Changes in Toll-like Receptor (TLR)-2 and TLR4 Expression and Function but Not Polymorphisms Are Associated with Acute Anterior Uveitis

John H. Chang,1,2 Taline Hampartzoumian,1 Beth Everett,1 Andrew Lloyd,1 Peter J. McCluskey,1,2 and Denis Wakefield1,2

PURPOSE. To investigate the expression and polymorphisms of Toll-like receptor (TLR)-2 and -4 in the peripheral neutrophils and monocytes of patients with acute anterior uveitis (AAU).

METHODS. Nine patients with active AAU and nine age- and sex-matched healthy control subjects were studied. TLR2 and -4 protein expression on CD16+ neutrophils and CD14+ monocytes were studied by flow cytometry. TLR function was investigated by whole-blood stimulation with lipopolysaccharide and peptidoglycan for TLR4 and -2 activation, respectively. Proinflammatory cytokine production in response to TLR stimulation was determined by multiplex cytokine bead arrays of the culture supernatant. TLR2 and -4 genotypes were determined by RFLP-PCR.

RESULTS. A significant reduction in the levels of TLR2 expression was observed on the neutrophils and monocytes of patients with active AAU compared with that of healthy control subjects (P < 0.05). IL-6 and IFN-γ production stimulated by TLR4 activation was significantly reduced in patients with AAU, compared with that in healthy control subjects (P < 0.05). In contrast, significantly increased production of IL-1β in response to TLR2 stimulation was observed in patients with AAU (P < 0.05). There was no correlation between the TLR2 or -4 genotypes and the observed differential functional responses to TLR stimulation.

CONCLUSIONS. There is a selective perturbation in the expression and function of TLR2 and -4, which could be consistent with a state of endotoxin tolerance, in patients with active AAU. The results support a role for microbial triggers and TLRs in the pathogenesis of AAU. (Invest Ophthalmol Vis Sci. 2007; 48:1711–1717) DOI:10.1167/iovs.06-0807

Acute anterior uveitis (AAU) is the most common form of potentially sight-threatening intraocular inflammatory disease.1–2 Extensive clinical and experimental evidence supports the role of microbial triggers, in particular certain Gram-negative bacteria (GBN) or their lipopolysaccharide (LPS), in the pathogenesis of noninfectious, immune-mediated AAU.2–3 Toll-like receptors (TLRs) are a family of pattern-recognition receptors of innate immunity that recognize unique molecular signatures of microbes, called pathogen-associated molecular patterns (PAMPs).3–5 TLRs are the first line of host defense and TLR activation by their respective PAMPs results in proinflammatory cytokine cascades and induction of both innate and adaptive immune responses. TLR4 recognizes LPS of GBN, whereas TLR2 responds to various lipoproteins, including components of Gram-positive bacteria, such as peptidoglycan.3–5 Both GNB and Gram-positive bacteria have been implicated in the pathogenesis of AAU.2,6–7 We have demonstrated the expression of TLR4 by resident antigen-presenting cells (APCs) in the normal human uvea and proposed a pathogenic mechanism whereby LPS of GNB could initiate uveitis by activation of intraocular TLR4 and the production of proinflammatory cytokines and chemokines for the recruitment of leukocytes to the eye.8 The expression and function of TLRs in clinical AAU has not been reported.

The purpose of the present study was to investigate the expression and function of TLR2 and -4 by the peripheral blood innate immune cells in active AAU.

METHODS

Patients and Clinical Samples

Patients with active AAU presenting to the Departments of Ophthalmology, St. Vincent’s Hospital and Sydney Eye Hospital were prospectively recruited. The study inclusion criterion was AAU with active inflammation presenting within 7 days of the onset of symptoms. Patients were excluded if there was concurrent chronic inflammatory disease that was unrelated to the uveitis or any recent infection in the preceding month. The study protocol was approved by the Institutional Review Board and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Medical history was obtained from all participants, including details of previous episodes of AAU, any associated systemic diseases, and the use of anti-inflammatory medications. All patients underwent slit-lamp biomicroscope ocular examinations, including assessment of anterior chamber (AC) flare and cells and dilated examination of the posterior segment to exclude intermediate uveitis or panuveitis. Age and sex-matched healthy control subjects without any history of ocular or systemic inflammatory disease were recruited. Blood samples were collected into sterile, anticoagulant (EDTA)-coated tubes and immediately transported to the laboratory for flow cytometry on fresh samples.

Flow Cytometry for TLR Expression on Peripheral Blood Neutrophils and Monocytes

Three-color flow cytometry was performed on freshly isolated whole-blood samples, to investigate the expression levels of TLR2 and -4 on the peripheral blood neutrophils and monocytes of patients with AAU and healthy control subjects. Briefly, 50 μL of freshly isolated blood samples were incubated with the following primary antibodies for 30

From the 1Inflammatory Diseases Research Unit, School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia; and the 2Department of Ophthalmology, St. Vincent’s Hospital, Sydney, NSW, Australia.

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Corresponding author: John H. Chang, School of Medical Sciences, University of New South Wales, Sydney 2052, Australia; jh.chang@unsw.edu.au.

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minutes on ice: FITC-conjugated anti-CD16 monoclonal antibody (mAb; 1 µg per 50 µL of blood, clone NKP15; BD Biosciences, Franklin Lakes, NJ), PE-conjugated anti-TLR2 (1 µg, clone TL2.1, ebioscience, San Diego, CA) or TLR4 mAb (1 µg, clone HTA125; ebioscience), and PerCP-conjugated anti-CD14 mAb (0.02 µg, clone MOP9; BD Biosciences). Isotype-matched irrelevant antibody controls were used to detect nonspecific staining. Flow cytometry lysing solution (FACS; BD Biosciences) was then added to each tube to lyse the red blood cells. The immunostained cells were washed three times with wash solution (FACS; BD Biosciences) and the cells fixed with 1% paraformaldehyde.

Neutrophils and monocytes were identified and gated according to their characteristic forward- and side-scatter flow cytometry profiles and their expression of CD16 (a neutrophil marker) or CD14 (a monocyte marker). A five-parameter flow cytometer (FACScan; BD Biosciences) was used for data acquisition. Ten thousand events were acquired for the neutrophil cellular gates and at least 2000 events for the monocyte gate. Analysis of the acquired flow cytometry data was performed with a cell counter (Beckman Coulter, Fullerton, CA). This facilitated the measurement of the percentage of CD16+ and CD14+ cells in each sample.

Bio-Rad Laboratories, Hercules, CA). Therefore, an MFI ratio of 1 represents no significant expression of the TLR under investigation, and an MFI ratio >1 represents higher levels of expression.

In Vitro Whole-Blood TLR Stimulation

Selective TLR2 and -4 stimulation was performed in vitro on whole-blood samples from patients with AAU and healthy control subjects. LPS of Salmonella typhimurium (10 ng/mL; Sigma-Aldrich, Castle Hill, NSW, Australia) and sonicated peptidoglycan of Salmonella typhimurium (100 µg/mL; Fluka, Buchs, Switzerland) were used to stimulate specifically TLR4 and -2, respectively. As LPS is a potent agonist of TLR4, stringent endotoxin-minimization techniques were used in all aspects of the experiments involving TLR stimulation, thus ensuring that any observed functional effects were not due to potential LPS contaminant. All reagents and materials used were certified LPS-free or depyrogated and were also regularly tested using a kit (Limulus Amebocyte Lysate [LAL] assay; Associates of Cape Cod, Inc., East Falmouth, MA) to ensure that there was no contaminating LPS (<0.05 endotoxin U/mL).

All TLR stimulation experiments were performed in duplicate. Samples of 900 µL of whole blood were incubated with 100 µL of cell culture media only (as a negative control) or TLR agonists (LPS or peptidoglycan) for 1 hour at 37°C and 5% CO2. The selected concentrations of TLR agonists and incubation times for effective TLR stimulation were determined by a series of dose- and time–response studies. The culture supernatants were collected, and the profile of cytokine production was studied by multiplex cytokine bead immunoassay. Custom-made multiplex cytokine bead arrays were used to study the secretion levels of five different LPS- and peptidoglycan-inducible cytokines (TNF-α, IFN-γ, IL-1β, IL-6, and IL-8/CXCL8) in the TLR-stimulated culture supernatants, according to the manufacturer’s instructions (Bio-Plex System; Bio-Rad Laboratories, Hercules, CA).

Quantitation of the total white cell and differential cell counts (neutrophils and monocytes) was performed with a cell counter (Beckman Coulter Counter; Beckman Coulter, Fullerton, CA). This facilitated the normalization of cytokine production to the numbers of the immune cells present within the TLR-stimulated blood sample.

Restriction Fragment Length Polymorphism-PCR for TLR2 and -4 Genotyping

Genomic DNA was extracted from the blood samples (UltraClean DNA BloodSpin; Mo Bio Laboratories, Carlsbad, CA) of patients with AAU and healthy control subjects, in whom in vitro TLR stimulation data were also obtained. TLR2 and -4 genotypes were determined by a restriction fragment length polymorphism (RFLP)-PCR method.9 Specifically designed PCR primers were used to amplify a region of the TLR2 and -4 gene spanning the respective single nucleotide polymorphism (SNP). Primers for TLR2 Arg753Gln genotyping were: forward, 5’ TTCTCAATTTGTCTTCTGATAAC 3’ and reverse, 5’ GGCACCTC-CAGGATGCTTCT 3’.9 Primers for TLR4 Asp299Gly genotyping were: forward, 5’ ATACTTAGACTACTCCTCCATG 3’ and reverse, 5’ TTTGAGAGATTGAGTTC 3’. The L2 Arg753Gln SNP was detected by cleavage with the restriction enzyme, Psfl, and the G allele of TLR4 Asp299Gly SNP was detected by cleavage with the restriction enzyme, Ncol (Fermentas Life Sciences, Burlington, Ontario, Canada). A known G/ Gly subject (for TLR4 Asp299Gly SNP) was used as a positive control for complete digestion. For each primer pair, PCR products were sequenced to confirm that the correct target sequence was being amplified. All mutations were confirmed by direct sequencing. The cleavage products were resolved and identified by a 12.5% polyacrylamide gel electrophoresis, in parallel with 100-bp DNA markers.

Statistical Analysis

Statistical analysis was performed with commercial software (Prism; GraphPad Software, San Diego, CA). Two-tailed Mann-Whitney test was used for comparison of nonparametric data between two groups. P < 0.05 was considered to be statistically significant in all analysis.

Results

Clinical Details of Patients with AAU

Nine patients (six males) with active idiopathic AAU satisfying the study inclusion and exclusion criteria were studied (mean age, 44 years). All but one of the patients had recurrent AAU. All patients had at least 1+ AC cells (range, 1+ to 4+ cells) at the time of the sample collection. Five of the patients with AAU had a uveitis-associated systemic disease (seronegative spondyloarthropathy). Only one of the patients was on any systemic anti-inflammatory treatment at the time of the study. Data analysis with or without inclusion of this patient did not affect the observed results. Nine age- and sex-matched (six males) healthy control subjects were also studied (mean age, 44 years). Seven of the nine patients with AAU were HLA-B27 positive, whereas all the healthy control subjects were HLA-B27 negative.

Reduced Expression of TLR2, but Not TLR4, on the Peripheral Blood Neutrophils and Monocytes of Active AAU

A high level of TLR2 and -4 expression was observed on CD16+ neutrophils of healthy subjects (Fig. 1).4,5 A significant reduction in the levels of TLR2 expression, as measured by the MFI, was observed on the peripheral blood neutrophils of patients with active AAU (median MFI, 2.7), compared with that of their age- and sex-matched healthy control subjects (median MFI, 3.3; P < 0.05, Fig. 1). In contrast, no significant difference was observed in the levels of TLR4 expression on the neutrophils of patients with AAU (median MFI, 2.3) compared with the healthy control subjects (median MFI, 2.5; P > 0.05; Fig. 1). In one of the patients with active AAU, a dramatic increase in the levels of both TLR2 (MFI, 25) and -4 (MFI, 30) expression were observed on the blood neutrophils (Fig. 2). This patient had a moderate to severe episode of AAU that was associated with ankylosing spondylitis.

Similar to that observed on the neutrophils, there was a significant reduction in the levels of TLR2 expression on the peripheral blood CD14+ monocytes in patients with active AAU (median MFI, 3) compared with that in age- and sex-matched healthy
control subjects (median MFI, 4; \( P < 0.05 \), Fig. 3). There was no significant difference in TLR4 expression levels on the CD14\(^+\) monocytes of patients with AAU, when compared with that in the healthy control subjects (\( P > 0.05 \); Fig. 3).

Selective Functional Hyporesponsiveness to TLR4 Stimulation in Patients with AAU

There were no significant differences observed in the neutrophil, monocyte, or total leukocyte counts between the patients with AAU and healthy control subjects (\( P > 0.05 \)). Nevertheless, cytokine production in response to TLR stimulation was standardized to the number of neutrophils and to the total white cell count in each sample.

IL-6 production stimulated by TLR4 activation (standardized to either the neutrophil or total leukocyte count) was significantly reduced (\( P < 0.05 \)) in the whole-blood samples from patients with AAU, compared with that in samples from healthy control subjects (Fig. 4). In contrast, there was no
FIGURE 3. Flow cytometry analysis of the level of expression of TLR2 and -4 on peripheral blood CD14+ monocytes in patients with AAU and healthy control subjects. Compared with that in healthy subjects (A), there was a shift of the fluorescence histogram plot to the left, corresponding to a reduction in the level of TLR2 expression on monocytes, in a patient with active AAU (B). (C) A significant reduction in the levels of TLR2 expression, as measured by the MFI, was observed on the peripheral blood monocytes of patients with active AAU (median MFI, 3), compared with that of their age- and sex-matched healthy control subjects (median MFI, 4; \( P < 0.05 \)). (D) In contrast, there was no significant difference observed in the levels of TLR4 expression on the monocytes of patients with AAU compared with that of healthy control subjects (\( P > 0.05 \)). Median values have been indicated on the graphs.

FIGURE 4. Selective functional state of LPS hyporesponsiveness in patients with AAU. Cytokine production in response to TLR4 and TLR2 whole-blood stimulation by LPS and PGN, respectively, were studied by multiplex cytokine bead arrays. (A) IL-6 production stimulated by TLR4 activation (standardized to the neutrophil count) was significantly reduced in the whole-blood samples from patients with AAU, compared to that in samples from healthy control subjects (\( P < 0.05 \)). (B) In contrast, there was no difference observed in the IL-6 production in response to TLR2 stimulation between the two groups (\( P > 0.05 \)). (C) Significant reduction in IFN-\( \gamma \) production in response to TLR4 stimulation (\( P < 0.05 \)), but not in response to TLR2 stimulation (D), was observed in patients with AAU compared with that in healthy control subjects. Horizontal lines: median values.
difference observed between the two groups in IL-6 production in response to TLR2 stimulation (P > 0.05). Therefore, rather than a global suppression of IL-6 production in response to TLR stimulation, there was a selective reduction in IL-6 production in response to TLR4 stimulation, but not in response to TLR2 stimulation, in patients with AAU. Similar results occurred with IFN-γ. There was significant reduction in IFN-γ production in response to TLR4 stimulation (P < 0.05), but not in response to TLR2 stimulation, in patients with AAU compared with that in healthy control subjects (Fig. 4).

Selective Functional Hyperresponsiveness to TLR2 Stimulation in Patients with AAU

Significantly increased production of IL-1β (standardized to either the number of neutrophils or of total leukocytes) occurred in response to TLR2 stimulation in whole-blood samples from patients with AAU compared with that in samples from healthy control subjects (P < 0.05, Fig. 5). TNF-α production induced by TLR2 activation of whole blood, relative to that induced by TLR4 stimulation, was also significantly increased in AAU when compared with that in healthy control subjects (P < 0.05). There were no differences observed in the IL-8/CXCL8 production in response to either TLR2 or -4 stimulation in patients with AAU, compared with that in healthy control subjects (P > 0.05, data not shown).

TLR2 and -4 Genotypes of Patients with AAU

TLR2 Arg753Gln genotyping by RFLP-PCR determined that all nine patients with AAU were homozygous (Arg/Arg at amino acid 753) for the wild-type TLR2 alleles. Except for one control subject, who was heterozygous (Arg/Gln) for the TLR2 Arg753Gln SNP, all the age and sex-matched healthy control subjects were also wild-type for the TLR2 gene. All the patients with AAU and the healthy control subjects were found to be homozygous for the wild-type TLR4 alleles (Asp/Asp) on TLR4 Asp299Gly genotyping. There was no correlation between the TLR2 or -4 genotypes, and the demonstrated differential functional responses to selective TLR stimulation.

DISCUSSION

This study reveals selective perturbations in the expression of TLRs in patients with AAU. In particular, the reduced expression and function of TLR2 or -4 during active AAU is further evidence supporting a pathogenic role for GNB triggers and TLR4 in the development of AAU.2,5,8

The present study demonstrates a change in the level of TLR expression on the innate immune cells in the systemic circulation of AAU. Specifically, a significantly reduced level of cell surface TLR2 protein expression was found on the neutrophils and monocytes in AAU, compared with that of the healthy control. This observation supports the proposed role of TLR activation by microbial products or their PAMPs in the pathogenesis of uveitis.3,8 Given that TLR2 and -4 stimulation may induce the internalization of the respective TLR and result in the downregulation of cell surface TLR2 or -4 expression.10–12 In vitro LPS stimulation has been shown to downregulate cell surface TLR2 and -4 expression on human neutrophils and monocytes.13–15 Similar findings have also been demonstrated in patients with AAU (manuscript in preparation). In support of these data, in vivo LPS stimulation by intravenous administration of LPS to healthy volunteers was found to downregulate cell surface TLR4 and -2 on peripheral blood neutrophils.14 Taken together, these studies show that microbial products that activate TLR2 or -4 can result in changes in the expression levels of either or both TLRs. The observed reduction in the expression level of TLR2 on the neutrophils and monocytes in AAU in the present study could be consistent with the consequences of TLR activation of these innate immune cells by Gram-negative (e.g., LPS) and/or Gram-positive (e.g., peptidoglycan) bacterial products. This would be in keeping with the clinical and experimental reports implicating the potential role of both Gram-negative and -positive bacteria in the pathogenesis of uveitis.2,16 Furthermore, a recent study has reported that LPS of Chlamydia trachomatis, which is strongly implicated in triggering HLA-B27-associated AAU, signals via TLR2 rather than TLR4.17 However, in the absence of data demonstrating reduction in the expression and function of TLRs during active uveitis compared with that in quiescent disease (in the same individual), it is unclear whether the observed changes reflect transient or chronic TLR downregulation. Repeated sampling of the same patients would be ideal; however, this may not be ethically justifiable.

It is interesting that we did not find changes in TLR4 expression on the innate immune cells of AAU given the numerous studies that have implicated the involvement of GNB in the pathogenesis of AAU.2,10 However, the present findings are not inconsistent with involvement of LPS or TLR4 activation in the development of AAU, as LPS stimulation can result in cross-desensitization of TLRs other than TLR4.18,19 For example, TLR2 expression on human neutrophils has been shown to be downregulated by LPS.15

![FIGURE 5. Selective functional state of TLR2 hyperresponsiveness in patients with AAU. Cytokine production in response to TLR4 and -2 whole-blood stimulation by LPS and PGN, respectively, were studied by multiplex cytokine bead arrays. (A) A trend toward reduced production of IL-1β in response to LPS stimulation was observed in patients with AAU compared with that in healthy control subjects (P = 0.06). (B) Significantly increased production of IL-1β (standardized to the neutrophil count) in response to TLR2 stimulation was observed in whole-blood samples from patients with AAU compared to that in healthy control subjects (P < 0.05). Horizontal lines: median values.](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932942/)
It is of interest that in one of our patients with AAU, marked upregulation of both TLR2 and -4 expression was observed on the neutrophils. Various studies have reported that in certain circumstances, PAMPs such as LPS and cytokines such as IL-10 may upregulate TLR2 or -4 expression on neutrophils.\(^{15,20}\) Furthermore, the in vivo surface expression of TLR2 and -4 was increased on neutrophils and monocytes in a study of patients with sepsis.\(^{21}\) There may be a dynamic change in the expression pattern of TLRs during the evolution of AAU, and it may vary between individuals. Thus, the observed level of TLR expression may depend on the precise timing of the study sample collection during the course of the disease in the individual patient.

Pre-exposure to LPS reduces sensitivity to a subsequent challenge with LPS; this transient functional state of LPS hypersensitivity is known as “endotoxin tolerance.”\(^{22}\) In healthy humans, a single intravenous injection of LPS has been shown to induce endotoxin tolerance in vivo, with significantly reduced production of IL-1β, TNF-α, and IL-6 on a second LPS stimulation, either in vitro or in vivo.\(^{23,24}\) Endotoxin tolerance is not a global suppression of immune function and the ability to respond to other non-LPS immunostimulants such as S. aureus or TNF-α remains unaffected.\(^{25-28}\)

In this study, we report perturbations in TLR function that could be consistent with endotoxin tolerance in patients with AAU, during active episodes of intraocular inflammation. TLR4 stimulation of whole blood resulted in a significantly reduced production of pro-inflammatory (and normally highly LPS-inducible) cytokines such as IL-6 and IFN-γ, in patients with AAU compared with that in healthy control subjects. In contrast, there was no impairment in the production of these same cytokines in response to TLR2 stimulation.

The highly specific nature of the alterations in immune function, with both evidence of reduced and enhanced TLR function, could be consistent with the observation of a functional state of endotoxin tolerance in patients with AAU. These findings are of relevance given the evidence supporting the role for microbial triggers, and in particular GNB, in the development of AAU. As all the study patients had active AAU at the time of sampling, the demonstrated LPS hypersensitivity could be consistent with that expected in persons who have been recently exposed to LPS with the associated functional consequence of TLR4 activation and endotoxin tolerance being observed. LPS-mediated activation of TLR4 may be one of the earliest initiating factors in the development of AAU.

However, endotoxin tolerance is a transient state, and the present study has not demonstrated a dynamic change in TLR function in AAU. In support of our hypothesis, a previous study has reported that patients with a history of AAU, but not with active uveitis, have higher functional responsiveness to LPS during inactive disease, as measured by cytokine production, as compared with that in healthy control subjects.\(^{25,26}\) Moreover, in vitro studies have reported that LPS stimulation of peripheral blood mononuclear cells (PBMCs) from patients with AAU is associated with increased production of TNF-α and IL-10.\(^{27,28}\) Others have reported that patients with AAU have higher functional responsiveness to LPS than do healthy subjects, in terms of TNF-α production, as determined by in vitro whole-blood stimulation.\(^{29}\) Such a heightened ability to respond to LPS during inactive disease may in fact predispose these individuals to the development of ocular inflammation by LPS-mediated TLR4 activation, with the state of endotoxin tolerance ensuing during active AAU, as hypothesized in the present study.

TLR2 and -4 genotypes of the patients with AAU were determined to investigate whether the different functional responses to selective TLR activation in patients with AAU (compared with that in healthy control subjects), were due to any of the reported functional polymorphisms in these TLR genes.\(^{30-32}\) These SNPs have been associated with various human inflammatory diseases such as rheumatoid arthritis and the susceptibility to bacterial infections.\(^{33-35}\) The Asp299Gly mutation of TLR4 has been shown to be associated with an endotoxin hyporesponsive phenotype in humans.\(^{30,34}\) However, all the patients with AAU in the present study were wild-type for the TLR4 gene. This finding indicates that the observed functional hyporesponsiveness to TLR4 stimulation in patients with AAU was not due to a known functional mutation in the TLR4 gene, but instead, it is supportive of a state of endotoxin tolerance resulting from the activation of the TLR4 signaling pathway by recent exposure to LPS or other PAMPs. The Arg753Gln SNP of the TLR2 gene has also been reported to be of functional significance.\(^{52}\) However, as for the TLR4 gene, none of the patients with AAU in the present study had this mutation of the TLR2 gene. Collectively, these results do not support a significant role for reported mutations in the TLR genes in the observed differential functional responses to TLR activation in patients with AAU, compared with that in healthy control subjects.

In summary, the findings of the present study implicate TLR activation in the pathogenesis of AAU. Demonstration of reduced TLR2 expression on systemic immune cells in AAU together with a functional state of endotoxin tolerance, provide further evidence to support the pathogenic role of microbial triggers or their PAMPs, in particular LPS of GNB, in the development of human AAU. Future studies involving greater numbers of patients with active and inactive uveitis should be performed to confirm and expand on the present findings.

References


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