EP-cadherin in muscles and epithelia of *Xenopus laevis* embryos

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Summary

EP-cadherin is a novel *Xenopus* Ca\(^{2+}\)-dependent adhesion molecule, which shares comparable homology with mouse E- and P-cadherins (Ginsberg, De Simone and Geiger; 1991, *Development* 111, 315–325). We report here the patterns of expression of this molecule in *Xenopus laevis* embryos at different developmental stages ranging from cleavage to postmetamorphic. EP-cadherin is already expressed in the oocyte and egg and can then be detected in close association with the membrane of all blastomeres up to late blastula stages. Starting at late gastrula stages, the level of EP-cadherin expression increases sharply in non-neural ectodermal cells, in the somites and in the notochord; it persists in endodermal cells and decreases rapidly in all migratory cells. During neurulation the level of EP-cadherin expression declines gradually in the nervous system and is undetectable here throughout later development except in the optic nerve and in the neural part of the olfactory organ. This pattern continues during later development so that in the tailbud stage and up to metamorphosis the most prominent staining is detected in the epidermis and skeletal muscle. After metamorphosis, the molecule gradually disappears from the muscle tissue and the major site of expression remains the skin.

EP-cadherin is invariably present in close association with the cell membrane. In the muscle it is associated with the sarcolemma at regions of myoblast–myoblast or myotube–myotube contact. In epidermal cells, EP-cadherin is usually coexpressed with E-cadherin. Yet, while E-cadherin staining is always restricted to the basolateral aspects of the cells, EP-cadherin is often distributed throughout the plasmalemma including the apical surface.

Key words: *Xenopus laevis*, development, cadherins.

Introduction

Cadherins are a family of homophilic Ca\(^{2+}\)-dependent cell adhesion molecules that exhibit considerable sequence homology and are highly conserved throughout evolution (Takeichi, 1988). These molecules are often located in adherens-type junctions, in an apparent association with the cytoskeleton (Geiger et al. 1984; Hirano et al. 1987; Boller et al. 1985), suggesting that they are involved in the control of cellular interactions during tissue differentiation. Furthermore a number of perturbation experiments (Gallin et al. 1986; Duband et al. 1987; Nose et al. 1988; Detrick et al. 1990) contribute to support the notion that cadherins are essential for the control of critical events of morphogenesis (Edelman 1985, 1986; Takeichi, 1988; Thiery, 1989).

More recently, it was demonstrated that the forced expression of cadherins in mesenchymal cells, following transfection with the appropriate cDNAs, augments cellular interactions leading to an apparent epithelialization. The latter studies have also shed some light on the possible physiological significance of the presence of multiple cadherins within the same species; it has been shown that cells bearing different types of cadherins or expressing different levels of the same cadherin display selective homotypic binding (Nagafuchi et al. 1987; Edelman et al. 1987; Hatta et al. 1988; Nose et al. 1988; Mege et al. 1988; Miyatani et al. 1989; Friedlander et al. 1989; Matsuzaki et al. 1990) yet the differential contributions of the various cadherins to morphogenetic events remain to be elucidated.

In an attempt to study the involvement of cadherins in embryonic morphogenesis, we have recently characterized the expression of different cadherin molecules in developing *Xenopus laevis*. One of the earliest cadherin detected is EP-cadherin (Ginsberg et al. 1991), which is encoded by a maternal transcript and is already present in the oocyte and unfertilized egg and which appears to be identical to the 'cadherin like protein' described by Choi et al. (1990) (B. Gumbiner, personal communication). Two other cadherins, XB-cadherin (Herzberg et al. 1991) and U-cadherin (Angres et al.
boiling Laemmli sample buffer; it was essential to reduce as much as possible the time needed for the preparation of the samples as EP-cadherin appears to be particularly sensitive to degredation. Early embryos were homogenized in 5 volumes of cold TBS containing 0.1% Triton X-100, 0.5% NP40 and a cocktail of protease inhibitors, the homogenate was then centrifuged in an Eppendorf table-top centrifuge for 5 min and a aliquot of the clear extract was mixed and boiled in Laemmli sample buffer. Samples were resolved by SDS-PAGE (Laemmli, 1970) on 7% or 10% polyacrylamide gels followed by electrophoretic transfer of the proteins to nitrocellulose paper (Towbin et al. 1979). The presence of EP-cadherin was revealed by an overnight incubation with the rabbit R-827 antiserum at an appropriate dilution or with the band-purified antibodies, followed by 125I-protein A and autoradiography.

Immunochemistry

Paraffin sections were prepared for staining using a previously published procedure (Levi et al. 1987; Gurdon et al. 1976); when this procedure was used to prepare sections of large metamorphic animals, the method was modified as described (Levi et al. 1990). For immunofluorescence, sections were deparaffinized in xylene (3 x 2 min), rehydrated and incubated sequentially with the primary antibody or the affinity-purified band-specific antibodies (10 μg/ml-1 in PBS, 5% foetal calf serum (FCS); overnight), and Texas-red-conjugated anti-rabbit IgG secondary antibodies (10 μg ml-1 each in PBS, 5% FCS; 2 h). For double staining we treated the sections simultaneously with the two primary antibodies followed by a mixture of Texas-red-conjugated anti-rabbit IgG antibodies and biotinylated anti-mouse IgG antibodies and by FITC-streptavidin; all secondary antibodies were from Amersham. In the case of early embryos, the staining was confirmed by using phycocerythrin-conjugated streptavidin (Biomedia Corp., Foster City, CA) for labeling and a barrier filter at 550 nm to reduce the intensity of the yolk autofluorescence. The sections were observed with either a Leitz epifluorescence microscope or Zeiss Axiohot microscope. Control sections were stained either with similar dilutions of purified rabbit IgG or with preimmune rabbit serum.

Enzymatic staining of early embryos

The use of immunohistofluorescence was not adequate to stain early embryos (before stage 13) due to high levels of autofluorescence and immunoperoxidase labeling was used instead. Albino Xenopus embryos were stained according to the method of Dent et al. (1989), using either anti-EP-cadherin or irrelevant antibodies and goat anti-rabbit antibodies conjugated to peroxidase (Jackson, USA). Following the enzymatic reaction, the embryos were dehydrated in alcohol and embedded in JB4 resin (Polysciences, Inc., PA). The embedded embryos were sectioned (2-3 μm) using an LKB Nova microtome and examined in a Zeiss Axiohot microscope.

Electron microscopy

Tadpoles were fixed with modified Karnovsky’s fixative (3% glutaraldehyde, 2% formaldehyde, 1% acrolein, 2.5% dimethyl sulfoxide in 0.1 M cacodylate buffer, pH 7.2) for 5 h at room temperature and 12 h at 4°C. The tissue was then postfixed with 2% OsO4 in cacodylate buffer containing 0.5% potassium dichromate and potassium ferrocyanide, the blocks were then dehydrated and embedded in Polybed 812 (PolySciences, USA). Sections were examined with a CM-12 transmission electron microscope (Philips, Netherlands), at 80 kV.

Materials and methods

Animals

Sexually mature Xenopus laevis were obtained either from the Service d’Élevage de Xenope of the Centre National de la Recherche Scientifique (Montpellier) or from Xenopus 1 Ltd (MI, USA). Embryos were obtained by artificial fertilization (Newport and Kirschner, 1982) and maintained in 10% filter-sterilized Holfreter’s solution at room temperature. Animals at more advanced stages were purchased from Nasco (Fort Atkinson, Wisconsin). Stages of development were determined according to Nieuwkoop and Faber (1967).

Antibodies

The preparation of the antibodies to Xenopus laevis EP-cadherin used in this study (R-827) has been previously described in detail (Ginsberg et al. 1991); it was obtained by injection in rabbits of a trpE fusion protein containing amino acids 149-366 of EP-cadherin. This antiserum stained A6 cells in culture as well as the periphery of the animal hemisphere of Xenopus early embryo. In this study, we have examined the tissue-restricted expression of EP-cadherin throughout early development and up to metamorphosis. We show that this molecule exhibits an expression profile distinct from that of either E- or N-cadherin, but that it is often coexpressed with these two molecules (i.e. E-cadherin in the skin, N-cadherin in the somites and muscle) displaying, however, a different subcellular distribution. We discuss here the significance of the differential expression of cadherins in early embryos and their different subcellular distribution.

Western blots

Cells and differentiated tissues were homogenized directly in
Fig. 2. Distribution of EP-cadherin during early embryogenesis. Immunoperoxidase labeling of early blastula with anti-EP-cadherin (R-827). Bar=20 μm.
Results

Characterization of anti-EP-cadherin (R-827) antibodies

The study of the EP-cadherin distribution was largely dependent on the use of a monospecific antibody (R-827), which was raised in rabbits against a bacterial fusion protein, containing a segment of EP-cadherin (Ginsberg et al. 1991). We considered it, therefore, of primary importance to demonstrate that these antibodies specifically recognize EP-cadherin and do not bind to other members of the cadherin family. This was conducted by comparing the reactivity of the antibodies with CHO cells which were stably transfected with EP-cadherin (as described in Ginsberg et al. 1991) to that obtained with CHO cells, which contain little or no cadherins. As shown in Fig. 1A, western blot analysis of these two cell lines using the R-827 antibodies revealed the presence of a 120×10^3 M_r protein in the transfected cells, which was absent from the parental cell line. A comigrating molecule was identified in a parallel western blot analysis carried out with the pan-cadherin antibody (R-156) directed against the highly conserved C-terminal 24 amino acids of N-cadherin (Geiger et al. 1990). Furthermore, immunostaining of the EP-cadherin-transfected cells by the R-827 antibodies showed intense staining in areas of cell–cell contact (Fig. 1C) which was absent from the parental cells (Fig. 1D). It is noteworthy that the forced expression of EP-cadherin in CHO cells was accompanied by morphological changes manifested in an apparent epithelialization (Ginsberg and Geiger, unpublished results).

EP-cadherin was also detected in an established Xenopus cell line, namely A6 cells, along with at least two additional cadherins (Ginsberg et al. 1991). Western blot analysis of A6 cell extracts with R-827 serum or affinity-purified antibodies to EP-cadherin resulted in the identification of a single band of 120×10^3 M_r comigrating with the band present in the transfected CHO cells. Additional cadherins, which are recognized in these cells by the pan-cadherin and anti-E-cadherin antibodies, did not react with the anti-EP-cadherin serum. Moreover, R-827 did not stain CHO or L cells transfected with mouse or chicken E-, P- or N-cadherins (data not shown).

Expression of EP-cadherin in early stages of Xenopus embryogenesis

The expression of EP-cadherin in developing Xenopus embryos was first analyzed by western blotting using the R-827 antibody. As can be seen in Fig. 1B, the 120×10^3 M_r EP-cadherin band was already detectable in the egg and persisted throughout the blastula and neurula stages. In the latter stages, an additional faint band of 220×10^3 M_r was also detected.

Immunohistochemical labeling of Xenopus blastulae with R-827 antibodies yielded a positive staining of essentially all blastomeres, which was concentrated along the plasmalemma and was particularly intense in areas of blastomere–blastomere contact (Fig. 2A,B). This observation supported the notion that EP-cadherin is a membrane-associated protein involved in cell–cell adhesion in the early embryo.

![Fig. 1](image-url)
Between the end of gastrulation and the onset of neurulation, we observed a strong increase in EP-cadherin expression in all non-neural ectodermal structures. This was particularly evident in the cement gland, which was already brightly stained in stage 14–15 embryos when its differentiation begins. All cells of the columnar epithelium of the cement gland showed a strong membrane-associated staining, which was distributed throughout all cell surfaces including the apical membrane (Fig. 3A). The staining for EP-cadherin was also increased throughout the epidermis (Fig. 3B). The underlying lateral plate mesoderm and somites were also positive and the staining was predominantly associated with the plasma membrane (Fig. 3B,C). The notochord was very brightly stained throughout development up to its degeneration (Fig. 3E,F). Migratory cells such as neural crest cells surrounding the notochord were never stained by anti-EP-cadherin antibodies (Fig. 3E).

The staining of the cells in the neural fold and the neural tube diminished gradually so that in the well-differentiated nervous system (stage 20 embryos) only a
faint immunoreactivity was detected. The large cells of the endoderm continued to show some EP-cadherin expression, localized prominently in regions of cell–cell contact (Fig. 3D); this staining persisted in the differentiating gut epithelia.

**Differential distribution of EP- and E-cadherins in the skin and in other epithelia**

As pointed out above, EP-cadherin was highly expressed by presumptive and differentiated epidermal cells throughout the development of the animal. During neurulation the expression of the molecule increases in non-neural ectodermal cells, concomitantly with epidermal differentiation (Fig. 3B). A similar increase of expression during epidermal differentiation has also been observed for E-cadherin (Levi et al. 1991). In order to elucidate the interrelationship between the two cadherins, we performed a series of double-staining experiments. Although the two cadherins were found in the same cells, their subcellular localization was not always identical. While E-cadherin was distributed only on the basolateral aspects of the polarized epithelia of the outer and inner layer of the epidermis of the larva, EP-cadherin was present all over the cell surfaces (Fig. 4A,B).

During later stages of development strong EP-cadherin staining was also present in the lateral line sensory organs of the premetamorphic skin and in the epithelium of the ducts of the glands of the postmetamorphic skin (Fig. 4C). During metamorphosis, at variance with E-cadherin which continued to be present even in degenerating epidermis (Levi et al. 1991), EP-cadherin staining decreased dramatically in degenerating areas of the skin (Fig. 4D).

EP-cadherin was also present in many other epithelia such as the pharyngeal floor (Fig. 3F), the gills epithelium, the Wollfian ducts and, faintly, in the gut epithelium. In the differentiated liver and in the pancreas, EP-cadherin immunoreactivity was undetectable.

**Distribution of EP-cadherin in muscles**

Skeletal muscle was found to be one of the major sites of expression of EP-cadherin up to metamorphosis. Myotomal cells were immunopositive at all stages of development. In the somites the myoblasts were clearly positive already before somite rotation (Fig. 3C,F), and remained so throughout development of axial muscles (Fig. 5A,B) and of smooth muscles (Fig. 5C). In premetamorphic animals, a strong EP-cadherin was highly expressed in the epidermis and in the underlying muscles, while E-cadherin was present only in the epidermis (Fig. 5D,E,F,G). To confirm that the staining observed in both the skin and the muscle

![Fig. 4. Distribution of anti-EP-cadherin immunoreactivity in the skin. (A,B) Double staining with R-827 anti-EP-cadherin antibody (A) and a monoclonal anti *Xenopus* E-cadherin (B) of larval skin (stage 41) showing distinct distribution of the two molecules. Premetamorphic skin (C) and forelimb of a stage 51 animal (D) stained with R-827. Note that only the newly formed epidermis of the limb is stained for EP-cadherin while the degenerating epidermis of the body (sk) is not. fl, forelimb; g, gland; ol, outer layer of the epidermis; sk, degenerating skin of the body; sl, sensory layer of the epidermis. Bar=30 μm.](image-url)
corresponded to genuine EP-cadherin, we checked extracts of the skin and the muscles dissected from the tail of a stage 53 animal for the presence of EP-cadherin by western blot analysis, using the R-827 antibodies. Fig. 5H,I shows that the antibodies recognized a 120 kDa protein in both tissues.

In the muscle, EP-cadherin immunoreactivity was apparently associated with the sarcolemma along all the length of the fiber. Furthermore staining was observed only in regions of cell–cell contact and was not detectable in aspects of the fiber that were not juxtaposed to other fibers (Fig. 5F). This observation suggested that EP-cadherin was involved in myotube–myotube or myotube–myoblast adhesion. To establish the nature of these cellular adhesions we have examined premetamorphic muscle at the electron microscopic level and stained this tissue for vinculin. The former analysis (Fig. 6B) confirmed that adjacent myotubes were closely attached to each other, often displaying electron-dense plaques associated with the sarcolemma. In addition, immunofluorescent labeling for vinculin was localized along the cell periphery in
regions of cell contact suggesting the presence of adherens-type junctions (Fig. 6A).

**Distribution of EP-cadherin in the nervous system and sensory organs**

The central and peripheral nervous systems were only very faintly stained by anti EP-cadherin antibodies throughout larval development, the only exception being the optic nerve, which was brightly stained at all stages analyzed (Fig. 7A,C). The optic nerve was stained from the lamina cribrosa up to the optic tectum. In transverse sections of the nerve (Fig. 7C) the staining did not have the punctuate appearance typical of antigens present on the axons but was most probably associated to another population of cells within the optic nerve, possibly oligodendroglia. A strong immunoreactivity was present in the meninges (Fig. 7B), and some staining was also present in cells of the neural epithelium lining the ependymal canal of the spinal cord. During the formation of the ear, EP-cadherin rapidly disappeared from the inner layer of the ectoderm after it thickened to form the otic placode. EP-cadherin immunoreactivity was present at low levels in the auditory epithelium and in the *crista extaerna*, a restricted region in the craniolateral part of the sensory epithelium (Fig. 7D). EP-cadherin was also present in the olfactory organ in most stages of development; the staining was already present in the olfactory placode and persisted in the nasal pit and in the Jacobson's organ (Fig. 7E).

**Discussion**

In this study, we examined the distribution of EP-cadherin during *Xenopus laevis* development. We show that this adhesion molecule is already present in the egg and persists throughout embryogenesis. The observation that EP-cadherin is present in the cleavage stage *Xenopus* embryo as well as its localization at regions of blastomere–blastomere contact suggests that this molecule is a 'primary' cell adhesion molecule in this species. Moreover, on the basis of examination with the pan-cadherin antibodies (Geiger *et al.* 1990), it appears that EP-cadherin might be one of the major cadherins present before MBT. Recently there were other reports describing the presence of cadherins in oocytes and blastula stage *Xenopus* embryo, these include the cadherin-like protein (CLP) (Choi *et al.* 1990), U-cadherin (Angres *et al.* 1991) and XB-cadherin (Herzberg *et al.* 1991). The CLP was since cloned and sequenced by Gumbiner and his colleagues and found to be essentially identical to EP-cadherin (personal communication). Molecular details about U-cadherin are still scarce. Of the 21 amino acids of U-cadherin sequenced 3 differences were detected when compared to EP-cadherin and the immunohistochemical data are insufficiently overlapping to draw a definitive conclusion. The recently described XB-cadherin shows 92% identity to EP-cadherin at the nucleotide and amino acid levels. This difference could, in principle, be accounted for by allelic polymorphism, though a direct evidence supporting this view is still missing. The fine molecular and cytological relationships between the various 'early cadherins' of *Xenopus* are still not elucidated and the possibility that multiple molecules are coexpressed at these stages cannot be excluded. This is especially relevant in view of the recent findings that closely related members of the cadherin family are coexpressed in mammalian brain (Suzuki *et al.* 1991). It is worth noting that the possibility that there are additional cadherins, which do not bear the conserved cytoplasmic domain, present during early development cannot be ruled out. This possibility is especially
attractive in view of the recent reports on cadherins that
differ in their C-terminal region (Ranscht and Bronner-
Fraser, 1991; Suzuki et al. 1991).

The role of EP-cadherin in adhesive interactions was
demonstrated by its forced expression in CHO cells,
which led to major morphological changes in the cells
concomitantly with the localization of the protein in
intercellular contacts. Its involvement in mediating

The arrest of EP-cadherin expression in early embryos impairs the
interactions between blastomeres (Ginsberg, Geiger,
Heasman and Wylie, unpublished results). A similar
perturbation of blastomere interactions was also obtained
by antibodies directed against U-cadherin
function as ‘primary cadherins’ in other species? In
mouse and chicken embryos, antibodies prepared
against a cadherin of differentiated epithelia (E-
cadherin/Uvomorulin in the mouse, L-CAM in the
chicken) do recognize a molecule present in the
cleavage stage embryo and involved in cell-cell
adhesion (Hyafil et al. 1980; Ogou et al. 1983; Damsky et
al. 1983; Shirayoshi et al. 1983; Vestweber and Kemler,
1984; Johnson et al. 1986; Vestweber et al. 1987; Gallin
et al. 1983, 1985, 1987; Thiery et al. 1984). In
Xenopus, however, E-cadherin is not present in early stages of
development, but starts to be expressed only during
epithelial differentiation (Levi et al. 1991). In view of
the fact that EP-cadherin shares strong homology sequence with E-cadherin (Ginsberg et al. 1991) and
that it has been reported, at least in one case, that cross-
reacting monoclonal antibodies against the amino
terminal region of the two molecules could be prepared
(Angres et al. 1991), it is possible that the antigen
recognized in early mouse and chicken embryo is, in

Fig. 7. Distribution of anti-EP-cadherin in the nervous system and sensory organs. (A,C) Longitudinal (A) and transverse
(C) sections through the optic nerve of stage 41 (A) and 51 (B) Xenopus. The optic nerve is positive after its exit from the
lamina cribrosa. (B) Staining of the spinal cord of a stage 51 tadpole. No staining is observed in the central nervous system
beside the meninges and the ependymal canal. (D) Auditory organ at stage 41; the crista externa and part of the sensorial
epithelium are stained. (E) Olfactory organ stage 41; the nasal pit and the Jacobson’s organ are stained. on, optic nerve;
ep, ependymal canal; mg, meninges; r, retina; ce, crista externa; ev, ear vesicle; np, nasal pit; Jo, Jacobson’s organ.
Bar=40 μm.
fact, not (or not only) authentic E-cadherin (or L-CAM), but a distinct cadherin related to EP-cadherin. Such explanation would account for the fact that a polyclonal anti-i-CAM antibody used for immunofluorescence labeling of Xenopus sections did stain both early embryos and differentiated epithelia (Levi et al. 1987). Such possible cross reactivities should be taken into account in the interpretation of immunochemical analysis of cadherin diversity.

As shown, following MBT, E- and N-cadherins appear in the Xenopus embryo (Levi et al. 1991; Detrich et al. 1990; Ginsberg et al. 1991) while the expression of EP-cadherin becomes more restricted to muscle and epidermis.

In skeletal muscle, EP-cadherin is localized along the plasma membrane of both myoblasts and myotubes. The strict distribution in areas of fiber–fiber contact suggests a role in generating adherens junctions (or similar structure) between adjacent muscle fibers. Indeed electron microscopic observation of Xenopus tail muscle revealed the presence of regions of close association between the plasma membranes of adjacent cells, displaying submembrane electron density typical of adherens junctions. EP-cadherin is the first cadherin to be detected in structurally mature skeletal muscle; however, at least two other cadherins have been reported to be present during early muscle development in other species. These include N-cadherin/A-CAM (Duband et al. 1988) and T-cadherin (Ramscht and Bronner-Fraser, 1991), which is transiently expressed in the somites at the moment of neural crest cell emigration.

How do these different adhesion molecules participate in the formation of a functional neuromuscular unit or the fusion of myoblasts and assembly of individual fibers into bundles remains still to be determined. This appears to be particularly challenging in Xenopus since muscular development in this species was reported to differ from that found in other species as multinucleation of mature fiber is not obtained by myoblast fusion, but by karyokinesis without subsequent cytokinesis (Boudjelida and Muntz, 1987). It appears that further studies of differentiating Xenopus muscle in culture will be needed in order to understand the specific roles played by N- and EP-cadherin in muscular development.

In the skin, EP-cadherin is co-expressed with additional cadherin molecule(s), yet their differential contributions to intercellular adhesion is not clear. An intriguing observation made in this study is that EP- and E-cadherins, which are expressed by the same skin cells, can differ in their subcellular distribution: while E-cadherin is present only in the basolateral domain of the epidermal cells, EP-cadherin is broadly distributed throughout the membrane, including its apical aspect. This suggests that in addition to the cell-type-specific expression of different cadherins, which is commonly considered to account for selective cell adhesion, subcellular targeting of these molecules could also be involved. The basis for this phenomenon is not clear, yet it is possible that selective interactions of the two cadherins with other membrane components or with the subplasmalemmal cytoskeleton leads to the differential distribution observed.

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