Editorial

Intravitreal Inflammation: From Benchside to Bedside

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Received 16 December 2012; Accepted 16 December 2012

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Inflammation plays a major role in the formation and in the progression of sight-threatening chorioretinal diseases such as diabetic retinopathy (DR), proliferative vitreoretinopathy (PVR), uveitis, and age-related macular degeneration (AMD). A greater understanding of the underlying pathological mechanisms is necessary for the development of better therapeutic agents and relies on the analysis of clinical specimens as well as on animal models. Contrary to the retina, the vitreous humour (VH) is a transparent gel that fills the posterior chamber of the eye and can be sampled without causing visual loss. In recent years, advances in the analysis of VH samples have highlighted new biological mechanisms of long-known diseases and have improved the accuracy of diagnostic procedures.

In this special issue, we report how the VH findings at the benchside can be translated to the bedside, and how this may help clinical practice. The papers have been contributed by a number of experts in the field and include both review articles that provide an overview of the work conducted to date, as well as original articles reporting recent discoveries and innovations. In order to highlight the translational relevance of VH analyses, most of the papers are focused on a specific disease entity. We hope that this series of manuscripts will be beneficial for clinicians in their diagnostic and therapeutic approaches towards intravitreal inflammatory conditions and for researchers in appreciating some of the recent innovations and their clinical implications in this field. Each of the manuscripts in this series is briefly highlighted as follows.

The paper by M. Angi et al. “Proteomic analyses of the vitreous humour” describes how to correctly collect and handle VH specimens and presents a clear workflow for proteomic analyses. This is significant since the VH is not a straightforward tissue to analyze due to its viscous consistency. Proteomic technologies have dramatically evolved over the past years, allowing identification of an increasing number of disease-specific proteins in the VH. Moreover, recent proteomic studies on the VH from animal models of autoimmune uveitis have highlighted new pathways associated to autoimmune triggers and intravitreal inflammation that could become the targets for much needed therapies.

Another example of the usefulness of proteomic analyses of the VH in translational research is presented by O. Simó-Servat et al. in “Usefulness of the vitreous fluid analysis in the translational research of diabetic retinopathy” who applied fluorescence-based difference gel electrophoresis (DIGE), as well as flow cytometry, to identify new candidates involved in the inflammatory process that occurs in DR. The authors provide evidence supporting the role of proinflammatory mediators such as cytokines (i.e., IL-1β, IL-6, IL-8, and TNFα), chemokines (i.e., MCP-1, SDF-1, and IP-10), and adhesion molecules (i.e., VCAM, ICAM-1, and VAP-1) in the pathogenesis of DR. Such persistent low-grade inflammation contributes to the damage of the internal blood-retinal barrier and to the development of proliferative diabetic retinopathy (PDR).

A. M. Abu El-Asrar et al. in “Osteopontin and other regulators of angiogenesis and fibrogenesis in the vitreous from patients with proliferative vitreoretinal disorders” and “High-mobility group box-1 and endothelial cell angiogenic markers in the vitreous from patients with proliferative diabetic retinopathy” investigate the role of osteopontin and other regulators of angiogenesis and fibrogenesis, such as high-mobility group box-1 (HMGB1) and connective tissue growth factor (CTGF) in the pathogenesis of proliferative...
vitreoretinal disorders with a concomitant increase of anti-
biogenic pigment epithelium-derived factor (PEDF) levels in
the VH. Moreover, the authors report that HMGB1, soluble
vascular endothelial-cadherin (sVE-cadherin), and soluble
endoglin (sEng) regulate the angiogenesis of endothelial cells
in PDR.

R. dell’Omo et al. in “Vitreous mediators in retinal hypoxic
disease” describe that serum adiponectin (APN) levels cor-
relate with blood inflammatory marker levels and with DR
as response to endothelium dysfunction, indicating the role
of APN as endogenous modulator of microvascular function
and inflammation.

S. N. Moysidis et al. in “Mechanisms of inflammation
in proliferative vitreoretinopathy: from bench to bedside”
describe the indirect activation of PDGFRα by non-PDGFs
as trigger that leads to development of PVR. In this pathway,
the intracellular reactive oxygen species (ROS) plays a key
role, leading to activation of Src family kinases (SFKs) that
promote phosphorylation and activation of PDGFRα. The
ROS could be one of the therapeutic targets of multimodal
approach.

D. Gollogorsky et al. in “Therapeutic interventions against
inflammatory and angiogenic mediators in proliferative dia-
abetic retinopathy” report the latest focus of targeted therapies
for proliferative diseases through the block of vascular adhe-
sion molecules such as ICAM-1, VCAM-1, inflammatory
factors including the interleukins, tumor necrosis factor
(TNF), insulin-like growth factor (IGF), and angiopoietins
(Ang-2).

Analysis of the VH is a valuable adjunct also for the
management of patients with uveitis and especially in the
diagnosis of neoplastic diseases masquerading as chronic
intraocular inflammation, as reported by E. M. Damato et
al. in “Vitreous analysis in the management of uveitis.” For
example, increased levels of T-cell cytokine, IL-6, in VH
is characteristic of uveitis, whereas increased levels of IL-
10 and in particular IL-10/IL-6 ratio greater than 1 should
prompt cytological analysis for the diagnosis of vitreoretinal
lymphoma. The involvement of VH in neoplastic diseases
and the pros and cons of performing VH biopsies in the clinical
practice are further discussed in the review article by M.
Asencio-Duran et al. entitled “Vitreous diagnosis in neoplastic
diseases.”

J. L. Vallejo-Garcia et al. in “Role of inflammation in
endophthalmitis” discuss the role of inflammation in infective
endophthalmitis, reporting that the damage to the retina in
this rare but severe diseases is mediated by the host immune
reaction through toll-like receptors, cytokines, HMGB1, and
αB-crystallin. A better understanding of the host immune
reaction and the cellular pathways leading to tissue damage
is also essential to improve clinical outcomes. Corticosteroids
are frequently administered with antibiotics but often do
not fully control the host immune reaction with consequent
visual loss. A novel TLR2 ligand, Pam3Cys, has demonstrated
encouraging results when administrated before the onset of
endophthalmitis and also when injected in combination with
intravitreal antibiotics.

J. B. Christoforidis et al. in “Intravitreal devices for the
treatment of vitreous inflammation” describe the importance
of the modulation of pharmacokinetics in the treatment of
chronic intraocular inflammation. Long-term treatments are
currently provided by drug-delivery devices, which include
nonbiodegradable and biodegradable devices. The therapeu-
tic agents that can be delivered are ganciclovir, fluocinolone
acetonide, triamcinolone acetonide, and dexamethasone. The
next small-scale biodegradable devices already described are
liposomes, microspheres, and nanoparticles from 0.01 to
1,000 μm in diameter.

J. B. Christoforidis et al. in “Systemic treatment of vitreous
inflammation” also report that many classes of systemic drugs
may be used alone or in combination to control intraocular
inflammation while closely monitoring side effects. Many of
these inflammatory disorders require long-term treatment,
and hence steroid-sparing agents, including antimetabolites,
alkylating agents, and biological agents, are being used.

The emerging topic of sterile endophthalmitis is pre-
presented by J. Marticorena et al. in “Sterile endophthalmitis after
intravitreal injections.” It is an infrequent complication of
intravitreal injections and seems to develop in the context of
the off-label use of drugs that have not been conceived for
intravitreal administration. Sterile inflammation secondary
to IVTA and IVB share many characteristics, such as the acute
and painless vision loss present in the vast majority of the
cases.

Inflammation also plays a major role also in the aging
retina, where free radicals and oxidized lipoproteins are
considered to be major causes of tissue stress. F. Parmeggiani
et al. in “Mechanism of inflammation in age-related macular
degeneration” report that the consequence is a parainflam-
amation, a chronic status which contributes to initiation
and progression of neurodegenerative diseases such as age-
related macular degeneration (AMD). The parainflammatory
deregulation that is already present in the early stage of
AMD may notionally support the preventive employment of
agents directed against the immune-inflammatory response
in combination with high-dose nutritional supplements.

We sincerely hope that the present special issue may
provide useful information to understand the mechanisms,
the clinical effects, and the novel treatments of inflammation
in which the vitreous is involved.

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