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Stimulation of tenascin expression in mesenchyme by epithelial-mesenchymal interactions

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ABSTRACT. Tenascin is an extracellular matrix glycoprotein with an unusually restricted tissue distribution in the developing embryo. The protein was independently discovered by several investigators, and has been given many different names. Synonyms of tenascin include cytotactin, J1, hexabrachion and glioma-mesenchymal extracellular matrix antigen. Whereas fibronectin is expressed rather uniformly in matrices of embryonic mesenchyme, tenascin is found in the mesenchyme at sites of epithelial-mesenchymal interactions. Tenascin is thus found close to epithelial basement membranes but it is probably not an integral basement membrane component. The distribution suggests that developing epithelial cells may produce locally active factors that stimulate tenascin synthesis in the nearby mesenchyme. Tenascin is composed of disulfide-bonded subunits of approximate M. between 200-280 kD. Using monoclonal antibodies to mouse tenascin, we find two major subunits of M. 260 and 200 kD from mouse fibroblasts. Work from many laboratories suggests that the different subunits arise by differential splicing of one mRNA. Rotary shadowing electron microscopy of the intact molecule suggests a six-armed structure connected by a central region. However, the different subunits are not co-ordinately expressed during embryogenesis, suggesting that tenascin can exist as different isoforms. The different isoforms may serve distinct functions. The function of tenascin is not well known, but it has been suggested that it alters the adhesive properties of cells and causes cell rounding.

Embryonic induction in development

Local cell interactions are crucial for morphogenesis during embryonic development. In several developing tissues, the fate of a particular cell type is controlled by signals derived from nearby cells. Such local interactions between dissimilar types of cells are referred to as embryonic induction, a phenomenon first decribed for lens development by Spemann (1901). Subsequently it has become clear that inductive interactions are instrumental for most stages of development in multicellular organisms (Spemann and Mangold, 1924; Nieuwkoop, 1977; Toivonen, 1979).

The importance of inductive interactions was originally established by tissue recombination experiments in amphibian and mammalian embryos (for recent reviews: Dawid and Sargent, 1986; Gurdon, 1987), but more recently, evidence for a role of cell interactions in development has also come from analyses of developmental mutants which affect development in *Drosophila* (Tomlinson and Ready, 1987; Hafen *et al.*, 1987), other insects (Doe and Goodman, 1985) and nematodes (Greenwald, 1985; Priess and Thomson, 1987). The identification of such mutants should make it possible to study embryonic induction at the molecular level. Several other recent findings have greatly increased interest in embryonic induction. Growth factors have been shown to act like inducer substances in some systems (Smith, 1987; Slack *et al.*, 1987), and mRNA for these or similar growth factors have been identified in inducer tissues (Kimelman and Kirschner, 1987; Weeks and Melton, 1987). In several models the response to induction can be analyzed at the molecular level. A common response is an increase in intercellular adhesion caused by changes in the composition of the extracellular matrix (Ekblom *et al.*, 1980, 1981) and the cell surface (Thiery *et al.*, 1982; Chuong and Edelman 1985; Vestweber *et al.* , 1985). Here we will focus on certain molecular responses of embryonic mesenchyme to inductive signals from developing epithelia.

Epithelial-mesenchymal interactions are required for organ development

Interaction between mesenchyme and epithelium are classical examples of inductive interactions. They are instrumental for the development of lung, kidney, liver, tooth, and most glandular organs such as the mammary, salivary and pancreatic glands (Grobstein, 1967). In these organs, branched epithelial sheets arise from a small epithelial bud, which in response to signals from mesenchyme starts to grow, differentiate and branch (Bernfield and Wessells, 1972; Saxén *et al.*, 1980). The branching of the epithelium is easy to detect by morphological techniques and has therefore been much studied.

The response of the mesenchyme to the presence of the developing epithelium is, with few exceptions, more subtle at the morphological level, although biological studies clearly have established that the mesenchyme responds to the presence of the branching epithelium. In several of the tissues, the mesenchyme around the epithelium becomes slightly more compact, suggesting that the expression of adhesion molecules has been altered as a result of the interaction. The nature of the molecules responsible for the changed compactness of the mesenchyme is not well known. In addition to changes in compactness of the tissue, the mesenchyme may also respond in a tissue-specific manner. An example of the latter is the appearance of androgen-receptors in mammary gland mesenchyme through an induction of mammary epithelium (Kratochwil and Schwartz, 1976; Heuberger *et al.*, 1982). Their presence in male mammary gland anlagen is a prerequisite for the androgen-induced killing of the epithelial cells. These studies are elegant demostrations of the importance of epithelial-mesenchymal

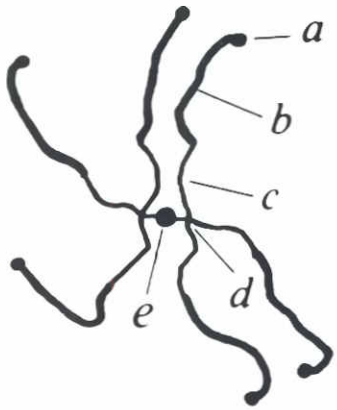

Fig. 1. *Model of tenascin based on rotary shadowing electron microscopy according to Erickson and Inglesias (1984). Abbreviations: a), the terminal nob of each arm; b), the thick distal segment which is about 55 nm long; c), the thin inner segment; d), two T-junctions; e), the central globular particle. Reprinted by permission from* Nature 311: *267-269, 1984, copyright 1984, Macmillan Magazines Ltd.*

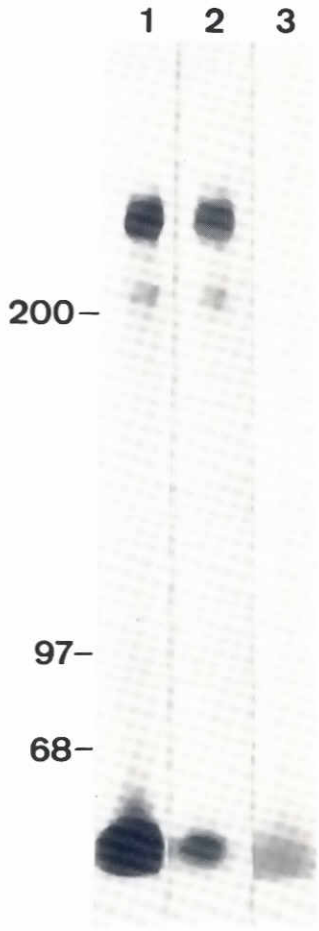

Fig. 2. *Immunoprecipitation with two different monoclonal antibodies, MTn 5 and MTn 12 (Aufderheide and Ekblom, 1988), reacting with mouse tenascin reveals two polypeptides of M, 260 and 210 kD. Fibroblasts were labeled with radioactive methionine, immunoprecipitated proteins from supernatants were separated under reducing conditions on a SDS-PAGE linear gradient gel (5-10% acrylamide), and radioactive bands were visualized by fluorography. Both the MTn 5 (lane 1) and the MTn 12 mAb (lane2) react with the similar polypeptides. Lane 3 is a precipitation without first antibody. Radioactivity in the lower part of all three lanes indicates the running front. Molecular mass markers in kD are on the left. Reproduced from Aufderheide and Ekblom.* The Journal of Cell Biology 107: *2431-2349, 1988; by copyright permission of the Rockefeller University Press.*

interactions, because they conclusively show that a soluble morphogenetic factor (testosterone) acts through the mesenchyme to activate a tissue interaction leading to a developmental response. A similar induction-dependent appearance of hormone receptors has also been demonstrated for the urogenital organs (Cunha *et al.*, 1986). The induction of hormone-receptors in urogenital tissues and mammary glands is a tissue-specific special event, and it is likely that there are also molecular responses common to most, if not all, mesenchymal cells located close to growing epithelial buds.

Epithelial-mesenchymal interactions affect the extracellular matrix

For many embryonic organs it has been shown that the development of basement membranes of epithelial cells is dependent on inductive tissue interactions. It has therefore been suggested that stimulation of extracellular matrix deposition is a major effect of embryonic induction (Ekblom *et al.*, 1986). The formation of the epithelial basement membrane in the developing kidney is dependent on embryonic induction (Ekblom *et al.*, 1980; Klein *et al.*, 1988). Similarly, mesenchyme is required for the proper assembly of basement membranes of developing salivary gland (Bernfield and Wessells, 1972), gut (Simon-Assmann *et al.*, 1988) and skin (Bohnert *et al.*, 1986). These examples show that inductive interactions between epithelium and mesenchyme can have a major influence on the composition of the matrix of the epithelial cells. Since these interactions are reciprocal, it is likely that the composition of the matrix of the mesenchymal cells likewise is influenced by inductive signals from the epithelium.

Most proteins of the mesenchymal matrix so far described seem to be constitutively expressed around embryonic mesenchymal cells. Interstitial collagens I and III and fibronectin, for example, are abundantly expressed in embryonic mesenchyme, in adult stroma and in scar tissue (Vaheri and Mosher, 1978; Ruoslahti *et al.*, 1983). The expression of the interstitial collagens and fibronectin is developmentally regulated but, with few exceptions, their expression is apparently not directly controlled by epithelial-mesenchymal interactions. In the developing kidney, some cells seem to lose these interstitial matrix proteins as a result of induction from the epithelial ureter (Linder *et al.*, 1975; Ekblom, 1981; Ekblom *et al.*, 1981), but this is a special case. Here, the cells that lose these interstitial matrix components convert from mesenchyme into epithelium, and the apparent loss of fibronectin and interstitial collagens is part of this unique conversion process. In most other tissues where no such conversions occur, the mesenchymal cells express interstitial collagens and fibronectin both before and after the epithelial-mesenchymal interaction (Thesleff *et al.*, 1979; Mauger *et al.*, 1983; Aufderheide and Ekblom, 1988). Thus, neither fibronectin nor interstitial collagens appear or disappear selectively in areas close to inducer epithelium in true mesenchyme predetermined to become stroma.

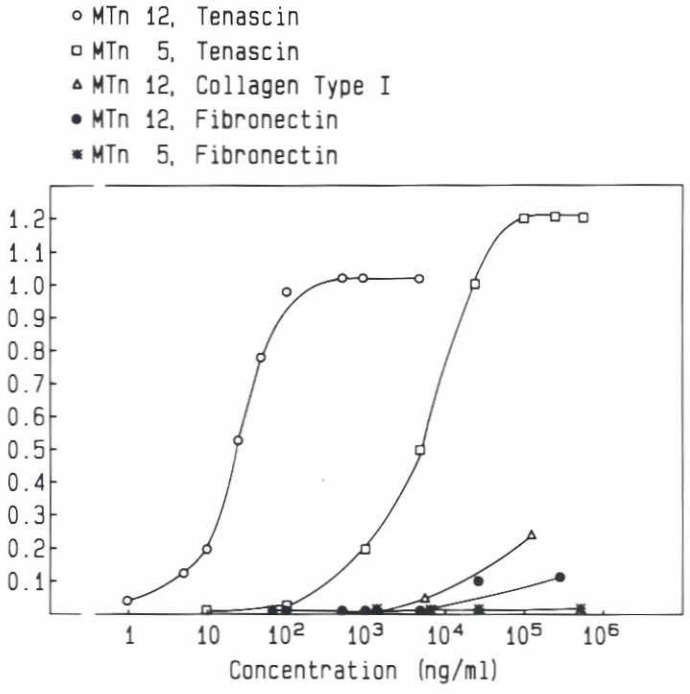

Fig. 3. *Enzyme-linked immunoabsorbent assay demonstrating specific binding of two monoclonals MTn 5 and 12 against mouse tenascin. Bound antibodies were detected by biotinylated anti-rat antibodies, a biotin-streptavidin-horseradish-peroxidase complex and an enzyme-catalyzed dye reaction. Measurements were done after 30 minutes at 450 nm. Wells of microtiter plates were coated with 0.5 ug of protein per well. (○) Antibody MTn 12/substrate tenascin; (□) MTn 5/tenascin; (△) MTn 12/Collagen type I; (●) MTn 12/Fibronectin; (*) MTn 5/Fibronectin. Reproduced from Aufderheide and Ekblom,* The Journal of Cell Biology 107: *2341-2349, 1988; by copyright permission of the Rockefeller University Press.*

Tenascin is a mesenchymal glycoprotein with a much more restricted tissue distribution than fibronectin. Recent evidence suggests that the expression of this protein is closely related to the occurrence of epithelial-mesenchymal interactions in the embryo (Chiquet-Ehrismann *et al.*, 1986). Hence in order to understand more about embryonic induction it is of considerable importance to obtain more information about the structure of this glycoprotein and the nature of the signals that stimulate its expression *in vivo* and *in vitro*.

Tenascin, an extracellular matrix glycoprotein of mesenchyme.

Tenascin was originally described as glioma-mesenchymal extracellular matrix (GMEM) antigen by Bourdon *et al.* (1983, 1985). It was shown to be composed of disulfide-bonded protein subunits of M, of about 230 kD, and it could be demonstrated to be a glycoprotein distinct from fibronectin and laminin, two well-characterized adhesive proteins of the extracellular matrix (Hynes, 1985; Martin and Timpl, 1987). GMEM was found to be absent from the central nervous system of adult brain, but was a prominent mesenchymal matrix protein in human CNS tumors. It was suggested that GMEM affected adhesion of cells (Bourdon *et al.*, 1983, 1985). Proteins similar to GMEM were independently discovered by several groups and it now seems clear that the M1 antigen (Chiquet and Fambrough, 1984 a,b), cytotactin (Grumet *et al.*, 1985), the J1 antigen (Kruse *et. al.*, 1985), hexabrachion (Erickson and Iglesias, 1984), and the GP 250 (Carter and Hakomori, 1981) are all the same protein as GMEM (Erickson and Taylor, 1987). The myotendinous antigen defined by a monoclonal antibody M1 (Chiquet and Fambrough, 1984 a, b) was renamed to tenascin by Chiquet-Ehrismann *et al.*, (1986) and this name has subsequently been used by most investigators in the field.

Although expression of tenascin at sites of epithelial-mesenchymal interactions is one of the most distinct characteristics of tenascin, it is also found in other locations. It is present in the glial matrix of the developing central nervous system (Bourdon *et al.*, 1983; Grumet *et al.* , 1985; Kruse *et al.*, 1985; Crossin *et al.*, 1987), developing cartilage (Mackie *et al.*, 1987; Vaughan *et al.*, 1987), and around muscle fibers (Chiquet and Fambrough, 1984 a,b). These can be considered specialized mesenchymal compartments, and in all these tissues tenascin expression seems to be more restricted than that of fibronectin.

Rotary shadowing electron microscopy of purified tenascin suggests that the intact molecule forms a spider-like structure with six arms connected by a central region. Because of this appearance, the name hexabrachion was suggested for the protein (Erickson and Iglesias, 1984). Each of the six arms has a terminal knob and a thicker distal segment. The thinner inner segments join to form a T-junction, and the two T-like structures are interconnected by the central region which in the middle has a thick globular region (Fig. 1). So far, all published data on tenascin from different sources has revealed the same basic structure (Erickson and Taylor, 1987; Vaughan *et al.*, 1987; Chiquet-Ehrismann *et al.*, 1988; Hoffman *et al.*, 1988). This is interesting since immunological techniques have shown heterogeneity of the apparent molecular mass of the individual subunits. In most cases immunoblotting or immunoprecipitation of extracts from various sources (tissues or cells) with antibodies reveal one large form of tenascin (M, 230-260 kD) and a smaller form of about 200 kD. An example of this polypeptide pattern is shown in the immunoprecipitation (Fig. 2) of medium of mouse fibroblasts using monoclonal antibodies to mouse tenascin (Aufderheide and Ekblom, 1988). These monoclonal antibodies do not react with fibronectin or collagen (Fig. 3) or with the smaller M, 170 kD forms of the J 1 complex (Kruse *et al.*, 1985). From some tissues, such as human tumors, larger forms with an apparent M, of 285 kD have been reported (Erickson and Taylor, 1987) and some antibodies react with 170 kD proteins (Kruse *et al.*, 1985). The reason for this heterogeneity is not altogether clear at the moment, and it is not known how the individual chains assemble to form the six-armed hexabrachion.

In initial studies on cytotactin (Grumet *et al.*, 1985) and the J1 antigen (Kruse *et al.*, 1985) the polyclonal antibodies that recognized the M, 200 kD polypeptide also recognized 180 to 160 kD polypeptides. Specifically-raised antibodies against the distinct polypeptides could, however, distinguish between the different forms, suggesting strongly that the smaller polypeptides of M, between 160 and 180 kD should not be considered analogous to tenascin but rather are unique proteins that can be associated with tenascin (Aufderheide and Ekblom, 1988; Faissner *et al.*, 1988; Hoffman *et al.* , 1988). Nevertheless, there remains some heterogeneity that cannot be explained by cross-reactivity of the antibodies with other proteins. There are apparently different types of tenascin polypeptides ranging from M,

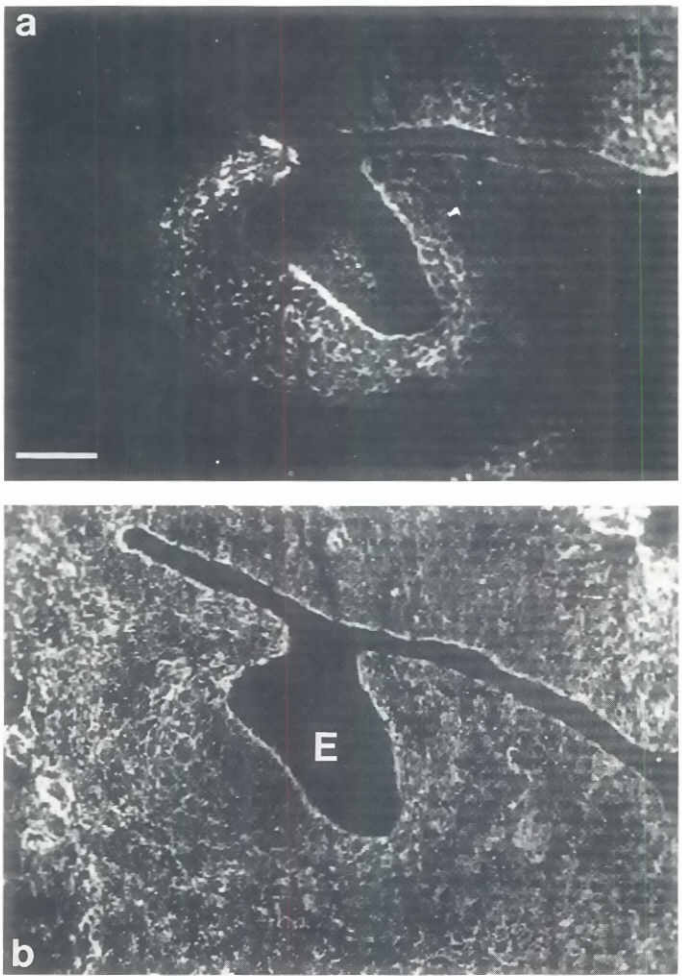

Fig. 4. *Distribution of tenascin (a) and fibronectin (b) in embryonic rat molar tooth. Indirect immunofluorescence demonstrates that fibronectin is distributed in all areas of mesenchyme, whereas tenascin is restricted to those mesenchymal cells close to the developing epithelial bud (E). Reproduced from Chiquet-Ehrismann* et al., Cell 47: *131-139 (1986); by copyright permission of Cell Press. Bar: 50 μm.*

of 200 kD to up to 260 kD, depending on the source and developmental stage of the tissue analyzed. It remains to be seen whether these differences are due to differential glycosylation or differences in the amino acid sequence of the polypeptides. The size of tenascin mRNA estimated by Northern blotting suggests that there are at least two mRNA forms, and thus at least two tenascin polypeptides differing in amino acid sequences are to be expected (Jones *et al.*, 1988; Pearson *et al.*, 1988).

Tenascin interacts with proteoglycans

Like other matrix proteins, tenascin probably interacts not only with cell surfaces, but also with other matrix components. Binding to proteoglycans seems to be a prominent feature of tenascin (Chiquet and Fambrough, 1984; Hoffman and Edelman, 1987; Faissner *et al.*, 1988; Hoffman *et al.*, 1988). The physiological significance of these molecular interactions is not known and other molecular interactions may exist. Tenascin can interfere with fibronectin-mediated cell adhesion (Chiquet-Ehrismann *et al.*, 1988), suggesting that cell behavior could be controlled by varying the ratio between fibronectin and tenascin. Therefore, it would be of importance to analyze tenascin-proteoglycan interactions and tenascin-fibronectin interactions in further detail. Many different proteoglycans have been described, but it is not yet known whether tenascin specifically interacts with special types of proteoglycans or does so with most of them.

Regulation of tenascin expression in mesenchyme by induction from epithelium

Interest in tenascin was greatly enhanced when Chiquet-Ehrismann *et al.*, (1986) showed that tenascin is expressed selectively at sites of epithelial-mesenchymal interactions (Fig. 4). It has long been speculated that the mesenchyme influences developing epithelia by depositing a special type of extracellular matrix (Grobstein, 1967; Bernfield and Wessells, 1972). The expression of tenascin at sites of the interactions raised the possibility that tenascin somehow could be involved in these interactions. Tenascin was found in the mesenchyme of developing epithelia in tooth, vibrissae and breast (Chiquet-Ehrismann *et al.*, 1986; Thesleff *et al.*, 1987) It remained unclear, however, whether tenascin appeared in the mesenchyme as a result of the interaction or whether it was present already at onset of development.

Studies on kidney development were the first to suggest that tenascin actually appears in the mesenchyme as a consequence of interaction (Aufderheide *et al.*, 1987). In the kidney, a part of the mesenchyme converts into new epithelium. It was found that tenascin appeared in the mesenchyme surrounding those new epithelial structures (Fig. 5). Tenascin was not present when the first interaction occurred. Induction of mesenchymal tenascin production by differentiating epithelia may be a common phenomenon and would explain the restricted distribution also in other tissues. Hence it was proposed that actively growing and differentiating epithelial sheets produce locally active factors that stimulate tenascin expression in mesenchyme (Aufderheide *et al.* , 1987; Aufderheide and Ekblom, 1988).

To test tenascin induction by epithelial cells experimentally in mouse models, monoclonal antibodies to mouse tenascin were raised (Aufderheide, 1988). They were then used to study the expression of tenascin during gut development. It is known that epithelial-mesenchymal interactions are required for gut development, and that the interactions are important for the formation of the epithelial cell matrix (Simon-Assmann *et al.*, 1988). The expression studies suggested that gut mesenchyme starts to express tenascin as a consequence of epithelial-mesenchymal interactions. This possibility was then studied in more detail by co-culturing embryonic mesenchyme with different cell lines. It was found that mesenchyme began to produce tenascin when co-cultured with certain epithelial cells but not when co-cultured with B16 melanoma cells (Aufderheide and Ekblom, 1988). Similar findings were independently reported by Inaguma *et al.*, (1988) for breast development. It was shown that tenascin appeared only in breast mesenchyme immediately surrounding the epithelia starting morphogenesis. It was found in embryonic glands from 13- to 16th day of gestation in mammary endbuds. These are characteristic structures of early developmental stages. In contrast, very little tenascin could be detected around elongating ducts of embyonic and adult glands, or in involuting mammary glands (Inaguma *et al.*, 1988). Experimentally-induced epithelial development in the

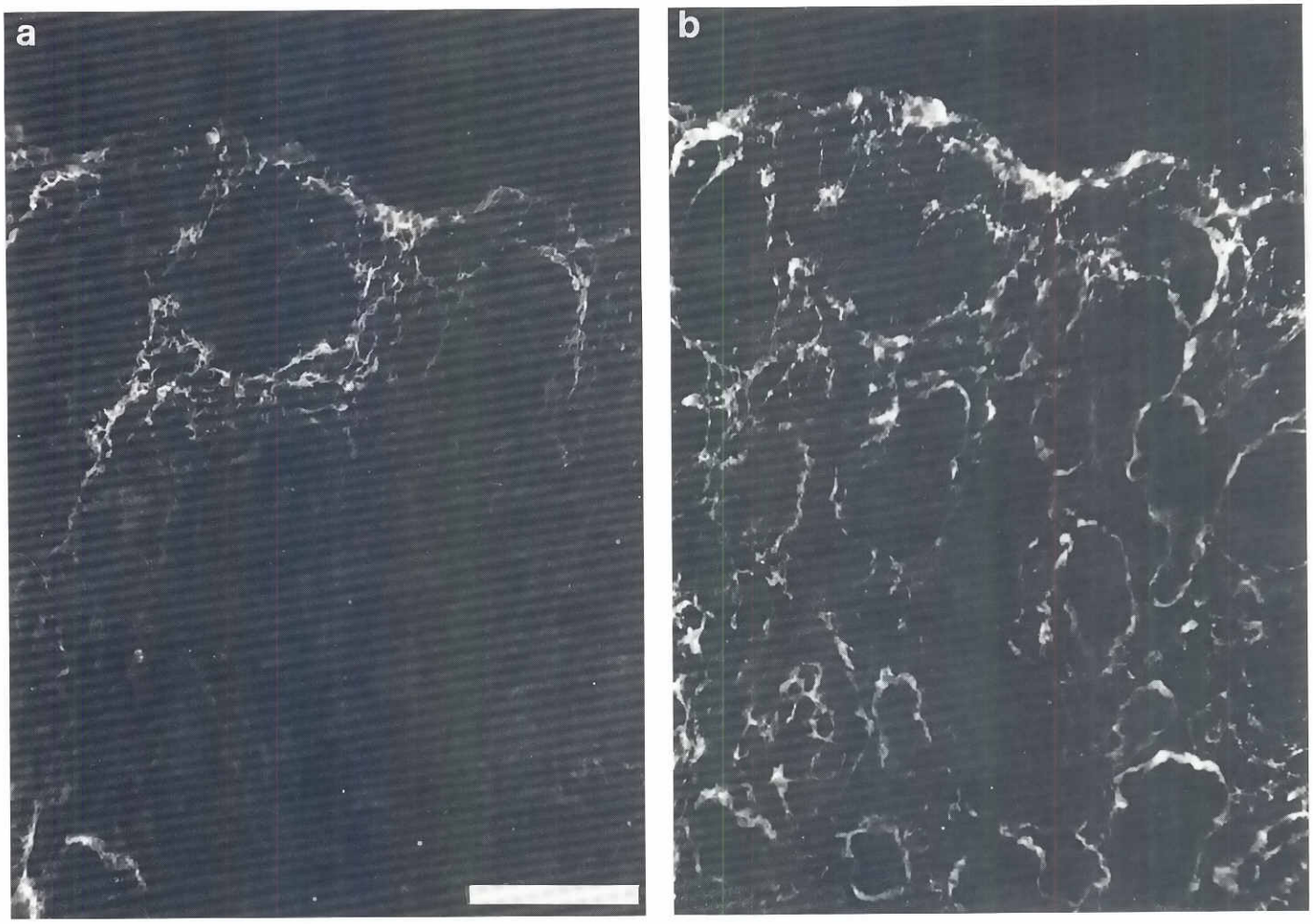

Fig. 5. *Distribution of tenascin (a) and fibronectin (b) in developing mouse kidney. Indirect immunofluorescence shows that fibronectin is distributed in all mesenchymal areas of the kidney and around all developing epithelial structures. Tenascin, in contrast, is seen only around the youngest epithelial structures, which in whole kidneys are located in the upper part of the cortex. Bar: 50 μm.*

mammary gland can apparently stimulate tenascin in the mesenchyme (Fig. 6).

In conclusion, available data from the developing kidney (Aufderheide *et al;* 1987) and gut (Aufderheide and Ekblom, 1988), developing and adult breast (Inaguma *et al.*, 1988) and tooth (Thesleff *et al.*, 1987) support the view that tenascin expression is stimulated by actively growing epithelia. The stimulatory capacity is not necessarily general for all epithelial sheets. This is clearly demonstrated in the developing breast and kidney. In the breast, tenascin expression can be seen only around certain parts of the elongating epithelium (Fig. 6). In the kidney, strong stimulation of tenascin expression is associated with the appearance of kidney tubules, whereas very little tenascin is found around the second epithelial sheet, the ureteric tree (Aufderheide *et al;* 1987). It is thus possible that in the kidney only the tubular epithelium and not the ureter epithelium secrete factors that stimulate tenascin production. The nature of these factors in unknown, and factors in the mesenchyme may also be involved.

It is noteworthy that growth factors such as transforming factor-β (TGF-β) can stimulate tenascin synthesis *in vitro* (Pearson *et al.*, 1988), and TGF-β is found in the embryo at sites of tenascin expression (Heine *et al,* 1987). TGF-β or other similar growth factors may thus act as local inducers of extracellular matrix production at sites of epithelial-mesenchymal interactions. It is not clear, however, whether TGF-β is a stimulator of tenascin synthesis during *in vivo* organogenesis.

Possible role of tenascin at sites of epithelial-mesenchymal interactions

Extracellular matrix proteins often have direct influences on the very cells that secrete them. Fibronectin is produced by fibroblasts and affects the behavior of fibroblasts (Vaheri and Mosher, 1978; Ruoslahti *et al.*, 1983). Laminin, a basement membrane protein (Timpl *et al.*, 1979) produced by epithelial cells is probably important for epithelial cell development (Ekblom *et al.*, 1980). Direct evidence for a role of laminin in epithelium development has recently been reported. Certain defined parts of laminin are required for the further development of the induced cells; antibodies against the A chain of laminin can per-

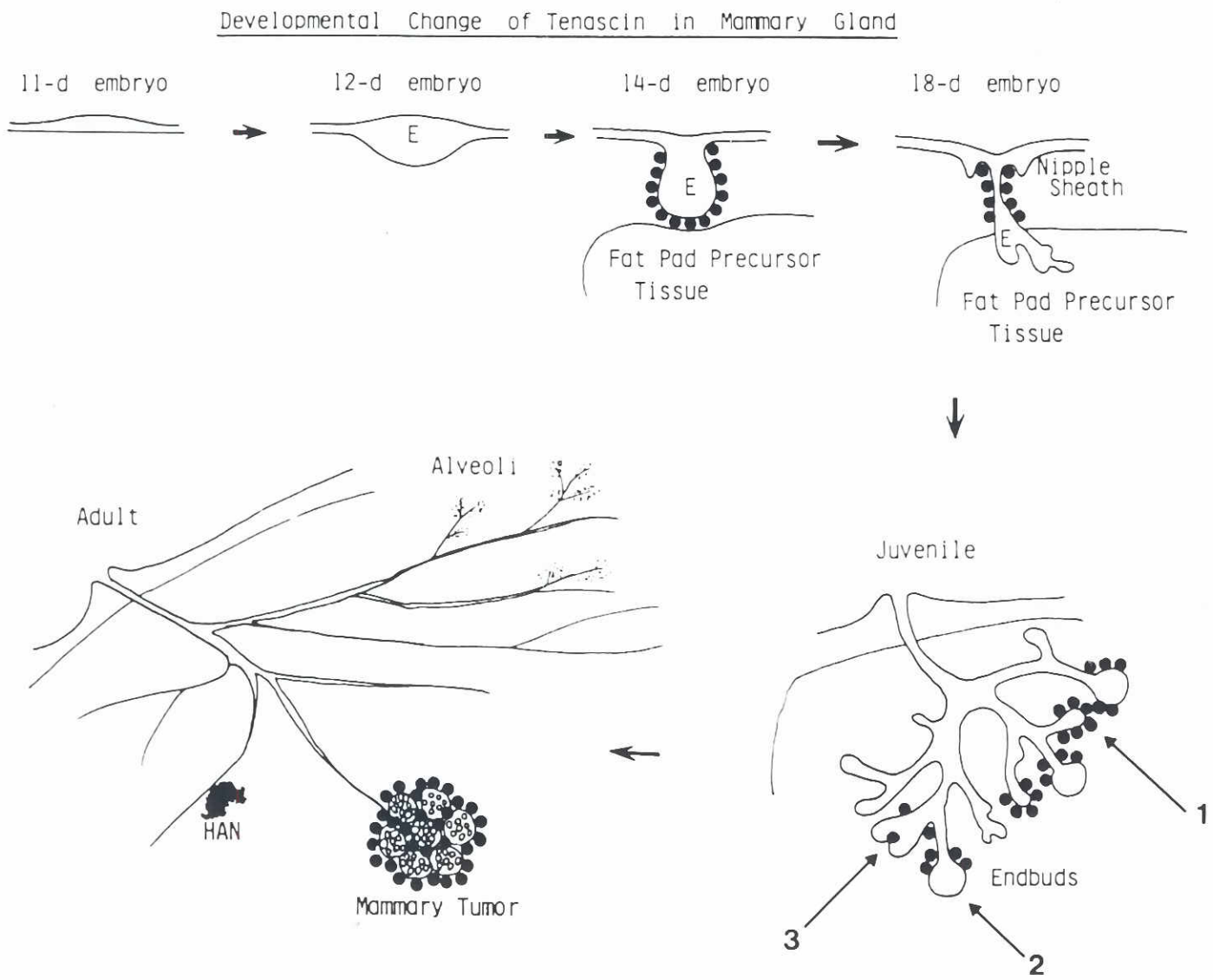

Fig. 6. *Scheme of tenascin expression during breast development. The black areas indicated strong tenascin expression. Tenascin can be seen only locally in mesenchyme around developing epithelium but only in certain areas during breast development. Abbreviations: HAN, hyperplastic alveolar nodule. For details, see Inaguma* et al., *1988. Reproduced from* Developmental Biology 128: *245-255, 1988; by copyright permission from Academic Press Inc.*

turb histogenesis of kidney tubules (Klein *et al.*, 1988). Hence, matrix proteins of epithelia are important for the epithelial cells themselves. By analogy, we suggest that tenascin expression in the mesenchyme could be important for the development of the mesenchymal cells in the kidney, and in the other developing organs expressing tenascin. The presence of tenascin can interfere with fibronectin action, an effect which probably is of major significance for development of mesenchymal cells (Chiquet-Ehrismann *et al.*, 1988). In many of the tissues expressing tenascin, the tenascin-positive areas seem to be slightly more compact that the surrounding mesenchyme (Chiquet-Ehrismann *et al.*, 1986; Thesleff *et al.*, 1987; Inaguma *et al.*, 1988). This does not appear to be the case for the developing kidney, however, and therefore the association between compactness and tenascin expression in the other tissues may be coincidental (Aufderheide *et al.*, 1987). Morphological comparisons of tissues with varying amounts of tenascin may thus not reveal the function of tenascin.

In order to understand more about the function of tenascin, direct functional tests should be performed. Some data on the function of tenascin in the developing nervous system is available (Kruse *et al.*, 1985; Chuong *et al.*, 1987). Technically, the easiest approach to test the role of tenascin in epithelial-mesenchymal interactions would be the application of anti-tenascin antibodies into organ cultures. Injection of antibodies or hybridomas secreting these antibodies into specific locations in the embryo has been performed for other matrix ligands (Bronner-Fraser, 1985; Jaffredo *et al.*, 1988), and could also be tried out for tenascin. Such studies may clarify the role of tenascin at sites of epithelial-mesenchymal interactions. It is important to note

that tenascin during embryogenesis can exist in different forms (Hoffman *et al.*, 1988). In the developing gut, for instance, only the smaller polypeptide chains appear to be made at early developmental stages (Aufderheide and Ekblom, 1988). The larger forms gradually appear with advancing development (Fig. 7). Such variations in chain synthesis may have profound effects on the biological properties of tenascin. A more precise mapping of the various domains of tenascin, their chemical structure, and binding to cells and matrix should help us to clarify the biological functions of tenascin.

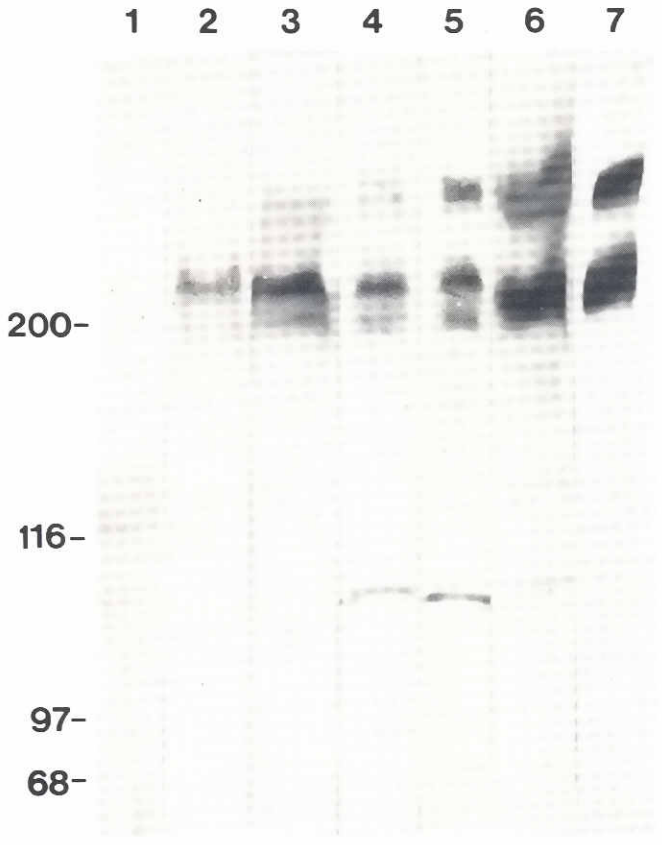

Fig. 7. *Sequential appearance of different tenascin polypeptides during embryonic gut development as shown by immunoblots of tissue extracts with mAb Mtn 12. Extracts were separated by SDS-PAGE, transferred to nitrocellulose filters, and detected by incubation with mAb, a biotinylated second antibody, a streptavidin-alkaline phosphate complex, and a color reaction. Extracts are from embryonic day 13 (lane 1), 15 (lane 2), 18 (lane 3), newborn (lane 5), adult (lane 6) and cultured fibroblasts (lane 7). Note that no tenascin could be seen in 13-day intestine, and that the bigger 260 kD tenascin polypeptide is not seen clearly until birth. Molecular mass markers in kD to the left. Reproduced from Aufderheide and Ekblom.* The Journal of Cell Biology 107: *2341-2349, 1988, by copyright permission of the Rockefeller University Press.*

Induction of stromal tenascin in carcinogenesis

The studies on tenascin during embryonic development may be useful for our understanding of certain aspects of carcinogenesis. Most solid tumors in humans are derived from epithelial cells. Very often, the malignant epithelial cells are surrounded by a rather abundant extracellular matrix. Tenascin seems to be part of this tumor matrix. Tenascin is expressed in stroma around epithelial malignancies of mammary gland but not in the stroma of benign tumors (Mackie *et al.*, 1987; Inaguma *et al.*, 1988). Tenascin thus seems to have some features of an oncofetal antigen. It is clear, however, that several normal adult tissues express some tenascin (Bourdon *et al.*, 1983; Hoffman *et al.*, 1988) although tenascin expression is not a prominent feature of the stroma of adult tissues. Apparently, carcinogenesis of epithelial cells leads to an increased production of factors that stimulate tenascin expression in the nearby stroma. The carcinomas may overproduce these factors, normally produced at high levels only during embryogenesis. The data suggest that carcinogenesis involves disturbances in inductive cell interactions between epithelium and mesenchyme. In order to understand the interactions of carcinoma cells and the nearby mesenchymal cells, we need more information on the basic mechanisms of embryonic induction in experimental model systems. It will therefore be of considerable interest to learn how the epithelial sheets induce tenascin expression in embryonic mesenchyme.

Concluding remarks

In many embryonic tissues, epithelial-mesenchymal interactions affect the composition of the extracellular matrix of the responding tissue. This has been previously shown clearly for the development of the epithelial cell extracellular matrix, the basement membrane (Ekblom *et al.*, 1980, 1981; Hay, 1983). Here we have reviewed data suggesting that mesenchymal cells from several parts of the embryo respond to the presence of epithelial sheets by starting to synthesize tenascin. In several embryonic tissues tenascin expression could thus be controlled by inductive tissue interactions. A similar induction apparently occurs when carcinoma cells meet stromal fibroblasts in adult tissues. Thus, identifying the factors that stimulate tenascin expression would be important for our understanding of embryonic induction, and development of some forms of cancer.

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