Microvasc Res 71: 103-107.

56. Rosenzweig HL, Martin TM, Jann MM, Planck SR, Davey MP, et al. (2008) NOD2, the gene responsible for familial granulomatous uveitis, in a mouse model of uveitis. Invest Ophthalmol Vis Sci 49: 1518-1524.

57. Rosenzweig HL, Galster K, Vance EE, Ensign-Lewis J, Nunez G, et al. (2011) NOD2 deficiency results in increased susceptibility to peptidoglycan-induced uveitis in mice. Invest Ophthalmol Vis Sci 52: 4106-4112.

58. Dziarski R, Gupta D (2005) Peptidoglycan recognition in innate immunity. J Endotoxin Res 11: 304-310.

59. Sorbara MT, Philpott DJ (2011) Peptidoglycan: a critical activator of the mammalian immune system during infection and homeostasis. Immunol Rev 243: 40-60.

60. Rosenzweig HL, Galster K, Vance EE, Ensign-Lewis J, Nunez G, et al. (2011) NOD2 deficiency results in increased susceptibility to peptidoglycan-induced uveitis in mice. Invest Ophthalmol Vis Sci 52: 4106-4112.

61. Clowers JS, Allensworth JJ, Lee EJ, Rosenzweig HL (2013) Investigation of the peptidoglycan sensing molecule, PGLYRP-2, in murine inflammatory uveitis. Br J Ophthalmol 97: 504-510.

62. Watanabe T, Kitani A, Murray PJ, Wakatsuki Y, Fuss IJ, et al. (2006) Nucleotide binding oligomerization domain 2 deficiency leads to dysregulated TLR2 signaling and induction of antigen-specific colitis. Immunity 25: 473-485.

63. Yang Z, Fuss IJ, Watanabe T, Asano N, Davey MP, et al. (2007) NOD2 transgenic mice exhibit enhanced MDP-mediated down-regulation of TLR2 responses and resistance to colitis induction. Gastroenterology 133: 1510-1521.

64. Watanabe T, Kitani A, Murray PJ, Strober W (2004) NOD2 is a negative regulator of Toll-like receptor 2-mediated T helper type 1 responses. Nat Immunol 5: 800-808.

65. Caspi RR, Silver PB, Luger D, Tang J, Cortes LM, et al. (2008) Mouse models of experimental autoimmune uveitis. Ophthalmic Res 40: 169-174.

66. Horai R, Caspi RR (2011) Cytokines in autoimmune uveitis. J Interferon Cytokine Res 31: 733-744.

67. Jiang G, Sun D, Kaplan HJ, Shao H (2012) Retinal astrocytes pretreated with NOD2 and TLR2 ligands activate uveitogenic T cells. PLoS One 7: e40510.

68. Lee EJ, Furtado JM, Brown B, Vance EE, Sacdal JP, et al. (2013) An unexpected role for the innate immune receptor NOD2 in suppression of experimental autoimmune uveitis. Invest Ophthalmol Vis Sci 2013, 54: E-abstract-2523.

69. Martin TM, Zhang Z, Kurz P, Rosé CD, Chen H, et al. (2009) The NOD2 defect in Blau syndrome does not result in excess interleukin-1 activity. Arthritis Rheum 60: 611-618.

70. Masumoto J, Yamazaki T, Ohta K, Nakayama J, Agematsu K (2009) Interleukin-1beta suppression in Blau syndrome: comment on the article by Martin et al. Arthritis Rheum 60: 2544-2545.