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Influence of viral infection on expression of cell surface antigens in human retinal pigment epithelial cells

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Abstract ● Background: Subacute viral infection is known to change the phenotype of infected cells, thereby causing immune-mediated tissue damage. The aim of this study was to investigate the expression of different cell surface molecules on human retinal pigment epithelial cells (RPEC) following viral infection, with special emphasis on those having immune-regulatory functions. ● Methods: Cultured RPEC were infected with cytomegalovirus (CMV), coxsackievirus B3 (CVB) or herpes simplex virus type I (HSV). Double-staining fluorescence technique was used for visualization of virus infection and cell surface markers in the same cells by laser microscopy. ● Results: CMV downregulated MHC class I antigens on RPEC, whereas CVB and HSV did not alter MHC class I antigen expression. No induction of class II antigens was observed in RPEC infected with CVB, HSV or CMV. The intercellular adhesion molecule ICAM-1 (CD54) was strongly expressed in uninfected RPEC, and a slight increase was observed after virus infection. Vascular cell adhesion molecule 1 (VCAM-1) was expressed in low amounts in both uninfected and infected RPEC. No expression of intercellular adhesion molecule 2 (ICAM-2), E-selectin ELAM-1 or lymphocyte-function-associated antigen 1 (LFA-1) was observed on RPEC before or after virus infection. ● Conclusion: Downmodulation of immune-regulating cell surface antigens has been suggested to provide a means of long-term survival of viruses in the infected cell, favoring establishment of persistent infection. Our observation in cultured human RPEC indicates that this mechanism might indeed contribute to the development of disease affecting retinal tissue.

Introduction

The etiologic factors leading to retinitis are often unknown. Whereas autoantigens [review 28] and immune mechanisms have been clearly shown to play a destructive role, suggesting a self-perpetuating mechanism [7, 9, 11, 22], the initial damaging event leading to exposure to autoantigens in vivo is rather unclear.

Host T-cells require major histocompatibility complex (MHC) molecules in order to respond to antigens. MHC class I molecules are involved in the presentation of cytoplasmic antigens to cytotoxic T-cells (CTL) and are important for the destruction of antigenically altered (e.g. virus-infected) cells. MHC class II antigens are responsible for presenting circulating antigens to helper T-cells [review 1]. Therefore, alteration of expression of human MHC molecules could be important in the development of autoimmune disease [20].

Adherence molecules are expressed especially on inflamed retinal tissue [14, 15] and seem to be involved in the autoimmune process [33]. Cytokine-mediated activation of retinal pigment epithelial cells (RPEC) may be important for autoimmune disease facilitated by MHC class II expression [21]. Particularly interferon-gamma

(IFN-γ) produced by T lymphocytes has been shown to induce expression of MHC class II (Ia) antigens on RPEC and vascular endothelial cells [8, 16] and seems to play a crucial role in the inflammatory process [6], most likely by enhancing presentation of retinal antigens [21]. Possible antigenic cross-reactivity of microbial antigens and retinal antigens has also been suggested [5, 29, 30].

The intercellular molecules 1 and 2 (ICAM-1 = CD54 and ICAM-2 = CD102) and vascular cell adhesion molecule 1 (VCAM-1 = CD106) are known as cellular adhesion molecules. ICAM-1 was initially identified as a widely distributed cytokine-counterreceptor for the lymphocyte-function-associated antigen 1 (LFA-1). The highest levels of ICAM-1 antigen are found on activated endothelium, with lower levels that increase in inflammation on multiple other cell types. High levels of ICAM-2 antigens are found on endothelium and lower levels on hemopoietic cells, including platelets, and on thymic stroma cells. Unlike ICAM-1, ICAM-2 is constitutively expressed and not responsive to lipopolysaccharides or cytokines. VCAM-1 was shown to be expressed by dendritic cells and crypt epithelium (basal part). The E-selectin ELAM-1 (=CD62E) was first identified as a cytokine-inducible surface antigen on endothelial cells. Expression of ELAM-1 has been clearly documented on acutely activated endothelium, where it participates in the recruitment of leukocytes at sites of acute inflammation. This adhesion molecule has also been identified in chronic inflammatory lesions of the skin and synovium. LFA-1 is the receptor for three members of the Ig supergene family of proteins ICAM-1, ICAM-2 and ICAM-3 (=CD50). LFA-1 has been shown to play a central role in homotypic and heterotypic cellular adhesion in immune and inflammatory responses and is expressed on lymphocytes, monocytes, and, more weakly, on neutrophils. LFA-1 is a heterodimer consisting of two subunits, alpha (CD11a) and beta (CD18). For further details see reference [31]. We did not expect the latter antigen to be expressed on human cultured RPEC but used the antibody as control to exclude contamination of the cultures.

Various viruses have been shown to affect retinal tissue in animals [review 10]. The most interesting virus in this respect is the murine coronavirus mouse hepatitis virus, which has been shown to induce retinitis in infected animals [23, 32].

In humans, virally induced chorioretinitis is known in congenital rubella and cytomegalovirus (CMV) infection. The latter virus is also the most common cause of retinitis in adults, primarily because of the recent high incidence of immunosuppressive situations associated with AIDS, whereas herpes simplex virus type I (HSV) and varicella zoster virus retinitis also occur in immunocompetent individuals [review 35].

In our previous study we showed that rather common human pathogenic viruses like respiratory viruses and enteroviruses or measles virus and adenovirus are also able to infect human RPEC [10].

One of the strategies used by viruses to cause persistent infection so as to evade host immunosurveillance is the interference with the expression or function of cell surface molecules [12, 13]. Moreover, such mechanisms might influence immune effector cells. We therefore studied the possible influence of viral infection of cultured RPEC on the hypothetical mechanisms, especially on MHC antigen and adherence molecule expression.

Materials and methods

Preparation of retinal pigment epithelium

Human RPEC were isolated from freshly enucleated bulbi from normal donors for corneal transplantation as described previously [3, 10]. Briefly, the corneoscleral disk was first removed, followed by the lens and vitreous body. The residual eye cup was sectioned with a longitudinal incision toward the optic nerve. Repeated rinsing with Dulbecco's phosphate-buffered saline (PBS), Ca^{2+}- and Mg^{2+}-free (Biochrom, Berlin, Germany), allowed prompt separation of the remaining vitreous body and neural retina from the retinal pigment epithelium (RPE) layer and detachment of the choroid from the sclera. The RPE adhering to Bruch's membrane on the obtained choroidal sheets were washed with PBS and treated three times with 0.25% trypsin EDTA solution (Biochrom) for 20 min at 37°C. The isolated cells were centrifuged at 300 *g* for 10 min, resuspended in cell culture medium RPMI 1640 (Biochrom), supplemented with 10% fetal calf serum (Biological Industries, Kibbutz Beth Haemek, Israel). Cells were seeded in 25-cm^2 tissue culture flasks (Becton Dickinson, Plymouth, UK) for 24 h at 37°C in a humidified atmosphere with 5% CO_2. The next day, nonadherent cells were removed and fresh culture media added. All adherent cells contained pigment granulae. Confluent cells were trypsinized, washed with PBS and seeded into two tissue culture flasks. After two or three passages, cells were used for virus transfection after seeding on Lab-Tec chamber slides (Nunc, Naperville, Ill.).

RPEC were grown in tissue culture flasks for several passages. After seeding, cells quickly came into contact with other RPEC and began to proliferate until confluence was achieved after approximately 1 week. In the first two to three passages RPEC still contained their typical pigment granulae. For viral infection, cells were transferred onto Lab-Tec chamber slides and kept under the same culture conditions for approximately 1 week until they were confluent.

Viral infection was achieved with various viruses on various passages (3 and 4) of RPEC.

Viruses

CMV strain AD169 (ATCC No. 538-VR) and coxsackievirus B3 (CVB; ATCC No. 30-VR) were obtained from the American Tissue Culture Collection at Rockville, Md. HSV type 1 strain Wal was described by Schroeder et al. [27].

RPEC were cultured on Lab-Tec chamber slides (Nunc) and infected with the various viruses on passages 3 and 4 as described previously [10]. For infection of RPEC, viruses were adjusted to a high multiplicity of infection (m.o.i. >1), which was determined by standard virological methods. Cells were kept in culture until cytopathic effects following infection with HSV and CVB were visible or for a maximum of 3 weeks after infection with CMV. Productive infection was confirmed by detection of viral antigens

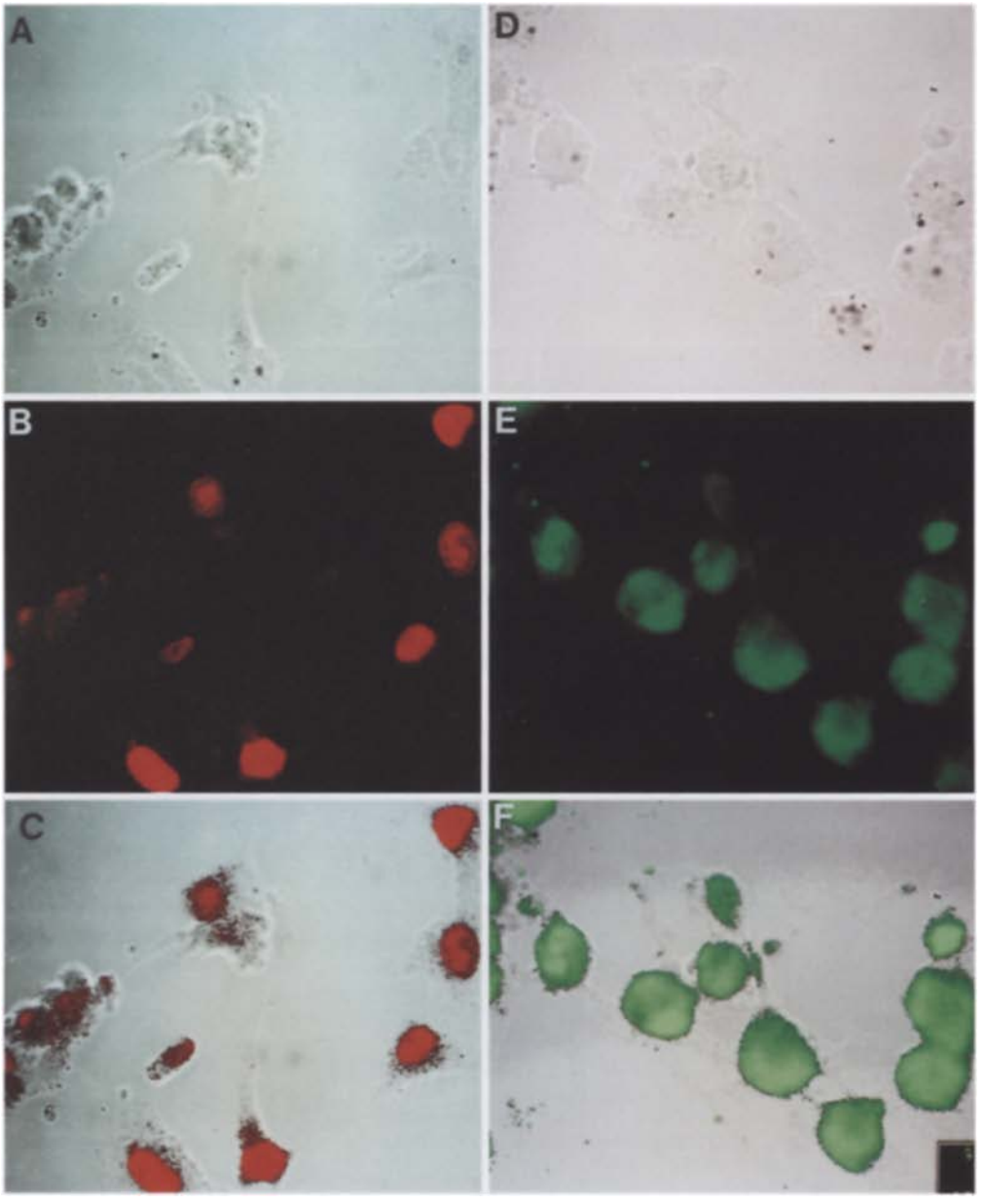

Fig. 1 Human RPEC infected with CMV (**A–C**) and CVB (**D–F**). **A, D** Cells in transmission scan. **B, E** Cells stained with antibodies to confirm virus infection and subsequently with a fluorescent antibody (**B** TRITC-conjugated; **E** FITC-conjugated), shown here in fluorescence scan. **C, F** Colored overlay of transmission and fluorescence scans. (Original magnification 63× oil, 20× zoom)

by immunofluorescence staining. Cells were washed twice with PBS, permeabilized with 70% methanol for 15 min at room temperature, washed again and incubated for 1 h with the corresponding antibodies. For detection of CMV infection a cocktail of monoclonal antibodies (mAb) was used consisting of an mAb directed to immediate early antigen (IEA, clone E-13, Clonatec, Biosoft, Paris, France), early antigen (EA, DuPont, Vienna, Austria) and pp65 (Clonab-CMV, Biotest, Dreieich, Germany). HSV infection was detected with mAb anti-HSV1/2 (CHA 437, Clonatec, Biosoft). Coxsackievirus infection was detected with a high-titer positive patient serum. As second antibodies we used a FITC-conjugated anti-mouse $F(ab)_2$ fraction of goat immunoglobulin (Bioresearch, Kaumberg, Austria) or a TRITC-conjugated rabbit anti-mouse IgG and a FITC-conjugated rabbit anti-human IgG or a TRITC-conjugated rabbit anti-human IgG (all from Dakopatts, Glostrup, Denmark), respectively.

Antibodies

The following antibodies were used:

Anti-MHC-class I (clone W6/32, IgG2a, dilution 1:40), anti-HLA class-II (clone DK22, IgG2a, dilution 1:40), anti-MHC-class II, alpha-chain (clone TAL.1B5, IgG1, dilution 1:40) (all from Dakopatts); anti-ICAM-1 (CD54, clone RR1/1, IgG1, dilution 1:50), anti-ICAM-2 (clone CBR-IC2/2, IgG2a, dilution 1:50), anti-LFA-1ß (CD18, clone R3.3, IgG1, dilution 1:50, (all from Bender MedSystems, Vienna, Austria); anti-ELAM-1 (alpha E-selectin, clone BBIG-E6, IgG1, dilution 1:50, British Biotechnology, Abingdon, UK); anti-VCAM-1 (clone E1/6, IgG1, dilution 1:50, 5th Leucocyte Typing Workshop, Boston, 1993).

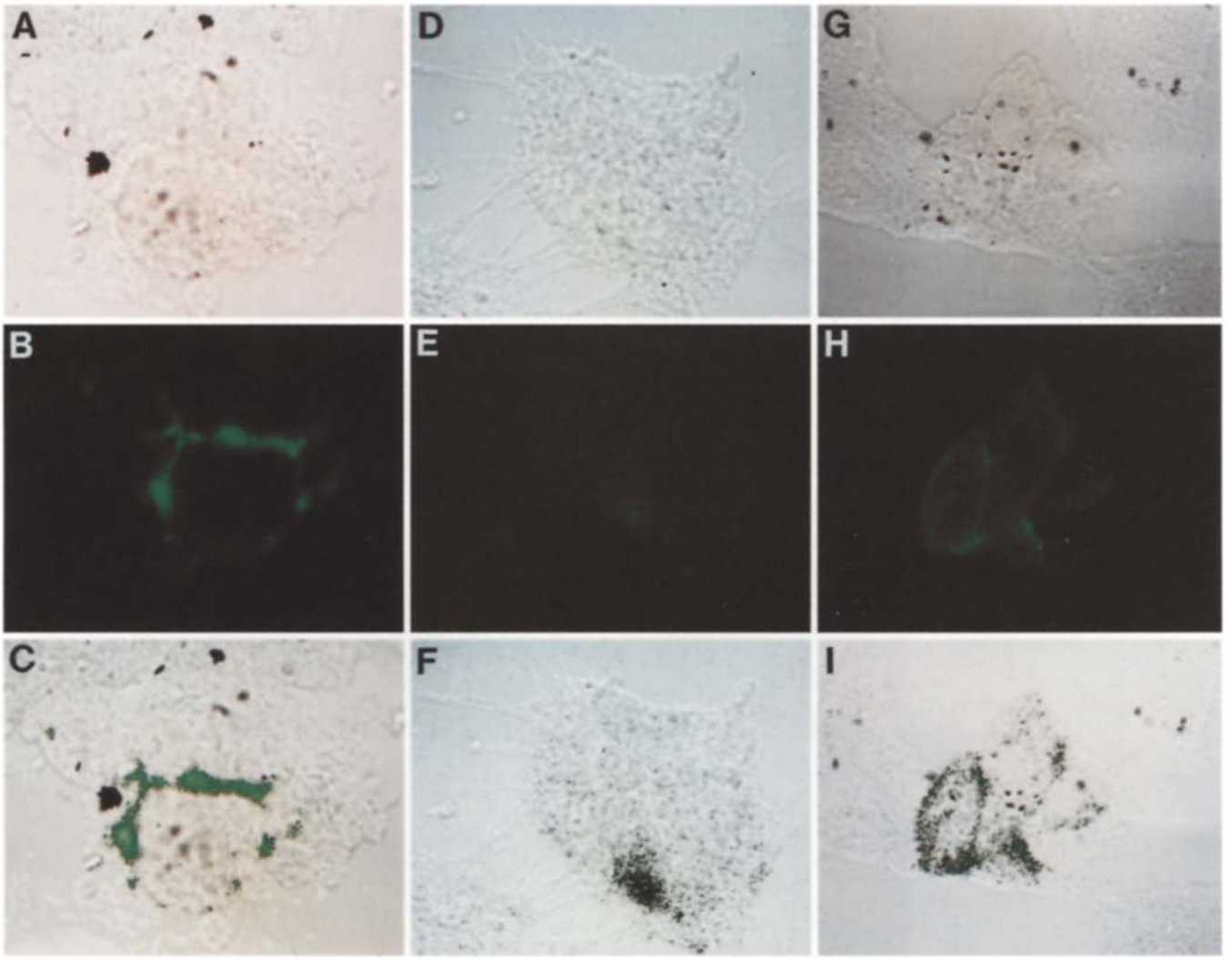

Fig. 2A–I Expression of cell surface markers in human RPEC. **A–C** Cells after staining with anti-MHC-class I antibody; D–F after staining with anti-MHC-class II antibody; **G–I** after staining with anti-ICAM-1 antibody. **A, D, G** Transmission scans; **B, E, H** fluorescence scans; **C, F, I** overlays. (Original magnification 63× oil, 40× zoom)

Immunofluorescence procedures

Cells grown on Lab-Tec chamber slides were washed twice with PBS and incubated on ice (unfixed) with one of the antibodies diluted in PBS and containing 1% bovine serum albumin and 0.05% sodium azide for 1 h. After washing thoroughly with PBS, cells were incubated with FITC-conjugated anti-mouse $F(ab)_2$ IgG on ice for 30 min. For double staining, virus-infected cells were permeabilized with 70% methanol for 15 min at room temperature, then washed and incubated for 1 h with the antibody used for detection of virus infection (see above), followed by a TRITC-conjugated rabbit anti-mouse or anti-human IgG for 30 min. Extensive washings with PBS were necessary to prevent background staining. Cell layers were not allowed to dry out. Cells were finally embedded in Moviol (Hoechst, Germany) to reduce fading during observation and examined in a laser scanning microscope (LSM10, Zeiss, Oberkochen, Germany). For FITC a 488-nm argon laser was used for excitation and a BP 530/30 filter for emission. For TRITC a 514-nm argon laser was used for excitation and a BP 575–640 filter for emission. Cells were observed and photographed in transmission scan and in fluorescence scan and presented as a false color overlay micrograph of FITC/TRITC and transmission.

Results

Infection of human-derived RPEC cultures with the rapidly growing viruses CVB and HSV produced typical cytopathic effects such as cell rounding and detachment of cells within 24 and 48 h. Infection with the slower growing CMV did not affect all cells visibly. As soon as a cytopathic effect was observed or after a maximum of 3 weeks in CMV-infected cells, viral infection of RPEC was confirmed by detection of viral structural proteins with monoclonal or polyclonal antibodies. Most of the cells in the culture were infected at the time the experiments were done, as can be seen from the clear nuclear (CMV) and cytoplasmic (CVB) fluorescence (Fig. 1).

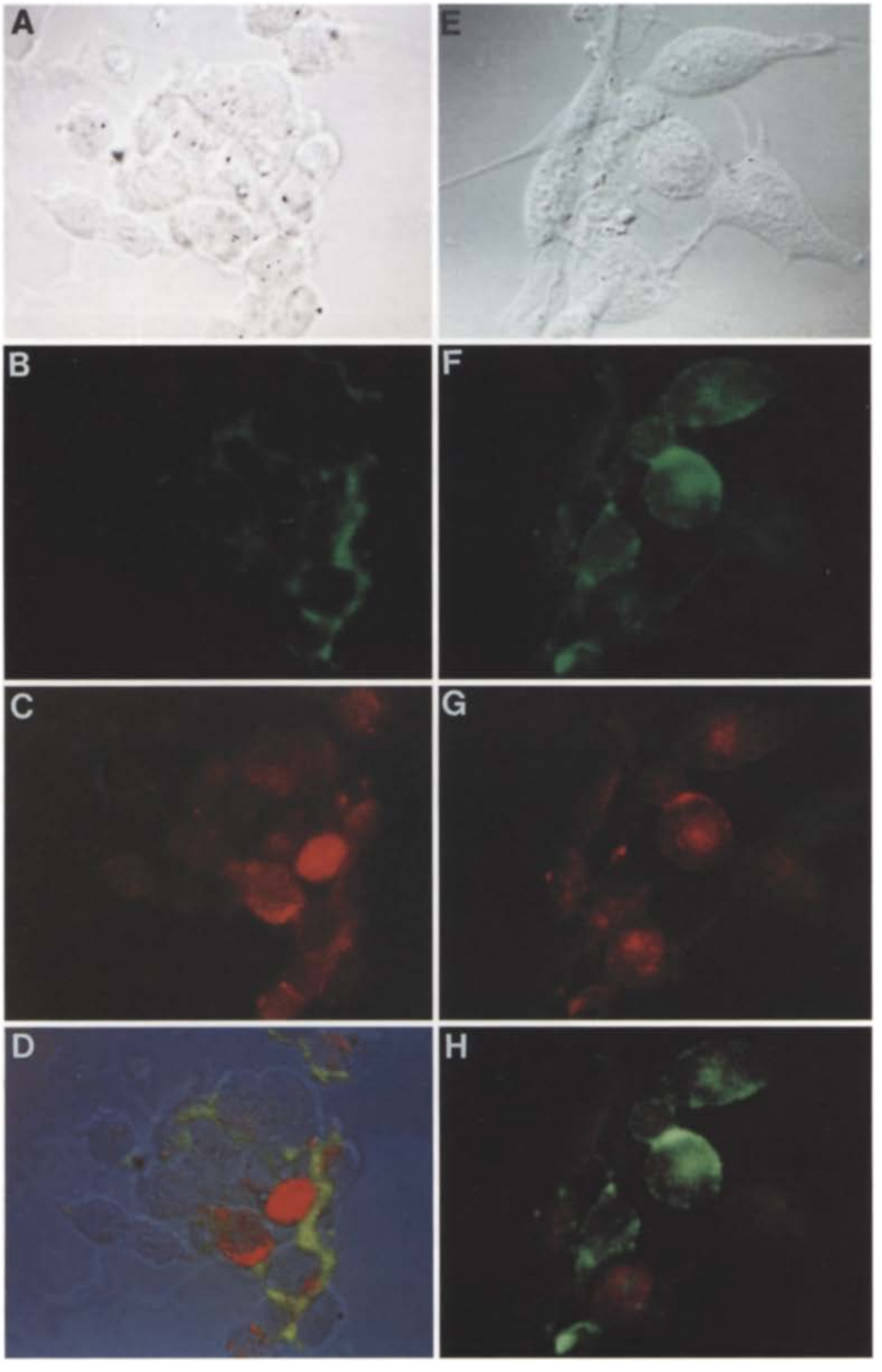

Fig. 3 Expression of MHC-class I (**A–D**) and ICAM-1 (**E–H**) in CBV-infected human RPEC. **A, E** The cells in transmission scan; **B, F** expression of the cell surface antigens by fluorescence scan; **C, G** staining in double fluorescence with an antibody against coxsackieviruses; **D, H** overlays of transmission and fluorescence scan. (Original magnification 63× oil, 20× zoom)

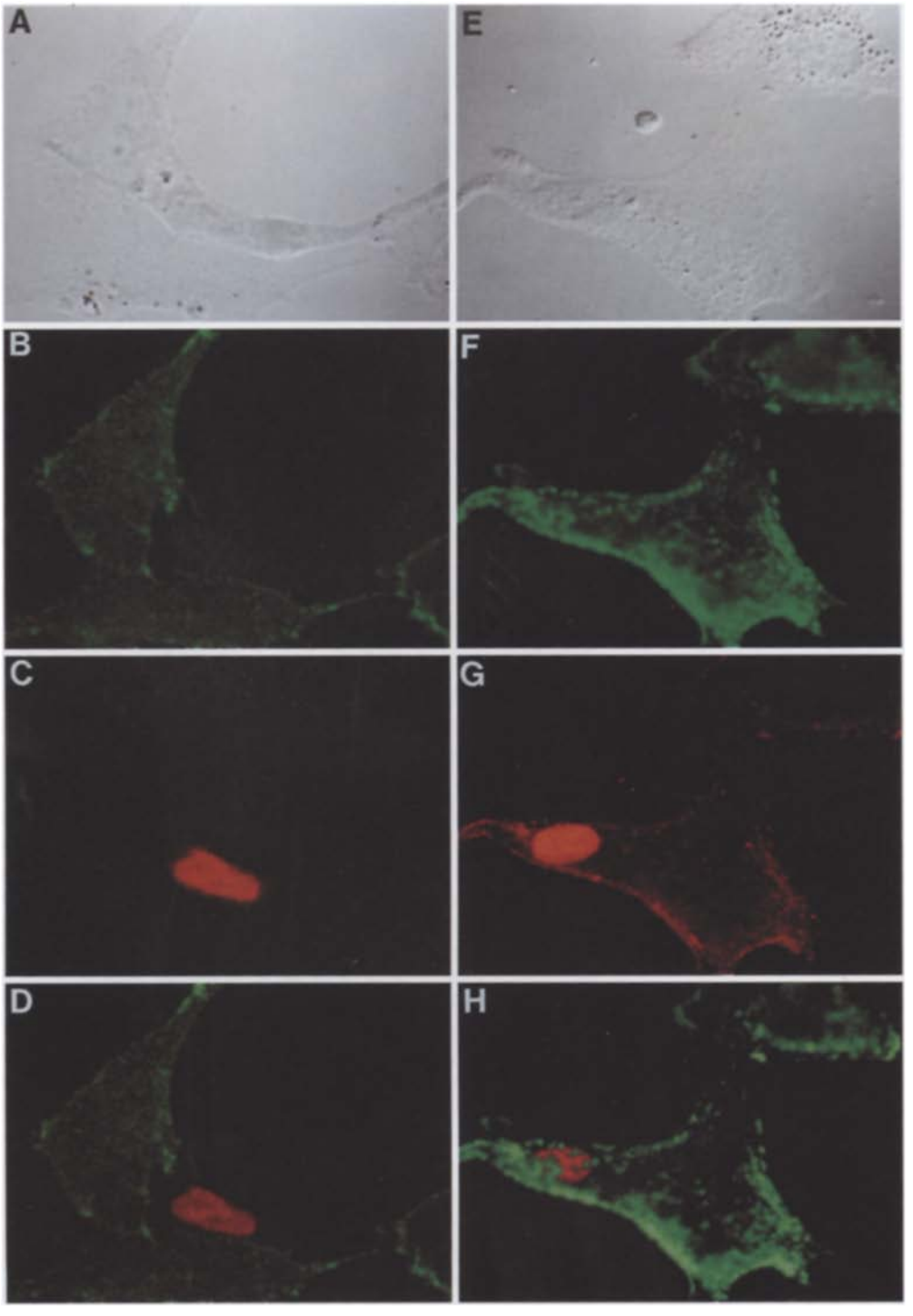

Fig. 4A–H CMV-infected RPEC. Expression of MHC class I (**A–D**) and ICAM-1 (**E–H**) in CMV-infected human RPEC. **A, E** The cells in transmission scan; **B, F** expression of the cell surface antigens by fluorescence scan; **C, G** staining in double fluorescence with an antibody against CMV; **D, H** overlays of transmission and fluorescence scans. (Original magnification 63× oil, 40× zoom)

The number of passages of cultured RPEC had no influence on the susceptibility of RPECs to virus infection, as we were able to demonstrate in our previous study [10].

MHC-class I was expressed in abundant amounts by native human RPEC in culture, whereas no expression of MHC-class II was observed (Fig. 2, Table 1). Also, ICAM-1 and VCAM-1 were constitutively expressed by RPEC, the first to a large extent, the latter weakly. No expression of ELAM-1, ICAM-2 or LFA-1 was observed.

After infection with CVB (Fig. 3) and HSV (not shown), MHC class I expression remained unaltered, and in both cases only a slight increase in fluorescence intensity of ICAM-1 was observed. The other cell surface antigens tested remained negative. A very faint immuno-

Table 1 Expression of cell surface antigens before and after infection with CMV, HSV or CVB3 observed after immunofluorescence staining. (↓↓ MHC class I expression strongly diminished after CMV infection of RPEC; ↑ ICAM-1 expression moderately increased after infection of RPEC with CMV, HSV or CVB3; –, +, ++, +++ relative fluoresence intensity)

Antibody	Before virus infection	Infection with CMV	Infection with HSV	Infection with CVB3
MHC class I	+++	+↓↓	+++	+++
MHC class II	–	–	–	–
ICAM-1	+	++↑	++↑	++↑
ICAM-2	–	–	–	–
VCAM-1	+	+	+	+
ELAM-1	–	–	–	–
LFA-1β	–	–	–	–

fluorescence indicated borderline expression of VCAM-1 in infected and uninfected cells (Table 1).

Interestingly, infection of RPEC with CMV led to a remarkable downregulation of MHC class I antigens from the cell surface (Fig. 4D), whereas expression of ICAM-1 was slightly increased (Fig. 4H) as shown with double staining. MHC class II was not upregulated on cultured human bulbus-derived RPEC as a direct consequence of virus infection in vitro. The other cell surface molecules tested remained unchanged.

Discussion

Retinal pigment epithelium is susceptible to growth of various viruses, but infection of the retina does not necessarily lead to severe destruction, as observed with HSV infection, one of the best-studied viruses in ocular disease [36]. As shown in animal experiments, mouse hepatitis virus is able to cause only mild inflammatory response but long-lasting disease [23, 24]. Viruses are known to be able to alter "self", thereby inducing an autoimmune response, and presumably a similar mechanism could also play a role in affecting the pigmented layer in humans. Autoimmunity to retinal antigens has been implicated in the pathogenesis of endogenous posterior uveitis and retinitis pigmentosa. Reid et al. [22] found that EBV-transformed human lymphocytes from patients with retinitis pigmentosa secreted higher levels of antiretinal antibodies than those from uveitis patients and normal controls, although all groups had low serum titers of antibodies. Albeit in the absence of cytopathic effects, persistent viral infection of retinal tissue has been described as leading to cellular dysfunctions [34]. CMV infection leads to downregulation of MHC class I in human fibroblasts and, as observed, in our experimental design. This seems to favor virus escape from the immune response [12, 20] and might support virus persistence in vivo. Also, other viruses such as HIV or adenoviruses which are able to induce persistent infections choose this type of strategy [19, 25, 26]. MHC class II was not upregulated on cultured human bulbus-derived RPEC as a direct consequence of virus infection in vitro, not ruling out the possibility that this could occur in vivo due to local production of IFN-γ by CMV-specific T-cells.

No decrease of adherence molecules was observed in virus-infected RPEC. Adherence molecules regulating interactions of immune effector cells are known to be involved in retinal inflammation [14, 15]. An important member of this class is ICAM-1, which has been shown to mediate lymphocyte binding to RPEC [17]. Basal expression of ICAM-1 on non-hematopoietic cells is usually rather low, but it can be induced by cytokines such as IFN-γ, tumor necrosis factor alpha (TNF-α) and interleukin-1beta (IL-1β). ICAM-1 is also constitutively expressed on unstimulated RPEC and can be induced in vivo by various cytokines, most importantly IFN-γ [2]. This mechanism might regulate leukocyte infiltration and might be important for the local immune response of the eye [review 4]. Lymphocyte binding to RPEC is normally ICAM-1-dependent, but ICAM-1-independent mechanisms have also been found on stimulated RPEC [17], suggesting the involvement of further cell surface molecules. Other investigators showed that HSV-1 induced an increase in ELAM-1, ICAM-1 and VCAM-1, whereas coxsackievirus induced an increase in ICAM-1 and VCAM-1 in endothelial cells. Cytokines such as TNF-α, IL-1, IL-4 and IL-6 were shown to effect the expression of adhesion molecules. TNF-α also upregulated VCAM-1 and ELAM-1 [31]. However, the adhesion molecules ELAM-1 and ICAM-2 were not found on RPEC, and no induction due to viral infection was observed.

As RPEC have been shown to function as antigen-presenting cells under certain circumstances [18], the modulation of immune regulatory cell surface antigens such as MHC class I or ICAM-1 by infectious agents observed in vitro might alter the immune response in vivo.

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