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Editorial

Heterogeneity of basement membranes in normal and pathologically altered tissues

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The basement membranes (BM) are ubiquitous structural components of the extracellular matrix of both normal and neoplastic tissues (Martinez-Hernandez and Amenta 1983). Originally considered to be an inert framework for cells or merely delineating tissue compartments (Vracko 1974), BM turned out to be actively involved in preserving the integrity of the organs but also contributing to many of their specialized functions (Gorstein 1988). These functions vary from tissue to tissue over a broad spectrum.

In view of the multifacetted nature of the BM in the body and the numerous functions ascribed to them in both health and disease, it is reasonable to assume that the BM from different anatomical sites differ from one another. In this article I will briefly review the evidence that the BM vary from one organ to another; that within the same organ different anatomical structures may be invested by structurally and biochemically different BM; that the fetal BM differ from the equivalent BM in the adult organism; that the pathologically altered BM differ from normal BM; and finally, that the BM of neoplastic cells differ from those produced by the normal cells.

Methodological considerations

The structure, function and biochemistry of normal and pathological BM have been reviewed *in extenso* (Kefalides et al. 1979; Martinez-Hernandez and Amenta 1983; Liotta et al. 1983, 1986; Bosman et al. 1985; Timpl and Dziadek 1986; Martin and Timpl 1987). This article will thus discuss only two major components of the BM – type IV collagen and laminin, the principal non-collagenous multidomain glycoprotein (Sasaki et al. 1988). Other macromolecules such as fibronectin (Ruoslahti 1988a), proteoglycans (Iozzo 1985; Ruoslahti 1988b) and entactin (Durkin et al.1988) will not be discussed, although many of these show differential distribution in various BM (Couchman 1987). The emphasis will be on immunohistochemical data primarily to demonstrate the usefulness of this technique for the study of the BM heterogeneity.

The contributions of the biochemical or biophysical approaches will not be included, since these data have been considered in aforementioned reviews. Each of these approaches has its own merits and weaknesses and ideally any systematic analysis should include more than one method of investigation. Moreover, any qualitative or quantitative data obtained by descriptive or analytical techniques should be correlated with one or more functional parameters to obtain insight into the physiological role or assign a pathogenetic significance to those findings. Admittedly, such multidisciplinary studies are relatively rare and we are still in a stage of gathering fragmentary data, whereas the global picture is only slowly emerging.

Embryonic and fetal BM

BM play an important role in embryogenesis (Sanders 1983). Laminin appears early in mammalian embryonic development and it may be detected immunohistochemically after first mitotic divisions of the fertilized egg (Wu et al. 1983). It is, however, interesting to note that the A and B chain of laminin are not synthesized synchronously and that the synthesis of other components of the BM (collagen type IV and entactin) occurs only after the embryo has reached the stage of blastocyst, i.e. approximately 2 days after the onset of laminin synthesis. The "early embryonic" laminin does not react with all monoclonal antibodies produced against laminin, indicating that it is indeed

different from laminin in fetal or adult BM (Wan et al. 1984; Wewer et al. 1987). As the embryonic development proceeds, laminin appears in the embryonic BM underlying the ectoderm and endoderm and in the structures evolving from these primitive germ layers. However, if one probes various embryonic BM with a battery of monoclonal antibodies to laminin, it becomes obvious that these BM differ considerably from one another in their immunoreactivity. Heterogeneous reactivity of BM with monoclonal antibodies may be seen throughout the fetal stages of development and during the morphogenesis of various organs (Wan et al. 1984). On the basis of these and similar results from other laboratories (Timpl and Dziadek 1986), one can conclude that the BM change considerably during prenatal development, and that the embryonic and fetal BM are at least immunochemically different from equivalent BM in the adults.

Anatomical differences between BMs

Electron microscopic studies have shown many years ago that there are significant differences among the BM from different anatomical sites (Martinez-Hernandez and Amenta 1983; Abrahamson 1987). The content of BM may fluctuate under various physiological conditions, as exemplified by decidua of pregnant uterus (Wewer et al. 1985; Damjanov 1985). With the advent of monoclonal antibodies these anatomical differences were confirmed and further elaborated (Hessle et al. 1984; Wan et al. 1984). Monoclonal antibodies to laminin (Jaffe et al. 1984; Horikoshi et al. 1988) have revealed considerable heterogeneity of BM along the nephron as well as between the glomerular and tubular BM (Leu et al. 1986). Testicular seminiferous tubules also show heterogeneity in that the hilar tubules react with some monoclonal antibodies that do not bind to the BM of the principal portion of the tubules (Leu et al. 1986).

Organ-specific monoclonal antibodies to collagen type IV have also been reported (Scheinman and Tsai 1984). However, many more monoclonal antibodies to collagen type IV do not discriminate between the BM in different tissues (Havenith et al. 1987). Thus, it appears that the monoclonal antibodies to laminin are better suited for studying the heterogeneity of BM than the antibodies to collagen type IV.

Protease treatment of tissue sections removes the laminin more easily from the BM than the collagen type IV (Leu and Damjanov 1988), suggesting that this collagen is more centrally located and thus less prone to enzymatic removal or degradation than the peripherally located laminin (Laurie et al. 1986). Predigestion of tissues with proteolytic enzymes may thus be used for the study of heterogeneity of BM with regard to their content of laminin.

Pathologically altered BM

Structural and biochemical defects have been reported in many BM (Abrahamson 1986). However, most of the progress was made in the study of glomerular BM (Timpl 1986). The glomerular BM of experimental animals made nephrotic loose heparan sulphate proteoglycan (Mynderse et al. 1983). In patients with Alport's syndrome a loss of the epitope recognized with the antibodies from patients with Goodpasture's syndrome was reported (Kleppel et al. 1987). The glomerular BM of diabetic patients express distinct lectin binding properties (Holthöffer et al. 1987), suggesting that the thickened and morphologically altered BM are also biochemically different from normal BM. Morphologically abnormal glomerular BM are typically found in hereditary nephritis, but with the present detection techniques a third of all patients will show no ultrastructural pathological changes (Yoshikawa et al. 1988). Major advances have been made in the elucidation of the BM changes in Goodpasture's syndrome (Butkowski et al. 1987; reviewed by Price and Wong 1988).

Tumour BM

Like the equivalent normal cells, tumour cells may produce various BM components and even assemble complete BM (Liotta et al. 1986; Martinez-Hernandez 1988). Benign tumours form BM that are structurally and biochemically indistinguishable from those in normal adult tissues (Willebrand et al. 1986); however, malignant tumours tend to form defective BM. In such tumours it is essentially impossible to determine whether the incompletely formed BM is due to faulty synthesis or due to destruction of the BM by the invading tumour cells (Barsky et al. 1983; Liotta et al. 1983).

The BM found in malignant tumours may be derived from the tumour cells, stromal cells or represent a mixture of both neoplastic and stromal cells (Damjanov et al. 1985; Havenith et al. 1988). The pattern of distribution of BM may vary from periacinar to pericellular (Miettinen et al. 1983; Donato et al. 1989). Overall, the malignant tumour contains less BM material than benign tumours

(Charpin et al. 1989) and the qualitative assessment of BM within tumours may provide additional information about their malignancy and invasiveness (Havenith et al. 1987).

Concluding remarks

The BM are complex, structurally and functionally heterogeneous components of both normal and neoplastic tissues. The heterogeneity of BM evolves during ontogeny of normal tissues and it becomes even more accentuated in neoplasia.

The complex functions of BM have not been fully explored. In view of the fact that these extracellular matrices reflect, on the one hand, the functional state and the basic biology of tumour cells and, on the other, that they interact with adjacent cells, future studies centering on the dynamic interaction of cells and BM could provide important information about both normal and neoplastic development.

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