Systemic inflammation and innate immune response in patients with previous anterior uveitis

M Huhtinen, H Repo, K Laasila, S-E Jansson, H Kautiainen, A Karma, M Leirisalo-Repo

Aim: To determine the presence of systemic inflammation and innate immune responsiveness of patients with a history of acute anterior uveitis but no signs of ocular inflammation at the time of recruitment.

Methods: Tumour necrosis factor α (TNF-α) production in response to bacterial lipopolysaccharide (LPS) was studied using whole blood culture assay; levels of TNF-α in culture supernatants, and soluble interleukin 2 receptor (sIL-2R) in serum were determined by chemiluminescent immunoassay (Lumilite); monocyte surface expression of CD11b, CD14, and CD16 and the proportion of monocyte subsets CD14dimCD16+ and CD14+CD16− were studied with three colour whole blood flow cytometry; and serum C reactive protein (CRP) levels were determined using immunonephelometric high sensitivity CRP assay.

Results: The CRP level (median, interquartile range) was significantly higher in 56 patients with previous uveitis than in 37 controls [1.59 (0.63 to 3.47) µg/ml v 0.81 (0.32 to 2.09) µg/ml; p=0.008]. The TNF-α concentration of the culture media per 10^5 monocytes was significantly higher in the patient group than in the control group in the presence of LPS 10 ng/ml (1193 to 2024) pg/ml v 935 to 1555 pg/ml; p=0.012) and LPS 1000 ng/ml (3280 (2709 to 4418) pg/ml v 2910 (2313 to 3358) pg/ml; p=0.011). The background TNF-α release into the culture media was low in both groups. CD14 expression of CD14+CD16− monocyes, defined as antibody binding capacity (ABC), was similar for the patients and controls (22 839 (21 038 to 26 020) ABC v 21 657 (19 854 to 25 646) ABC).

Conclusions: Patients with previous acute anterior uveitis show high innate immune responsiveness that may play a part in the development of ocular inflammation.

Acute anterior uveitis (AAU) of unknown aetiology is an inflammatory disorder that occurs in the iris or anterior ciliary body and lasts no more than 3 months. About 50% of the patients have HLA-B27 antigen. In half of those who are HLA-B27 positive, AAU occurs with spondyloarthropathy (SpA), including ankylosing spondylitis, reactive arthritis who are HLA-B27 positive, AAU occurs with spondyloarthropathy (SpA), including ankylosing spondylitis, reactive arthritis. Although most patients with AAU lack clinical infection, laboratory findings suggest the presence of systemic inflammation in the acute phase of the disease. Therefore, it is possible that innate and adaptive immune responses play a part in the development of ocular inflammation.

LPS activates monocytes, important cellular elements of the innate immune system, via CD14 and Toll-like receptors. Activated monocytes generate tumour necrosis factor α (TNF-α) and other cytokines, including interleukin 6 (IL-6). They induce the liver synthesis of C reactive protein (CRP), an acute phase protein, and play a key part in the activation of adaptive immune responses. Both LPS and proinflammatory cytokines can strengthen phagocyte functions in several ways. They prime monocytes, and enhance their maturation. Indeed, in healthy subjects, the majority of monocytes are strongly positive for CD14 (CD14bright) and negative for high affinity Fcγ-III receptor (CD16). However, in a variety of disorders with features of systemic inflammation, up to 50% of monocytes are weakly positive for CD14 (CD14dim) and co-express Fcγ-III receptor (CD16). Such monocytes exhibit enhanced capacity to produce TNF-α. The anterior chamber of the eye is an immunologically privileged site, which possesses the capacity to inhibit both innate and adaptive immune reactions. Taking into account the functional heterogeneity of phagocytes, we reasoned that hyperreactive monocytes emigrating into the eye would more likely be capable of breaking down the mechanisms of innate immune privilege compared with low responder cells. We therefore assessed innate immune responsiveness and the presence of systemic inflammation in patients with previous AAU. We quantified LPS induced TNF-α production in whole blood ex vivo to study the innate response. To assess the presence of systemic inflammation we measured serum levels of CRP and soluble interleukin 2 receptor (sIL-2R), a marker of lymphocyte activation, and monocyte surface expression of the β2-integrin CD11b/CD18, a marker of phagocyte activation. Finally, we quantified the cell surface expression of CD14, CD16, and CD11b to identify monocyte subsets with distinct functional capacities.

SUBJECTS AND METHODS

Subjects
A total of 64 patients with a history of idiopathic acute or recurrent anterior uveitis were recruited to the present study, which was carried out at the Helsinki University Eye Hospital.

Abbreviations: AAU, acute anterior uveitis; ABC, antibody binding capacity; CRP, C reactive protein; EIA, endotoxin induced uveitis; EIU, endotoxin induced uveitis; LPS, lipopolysaccharide; sIL-2R, soluble interleukin 2 receptor; SpA, spondyloarthropathy; TNF-α, tumour necrosis factor α.
between September and December 1999. The study protocol was approved by the institutional review board and was conducted according to the tenets of the Declaration of Helsinki. A visual acuity test, tonometry, a slit lamp examination, and an evaluation of the fundus with a 90 dioptre lens, or indirect ophthalmoscopy, and a three mirror lens when necessary, were performed. Five patients were shown to have ongoing AAU. Data concerning age, sex, age at onset of first uveitis, number of attacks, complications, and systemic symptoms and disorders were collected on standard forms. In addition we asked about the use of anti-rheumatic drugs known to inhibit TNF-\(\alpha\) production.13–16 A rheumatological survey with sacroiliac x-ray examination was performed on the patients with low back pain or peripheral joint symptoms suggestive of ankylosing spondylitis or other forms of SpA. Patients fulfilling the criteria of the European Spondyloarthropathy Study Group17 were diagnosed as having seronegative SpA. Parallel blood samples were collected from the patients and also from 37 volunteers (26 women, 11 men, mean age 42 years, SD 10.1) from the hospital and laboratory staff who were not on medication and had no signs of infection.

Reagents

The reagents used were pyrogen free heparin (Lövens, Ballerup, Denmark); Dulbecco’s phosphate buffered saline (PBS) and RPMI 1640 medium (both from Life Technologies Ltd, Paisley, Scotland); Escherichia coli O111:B4 lipopolysaccharide (LPS, Sigma Chemical Company, St Louis, MO, USA); TNF-\(\alpha\) sample diluent (Diagnostic Products, Los Angeles, CA, USA); fluorescein isothiocyanate (FITC) conjugate of mouse anti-CD11b mAb (IgG1, clone BEAR 1), phycoerythrin (PE)-CY5 (PC5) conjugate of anti-CD16 mAb (IgG1, clone 7G8), and PC5 conjugate of irrelevant mouse mAb IgG1 (clone 679.1Mc7) (all from Immunotech, Marseilles, France); RPE conjugate of anti-CD14 mAb (IgG2a, clone TÜK4) and RPE conjugate of irrelevant mAb (IgG2a, clone DAK-G05) (both from Dako A/S, Glostrup, Denmark); FACS lysing solution (Becton Dickinson, San Jose, CA, USA). QuantibRITE PE bead standards were obtained from Becton Dickinson.

Blood samples

Parallel blood samples were obtained by phlebotomy on a given day from one to three patients and a healthy control subject. Two samples of whole blood were collected from each subject. One sample was taken into a polystyrene tube (Falcon No 2058, Becton Dickinson Labware, Lincoln Park, NJ, USA) containing pyrogen free heparin (10 IU/ml blood), cooled immediately at 0°C, and aliquoted within an hour of the sampling for whole blood culture and the staining of cell surface markers. The other sample was taken into a glass tube (Venoject VE-100PZX, Terumo Europe NV, Leuven, Belgium) and similarly cooled. Serum was separated by centrifugation at 4°C and stored in aliquots at −70°C until used.

Methods

Whole blood culture

LPS stock solution (400 mg/ml in PBS) was stored in 20 ml aliquots at −20°C. Samples of 100 ml of heparinised blood were added into polypropylene tubes (No 352063, Becton Dickinson) containing 800 µl of RPMI 1640 and 100 µl of LPS (final concentrations 1000 ng/ml and 10 ng/ml) in PBS, or PBS only. After incubation for 4 hours at 37°C in 5% carbon dioxide, the supernatants were separated by centrifugation, snap frozen, and stored at −70°C. The TNF-\(\alpha\) levels were determined within 2 weeks. The intra-assay variation was 9% and 7% for the 1000 ng/ml and 10 ng/ml LPS concentrations, respectively, and the interassay variation was 12% for both concentrations.

Determination of TNF-\(\alpha\) and sIL-2R

The culture supernatants at −70°C were thawed and diluted 1:5 with TNF-\(\alpha\) sample diluent. The TNF-\(\alpha\) levels of the culture supernatants and the sIL-2R levels of the serum samples were determined by Immulite (Diagnostic Products), a chemiluminescent immunoassay system. The detection limits of TNF-\(\alpha\) and sIL-2R were 4 pg/ml and 10 U/ml, respectively. The TNF-\(\alpha\) levels were corrected for dilution.

### Table 1 Characteristics of 56 patients with previous acute anterior uveitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Number of women/men</td>
<td>25/31</td>
<td>44.6%</td>
</tr>
<tr>
<td>Mean age, years, (SD)</td>
<td>42 (12.9)</td>
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<tr>
<td>Mean age at first iritis, years, (SD)</td>
<td>34 (11.3)</td>
<td></td>
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<tr>
<td>Median cumulative number of iritis episodes, (range)</td>
<td>10 (1–51)</td>
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<tr>
<td>Number of patients positive for HLA-B27, (%)</td>
<td>49 (88)</td>
<td></td>
</tr>
<tr>
<td>Number of patients with fibrin exudates, (%)</td>
<td>32 (57)</td>
<td></td>
</tr>
<tr>
<td>Number of patients with chronic eye disease*, (%)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Number of patients with eye complications, (%)</td>
<td>14 (25)</td>
<td></td>
</tr>
<tr>
<td>Number of patients with spondyloarthropathy, (%)</td>
<td>12 (21)</td>
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*A iritis has not resolved within 3 months.

Figure 1 Analysis of patients’ CD14 and CD16 cell surface markers on CD11b positive monocytes. Aliquots of heparinised blood were triple labelled with fluorescent mAbs, as described in the Methods section. CD11b positive cells were delineated by R1 (A) and monocytes by R2 (B) and a CD14(FL2)/CD16(FL3) dot plot was developed from the monocytes (that is, the events co-locating in R1 and R2) (C). The proportion of CD14\(^+\)/CD16\(^+\) monocytes was 13.4%. CD14 expression, median of the number of PE molecules bound by cells; CD16 expression, relative fluorescence units (RFU); upper horizontal zone, CD14\(^+\) monocytes; middle horizontal zone, CD14\(^-\)/CD16\(^+\) monocytes; bottom zone, non-specific PE fluorescence of cells stained with PE conjugated irrelevant mAb; vertical zone on right, CD16\(^+\) monocytes; vertical zone on left, non-specific PC5 fluorescence.
Table 2  C reactive protein (CRP) levels

<table>
<thead>
<tr>
<th>Subjects</th>
<th>CRP (µg/ml) median (interquartile range)</th>
</tr>
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<tbody>
<tr>
<td>Patients, n=56</td>
<td>1.59 (0.63–3.47)*</td>
</tr>
<tr>
<td>Controls, n=37</td>
<td>0.81 (0.32–2.09)</td>
</tr>
<tr>
<td>Patients with SpA, n=12</td>
<td>1.27 (0.37–2.52)</td>
</tr>
<tr>
<td>Patients without SpA, n=44</td>
<td>1.68 (0.81–3.60)</td>
</tr>
</tbody>
</table>

*Significantly different from control (p=0.008); †spondyloarthropathy.

Determination of CRP level
Immunonephelometric high sensitivity CRP assay (Dade Behring, Marburg, Germany) was used to determine serum CRP levels (detection limit 0.18 µg/ml). At serum CRP levels of 0.58 µg/ml and 3.55 µg/ml, the intra-assay variation was 3% and 2%, respectively, and the interassay variation was 4% and 3%, respectively.

Flow cytometry
Three colour flow cytometry was used. The cell labelling was as described previously. Briefly, two 25 µl aliquots of heparinised whole blood in polystyrene tubes (No 352054, Becton Dickinson) were triple labelled at 0°C by the addition of pretitrated amounts of FITC conjugated CD11b mAb into both tubes, PE conjugated CD14 mAb (tube 1) or irrelevant PE conjugated IgG1 mAb (tube 2), and PC5 conjugated CD16 mAb (tube 1) or irrelevant PC5 conjugated IgG1 mAb (tube 2). After being stained for 20 minutes at 0°C, erythrocytes were lysed by the addition of 1:10 diluted ice cold FACS lysing solution. After a 3 minute incubation at a cold temperature, the cells were separated by centrifugation and resuspended in 2 ml of FACS lysing solution at room temperature. Leucocytes were pelleted by centrifugation and resuspended in 1% formalin at 0°C. Data were acquired by a flow cytometer within 6 hours.

A FACSort flow cytometer (Becton Dickinson) and CellQuest software were used to obtain the data. After appropriate spectral compensation, the instrument settings were not changed during the study. An electronic live gate for CD11b positive monocytes was set as follows: firstly, the CD11b positive events were delineated in the side scatter (SSC)/CD11b (fluorescence-1 axis, FL1) dot plot by the region R1 (Fig 1A); secondly, SSC/forward scatter (FSC) dot plot (Fig 1B) was created from R1, and R2 was set to delineate the monocyte population. At least 1×10^6 monocytes (that is, events colocating in R1 and R2) were collected. The QuantiBRITE PE bead standards (that is, beads conjugated with four known levels of PE) were run weekly during the study period.

The data were analysed using QuantiCalc software (Verity Software House, Topsham, ME, USA). The QuantiBRITE PE data were used to calibrate the FL2 axis in terms of PE molecules. Using the CD14(FL2)/CD16(FL3) dot plot (Fig 1C), CD14^+CD16^+ and CD14^-CD16^- monocyte subsets were identified. According to the manufacturer, the ratio of fluorescein to protein was 1 in the RPE conjugate of the CD14 mAb used. CD14 expression was reported as the antibody binding capacity (ABC) (that is, the median number of PE molecules bound by the monocyte). To assess the CD11b expression, a CD11b fluorescence (FL1) histogram was created from the monocyte population, and the CD11b fluorescence intensities were reported as relative fluorescence units (RFU) (that is, median channel number of the fluorescent cell population).

Monocyte count
The monocyte count was determined using a flow cytometer as the cell counter, as described previously. The time needed to collect data from 1×10^6 monocytes was recorded. The arithmetic mean of the monocyte count of tubes 1 and 2 was determined.

Data analysis
Out of the 64 patients included in the study, five with AAU and three others with incomplete data in the culture assay and cell surface marker study were excluded from the data analyses. The results are presented as median values, and the interquartile range (IQR) is provided. The patients and control groups were compared with the use of the Mann-Whitney U test using the exact p values. The relation between the monocyte count and TNF-α level was assessed with a Spearman rank correlation coefficient (r) and its 95% confidence interval (CI), and with a locally weighted scatter plot smoother (LOWESS). Three patients were on antirheumatic drugs and indicated in the figure as follows: ▲, aurothiomalate; ■, hydroxychloroquine; ▼, sulphasalazine.

RESULTS
The clinical characteristics of the 56 patients are presented in Table 1. One quarter of the AAU patients had developed eye
Figure 3 TNF-α levels in whole blood culture supernatants. The difference between the patients’ cell supernatants (n=56) and control cell supernatants (n=37) was statistically significant (Mann-Whitney U test) at 1000 ng/ml (p=0.011) and 10 ng/ml (p=0.012). LPS, *Escherichia coli* lipopolysaccharide. Open circles, outliers.

Table 3 Proportions of monocyte subsets, and CD14 expression levels of CD14<sup>dim</sup>CD16<sup>-</sup> monocytes

<table>
<thead>
<tr>
<th>Monocyte subset</th>
<th>Patients (n=56)</th>
<th>Controls (n=37)</th>
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<tbody>
<tr>
<td>CD14&lt;sup&gt;dim&lt;/sup&gt;CD16&lt;sup&gt;-&lt;/sup&gt;, Proportion, %</td>
<td>86.0 (82.3–88.1)</td>
<td>85.6 (82.8–89.0)</td>
</tr>
<tr>
<td>CD14 expression, ABC</td>
<td>22 839 (21 038–26 020)</td>
<td>21 657 (19 854–25 646)</td>
</tr>
<tr>
<td>CD14&lt;sup&gt;dim&lt;/sup&gt;CD16&lt;sup&gt;-&lt;/sup&gt;, Proportion, %</td>
<td>4.5 (3.2–6.7)</td>
<td>4.3 (2.8–6.4)</td>
</tr>
</tbody>
</table>

Data are median [interquartile range]; ABC, antibody binding capacity.

complications such as persistent synchia, cataract, glaucoma, and macular oedema. SpA, which did not correlate with complications or with the chronicity of the eye disease, was detected in one fifth of the patients. Three patients were taking antirheumatic drugs for SpA; one was on sulphasalazine, another was on hydroxychloroquine, and the third took aurothiomalate.

The CRP concentration of the AAU patients was significantly higher than that of the normal controls (p=0.008). The CRP levels of the patients with (n=12) SpA and those without (n=44) SpA were comparable (Table 2). For two of the patients on antirheumatic drugs, the CRP values were higher than the median CRP value of the other patients (1.03 µg/ml, 3.62 µg/ml, and 10.00 µg/ml). The SIL-2R levels of the patients’ sera (334 (267 to 417) IU/ml) and control sera (394 (284 to 478) IU/ml) were comparable. The CD11b expression level of the patients’ monocytes (92 RFU (87 to 104)) was similar to that of the control monocytes (86 (80 to 100) RFU).

The TNF-α levels of the whole blood culture media (LPS concentration 10 ng/ml) correlated positively with the blood monocyte counts (Fig 2A); however, when standardised by the monocyte count, this correlation disappeared (Fig 2B). The median TNF-α concentration standardised by the monocyte count (Fig 3) was significantly higher in the patient group than in the control group (1473 (1193 to 2024) pg/ml vs 1320 (935 to 1555) pg/ml; p=0.012). The difference was significant also for the 1000 ng/ml LPS concentration (3280 (2709 to 4418) pg/ml vs 2910 (2313 to 3358) pg/ml; p=0.011). If the TNF-α level was not standardised by the monocyte count, the difference between the patients and controls was not statistically significant (515 (376 to 701) pg/ml vs 415 (304 to 610) pg/ml for the 10 ng/ml LPS concentration, and 1143 (938 to 1506) pg/ml vs 1030 (848 to 1348) pg/ml for the 1000 ng/ml LPS concentration). The basal TNF-α levels were low in both of the subject groups. The monocyte counts (≥10<sup>5</sup>/µl) of the patients and controls were comparable (0.34 (0.29 to 0.46) vs 0.35 (0.28 to 0.44)). The TNF-α levels of the SpA group and non-SpA group were similar (data not shown).

When the patients and controls were compared, the proportions of CD14<sup>dim</sup>CD16<sup>-</sup> monocytes and CD14<sup>+</sup>CD16<sup>-</sup> monocytes were comparable. The median CD14 expression of patients’ CD14<sup>dim</sup>CD16<sup>-</sup> monocytes was similar to that of the CD14<sup>dim</sup>CD16<sup>-</sup> control monocytes (Table 3).

DISCUSSION

The results show that monocytes of people with a history of AAU, as determined by a whole blood assay, release TNF-α in response to LPS more than do monocytes of healthy subjects. The difference was significant in the presence of a low concentration of LPS (10 ng/ml) (that is, under conditions in which monocyte activation is mediated specifically via high affinity CD14 receptors for complexes of LPS and serum LPS binding protein). The difference was significant also with a high, non-physiological LPS concentration (1000 ng/ml), in which cell activation occurs non-specifically via low affinity LPS receptors on monocytes. These findings suggest that the patients’ monocyte hyperresponsiveness is not confined to the high affinity CD14 receptor pathway but may also involve other cell surface receptors and their intracellular signalling pathways. The results agree with our previous findings indicating that monocytes of the patients with a history of *Yersinia* arthritis show enhanced responses to high concentrations (0.1–10 µg/ml) of LPS. Because monocyte purification procedures cause cell loss and changes in monocyte function, which may be misleading, in the present study we employed a whole blood setting tailored to evaluate responsiveness of monocytes in vivo. In experimental endotoxin-induced uveitis (EIU), and probably in patients with AAU, mononuclear phagocytes are recruited into the anterior uvea. Upon emigration into the eye, monocytes become activated. If hyperreactive in terms of TNF-α production, they may be capable of breaking down innate immune privilege in the eye. Indeed, in experimental EIU, exogenous IL-6 abolished immune privilege in the eye.

There are several mechanisms for enhancing monocyte TNF-α production in response to low levels of LPS. Firstly, LPS and humoral mediators of inflammation can prime monocytes. In our study, however, the TNF-α levels in the culture media of SpA monocytes, which may be susceptible to priming by LPS from the gut, were similar to those of non-SpA monocytes. Secondly, CD14<sup>dim</sup>CD16<sup>-</sup> monocytes associate with increased TNF-α production; yet their proportion was not increased in the present study. Thirdly, genetic factors may affect innate immune responsiveness. The TNF-α gene shows promoter region polymorphism, and the TNF-2 allele has been associated with high, inducible levels of...
TNF-α, but not in all studies. In our study, the differences in the CD14 expression level between the patients and controls were not significant; this finding suggests that CD14 density may not explain the difference in LPS responsiveness. Finally, the HLA-B27 gene itself may have a modulatory role in the activation of the innate immune system. Indeed, using Hela cells transfected with HLA-B27 gene, Ikawa et al. provided evidence suggesting that HLA-B27 may be associated with the activation of otherwise silent intracellular signal transduction pathways and, consequently, contribute to the activation of innate immune genes. These findings, obtained using transfected cells in continuous culture in vitro, are, in fact, in agreement with our results of a whole blood assay, which mimics in vivo conditions in patients.

CRP serves as a marker of systemic inflammation; 95% of serum samples from healthy subjects have CRP levels of <2 mg/ml, whereas patients with coronary heart diseases have two times higher CRP levels, denoting ongoing systemic inflammatory reaction. In our study, the CRP levels were significantly higher in the patients than in the controls. This finding suggests that the patients who had no signs of active uveitis at the time of the study had ongoing low level systemic inflammation. The reason for such a chronic inflammatory reaction is not known, but it may involve stimulation of innate responses by microbial components, such as LPS, leaking from the gut into the circulation. Indeed, increased intestinal permeability and enhanced systemic leakage of LPS from the gut occur in patients with chronic inflammatory bowel disease, known to be associated with SpA.

In our study, however, the CRP levels of the SpA patients were lower, although not significantly lower, than those of the non-SpA patients. Interestingly, LPS occurs in healthy subjects at concentrations of up to 20 pg/ml of peripheral blood and up to 1 ng/ml of portal venous blood. It is possible, but not proved, that monocytes of our patients developed stronger responses to physiological concentrations of LPS than do monocytes from the control subjects. Such a hyperreactivity may promote chronic phagocyte activation. This possibility may not be excluded by the finding that the patients' monocytes had normal CD11b expression level. Indeed, in sepsis patients with organ failure, the high monocyte CD11b levels detected on admission to the hospital decreased to normal within the first week of hospitalisation, while the CRP level remained persistently high. Finally, the difference in the CRP levels in our study was not a result of the differences in chronic inflammation caused by chronic T cell activation because the serum sIL-2R levels of the patients and controls were comparable. Taken together, our results give credence to the view that the patients studied had smouldering systemic inflammation promoted by innate mechanisms.

In conclusion, in comparison with healthy subjects, the patients with a history of AAV in our study had elevated levels of circulating CRP, and their monocytes generated higher levels of TNF-α ex vivo in response to LPS; these findings suggest that the patients’ innate immune responsiveness was high. Although the reason for the difference is not known, an increased inflammatory reactivity may have rendered the subjects susceptible to ocular inflammation by overcoming the mechanisms that maintain innate immune privilege in the eye.

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REFERENCES

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