

Leading article – Hepatology series

Hepatocyte-matrix interactions

The normal hepatic sinusoid consists of a fenestrated endothelial capillary, behind which, and adjacent to the border of the hepatic pallisade, is the space of Disse. This term is in some respects a misnomer, for within it are the hepatic lipocytes (fat storing or Ito cells) and a specialised basement membrane-like matrix, which consists predominantly of type IV collagen, laminin, and proteoglycans. Extracellular matrix is an integral part of multicellular organisms, providing structural integrity and support to cells. Current evidence indicates that matrix is not merely a simple scaffolding but a dynamic modulator of cell phenotype and behaviour. There is now evidence that the basement membrane-like matrix of the liver can change the phenotypic characteristics and growth of lipocytes, endothelial cells, and hepatocytes.¹⁻⁴ Recent developments in matrix biochemistry and cell biology have offered a fascinating insight into the complex interaction of hepatocytes and their surrounding matrix in both health and disease. The importance of extracellular matrix was first appreciated in hepatocyte culture studies.

Evidence for a biological effect of extracellular matrix

When isolated mature hepatocytes are cultured on a non-physiological substratum such as tissue culture plastic, the cells attach poorly and have a limited viability.⁴ If a simple native substrate such as type I collagen is used, cell survival can be increased but the hepatocytes rapidly lose their normal appearance, becoming flattened, and specific gene functions such as cytochrome P⁴⁵⁰ and albumin expression rapidly diminish.⁵

In contrast, when hepatocytes are plated onto a model basement membrane, such as that derived from the Engelbreth Holm Swarm sarcoma (EHS), or in coculture with epithelial cells, they retain their normal cell polarity and structure, and the products of constitutively expressed genes such as albumin continue to be secreted for prolonged periods of culture.⁵⁻⁷ The EHS model basement membrane will also modulate hepatocyte growth and turnover, inhibiting cellular proliferation even in the presence of favourable growth factors.^{8,9} Hepatocytes cultured on EHS also exhibit a reduction in the expression of the cMyc oncogene and reduced DNA synthesis.⁹⁻¹¹ In short, the EHS cell culture model provides strong evidence of a biological interaction between a normal physiological basement membrane matrix and the hepatocyte, the result of which is the maintenance of hepatocyte polarity and differentiated cell function.

Is there then a single component contained within the EHS substratum that interacts with the hepatocyte to affect specific gene expression that is missing from plastic or simple substrata? Or is it the coordinated interaction of several matrix components (EHS contains laminin, type IV collagen, heparan-sulphate-proteoglycan, entactin, and other proteins) with the cell that effects the maintenance of a normal phenotype? The answer at present is unclear. First it should be noted that EHS is not a perfect model of the normal liver matrix as some dedifferentiation of hepatocytes cultured on this substratum can be detected.¹² Work in liver endothelial cells suggests that matrix prepared from human amnion is more effective at maintaining physiological phenotype than

EHS.² Nonetheless, the EHS model has provided the means to analyse the contribution of individual matrix components. The elegant studies undertaken by Bissell *et al* showed that none of the individual major matrix proteins used as a culture substratum would maintain hepatocyte function as effectively as the complete EHS gel complex.⁵ It is also known that hepatocytes express a series of integrin and non-integrin receptors for a series of matrix constituents.¹³ Predictably though, the hypothesis that it is simply a matrix complex which is required to maintain normal hepatocyte function in culture cannot explain all reported observations. If instead of a native type I collagen substrate, partially denatured type I collagen (or gelatin) is used, viable hepatocytes with a differentiated phenotype that will express cytochrome P⁴⁵⁰ can be cultured.¹⁴ Hydrating collagen substratum, in effect forming a collagen gel, is also associated with partial maintenance of albumin expression and trabecular organisation of hepatocytes.⁸ Albumin secretion can be restored to dedifferentiated flattened cells grown on type I collagen by the addition of dilute soluble EHS or laminin.¹⁵ Similar effects are seen when a collagen gel sandwich is used to culture hepatocytes. This is associated with albumin expression for up to six weeks compared with less than one week for equivalent monolayer culture.¹⁶

What then do these culture experiments using denatured single collagens or collagen sandwiches tell us of the nature of hepatocyte-matrix interaction? A common feature of these studies is the association of a more cuboidal cell shape with differentiated cell phenotype and expression of the genes for cytochromes and albumin. The data can be interpreted in several ways. At the simplest level they suggest that the three dimensional structure of the matrix and availability of ligands for cell binding may be important determinants of the hepatocyte's response to matrix constituents either alone or in combination. Research in other cell lines has suggested that the mechanical properties of the substratum are important in the maintenance of cellular differentiation.^{14,17} The stimuli which the cell receives from the matrix can then initiate changes in gene expression with temporally related changes in cell structure which result directly from the same signals or are determined by concomitant but separate cell-matrix interaction. Alternatively, it is possible that a fundamental determinant of matrix-initiated cellular differentiation is a change in cell shape and size. This would be mediated via cytoskeletal proteins which may then influence nuclear and cytoplasmic events by as yet undetermined mechanisms such as changes in nuclear and cytoplasmic pores or direct interaction with nuclear matrix. Recent studies have suggested that matrix stimulated activation of specific albumin regulating factors will only occur when the matrix on which the cell is grown promotes a cuboidal differentiated cell morphology.¹⁸

Mechanisms of cell-matrix interaction

1 INTEGRIN AND NON-INTEGRIN RECEPTORS

How do the cells adhere to a substratum, what cellular elements interact with the matrix, and what mechanisms signal changes in the intracellular milieu? The adhesion

molecules and receptors that mediate cell-matrix binding can be divided into two groups, the integrin and the non-integrin matrix receptors. Integrins are heterodimers that consist of non-covalently bonded α and β chains,¹⁹ with the latter stabilised by interchain disulphide bonding. The complete integrin consists of a head or ligand binding region made up of both the N terminal regions of the α and β subunits; a body which incorporates a hydrophobic membrane spanning domain, and two cytoplasmic linked domains. Cytoplasmic domains have been associated with cytoskeletal proteins including talin and α -actinin. They interact with the actin based cytoskeleton, and when stimulated may cause cytoskeletal rearrangement and have been shown to activate other cytoplasmic signalling pathways, thus acting as true trans-membrane receptors.¹⁹ Integrins may mediate both cell-matrix and cell-cell interaction. Changes in the α and β subunit combinations and alternative splicing are employed to determine and establish integrins of differing ligand specificity. Cells can influence not only integrin expression but under specific circumstances may 'activate' previously inactive integrins by exposing the ligand binding region through a molecular switch mechanism associated with a conformational change in the integrin molecule itself.¹⁹

The precise intracellular effects of ligand-integrin interactions remain to be determined in hepatocytes, but studies using other cell lines suggest that specific recognition sequences present on the ligand (such as RGD) complement an area within the binding region of the integrin which induces a change in the cytoplasmic domain.²⁰ Phosphorylates of tyrosine and protein tyrosine kinase, related to the *src* oncoprotein seem to be important as links between the integrin and intracellular signalling pathways.¹⁹ Tyrosine phosphate is found concentrated at points of cell-matrix and cell-cell contact in other cell lines studied.^{21,22} Heparan sulphate proteoglycan, laminin, and collagen have all been shown to be linked across cell membranes to cytoskeletal elements,^{23,24} and cytoskeletal proteins have been demonstrated to be condensed at cell-cell and cell-matrix interfaces.^{23,24} Current research suggests that integrins are similarly located and may therefore provide a physical link between matrix and the cytoskeleton.¹⁹ Heparan sulphate proteoglycan linked to the cytoskeleton can be copurified with attached nuclei, providing a possible link between matrix-integrin interaction and nuclear events.²⁴ Matrix components may also enhance cell-cell interactions.²⁵ The induction of the AP1 transcription factor, and through this mechanism stimulation of cytokine expression, has also been demonstrated from integrin-ligand interaction.²⁶

Interaction may also affect the intracellular milieu by changing the intracellular pH.¹⁹ Integrins binding to fibronectin, collagens, and laminin have been described in hepatocytes.^{13,27,28} Thus, the integrin family of molecules provides a mechanism whereby interaction with the extracellular matrix can cause rearrangement of the cellular cytoskeleton and signal changes in gene transcription through the activation of oncogenes and nuclear transcription elements.

Hepatocytes also express non-integrin, matrix binding proteins. Rat hepatocytes express three glycoproteins which have affinity for type I collagen. Activity of type I collagen binding by hepatocytes can be inhibited by antibodies raised against these glycoproteins.²⁹ In addition, a 32 kD laminin receptor has been described.³⁰ Molecular studies indicate that this receptor is expressed at low levels only in normal adult hepatocytes but that expression is increased in hepatoma cells and fetal hepatocytes.^{31,32} This adds a further regulator to receptor-matrix interaction and implies that specific receptor expression may be influenced by nuclear events or in response to a change in matrix. In common with many cells, hepatocyte and hepatoma cell lines have been shown to

express cell/cell adhesion molecules of the immunoglobulin superfamily and cadherins. It is not known whether there is non-integrin/integrin interactions in hepatocytes to activate integrin receptors as has been described in other cell types such as leukocytes.¹⁹

2 EXTRACELLULAR MATRIX AND CYTOKINES

A further level of complexity to hepatocyte-matrix interaction results from the propensity of the matrix to act as a reservoir and presenter of cell growth factors and cytokines. For example, one fragment of laminin contains a structure of 25 epidermal growth factor (EGF)-like repeats. When cleaved from laminin this protein is powerfully mitogenic and may explain the growth promoting properties that laminin has been shown to have cells expressing EGF receptors.³³ Similar properties have been described for thrombospondin and tenascin, two other matrix components.³⁴ That specific laminin receptors are differentially regulated in foetal, regenerating, and quiescent adult hepatocytes may not simply, therefore, be important for adhesive or structural reasons and may relate to the need for growth and development. Other matrix components are associated with the binding and presentation of cytokines. These include basic fibroblast growth factor (bFGF) which binds to heparan sulphate proteoglycan⁴ and can be released by the activity of plasmin which in turn may be activated by matrix bound tissue plasminogen activator (tPA). The presence of matrix bound tPA is itself important because the tPA-plasmin cascade is an activator of the matrix degrading metalloproteinase enzyme family (see below). In contrast to bFGF, binding of TGF β ₁ to type IV collagen may result in an enhanced or prolonged activity of this cytokine, possibly because of presentation or protection of the molecule.⁴ Other growth factors have been shown to bind to matrix components and include platelet derived growth factor (PDGF), interferon- γ (INF γ), acidic fibroblast growth factor (aFGF), and granulocyte colony stimulating factor (GM-CSF).⁴

3 MATRIX TURNOVER

A third mechanism by which hepatocyte behaviour can be regulated via interaction with the extracellular matrix is as a result of matrix turnover or modification by hepatocytes or other cells. Hepatocytes may produce heparan sulphate proteoglycans but 'in situ' hybridisation studies suggest the major source of type IV collagen is lipocytes, while laminin is derived predominantly from lipocytes and endothelial cells.³⁵ Activated lipocytes (myofibroblasts) are also the major source of the interstitial collagens (type I and III) which are produced in excess during liver fibrosis and cirrhosis and replace the normal basement membrane matrix.

Lipocytes are attractive candidates to regulate matrix turnover in both health and disease. They have been shown to express a 72 kDa type IV collagenase/gelatinase³⁶ with activity against the normal liver matrix, tissue inhibitor of metalloproteinase-1 (TIMP-1),³⁷ a potent inhibitor of the matrix degrading metalloproteinases and they also express interstitial collagenase, an enzyme with degradative activity against the excess interstitial collagens that characterise fibrosis.³⁸ In addition, Kupffer cells express a 95 kDa type IV collagenase/gelatinase which also degrades the normal liver matrix.³⁹ A potential mechanism by which hepatocytes may regulate metalloproteinase activity is by cleavage of tPA (see above) to activate plasmin which in turn activates latent metalloproteinases secreted by lipocytes and Kupffer cells. The interplay of these enzymes and their activators and inhibitors and the disruption of normal hepatocyte-matrix interactions is currently thought to be of major importance in the pathogenesis of liver injury.

The extracellular matrix is not uniform across the liver acinus. There is a gradient in matrix composition from the portal triad to the central vein, with relative preponderance of type III collagen and fibronectin adjacent to the central vein compared with the predominance of type IV collagen and laminin adjacent to the portal triad.⁴⁰ This finding has led to the suggestion that the hepatocyte pallisade may represent a lineage system within which cells mature as they pass from a peri-bile ductular position to mature perivenular hepatocytes.⁴⁰ If this hypothesis is proved it suggests that 'physiological' changes in matrix composition may be utilised in health to configure the developing hepatocyte either directly, or as the result of sequestration of particular growth factors and cytokines, the type of which would alter according to the specific matrix components. During cholestasis, periportal hepatocytes have been shown to express integrins normally associated with bile duct epithelium.²⁷ Whether this is the first stage in a phenotypic response of immature hepatocytes to cholestasis remains speculative.

Changes in cell-matrix interaction during disease

How can these, largely in vitro, observations be linked to the behaviour of hepatocytes in health and disease? A simple extrapolation from the basic hepatocyte culture experiments suggests that matrix degradation during liver injury may be associated with a loss of specific hepatocyte gene function, and promotion of cellular proliferation. Furthermore, during hepatic fibrosis there is replacement of the normal matrix with interstitial or fibrillar collagens (predominantly types I and III). Deterioration in hepatocyte function might therefore result from depriving the hepatocyte of normal matrix signalling in addition to any architectural disturbance that may occur. In progressive fibrosis there is evidence to indicate that synthetic functions of the liver are impaired proportionately to the degree of capillarisation,⁴¹ that is, to the accumulation of interstitial collagens within the space of Disse. Hepatocyte function may also be affected indirectly during fibrosis; recent research has shown that changes in matrix composition may reduce the size of fenestrae in endothelial cells.² Such a change, in combination with the capillarisation of the space of Disse, might reduce macromolecular exchange between the sinusoids and the hepatocytes.

Hepatocyte injury may also influence receptor expression and activation as described above. Activation and deactivation of integrins as a result of stimulation of other integrin and non-integrin receptors has been described in platelets and lymphocytes but has not yet been studied in hepatocytes. Studies in which rats have been fed ethanol have suggested that there is reduced ability of hepatocytes to bind to laminin, type I collagen, and fibronectin; a possible explanation for which is that there is reduced expression or activation of specific receptors for these matrix components.⁴² Evidence of a direct change in hepatic receptor type during disease comes from studies recently described by Volpes *et al.* Using antibodies directed against specific integrins, the authors show de novo expression of specific integrin receptor patterns by hepatocytes during inflammatory liver disease and in periportal hepatocytes during cholestasis (see above).²⁷ De novo expression of specific integrins with attachment affinity for type I collagen, laminin, and fibronectin has also been documented in chronic hepatitis B in both lobular and periportal hepatocytes, particularly in those cells in close proximity to lymphocyte infiltrates.⁴³

Conclusion

There is considerable evidence in vitro that, through several mechanisms, a change in hepatocyte phenotype, polarity,

proliferation, and function can be mediated via interaction with the surrounding matrix. In vivo, disease states are associated with changes in matrix components and in the expression of matrix degrading enzymes and their inhibitors by non-parenchymal cells. Hepatocyte function in disease may be perturbed by degradation of the normal matrix and its replacement with interstitial collagens by activated lipocytes. Release of specific growth factors from matrix or changes in matrix presentation of cytokines may also occur as a result of matrix degradation or a change in matrix composition. Altered integrin receptor expression by hepatocytes during disease provides a mechanism by which the cellular response to normal and abnormal matrix may be further modulated. Further research in this field is currently aimed at elucidating the precise mechanism(s) that regulate each of these factors and at determining their influence on hepatocyte-matrix interaction and thus their importance in liver injury.

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Review editor's note

Not so long ago, it was observed that if the size of medical textbooks continued to increase at its present rate, like dinosaurs they would become victims of their own bulk: they would be too heavy to lift. *Gut*, too, has been growing in size – initially in depth and, more recently, in length and breadth as well. This reflects the increasing quality and quantity of papers submitted, commensurate with the increasing quality and quantity of gastrointestinal research. There is no worry, as yet, of our journal sharing the same fate as the dinosaur. Nevertheless, there is a widely held view that over the years a growing proportion of *Gut* has become less accessible to its readership. This is, perhaps, a natural result of the sophistication and specialisation of science. There are few of our readers who are au fait in equal measure with stimulus-secretion coupling, cell-cycle kinetics, T cell receptor interaction, anal sphincter physiology, and the psychodynamics of the irritable bowel.

Clearly, *Gut* will always remain faithful to its aim of publishing high quality contributions in scientific gastroenterology but the editorial board feels it may be timely and appropriate to include, on a regular basis, some less weighty material, which might reflect the issues in what is

sometimes termed ‘the real world’ – here defined as the world in which we spend our time devoted to the art and craft rather than the science of gastroenterology. Initially, we have sought contributions in two areas.

Firstly, in keeping with our translation into an international journal, we will be inviting distinguished members of our international advisory board to comment in ‘International Gastroenterology’ on issues of importance in their own countries. Secondly, mindful of Toynbee’s dictum that those who do not learn the lessons of history are condemned to repeat them, we shall invite members of our parent society to share with us the benefits of their experience in ‘Personal Viewpoint’. In the midst of the endoscopic revolution, we would do well to remember that the retrospectroscope is a most powerful instrument.

We would be happy to consider publication of unsolicited contributions in either of these formats, and hope that this new section of the journal will provide some reader friendly relief on those occasions when the sheer volume of science seems somewhat indigestible.

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