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Short Communication Open Access

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

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Short Communication

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 NLRPs 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.

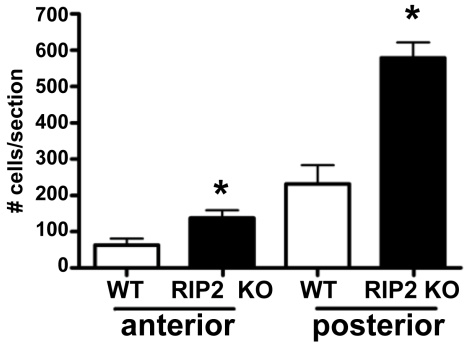

Figure 1: The NOD2-RIP2 pathway is protective in PGN-induced uveitis. RIP2 KO mice and C57BL/6J controls were intravitreally injected with 1 μg PGN. The cellular influx into anterior and posterior segments of the eye at 24 h was quantified histologically. Data are mean+SEM of individual mice (average 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.

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