0014-4754/95/100851-02$1.50 + 0.20

Multi-author Reviews

Extracellular matrix in animal development

Role of extracellular matrix in animal development – an introduction

The editors wish to thank Dr. P. Ekblom for having coordinated this review.

P. Ekblom

Department of Animal Physiology, Uppsala University, Biomedical Center, Box 596, S-75124 Uppsala (Sweden), Fax +46 18 50 80 95

Today it is widely accepted that extracellular matrix components are vital for development in animals. The scientists who initiated research on extracellular matrix (ECM), the leather chemists, probably could not imagine that research on ECM by the end of the century would take centre stage in a wide variety of biological and medical disciplines. Embryologists were among the first biologists to realize the potential role of extracellular matrix for cell behaviour. Long before it was possible to characterize the individual ECM components at the molecular level, embryologists suggested that ECM could provide important differentiation signals for the developing cells[7-9]. It seems clear today that this basic concept is correct, and signal transduction pathways initiated by extracellular matrix components are intensively studied by a large number of laboratories[2].

Extracellular matrix consists of collagens, adhesive glycoproteins and proteoglycans. In each class a large number of family members have been characterized, and it is naturally beyond the scope of this issue to cover all these molecules. Since the discovery of a novel type II collagen in 1969, extracellular matrix scientists have continuously and with increasing speed discovered new collagens, glycoproteins and proteoglycans[4,11,14]. It is to some extent a matter of taste which one of the many discoveries should be considered a breakthrough. What matters is that as a result of a large body of evidence we now have a fairly good overview of the composition of the extracellular matrix in all parts of the body. In many cases we also have some insignt into the physiological roles of some of the components.

Interest in extracellular matrix was greatly enhanced by the discovery of cellular receptors for the matrix. In the late 1980s integrins were identified as major extracellular matrix receptors[12]. A large number of cell biology studies have firmly established the paramount importance of the interactions between ECM and integrins for cell behaviour, and in some cases the suggestions are supported by recent genetic evidence[10]. More recently, other ECM receptors such as the dystroglycan complex have been identified[6]. With the ligands and receptors available, a large number of sophisticated and accurate biological studies have been performed. The importance of ECM components as major local factors for cell survival and differentiation is now indisputable. The major discoveries have become textbook knowledge, and need not to be repeated here.

Some of the pioneering work suggesting a role for extracellular matrix was performed by C. Grobstein in the 1950s[7,8]. He was particularly interested in the interactions between epithelium and mesenchyme during embryogenesis. He and others could show that the differentiation of epithelium requires the presence of mesenchyme, and vice versa. He speculated that the ECM could be involved in the interactions. Although we have learned to understand many aspects of extracellular matrix biology in other systems, the role of ECM in epithelial-mesenchymal interactions has not yet been well defined. Many researchers are now becoming interested in this classical phenomenon, known to be crucial for tissue histogenesis. Most of the reviews in this volume focus on interactions between epithelium and mesenchyme.

An exciting discovery in the field was that an extracellular matrix protein, tenascin, is expressed at sites of epithelial-mesenchymal interactions in the embryo[1]. It is suggested that tenascin could be involved in these interactions. Yet, as Chiquet-Ehrismann describes, mice lacking tenascin-C develop normally. We now know that there are many tenascins and the first described is called tenascin-C. It will be important to study this family further. Another interesting family of molecules for embryologists is the syndecan family[3]. Like tenascins, some of the family members are associated with epithelial-mesenchymal interactions. Salmivirta and Jalkanen provide an in-depth coverage of the biochemistry of the different syndecans, and point out the different binding potentials for these molecules. The syndecans are transmembrane proteoglycans and are thus potential receptors for extracellular matrix components. Both the tenascins and the syndecans continue to fascinate embryologists basically because of their

peculiar expression pattern, which suggest that some of the members should be involved in epithelial-mesenchymal interactions. Curiously, we still do not know very much of the physiological roles of these molecules. Hopefully, these reviews will stimulate further research in this area.

The basement membrane is a thin sheet of extracellular matrix separating the mesenchyme and the epithelium. Basement membranes are produced early during tissue development. As soon as the biological importance of epithelial mesenchymal interactions became evident, it was speculated that basement membrane components could be involved in the interactions. Major advances in the understanding of basement membrane composition were made in the 1980s[4,14]. As will be evident in two papers, these advances have now made it possible to study the role of basement membrane compoments during epithelial-mesenchymal interactions in more precise molecular terms. The papers of Simon-Assmann and Dziadek advance the concept that basement membranes form as a result of interactions between mesenchymal and epithelial ECM components. Some basement membrane proteins such as nidogen seem to be produced exclusively by mesenchyme, and recently it has been shown by antibody perturbation experiments that binding of mesenchymal nidogen to laminin disturbs epithelial morphogenesis in vitro[5]. This suggests that epithelial-mesenchymal interactions in part are mediated by interactions between mesenchymal and epithelial ECM components. We can expect that research in this area will flourish, and the papers of Simon-Assman and Dziadek are therefore particularly timely. They introduce many of the basic concepts and problems and provide good background for further studies.

In most parts of the developing embryo, mesenchymal cells and epithelial cells will continue to keep their basic morphological phenotype. But in some parts of the developing embryo the normal developmental program leads to a conversion of an epithelium to mesenchyme, or vice versa. Conversion of mesenchyme to epithelium occurs in the developing kidney[8], a much studied event where laminin-integrin interactions seem to be particularly important. This process has recently been extensively reviewed[13], and we have here chosen to focus on the reverse process, the formation of mesenchyme from a polarized endothelial cell. This occurs during development of the heart. Muscle formation is naturally a major event during cardiac development, but heart valves and septa have to form simultaneously. To accomplish that, some polarized endothelial cells will break loose from one part of the tube-like heart anlagen, and differentiate into endocardial cushion tissue. The endocardial cushion tissue then forms septa and heart valves and produce a special form of ECM. This process is accompanied by high expression of novel ECM components, the fibulins. As discussed by Rongish and Little, many other ECM are involved in endocardial cushion tissue formation. Since the cushion tissue forms major parts of the heart septa and the valves it is important to sort out the respective roles of the ECM components in the formation of the endocardial cushion tissue.

The last paper by Klein covers a slightly different topic, the role of ECM in bone marrow development. Circulating blood cells differentiate and mature in the bone marrow, and only break loose into the circulation once they have reached a certain degree of differentiation. The cells must thus initially adhere to the bone marrow microenvironment, but later they must lose that capacity. It is still unclear how adhesion and de-adhesion are controlled in the bone marrow. Interestingly, there is increasing evidence that extracellular matrix might be involved both in adhesion and de-adhesion. ECM-mediated de-adhesion might be particularly important in the bone marrow, where de-adhesion is part of the normal differentiation program. Klein discusses adhesive and anti-adhesive ECM components of the bone marrow, and introduces some of the methods used to study these phenomena. The phenomenon of anti-adhesion is also covered by Chiquet-Ehrismann.

All contributors have done an excellent job and have produced comprehensive, critical and well-written reviews, and I thank them very much for their efforts.

1 Chiquet-Ehrismann, R., Mackie, E., Pearson, C. A., and Sakakura, T., Tenascin: an extracellular matrix protein involved in tissue interactions during fetal development and oncogenesis. Cell *47* (1986) 131–139.
2 Clark, E. A., and Brugge, J. S., Integrins and signal transduction pathways: the road taken. Science *268* (1995) 233–239.
3 Bernfield, M., Kokenyesi, R., Kato, M., Hinkes, M. T., Spring, J., Gallo, R. L., and Lose, E. J., Biology of syndecans: a family of transmembrane heparan sulphate proteoglycans. A. Rev. Cell Biol. *9* (1993) 511–540.
4 Burgeson, R. E., New collagens, new concepts. A. Rev. Cell Biol. *4* (1988) 551–579.
5 Ekblom, P., Ekblom, M., Fecker, L., Klein, G., Zhang, H., Kadoya, Y., Chu, M., Mayer, U., and Timpl, R., Role of mesenchymal nidogen for epithelial morphogenesis in vitro. Development *120* (1994) 2003–2014.
6 Ervasti, J., and Campbell, K. P., A role for the dystrophin-glycoprotein complex as a transmembrane linker between laminin and actin. J. Cell Biol. *122* (1993) 809–823.
7 Grobstein, C., Tissue interaction in the morphogenesis of mouse embryonic rudiments in vitro, in: Aspects of Synthesis and Order of Growth, pp. 233–256. Ed. D. Rudnick. Princeton University Press, Princeton 1955.
8 Grobstein, C., Mechanisms of organogenetic tissue interaction. J. Natl Cancer Inst. Monogr. *26* (1967) 279–299.
9 Hay, E. D., Interaction of embryonic cell surface and cytoskeleton with extracellular matrix. Am. J. Anat. *165* (1982) 1–12.
10 Hynes, R., Genetic analyses of cell-matrix interactions in development. Curr. Opin. genet. Dev. *4* (1994) 569–574.
11 Kjellén, L., and Lindahl, U., Proteoglycans – structure and interactions. A. Rev. Biochem. *60* (1991) 443–475.
12 Ruoslahti, E., and Pierschbacher, D., New perspectives in cell adhesion: RGD and integrins. Science *238* (1987) 491–497.
13 Sorokin, L., and Ekblom, P., The development of tubular and glomerular cells of the kidney. Kidney Int. *41* (1992) 657–664.
14 Timpl, R., and Brown, J., The laminins, Matrix Biol. *14* (1994) 275–281.