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Developmental Pattern of Expression of the Mouse α1(XI) Collagen Gene (*Col11a1*)

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ABSTRACT **Fibrillar networks are intimately involved in several morphogenetic processes which underlie the harmonious development of the vertebrate embryo. Recent genetic evidence has demonstrated that the minor types V and XI collagen are key regulators of types I and II fibrillogenesis in non-cartilaginous and cartilaginous matrices, respectively. A comprehensive understanding of the expression and regulation of the genes coding for the chains of the minor collagen types is therefore relevant to animal morphogenesis and development. The present study was undertaken to elucidate the embryonic pattern of expression of the gene coding for the mouse α1 chain of type XI colagen (*Col11a1*) using the technique of in situ hybridization. Transcripts of the *Col11a1* gene were detected as early as 11 days of gestation. The α1(XI) transcripts were found to accumulate mostly in cartilaginous tissues, such as the chondrocranium and the developing limbs. Like the major cartilage-specific collagen (type II), *Col11a1* expression was also noted in the neuro-epithelium of the brain. However, α1(XI) transcripts accumulated in several other non-cartilaginous sites. They include odontoblasts, trabecular bones, atrioventricular valve of the heart, the tongue, the intestine, and the otic vesicle. Altogether, the data confirm that *Col11a1* has a broader spectrum of expression than previously thought. This finding raises the possibility that the α1(XI) chain may participate in the formation of stage- and tissue-specific trimers with distinct functional properties.**

Key words: Type XI collagen, Extracellular matrix, Gene expression

INTRODUCTION

In addition to being responsible for the biochemical properties of most tissues, collagenous networks are also intimately involved in a variety of morphogenetic processes (reviewed by Linsenmayer, 1991). Transgenic and gene targeting experiments have dramatically illustrated the latter role by documenting impaired development of mice harboring defective collagen genes. This large body of work includes transdominant overexpression of mutated versions of the genes coding for the α1(I), α1(II), α1(IX), and α1(X) collagen chain (Schnieke et al., 1983; Garofalo et al., 1991; Vandenberg et al., 1991; Nakata et al., 1993; Jacenko et al., 1993); inactivation of the genes coding for the α1(I), α1(IX), and α1(X) collagen chain (Stacy et al., 1988; Fassler et al., 1994; Rosati et al., 1994); and targeted mutagenesis of the gene coding for the α2(V) collagen chain (Andrikopoulos et al., 1995). Additionally, the craniofacial and skeletal abnormalities characteristic of the mouse *cho* (for *cho*ndrodysplasia) have been recently associated with a frame-shift mutation in the gene coding for the α1 chain of type XI collagen (*Col11a1*) (Li et al., 1995).

Earlier indirect evidence and the genetic studies cited above indicate that types V and XI collagen regulate the growth and tridimensional assembly of the types I and II fibrillar networks in non-cartilaginous and cartilaginous matrices, respectively (Birk et al., 1988, 1990; Mendler et al., 1989; Andrikopoulos et al., 1995; Li et al., 1995). In addition to serving comparable roles in fibrillogenesis, types V and XI collagen can give rise to hybrid trimers whose functional significance remains obscure (reviewed by Brewton and Mayne, 1994). Our cloning work provided the first evidence against the previously held belief that type XI is exclusively produced by cartilaginous cells, since we identified α1(XI) transcripts in cells of non-cartilaginous origin (Bernard et al., 1988). At about the same time a biochemical analysis of adult bovine bone demonstrated assembly of the α1(XI) protein with the α1 and α2 subunits of type V (Niyibizi and Eyre, 1989). Hybrid trimers were later reported in the bovine vitreous and in a human rhabdomyosarcoma cell line (Mayne et al., 1993; Kleman et al., 1992). Co-expression of the α1(XI) and α2(V) genes was also observed in bovine arterial smooth muscle cells and other tumor and virally transformed human cells (Brown et al., 1991; Yoshioka and Ramirez, 1990).

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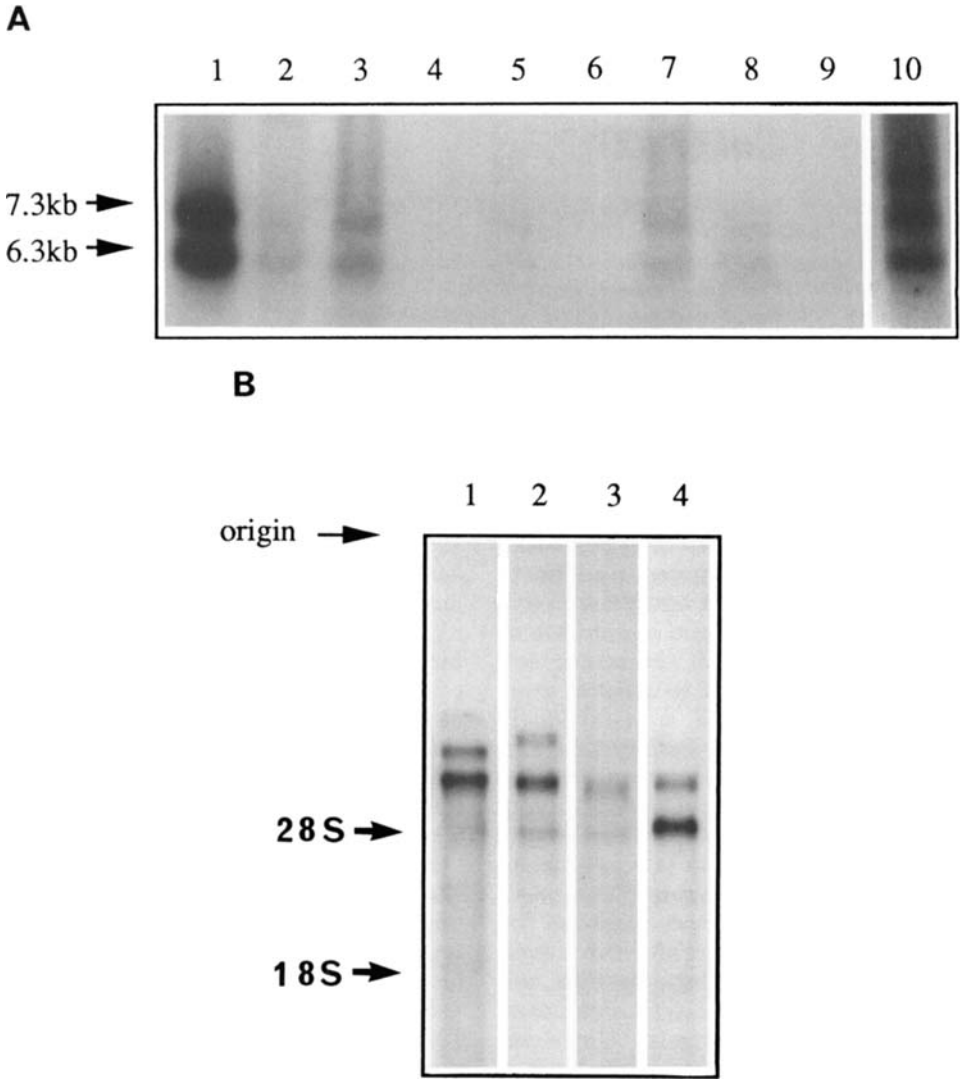

Fig. 1. Northern blot analysis of α1(XI) expression in the mouse embryo. **A:** Total RNA (20 μg) isolated from human A-204 cells (**lane 1**) and from limbs (**lane 2**), vertebrae (**lane 3**), heart (**lane 4**), brain (**lane 5**), liver (**lane 6**), tail (**lane 7**), skin (**lane 8**), kidneys (**lane 9**), calvaria (**lane 10**) of 18 d.p.c. mouse embryos was hybridized to probe mHY1. Arrows indicate transcripts of mouse α1(XI) collagen gene. **B:** Poly $(A)^+$ RNA (1 μg) from 18 d.p.c. embryonic mouse limbs was hybridized to cDNA probes coding for mouse α1(XI) (**lane 1**), mouse α1(V) (**lane 2**), human α2(XI) (**lane 3**), and mouse α2(V) (**lane 4**) chains, respectively. The estimated sizes of transcripts are: 7.3 and 6.3 kb in α1(XI); 7.7, 7.4, 6.3, and 4.8 kb in α1(V); 6.1 and 4.8 kb in α1(XI); 6.3 and 5.0 kb in α2(V). Arrows indicate the relative positions of the 28 and 18 S ribosomal RNA.

Based on this evidence, Nah et al. (1992) recently performed a preliminary survey of the pattern of the α1(XI) collagen gene expression during vertebrate embryogenesis using as a model the chick embryo. The study revealed that some of the α1(XI)-positive tissues of the chick coincide with the sites known to produce α1(II) collagen in the mouse (Cheah et al., 1991). Moreover, α1(XI) transcripts were found to accumulate in organs of the chick, which in the mouse have been shown to contain α2(V) collagen-producing sites (Andrikopoulos et al., 1992). The informative value of these correlations is unfortunately limited by two major differences in the experimental designs of the α1(XI) compared to the α1(II) and α2(V) studies. First, embryonic expression of α1(XI) collagen was examined in the chick and not in the mouse, the organism where the patterns of the α1(II) and α2(V) collagen genes have been described in the greatest details (Nah et al., 1992; Cheah et al., 1991; Andrikopoulos et al., 1992). Second, the α1(XI) analysis could not determine the precise sites of gene expression within each of the positive organs because it relied mostly on Northern rather than in situ hybridization data (Nah et al., 1992). The present study was therefore undertaken to provide a more reliable picture of the overall pattern of expression of the fibrillar collagene genes during the development of the same vertebrate embryo, notably the mouse.

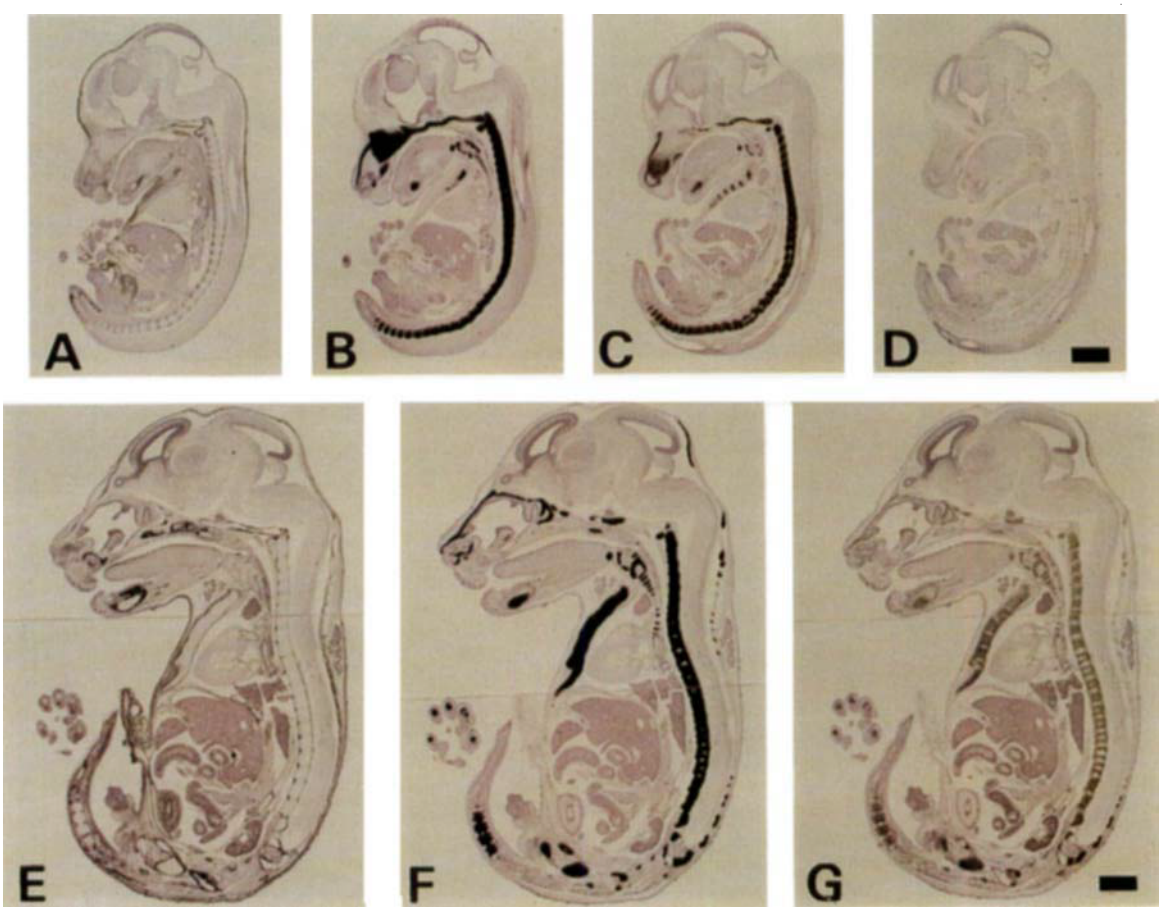

Fig. 2. Developmental expression of mouse collagen genes. Semi-serial sections are from a 14.5 d.p.c. embryo (top panels) and from a 16.5 d.p.c. embryo (bottom panels). From left to right, the probes are for α1(I) (**A,E**), α1(II) (**B,F**), and α1(XI) (**C,G**) collagen. In **D** is the negative control section which was pre-treated with RNase. Bar = 1 mm.

RESULTS AND DISCUSSION

As a first step toward defining the developmental pattern of *Col11a1* gene expression, we initially evaluated the presence of α1(XI) transcripts in the whole embryo at 11, 12, and 14 days post coitum (d.p.c.), as well as in different tissues of 18 d.p.c. mice by amplifying reverse transcribed RNA with the polymerase chain reaction technique (RT-PCR). *Col11a1* transcripts were readily detectable at all stages of development; they were also present in limbs, vertebrae, heart, brain, liver, tail, kidney, calvaria, lung, muscle, and intestine of 18 d.p.c. embryos (data not shown). A subsequent Northern analysis identified α1(XI) mRNA in the limbs, vertebrae, brain, tail, skin, and calvaria, but not in the heart, liver, and kidney, of 18 d.p.c. embryos (Fig. 1A). As a point of comparison, we hybridized mRNA from 18 d.p.c. embryonic limbs to α1(XI), α2(XI), α1(V), and α2(V) collagen probes (Fig. 1B). Size differences among the different collagens are mostly due to the variation in the length of the amino-terminal peptide-coding regions, whereas the multiple bands reflect the utilization of alternative polyadenylation sites (reviewed by Vuorio and de Crombrugghe, 1990).

Next, we performed a series of in situ hybridizations in order to identify the precise sites of *Col11a1* gene expression. To this end, we compared the hybridization pattern of the α1(I), α1(II), and α1(XI) collagen genes using sagittal sections of 14.5 and 16.5 d.p.c. embryos. At both stages of mouse development, α1(XI) signals were located in the vertebral column, the nasal septum, Meckel's cartilage, the sternum, the primordia of hyoid and thyroid cartilages, and the cartilage of the developing feet (Fig. 2C,G). As expected, accumulation of α1(I) and α1(II) collagen transcripts was mutually exclusive, with the latter particularly strong in the same cartilaginous sites that express high amounts of α1(XI) mRNA (Fig. 2).

Previous immunohistochemical and in situ hybridization experiments have revealed transient α1(II) collagen accumulation in a few non-cartilaginous tissues of the mouse embryo, such as the developing heart and brain (Thorogood and von der Mark, 1986; Kosher and

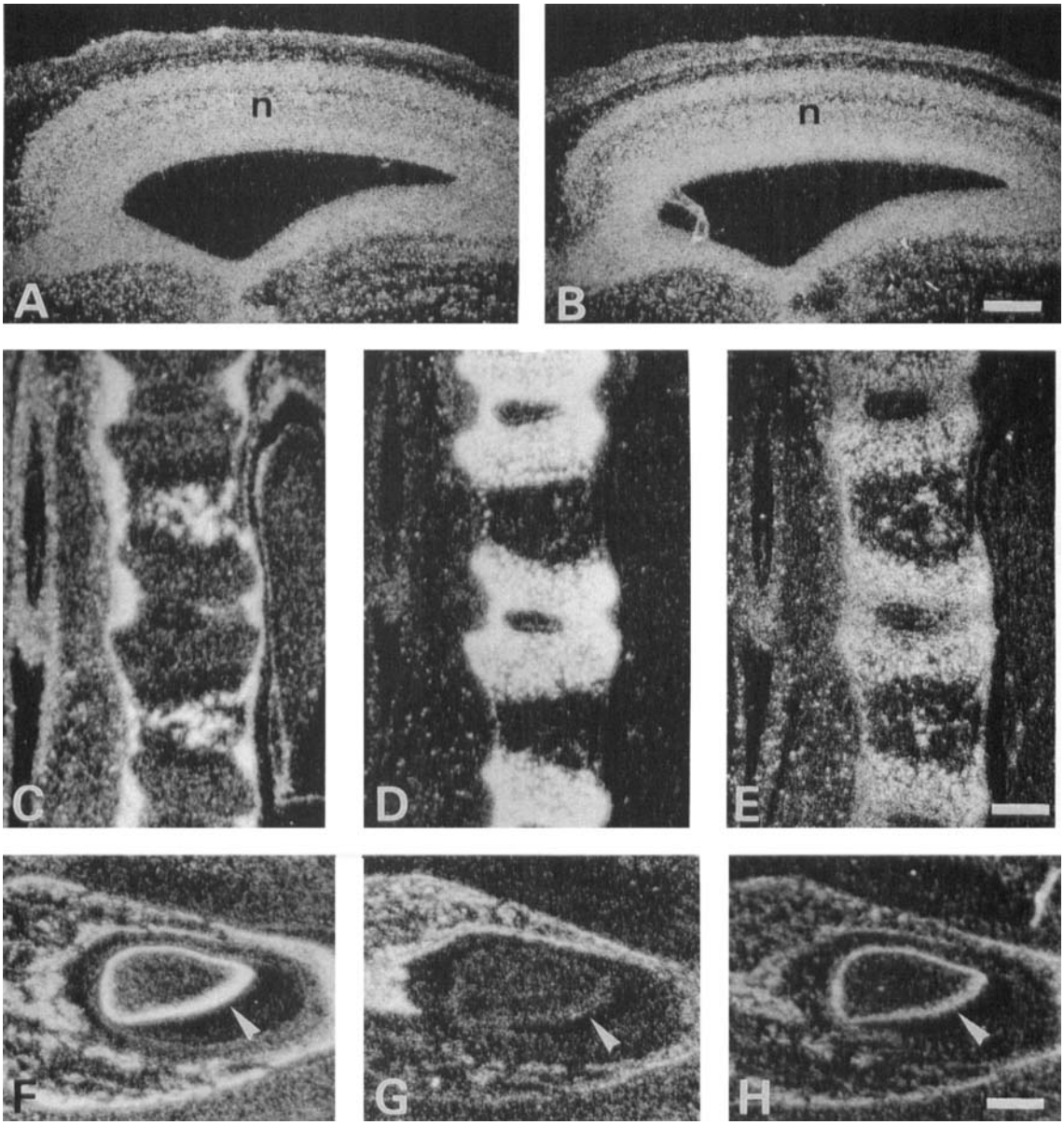

Fig. 3. Dark field analysis of collagen expression in the neuro-epithelium, vertebral column and mandibular bone. Serial sections of the telencephalon (**A,B**) are from 16.5 d.p.c. embryo, and the lumbar vertebral column (**C–E**) and the mandibular bone (**F–H**) from an 18.5 d.p.c. embryo hybridized to probes for α1(I) (C,F), α1(II) (A,D,G), and α1(XI) (B,E,H) collagen. In the mandibular arch (F–H), the odontoblasts are indicated with arrowheads. The letter "n" indicates neuro-epithelium. Bar = 200 μm.

Solursh, 1989; Cheah et al., 1991). Upon re-examining the sections at higher magnification, we were able to detect α1(XI) transcripts in the neuro-epithelium of the brain (Fig. 3B). Aside from confirming the Northern data of Nah et al. (1992), the finding localized the α1(XI) transcripts in the same non-cartilaginous tissue and at about the same developmental stage as the α1(II) collagen gene product (Fig. 3A) (Cheah et al., 1991). Since the α3 chain of type XI is believed to be a post-translational variant of α1(II), our result raises the possibility that α1(II) gene expression in the neuro-epithelium of the brain might be related to the production of some type XI collagen, in addition to type II trimers.

Aside from confirming co-expression of α1(XI) and α1(II) collagens in non-cartilaginous tissues, the high magnification analysis revealed several sites in which α1(XI) and α1(I) collagen transcripts accumulate together. In addition to cartilage, strong α1(XI) mRNA signals were in fact noted in the perichondrium and the trabecular bone of the lumbar vertebral column (Fig. 3E). The α1(I) and α1(XI) collagen genes were transcriptionally active in the mandibular bones too, with

odontoblasts containing significant amounts of both transcripts and lacking those of the α1(II) gene (Fig. 3F,G,H). The α1(XI) transcripts were also noted to accumulate in the atrioventricular valve, pulmonary valve, and artery of the developing heart (Fig. 4A). Furthermore, the α1(XI) signal was strong in the tongue, the intestine, and the otic vesicle of the mouse embryo (Fig. 4B,C,D). These last sites are the same ones in which we previously observed substantial accumulation of α2(V) mRNA (Andrikopoulos et al., 1992). This finding further strengthens the closer relationship between these two collagen chains compared to other subunits of types V and XI collagen. Along these lines, the co-expression of the two genes in some tissues is consistent with our recent identification of a common regulatory element in the promoter of the genes coding for the human α2(V) and α1(XI) chains (Yoshioka et al., 1995).

In conclusion, we confirmed and extended previous data on the identity and spectrum of α1(XI) collagen-producing tissues. In doing so, we elucidated for the first time the spatiotemporal pattern of expression of this minor fibrillar collagen gene during mouse embryogenesis. We confirmed that transcription of the *Col11a1* gene is not restricted only to α1(II) collagen-producing tissues; we extended the number of α1(XI) collagen positive sites to a larger variety of tissues than previously recognized; and we interpreted some of the in situ data as suggesting that the α1(XI) collagen chain may participate in the formation of several tissue- and stage-specific trimers with distinct functional properties. One such property could be to expand the ability of regulating the tridimensional assembly of fibrillar macro-aggregates by varying the biochemical composition of the minor collagen trimers.

EXPERIMENTAL PROCEDURES

RNA Analysis

RNA was isolated from different developmental stages using the acid-guanidine method (Chirgwin et al., 1979). Poly $(A)^+$ RNA was purified by oligotex 30 (Japan Synthetic Rubber Co., Tokyo, Japan) and subjected to Northern analysis as previously described (Yoshioka and Ramirez, 1990; Yoshioka et al., 1995). The Northern analysis employed cDNAs coding for mouse α1(XI), α1(V), and α2(V) collagen [clones mHY1 (Yoshioka et al., 1995), mHY8 (Yoshioka, unpublished data), and KA311 (Andrikopoulos et al., 1992)] and for human α2(XI) collagen [clone HY9 (Yoshioka, unpublished data)]. RT-PCR amplifications were performed for 35 cycles with 2.5 U of Taq DNA polymerase at 94°C for 1 min, 60°C for 2 min, 72°C for 3 min, followed by final extension at 72°C for 7 min (Wang et al., 1989). The nucleotide sequences for the primers used in these reactions are:

forward direction: 5′-GACACACTGAAAGCATC-CAG-3′[α1(XI)],
5′-AAGAGAGGTATCCTGAC-CCT-3′(β actin).

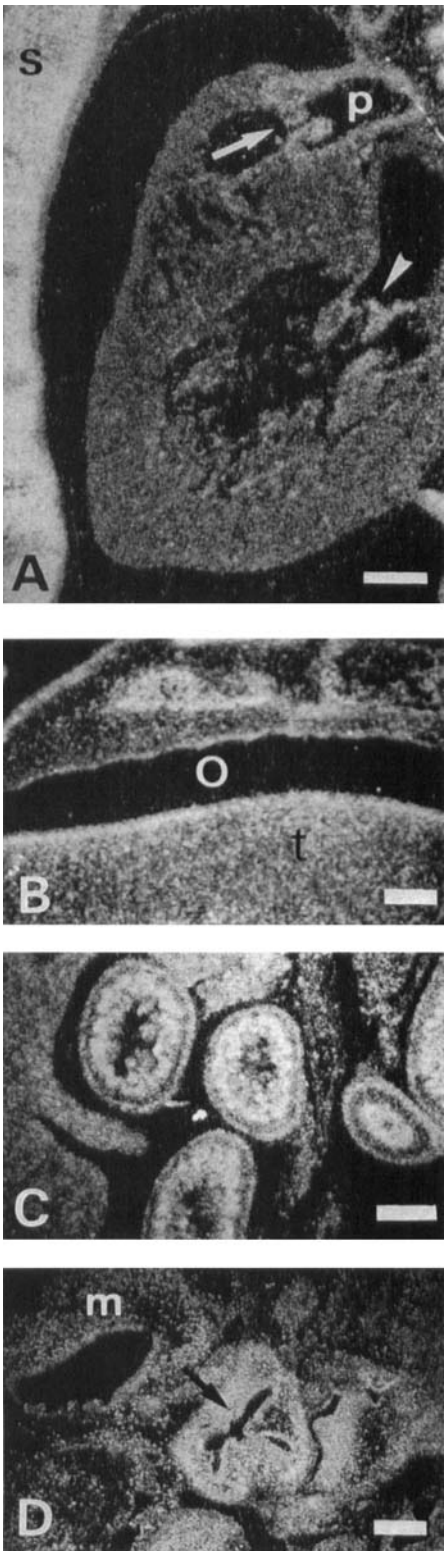

Fig. 4. Dark field analysis of α1(XI) expression in the heart, tongue, intestine, and otic vesicle. **A:** Hybridization of the α1(XI) probe to a 16.5 d.p.c. embryonic heart. Highlighted are the atrioventricular (arrowhead) and pulmonary (arrow) valves. **B,C,D:** α1(XI) hybridization in the tongue and intestine of 16.5 d.p.c. embryo, and the otic vesicle (arrow in D) of 14.5 d.p.c. embryo. s, sternum; p, pulmonary artery; t, tongue; o, oral cavity; m, metencephalon. Bar = 200 μm.

reverse direction: 5′-GGCAGCAGTGAT-TCCTAAAC-3′[α1(XI)], 5′-TACATGGCTGGGGTGTTGAA-3′(β actin).

In Situ Hybridizations

Balb/C mouse embryos at 14.5, 16.5, and 18.5 d.p.c. were collected, and fixed in 4% paraformaldehyde in 0.01 M phosphate buffer saline (PBS, pH 7.4) overnight at 4°C. Whole embryos were dehydrated in a graded series of ethanol and embedded in paraffin. Consecutive sections were cut at 5 μm and were then processed for in situ hybridization. The hybridization procedures used in this study were essentially the same as those described elsewhere (Hayashi et al., 1986; Iyama et al., 1991). In situ probes included mouse α1(XI) (Yoshioka et al., 1995), α1(II) (Andrikopoulos et al., 1992), and α1(I) collagen (Yoshioka, unpublished data); their sizes are 1,810, 618, and 250 bp, respectively. The cDNAs were labeled with ^{35}S-thymidine 5′-[α-thio] triphosphates (TTP) (Dupont, Boston, MA) by nick-translation to a specific activity of 1.8–4.5 × 10^8 cpm/μg DNA. After hybridization, slides were washed under conditions of high stringency as previously described (Hayashi et al., 1986; Iyama et al., 1991). The dried tissue sections were dipped into Kodak NTB-2 emulsion and exposed for 3–7 days at 4°C. The sections were counterstained with hematoxylin. Differential expression of each collagen mRNA in comparable tissue sections provided a good internal control. As a negative control, parallel sections were also digested before hybridization with 2 mg/ml of RNase for 1 hr at room temperature.

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