Glycosaminoglycans facilitate the movement of fibroblasts through three-dimensional collagen matrices

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Summary

The effect of glycosaminoglycans on the invasion of choroid fibroblasts into type I collagen gels was studied. Both hyaluronate and chondroitin sulphate, when incorporated into the gel, facilitated invasion of the collagen matrix, although hyaluronate was considerably more effective. Hyaluronate-induced fibroblast invasion was markedly concentration-dependent, being reduced at both high and low concentrations. Increased cell invasion appeared to correlate with denser packing of collagen fibrils within the gel, since the same effect could be achieved by increasing the collagen concentration of native, i.e. glycosaminoglycan-free gels. Scanning electron microscopy of the interior of the collagen gels suggested that changes in packing arrangement of fibrils in gels that had polymerized in the presence of glycosaminoglycans might account in part for different rates of cell invasion.

Key words: glycosaminoglycans, cell movement, collagen matrices.

Introduction

The movement of cells through extracellular matrices is intrinsic to many tissue processes such as wound healing, tumour metastasis, differentiation and ovulation. Glycosaminoglycans (GAGs) constitute one of the major matrix components and each GAG interacts with matrix collagen in a specific and highly structured manner (Turley et al. 1985a), either directly or indirectly through binding proteins such as hyaluronic acid binding protein (Delpech & Delpech, 1984) or other adhesive molecules, e.g. fibronectin (Isemura et al. 1982). GAGs have long been considered to influence the movement of cells, particularly during embryogenesis. In particular, hyaluronate has been proposed as a promoter of neural crest (Pratt et al. 1975) and corneal mesenchymal cell (Toole & Trebst, 1971) migration during development, but has also been correlated with inhibition of vascularogenesis in chicken limb bud development (Feinberg & Beebe, 1983). In contrast, high concentrations of hyaluronate have been correlated with invasiveness of the rabbit V₂ carcinoma, suggesting that the GAG facilitates tumour cell metastasis (Toole et al. 1979).

There is considerable evidence for GAG-modulated effects on cell movement in a variety of in vitro systems. For instance, heparin has been shown to stimulate capillary endothelial cell migration on two-dimensional substrata (Azizkhan et al. 1980), but to suppress completely neural crest cell migration into three-dimensional collagen gels (Turley et al. 1985a); chondroitin sulphate has been reported to increase the speed of movement of neural crest cells in collagen gels (Turley et al. 1985a), but to have little effect on neutrophil migration in Boyden chambers or on two-dimensional substrata (Forrester & Wilkinson, 1981). Hyaluronate has also been shown to inhibit leucocyte locomotion and neural crest cell migration on two-dimensional substrata (Forrester & Wilkinson, 1981; Balazs & Darzynkiewicz, 1973) and in three-dimensional matrices (Brown, 1982; Turley et al. 1985a; Forrester & Wilkinson, 1981), especially at high molecular mass. In contrast, hyaluronate promotes the migration of cardiac cushion cells (Bernanke & Markward, 1984), chick embryo mesoderm cells (Saunders & Prasad, 1983) and wound fibroblasts (Doillon & Silver, 1986), into hydrated collagen gels in vitro.

It would seem therefore that no general rules for the effect of GAGs on cell migration have, as yet, emerged. Much depends on the cell type, the nature of the GAG, and its relationship to the collagen matrix. In order to investigate these interactions further, we have studied the invasiveness of choroid fibroblasts into hydrated collagen gels, incorporating hyaluronate and other GAGs. The results show that high molecular weight hyaluronate and chondroitin sulphate at certain concentrations facilitate the movement of fibroblasts into collagen gels, in contrast to the inhibitory effect of hyaluronate on neutrophil
migration using an identical system (Brown, 1982). These effects may be related to the different means of translocation adopted by each cell type in three-dimensional matrices, and may have implications for the selective control of cell movement by the extracellular matrix.

Materials and methods

Cells and culture media
Choroid fibroblasts were obtained from the eyes of 10-day-old chick embryos by the method of Buultjens & Edwards (1977). After isolation, the cells were seeded into tissue-culture bottles containing growth medium (HEFT) consisting of Eagle’s Minimal Essential medium (Glasgow modification) (Flow Laboratories) containing 10% (v/v) foetal calf serum (Gibco), 1% (w/v) antibiotic + antimycotic (penicillin 100 μg ml⁻¹, streptomycin 100 units ml⁻¹, and fungizone 50 units ml⁻¹) and 5% (v/v) tryptose phosphate broth (Oxoid Ltd) buffered with 20mM-Hepes (N-2-hydroxyl piperazine-N’-2-ethane sulphonic acid), pH 7.4, and maintained at 37°C for use the following day. The purity of the cultured cells was checked by direct observation and only cultures that were free of any contaminating pigment epithelial cells were used in experiments.

Materials incorporated into the collagen gel matrices
The source of collagen used was Vitrogen 100 (Collagen Corporation, Palo Alto, CA, USA). High molecular weight (10⁶) hyaluronic acid (Healonid) was obtained from Pharmacia (Milton Keynes, England). Low molecular weight (1×10⁴ to 5×10⁴) hyaluronate was obtained from Northeast Biomedical Laboratories (Uxbridge, England). Bovine fibronectin was isolated from calf serum by affinity chromatography on a gelatin-Sepharose column as described by Engvall & Ruoslahti (1977). Chondroitin sulphate (type C from shark cartilage) was obtained from Sigma. Heparin (Sigma) 50 μg ml⁻¹ was incorporated into collagen gels (see below) but the gels were unstable and failed to polymerize adequately. All the substances being investigated were dissolved in serum-free HEFT to prepare fresh stock solutions.

Preparation of collagen gels
Collagen gels were reconstituted from rat tail tendons or vitrogen solutions in a similar manner to that described by Elsdale & Bard (1972). A 5 ml or 3 ml sample of the collagen stock solution (3 mg ml⁻¹, pH 4.0), depending on the final concentration required, was mixed at 4°C with 0.5 ml (or 0.3 ml) of 10× Eagle’s MEM and 50 μl of 0.142M-NaOH to restore physiological pH and ionic strength. This was then diluted with growth medium or growth medium containing one or more of the substances being investigated (and mixed thoroughly) to give a final collagen concentration of 2.5 mg ml⁻¹ (approx.) or 1.5 mg ml⁻¹. The collagen solution (2-0 ml well⁻¹), with or without the added test materials, was then immediately placed in clear tissue-culture plastic multiwells of 35 mm diameter (Nunc Plastics). The samples were incubated for 2 h at 37°C in a humid atmosphere to polymerize the collagen before the addition of cells and medium to the gel surface.

Invasion assay by visual methods
Collagen gels were prepared as described above and 2.5×10⁵ cells were seeded onto each gel in 3 ml HEFT medium. The leading front of the cell population (Zigmond & Hirsch, 1973) was measured after 48 and 72 h, using the calibrated fine focus on a Leitz Diavert microscope at a magnification of ×100. Ten readings were taken from each of three replicate gels and the mean ± S.E. was calculated for each of the different gel compositions tested.

The distribution of cells within the gel matrix was deter-

Fig. 1. A. Choroid fibroblasts seeded onto the surface of a collagen gel show random distribution and orientation. ×260. B. Same gel as A, showing invasive choroid fibroblasts within the collagen gel at a lower focal plane. Note typical polarized morphology. ×510.
mained after 25 h by counting the number of cells present in 10 randomly chosen fields from each of three replicate gels and the mean ± s.e. was calculated for each of the different gel compositions tested, at a depth of 70 μm.

**Scanning electron microscopy**

Collagen gels containing various GAGs were prepared on glass coverslips and fixed in 4% (v/v) glutaraldehyde in phosphate-buffered saline (PBS), pH 7.4, or in 2.5% (v/v) glutaraldehyde containing 1.5% (v/v) paraformaldehyde, 2.5% (v/v) dimethylsulphoxide in 0.1 M-sodium cacodylate buffer at pH 7.4 for 1 h at room temperature. Cetylpyridinium chloride (1%, w/v; Sigma, UK) was added to the second fixative in order to prevent loss of glycosaminoglycans (Turley *et al.* 1985). Gels were washed extensively with 0.1 M-sodium cacodylate buffer, pH 7.4, dehydrated in a graded series of ethanol solutions, and critical-point dried in CO2. The coverslips were mounted on stubs with colloidal silver adhesive, sputter-coated with 15 nm platinum, and examined in a Jeol JSM-35CF scanning electron microscope at 10 kV. During hydration, some degree of gel shrinkage occurred and cracks appeared on the gel surface. Micrographs of the gel interior, were taken through these cracks in order to obtain information on the fibrillar arrangement within the gel.

**Results**

**Choroid fibroblast invasion of collagen gels**

Choroid fibroblasts seeded onto hydrated collagen gels rapidly adhered to and invaded the gel matrix (Fig. 1A). Cells on the surface of the gel were distributed in a random orientation with numerous interdigitations. Cells invaded the gel singly and adopted a typical bipolar, spindle-shaped morphology (Fig. 1B).

The extent of fibroblast invasion was dependent on the density of the collagen matrix (Fig. 2). Increasing the concentration of collagen in the matrix produced greater cell invasiveness, up to a concentration of 2.5 mg ml⁻¹. Gels of <0.5 mg ml⁻¹ collagen were too unstable to support cell invasion and generally became disorganized by contraction. Gels of >3.5 mg ml⁻¹ were too concentrated to permit measurable invasion. Similar observations have been made previously by Schor *et al.* (1981).

**Effect of hyaluronate on choroid fibroblast invasion of collagen gels**

Incorporation of hyaluronate into the collagen gel induced some morphological changes in the cells migrating through the matrix (Fig. 3A, B). The cells tended to be less grouped and on occasions showed a degree of parallel alignment (Fig. 3A). The cells readily invaded hyaluronate-containing collagen gels, and assumed a long spindle-shaped morphology compared to the more compact cell forms in gels without hyaluronate (Fig. 3B).

The extent of gel invasion into hyaluronate-containing collagen gels was greatly facilitated (Table 1) both in terms of cell numbers invading the gel and in distance migrated by the leading front of cells. The effect of hyaluronate was more marked with a less dense collagen gel (1.5 mg ml⁻¹ >2.5 mg ml⁻¹) and with a higher molecular weight hyaluronate. In addition, the increase in gel invasion by choroid fibroblasts correlated with increases in the concentration of hyaluronate up to a maximum of 1 mg ml⁻¹ hyaluronate, after which this effect sharply declined (Fig. 4), and approached background levels at 2 mg ml⁻¹ hyaluronate.

**Effect of other glycosaminoglycans on choroid fibroblast invasion of collagen gels**

Choroid fibroblasts migrating into collagen gels containing chondroitin sulphate showed similar morphology to cells in standard gels (data not shown). Chondroitin sulphate also facilitated the movement of choroid fibroblasts into the gel but less effectively than hyaluronate (Table 2). In order to correlate these effects with the viscous properties of hyaluronate and chondroitin sulphate, gels with these polymers at equal viscosity were

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**Table 1. Effect of hyaluronic acid on choroid fibroblast invasion of hydrated collagen gels**

<table>
<thead>
<tr>
<th>Collagen (mg ml⁻¹)</th>
<th>Hyaluronic acid (mg ml⁻¹)</th>
<th>Distances migrated (μm ± s.e.)</th>
<th>Cell numbers at a depth of 70 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10⁻⁶ M&lt;sub&gt;s&lt;/sub&gt;</td>
<td>10⁻⁵·10⁻⁴ M&lt;sub&gt;s&lt;/sub&gt;</td>
<td>48 h</td>
</tr>
<tr>
<td>1·5</td>
<td>–</td>
<td>–</td>
<td>73 ± 4</td>
</tr>
<tr>
<td>1·5</td>
<td>–</td>
<td>1·0</td>
<td>170 ± 7</td>
</tr>
<tr>
<td>1·5</td>
<td>1·0</td>
<td>–</td>
<td>185 ± 7</td>
</tr>
<tr>
<td>2·5</td>
<td>–</td>
<td>–</td>
<td>168 ± 7</td>
</tr>
<tr>
<td>2·5</td>
<td>–</td>
<td>1·0</td>
<td>169 ± 7</td>
</tr>
<tr>
<td>2·5</td>
<td>1·0</td>
<td>–</td>
<td>203 ± 5</td>
</tr>
</tbody>
</table>

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Fig. 3. A. Choroid fibroblasts on surface of hyaluronate-containing (2 mg ml⁻¹) collagen (1 mg ml⁻¹) gel. Note exaggerated spindle-shaped morphology and the approximately parallel orientation of the cells. ×260. B. Same gel as A, showing invasive choroid fibroblasts within the collagen gel at a lower focal plane. These cells show markedly elongated spindle-shaped morphology.

Fig. 4. Dose-response curve showing relationship between hyaluronate concentration within a collagen gel (1.5 mg ml⁻¹) and invasiveness of choroid fibroblasts.

prepared (Forrester & Lackie, 1981) and compared with similar gels containing a non-GAG sugar polymer, dextran, for cell invasiveness. It can be seen from Table 3 that equally viscous polymer solutions produced a wide range of cell invasion responses in collagen gels, indicating that the invasion-promoting effects of these molecules were not merely a result of changes in viscosity of the interfibrillar gel matrix.

Attempts were also made to study the effects of heparin on choroid fibroblast invasion into collagen gels. However, the stability of the gel was extremely poor at heparin concentrations of 50 μg ml⁻¹ and gels with lower concentrations of heparin underwent extensive disruption, rendering accurate measurement of cell invasion impossible. A recent study (Guidry & Grinnell, 1987) has confirmed that heparin inhibits polymerization of collagen gels.

Choroid fibroblast invasion of model tissue matrices

Cells in vitro migrate through collagenous matrices that contain more than one GAG, plus several other matrix components such as fibronectin and other cell-adhesion proteins. We therefore studied the invasion of choroid fibroblasts into collagen gels that contained hyaluronate, chondroitin sulphate and fibronectin (Table 4). It can be seen that hyaluronate and chondroitin sulphate promote cell movement in a synergistic manner. In addition, incorporation of fibronectin into the matrix further enhances this response, although fibronectin alone has no effect on invasion.

Structure of GAG-containing collagen gels

An interpretation of the foregoing results might be that GAGs physically modify the three-dimensional structure of the gel to facilitate or hinder the movement of fibroblasts through its substance. Accordingly, gels containing various components were fixed either with glutaraldehyde in PBS alone or in glutaraldehyde and formaldehyde with cetylpyridinium chloride to preserve the highly hydrated GAG molecules, and studied by scanning electron microscopy (see Materials and methods). With fixation by glutaraldehyde alone the gels usually
Table 2. Effect of chondroitin sulphate on choroid fibroblast invasion of hydrated collagen gels

<table>
<thead>
<tr>
<th>Collagen (mg ml⁻¹)</th>
<th>Chondroitin sulphate (mg ml⁻¹)</th>
<th>Distance migrated (µm ± S.E.)</th>
<th>Cell numbers at a depth of 70 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>48 h</td>
<td>72 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 ± 2</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>1-5</td>
<td>1-0</td>
<td>73 ± 4</td>
<td>133 ± 8</td>
</tr>
<tr>
<td>0-5</td>
<td>-</td>
<td>168 ± 7</td>
<td>220 ± 8</td>
</tr>
<tr>
<td>2-5</td>
<td>1-0</td>
<td>172 ± 8</td>
<td>202 ± 9</td>
</tr>
</tbody>
</table>

Table 3. Effect of equisivous carbohydrate polymers on choroid fibroblast invasion of collagen gels

<table>
<thead>
<tr>
<th>Collagen (mg ml⁻¹)</th>
<th>Polymer*</th>
<th>Distance migrated (µm ± S.E.)</th>
<th>Cell numbers at a depth of 70 µm</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>48 h</td>
<td>72 h</td>
</tr>
<tr>
<td>1-5</td>
<td>Hyaluronate (0-5 mg ml⁻¹)</td>
<td>79 ± 6</td>
<td>91 ± 7</td>
</tr>
<tr>
<td>1-5</td>
<td>Chondroitin sulphate (10 mg ml⁻¹)</td>
<td>33 ± 9</td>
<td>30 ± 15</td>
</tr>
<tr>
<td>1-5</td>
<td>Dextran (8-8 mg ml⁻¹)</td>
<td>104 ± 6</td>
<td>118 ± 7</td>
</tr>
</tbody>
</table>

*The viscosities of the polymer incorporated into the gel were taken from Forrester & Lackie (1981).

Table 4. Choroid fibroblast invasion of model extracellular matrix

<table>
<thead>
<tr>
<th>Collagen (mg ml⁻¹)</th>
<th>Hyaluronic acid (mg ml⁻¹)</th>
<th>Chondroitin sulphate (mg ml⁻¹)</th>
<th>Fibronectin (µg ml⁻¹)</th>
<th>Distance migrated (µm ± S.E.)</th>
<th>Cell numbers at a depth of 70 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td></td>
<td></td>
<td></td>
<td>73 ± 4</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>1-5</td>
<td>0-5</td>
<td>-</td>
<td>100</td>
<td>185 ± 7</td>
<td>127 ± 8</td>
</tr>
<tr>
<td>1-5</td>
<td>0-5</td>
<td>1-0</td>
<td>-</td>
<td>188 ± 8</td>
<td>42 ± 6</td>
</tr>
<tr>
<td>1-5</td>
<td>0-5</td>
<td>1-0</td>
<td>-</td>
<td>156 ± 7</td>
<td>12 ± 22</td>
</tr>
<tr>
<td>1-5</td>
<td>0-5</td>
<td>1-0</td>
<td>-</td>
<td>135 ± 8</td>
<td>53 ± 2</td>
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<tr>
<td>1-5</td>
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<td>1-0</td>
<td>-</td>
<td>109 ± 8</td>
<td>92 ± 3</td>
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<td>1-5</td>
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<td>1-0</td>
<td>-</td>
<td>74 ± 5</td>
<td>45 ± 7</td>
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<tr>
<td>1-5</td>
<td>0-5</td>
<td>1-0</td>
<td>-</td>
<td>176 ± 7</td>
<td>134 ± 4</td>
</tr>
</tbody>
</table>

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collapsed during processing and, although differences between gels were observed interpretation of the changes in terms of gel structure was difficult. With combined glutaraldehyde, formaldehyde and cetylpyridinium chloride fixation, the three-dimensional structure was partially preserved, although there was still contraction of the gels during processing and a tendency for salt precipitation. Gels prepared from collagen alone at 1-5 mg ml⁻¹ concentration were composed of a random network of fibrils, of considerably varying thickness (mean 0-30, range 0-14–0-71 µm). Interfibrillar distances and spaces also varied widely (Fig. 5A). At higher concentrations of collagen (2-5 mg ml⁻¹), fibril diameters showed a similar range of size (mean 0-25, range 0-09–0-54 µm), although there appeared to be fewer thick fibrils (Fig. 5B).

Gels composed of collagen (1-5 mg ml⁻¹) and hyaluronic acid (1-0 mg ml⁻¹), contained more interfibrillar material (Fig. 5C). Fibril diameter appeared more uniform, as did the interfibrillar spaces. In lower concentrations of hyaluronate (0-25 mg ml⁻¹) the gels appeared to be particularly unstable and developed larger gaps during processing (Fig. 5D).

Similar findings were noted with collagen gels containing chondroitin sulphate. At high concentrations of chondroitin sulphate (10 mg ml⁻¹) fibril diameter was more uniform and fibril packing was more regular than with lower concentrations of chondroitin sulphate (1 mg ml⁻¹) (Fig. 5E,F), although wide spacing of the gel fibrils was less of a feature than with gels containing low concentrations of hyaluronate. These gels, however, are not directly comparable in terms of hydrodynamic volume, viscosity or concentration of their glycosaminoglycan components.

Discussion

This study has shown that glycosaminoglycans facilitate the invasion of three-dimensional collagen matrices by choroid fibroblasts. The effect depends on various factors, including the type of glycosaminoglycan promoting movement (hyaluronate producing a greater effect than chondroitin sulphate), the concentration of glycosaminoglycan, and the density of the collagen matrix. This...
suggests that the physical properties of the matrix regulate the movement of the cells into the matrix rather than that there is any direct effect of matrix components on the cells.

The specific interactions of GAGs with structural matrix proteins such as collagen have important effects on the physical properties of the matrix. For instance, heparin considerably alters the gelling properties of collagen solutions in vitro (Turley et al. 1985b), perhaps due to its high-affinity binding of the –COOH terminus of type I collagen (Keller & Kuln, 1986). Hyaluronic acid acts as a space-occupying molecule within collagen
matrices (Turley & Ericson, 1984) due to its very large hydrodynamic volume (for review, see Comper & Laurent, 1978). Both hyaluronate, which is composed of alternating N-acetyl-β-D-glucosamine and β-D-glucuronic acid residues, and chondroitin sulphate, which is the N-acetyl-D-galactosamine analogue of hyaluronate with additional sulphate groups at the C-4 and C-6 positions, behave in solution as very stiff chains (Scott & Tigwell, 1978). Direct interactions with collagen, therefore, are probably less important than indirect associations through other connective-tissue matrix-adhesive proteins such as fibronectin. In contrast, non-stiffened GAGs, such as dermatan and heparan sulphate, with a greater number of free hydrogen-bonding groups, have a greater capacity for direct intermolecular interactions with collagen and cell membranes.

Facilitation of fibroblast movement through collagen gels by GAG, especially hyaluronate (Fig. 4, Tables 1, 2) may be due to one of several mechanisms. These large space-filling molecules may impart stiffness to the gel and open up tissue planes (Toole et al., 1979), thereby providing a more stable collagen substratum on which the cells can exert traction (Guidry & Grinnell, 1987). However, it is also possible that hyaluronate and chondroitin sulphate affect migration by their effects on collagen fibril formation and packing. Gels containing high concentrations of hydrophilic GAGs, such as the vitreous gel and the corneal stroma, are composed of thin, regularly oriented collagen fibrils. Scanning electron microscopy studies (see above) have also shown that gels containing hyaluronate and chondroitin sulphate produce thinner collagen fibres and their packing arrangement may have affected cell migration.

In vitro studies by other groups have demonstrated these migration-modulating effects of hyaluronate (Bernanke & Markwold, 1984; Saunders & Prasad, 1983; Forrester & Wilkinson, 1981; Balazs & Darzynkiewicz, 1973) in collagen gels (Brown, 1982). Turley et al. (19856) have shown that high concentrations of hyaluronate in a collagen gel inhibit neural crest cell migration. However, low concentrations of hyaluronate, which did not normally affect neural crest cell migration, in a low-concentration collagen gel, promoted cell movement in a high-concentration collagen gel. These results indicate that fibril packing within the collagen gel affects cell movement.

Other factors apart from gel stability and fibril packing may also be important in the enhanced migration of fibroblasts and of neural crest cells through hyaluronate-containing gels. Both hyaluronate (Forrester & Lackie, 1981; Ericson & Turley, 1983) and chondroitin sulphate (Rich et al. 1981; Knox & Wells, 1979) reduce adhesion of cells to a variety of substrata. This effect seems unrelated to the viscosity of these polymers (Forrester & Lackie, 1981), as is the case with their effects on migration (Table 3). Increasing concentration of hyaluronate in the substratum adhesion site of certain cell types is associated with increasing detachment of the cells from the substratum (Kraemer & Barnhardt, 1978; Barnhardt et al. 1979). Since hyaluronate and chondroitin sulphate bind to collagen indirectly via fibronectin (Turley et al. 19855), it is likely that they present a relatively non-adhesive surface to migrating cells. Migration of cells depends on optimal adhesion to the substratum, i.e. it must be neither too strong to inhibit forward movement nor too weak to prevent the generation of tractional forces (for review, see Lackie & Wilkinson, 1984). Hyaluronate, within a specific concentration range, may render the collagenous substratum suitably non-adhesive to promote movement of fibroblasts, which normally form very strong adhesive interactions with collagen (Kolega, 1982).

In conclusion, this study has shown that hyaluronate and chondroitin sulphate facilitate migration of fibroblasts through collagen matrices in vitro, which is the reverse of their effects on neutrophil migration (Brown, 1982). Thus the precise composition of the extracellular matrix may selectively influence the traffic of different cell types through its substance, which may imply a regulatory role for extracellular matrix components in processes such as wound healing, differentiation and others in which cell movement is a significant feature. Indeed, Schor et al. (1981) have demonstrated such a role for fibronectin in the differential regulation of normal and transformed cells in collagen matrices.

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References


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