Immunolocalization of Integrins in the Human Retina

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Robert N. Mixon,* Joseph E. Robertson,* Stephen R. Planck,*‡ and James T. Rosenbaum*‡

Purpose. Integrins are cell surface proteins that participate in interactions between cells and with extracellular matrix. Binding of integrins to their ligands influences cell activities including proliferation, migration, and differentiation. Expression of integrin subunits from three different subfamilies was examined in human retina.

Methods. Integrins were detected in frozen sections of two human retinas with an avidin-biotin-complex immunohistochemical technique, using nine different monoclonal antibodies specific for \( \alpha_2, \alpha_5, \alpha_6, \alpha_{
\text{V}} \), and \( \beta_1, \beta_2, \) and \( \beta_3 \). One retina was from a patient who had conjunctival squamous cell carcinoma, and the other was from uninvolved regions of an eye with a choroidal melanoma.

Results. All integrins tested were detectable in consistent patterns in two retinas. All except \( \alpha_2 \) and \( \alpha_4 \) were stained vibrantly in retinal and choroidal vessels. All alpha subunit staining of vessels showed overlap or close proximity to \( \beta_1 \) staining. In addition to vessels, \( \beta_1 \) was also present in the internal limiting membrane; \( \alpha_2, \alpha_5, \alpha_6, \alpha_{
\text{V}} \), and \( \beta_2 \) were all found throughout much of the neural retina, albeit with distinctive staining patterns. Other than in association with vessels, \( \alpha_3 \) and \( \alpha_4 \) were not detected in neural retina, and \( \beta_3 \) was only weakly detected in the nerve fiber layer; \( \alpha_3 \) and \( \beta_2 \) were expressed in the retinal pigment epithelium; \( \beta_1 \) and \( \beta_2 \) were strongly expressed in drusen present in one of the eyes.

Conclusion. Nine integrin subunits have been found to have unique distributions in adult human retina. An understanding of the distribution in normal retina can serve as a useful contrast to patterns of staining associated with retinal diseases. Invest Ophthalmol Vis Sci. 1994;35:3466-3474.

Whether in culture or in tissue, cells of all types lay down a network of proteins and proteoglycans on which to adhere and develop. This extracellular matrix (ECM) is now thought not only to anchor cells but also to affect their differentiation and behavior. Extracellular matrix proteins include fibronectin, laminin, collagens, and vitronectin. Signals from the ECM and sometimes from adjacent cells are transduced to intracellular regulatory systems via a class of integral membrane proteins called integrins. Each integrin is specific for a given ECM protein or, in some cases, a few proteins; conversely, each ECM protein serves as a ligand for a small number of integrins. Integrins are heterodimers consisting of one \( \alpha \) subunit (from a minimum of 11 different types) and one \( \beta \) subunit (from at least six different types). Families of integrins are distinguished by their \( \beta \) chains. For example, in the \( \beta_1 \) family of heterodimers, the \( \beta_1 \) subunit forms heterodimers with three known ligand specificities. In this example, \( \alpha_1, \alpha_2, \) or \( \alpha_3 \) confer collagen-binding, \( \alpha_5, \alpha_6, \) or \( \alpha_\text{V} \) conffers fibronectin-binding, and \( \alpha_1, \alpha_2, \alpha_5, \text{or } \alpha_\text{V} \) conffers laminin-binding capability. The \( \beta_2 \) family mediates adhesion of leukocytes to each other or to vascular endothelium. The \( \beta_3 \) family includes the major integrin receptor for fibronectin in platelet membranes as well as a vitronectin receptor.

Several ECM proteins have been identified in the human retina. Fibronectin and laminin are located in the inner limiting membrane (ILM) and vessel walls. They may aid in the attachment of the ILM to the vitreous and to Müller cell processes. A role for laminin in retinal differentiation is suggested by a

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Integrins in Human Retina

### TABLE 1. Human Integrin Antibodies and Ligands

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Possible Dimer(s)</th>
<th>Possible Ligand(s)</th>
<th>Antibody (Source)*</th>
</tr>
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<tr>
<td>β1</td>
<td>α1-δβ1, α6β1</td>
<td>Extracellular matrix: collagen, laminin, fibronectin, fibronogen</td>
<td>DF5 (Chemicon)52,55</td>
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<tr>
<td>β2</td>
<td>α1β2, α3β2, α5β2</td>
<td>ICAM-1 and 2, C3b, rhinovirus</td>
<td>P4H9 (Oncogene Sciences)54</td>
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<td>β3</td>
<td>α1β2β3, α3β3</td>
<td>Fibronectin, vitronectin, VWF, OP, BSPI, thrombospondin, fibronogen</td>
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<td>α2</td>
<td>α2β1</td>
<td>Collagen types I, IV, laminin</td>
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<td>α3</td>
<td>α3β1</td>
<td>Laminin, collagen type I, fibronectin</td>
<td>P1B5 (Oncogene Sciences)35,50,58,50</td>
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<td>α4</td>
<td>α1β4, α2β4, α3β4, α4β4</td>
<td>Fibronectin (alternative splice site), VCAM-1</td>
<td>HP2/1 (AMAC)48,49</td>
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<td>α5</td>
<td>α5β1</td>
<td>Fibronectin (RGD site)</td>
<td>SAM1 (AMAC)</td>
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<td>α6</td>
<td>α6β1, α6β3, α3β3</td>
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<td>GOH1 (AMAC)9,48,50,61</td>
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<td>αv</td>
<td>αvβ1, αvβ2, αβ3, αβ3</td>
<td>αβ1: fibronectin, RGD</td>
<td>Anti-αv (Chemicon)62,63</td>
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<td>αβ3: vitronectin, RGD, fibronogen, VWF, OP, BSPI</td>
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</table>

RGD = Binds to GRGDSP peptide on affinity column; VWF = von Willebrand factor; OP = osteopontin; BSPI = bone sialoprotein 1.
* Sources: Chemicon International, Inc., Temecula, CA; Oncogene Sciences, Inc., Uniondale, NY; AMAC, Inc., Westbrook, ME; Dr. Virgil Woods, University of California, San Diego, CA.

correlation of laminin expression with the differentiation of rod photoreceptors and by interactions in vitro between laminin and photoreceptors.13 Additional ECM components, such as collagen and heparin sulfate proteoglycan, have also been identified in human retinal vessels and Bruch's membrane.15 Immunohistochemical assays on frozen sections of human retinas showed collagen types I, III, and IV (no type V) fibronectin and laminin in Bruch's membrane and around the retinal pigment epithelium (RPE).16

Despite the apparent importance of the ECM in the retina, little is known about the receptors for ECM proteins, i.e., integrins, in the human retina. Retinal pigment epithelial cells have been found to express the β1 integrin.17-18 Duguid and colleagues found by immunostaining that α2 was strongly expressed throughout the neural retina internal to the external limiting membrane, especially in the nuclear layers, and weakly in the retinal vascular endothelium.19 In chick and rat retinas, adhesion of the RPE to the basal lamina involves an integrin-fibronectin interaction, but adhesion of the RPE to the neural retina involves other linkage(s).20 Integrins are developmentally regulated at both transcriptional and posttranslational levels in embryonic avian retinas.21,22

Because of the obvious potential importance of integrin expression in retinal function and development, we have undertaken a more comprehensive survey of integrin expression in the human retina. Our immunohistochemical approach involved monoclonal antibodies specific for the separate integrin subunits; these antibodies have been characterized previously.

### MATERIALS AND METHODS

#### Tissue

Patient 1 was a 59-year-old man with a clinical diagnosis of squamous cell carcinoma of the palpebral and bulbar conjunctiva. The right orbit was exenterated, and the posterior region of the globe was removed. Samples of the inferior retina were frozen. Patient 2 was a 56-year-old woman with a clinical history of choroidal melanoma of the left orbit with extrascleral

### TABLE 2. Summary of Results From Staining Two Different Retinas

<table>
<thead>
<tr>
<th>Integrin</th>
<th>Vessels*</th>
<th>Drusen†</th>
<th>RPE</th>
<th>Rods</th>
<th>Cones</th>
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<th>ONL</th>
<th>OPL</th>
<th>INL</th>
<th>IPL</th>
<th>GC</th>
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RPE = Retinal pigment epithelial cells; OLM = outer limiting membrane; ONL = outer nuclear layer; OPL = outer plexiform layer; INL = inner nuclear layer; IPL = inner plexiform layer; GC = ganglion cell layer; NFL = nerve fiber layer; ILM = inner limiting membrane; e = endothelia; m = muscularis; em = endothelia and muscularis.

* Retinal and choroidal vessels were always stained similarly.
† Drusen were present only in eye 2. All drusen were positive for β2; only one was positive for β2
Antibodies

All anti-integrin antibodies used were mouse monoclonal antibodies and are listed in Table 1. Nonimmune mouse monoclonal IgGs of the appropriate subclasses (Sigma, St. Louis, MO) were used as negative controls.

Immunostaining

Slides were single stained for individual integrin subunits and sometimes double labeled to confirm association of an alpha subunit and a beta subunit with the same structure. Double-label protocols were simply two iterations of the single protocols before color visualization. Slides were fixed in 5% neutral-buffered formalin in Tris-buffered saline (TBS) pH 7.5 for 10 minutes at room temperature and blocked with 2% horse serum in TBS for 20 minutes. Sections were incubated either overnight at 4°C with mouse monoclonal primary antibody (or for 1 hour at room temperature when using DF5 antibody) and then washed in TBS. Rabbit anti-mouse secondary antibody (Vector Laboratories, Burlingame, CA) was applied for 30 to 60 minutes at room temperature, and, after another TBS wash, enzyme substrates were added, and the reaction was visualized. Substrates used were 5-bromo-4-chloro-3-indolyl phosphate–nitro blue tetrazolium (BCIP–NBT) or Fast Red (BioGenex, San Ramon, CA) for alkaline phosphatase and 3-amino-9-ethylcarbazole (AEC, BioGenex) for horseradish peroxidase. Some sections were counterstained with hematoxylin. Immunostaining was scored on the following scale: −, ±, +, ++, where − = no perceivable staining, ± = weak staining, + = moderate staining, and ++ = strong staining. Slides were photographed with a Zeiss Axioskop photomicroscope (Zeiss, Oberkochen, Germany) using Kodak Ektar 100 film (Eastman Kodak, Rochester, NY).

RESULTS

The location of three β and six α integrin subunits was examined in human adult retina and choroid by immunostaining with a panel of monoclonal antibodies. A semiquantitative analysis of the results for each structure is presented in Table 2. Figures 1 and 2 show photomicrographs of sections stained for several β and α subunits, respectively. The negative controls shown in Figures 1 and 2 were obtained for the specific staining indicated in the figure legends but are also representative of the negative controls obtained while staining for other integrin subunits. Photoreceptor cones sometimes displayed modest staining in these controls. The immunostaining results will be presented in groups according to integrin ligand.

The β1 subunit dimerizes with at least nine different α subunits to form receptors for many ECM proteins (Table 1). In both endothelial and muscularis layers of retinal and choroidal vessels, β1 was detected vibrantly (++) and was also expressed moderately (+) in the inner limiting membrane of the retina (Figs. 1A, 1C). Eye #2 had drusen that were also strongly positive for β1 (Fig. 1C).

α2 and α5 dimerize with β1 to form receptors for collagens and laminin (α5β1 binds fibronectin also).
FIGURE 2. Immunolocalization of integrin α subunits in normal human retina. All staining involved alkaline phosphatase-based visualization with Fast Red as the chromogenic substrate. Panels A and B were counterstained with hematoxylin. Panels A and B were sections of retina from patient 1; panels C to H were from patient 2. (A) α2 staining. (B) Negative control for (A). (C) α3 staining. (D) Negative control for (C). (E) α4 staining. (F) α5 staining. (G) α6 staining. (H) αv staining is faint but above background in vessels (arrows). Original magnification, ×220.

Staining patterns for these subunits were similar, but not identical. Both α2 (Fig. 2A) and α3 (Fig. 2C) were detected in the retina from the inner limiting membrane through the outer nuclear layer and in vessels. Only α3 staining was detectable over background in photoreceptor outer segments, whereas only α5 was clearly present in the outer limiting membrane. α2 staining was most intense in neuronal nuclear areas, whereas α3 staining was most intense in vessels.

α5 confers only laminin binding properties to β1 and was seen exclusively in vascular endothelia (Fig. 2G). Sections stained for both α5 (purple stain not seen in the absence of β1) and β1 (red) distinctly exhibited overlapping staining (dark purple–black) in vascular endothelia, but only β1 stain in vascular muscularis (Fig. 1F).

α4 and α2 are subunits of fibronectin receptors. Although staining for α4 was generally more intense than for α5, both subunits were detected in retina from ganglion cells through the photoreceptor outer segments (Figs. 2E, 2F). Retinal pigment epithelial cells also expressed α4. Vessel staining was apparent for α2, but questionable for α4. α2β1 is another fibronectin receptor; α2 was detected in the neural retina as described above (Fig. 2C).

α binds β1 to form a fibronectin receptor, and it binds β3 to form a receptor for at least six ECM proteins (Table 1). The α subunit was visualized as light staining in retinal and choroidal vessel endothelia (Fig. 2H). β2 also was seen in vessels and was seen weakly in the nerve fiber layer (Fig. 1H).

β2 differs from the other integrin subunits selected for this study in that the ligands for β2-containing heterodimers are located on cell surfaces instead of the ECM. For β2 staining, retinal and choroidal vessels stained strongly, the entire neural retina stained lightly to moderately, and the RPE stained weakly (Fig. 1E). One of two drusen stained for β2 (not shown).

DISCUSSION

Integrins form a class of cell surface proteins that serve as receptors for ECM proteins or other cell surface proteins. Integrins that bind laminin and collagen may be important in interactions with basal lamina. Integrins that bind fibronectin and vitronectin may have primary roles in development, wound healing, and inflammation. Integrins involved in cell–cell interactions function in leukocyte homing during inflammation. Inappropriate or defective integrin expression can contribute to tumor metastasis or to such diseases as leukocyte adhesion deficiency.3,4,7,23–30

In the most comprehensive study to date, we have shown that nine subunits that dimerize to form functionally different integrins have unique expression patterns in adult human retinal tissue. The sections were taken from uninvolved regions of eyes with two different types of cancer. Because both eyes had similar staining patterns, we propose that the patterns observed are representative of normal adult retina. Colocalization of an α subunit and a β subunit known to form a heterodimer (e.g., α1, α2, α3, or α5 with β1) only implies the possible presence of the corresponding heterodimer.5 Biochemical evidence such as shown by the ability of β1-specific antibody to preclear all α2 subunits on platelets and long-term activated T cells11 or immunologic evidence obtained with dimer-specific antibodies will be needed to verify that a given heterodimer is present.

Retinal and choroidal vessels were strongly positive for all the integrins studied here, except α2 and α4, which were weakly positive. Vascular endothelia have been found to express integrins in several different tissues. In the normal lung, vascular endothelium was found to express α1, α2, α3, α5, α6, αv, and β3.32 Placental vascular endothelia were positive for α1, α2, α3, α4, α5, α6, αv, β3, and β4,5 and investigators of integrins in lymphoid tissues noted that α3β3 was expressed strongly in vessels as well.53 Our results for the relatively normal retina correspond well to these findings considering that we did not study α1 or β4.

The omnipresence of integrins in vessels and their apparent concentration there, compared to other retinal structures, strongly suggests functions in directing circulating lymphocytes, monocytes, platelets, and coagulation factors into the retina. In this way, integrin-mediated mechanisms could be important in immunologic disorders of the retina and choroid, such as chorioretinitis or sympathetic ophthalmia. Vascular integrins may also serve as portals of entry for bacteria;
for example, \( \beta_1 \) is able to bind the bacterial protein invasin.\(^\text{34} \)

Several subunits were detected in various layers of the neural retina, including \( \alpha_2, \alpha_3, \alpha_4, \alpha_5, \) and \( \beta_2 \). None of the alpha subunits, except \( \alpha_3 \), was expressed strongly in a majority of cell types. Expression of \( \alpha_2 \) was noted in the entire neural retina and retinal vascular endothelium. This is consistent with the findings of Duguid et al\(^\text{19} \), who observed strong retinal staining internal to the outer limiting membrane, especially in the outer and inner nuclear layers, as well as endothelial staining. \( \alpha_2\beta_1 \) (and \( \alpha_5\beta_1 \)) can mediate cell–cell adhesion\(^\text{39,30,35–37} \); this ability could help to maintain retinal structure.

The inner and outer limiting membranes also were positive for several integrins: ILM—\( \alpha_2, \alpha_3, \alpha_4, \alpha_5, \beta_2 \); OLM—\( \alpha_3, \alpha_4, \alpha_5, \beta_2 \). Regarding \( \beta_1 \) and \( \alpha_4 \), which can serve as collagen receptors, expression at the ILM may help the neural retina to adhere to the cortical vitreous, whose major component is collagen fibrils\(^\text{38,39} \); type II collagen is the major type in the vitreous, with type IV predominating in the vitreous base.\(^\text{40,41} \) In addition, expression of \( \alpha_3 \) and \( \beta_1 \) in the ILM may relate to the presence of fibronectin and laminin in that structure.\(^\text{12–14} \)

The only integrins detected in RPE cells were \( \alpha_4 \) and a slight amount of \( \beta_2 \). Many integrins have been detected in epithelia of other tissues, such as lymphoid,\(^\text{53} \) breast,\(^\text{46} \) endometrium,\(^\text{45} \) and lung.\(^\text{52} \) Retinal pigment epithelial cells share antigenic features with simple and glandular epithelia and myoepithelial cells.\(^\text{44} \) Because RPE cells are highly specialized and serve multiple functions different from epithelia in other tissues, it may not be surprising that integrin expression here is unique. In any case, the RPE may use \( \alpha_4\beta_1 \) to adhere to fibronectin in its basement membrane (Bruch’s) and surrounding ECM.\(^\text{16} \) One would have expected RPE cells also to express laminin receptors because Bruch’s membrane contains laminin\(^\text{15} \) and because their migration in vitro is laminin dependent.\(^\text{45} \)

We observed the \( \beta_1 \) and \( \beta_2 \) subunits in drusen. Extracellular matrix molecules, but not integrins, have been examined in drusen previously.\(^\text{46} \) Indirect immunofluorescence studies have located the following ECM molecules in drusen: collagen types I, III, IV, and V; fibronectin; laminin; heparin sulfate proteoglycan; IgG, and IgM. Of these, only collagen type I presented a diffuse pattern similar to the distribution we observed for \( \beta_1 \). In that study, the composition of the ECM in drusen varied greatly among eyes and even within a given area of an eye.\(^\text{56} \)

In most tissues, cells express the collagen–laminin receptors \( \alpha_1\beta_1, \alpha_2\beta_1, \alpha_3\beta_1, \) and \( \alpha_4\beta_1 \). We observed \( \alpha_2 \) and \( \alpha_3 \) but not \( \alpha_5 \) in the retina, which indicates a specific repertoire different from other tissues. These integrin subunits may play a role in photoreceptor differentiation by way of adhesion to laminin.\(^\text{13} \) Expression of \( \alpha_2\beta_1 \) (a fibronectin receptor) was weak everywhere except in vessels, as has been observed in other tissues.

Overall, \( \beta_2 \) seemed to be one of the most widely distributed subunits in the retina. This was surprising because \( \beta_2 \) is known primarily to play a role in cell–cell adhesion among only leukocytes and vascular endothelial cells and has not been identified previously in other tissues.\(^\text{57} \) Among the known ligands for \( \beta_2 \) containing heterodimers are cells that express ICAM-1 or ICAM-2, as well as factor X, fibrinogen, and C3Bi; these molecules all participate in inflammatory processes.\(^\text{47} \) Future studies, which will include using controls such as absorption and different \( \beta_2 \)-specific antibodies, will be needed to substantiate this unusual finding. If it is true, \( \beta_2 \) may serve to uphold retinal structure, facilitate inflammation, or provide an undiscovered function.

Because \( \alpha_3, \alpha_4, \) and \( \alpha_5 \) antibodies did label retinal structures but colabeling with \( \beta_1 \) did not occur, these \( \alpha \) subunits may be paired with different \( \beta \) subunits. For example, \( \alpha_4 \) can pair with \( \beta_1 \) or \( \beta_4 \).\(^\text{48} \) Alternatively, \( \beta_1 \) in these structures may have been inaccessible to the antibody.

Our results showing widespread expression of integrins in the adult human retina can be used as a basis for comparison with integrins in retinal diseases. Because of the central importance of integrins to cell function, tracking them may be useful in understanding the pathogenesis of retinal diseases. Proliferative retinal membranes are known to contain large amounts of ECM proteins,\(^\text{49,50} \) which could serve not only as anchors for cells during membrane cell proliferation and migration but also as ligands for integrin receptors that modulate intracellular processes. This idea is substantiated by our studies described in the accompanying article.\(^\text{51} \)

**Key Words**
integrin, human retina, immunolocalization, cell-adhesion molecules

**Acknowledgment**

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**References**

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34. Isberg RR, Leong JM. Multiple beta-1 chain integrins are receptors for invasin, a protein that promotes bacterial penetration into mammalian cells. Cell. 1990;60:861–871.


