Homeobox Genes Msx-1 and Msx-2 Are Associated with Induction and Growth of Skin Appendages

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The mechanism involved in the morphogenesis of skin appendages is a fundamental issue underlying the development and healing of skin. To identify molecules involved in the induction and growth of skin appendages, we studied the expression of two homeobox genes, Msx-1 and Msx-2, during embryonic chicken skin development. We found that i) both Msx-1 and Msx-2 are early markers of epithelial placodes for skin appendages; ii) both Msx-1 and Msx-2 are expressed in the growing feather bud epithelia but not in the interbud epithelial; iii) although mostly overlapping, there are differences between the expression of the two Msx genes, Msx-1 being expressed more toward the anterior whereas Msx-2 is expressed more toward the distal feather bud; iv) there is no body-position-specific expression pattern as was observed for members of the Hox A-D clusters; v) in the feather follicle, Msx-1 and 2 are expressed in the collar and barb ridge epithelia, both regions of continuous cell proliferation; vi) when feather-bud growth was inhibited by forskolin, an activator of adenylyl cyclase, the expression of both genes was reduced. These results showed that Msx genes are specifically expressed in epithelial domains destined to become skin appendages. Its function in skin-appendage morphogenesis may be twofold, first in making epithelial cells competent to become skin appendages and, second, in making epithelial cells maintain their potential for continuous growth. Key words: Hox genes/mssh/embryonic induction epithelial-mesenchymal interaction/feather/hair/protein kinase A (PKA)/cyclic adenosine monophosphate (cAMP)/forskolin. J Invest Dermatol 104:711–719, 1995

Homeobox genes are transcription factors that contain a conserved 183-bp DNA sequence called the homeobox (reviewed in [1]). They were first discovered in Drosophila, where gene mutations caused homeotic transformations in which one part of the body (e.g., antenna) was transformed into another part (e.g., leg) [2]. Vertebrate homeobox-containing genes are categorized into different classes, among which are Hox complexes, POU-en (enlarged),Dll (distalless), msh (muscle segment homebox), etc. [3,4]. Among many functions, homeobox genes have been shown to determine the morphology of the skeleton [5,6] and the phenotype of hematopoietic cells [7]. Homeobox genes are also involved in normal growth control [8,9] as well as tumorigenesis [9–11]. The potential functions of Hox genes in skin biology has recently been reviewed [12–14]. Still additional studies on the importance of the homeobox gene family in skin biology and pathology remains to be performed.

One of the major groups of homeobox genes are Hox genes, which are homologs to the Drosophila Antenna and bithorax complexes. In vertebrates they form four paralogous gene clusters located on four different chromosomes [1]. We have found that Hox genes are distributed with an anterior-posterior gradient within the feather buds [15]. Hox genes (C6, C8, and D4) are also shown to have a body-position-specific expression pattern, suggesting a role in specifying specific skin domains [16,17]. Indeed many Hox genes (most of the Hox B cluster, and many members of the A, C, and D clusters) are expressed in developing skin in a dynamic fashion [18,19]. Among those studied in more detail, Hox B6 is transiently expressed in embryonic epidermis [20], whereas Hox C4 is expressed in suprabasal keratinocytes [11]. These data suggest that Hox genes are involved in the differentiation of epidermis.

Another group of homeobox genes are the Msc genes, which are homologues of the msh gene of Drosophila [21]. Two known members of this group, Msc-1 [22,23] and Msc-2 [24–27], formerly named Hox-7 and Hox-8 (see [28] for new nomenclature) have been found in a variety of vertebrate and non-vertebrate species [29,30]. In chicken and mouse embryos, where their expression pattern has been studied in greater detail, they are expressed in very overlapping, but distinct, sites in a variety of organs such as the neural crest, pharyngeal arches, eyes, limb buds, heart, teeth, etc. [22–26,31–33]. The highly dynamic expression patterns of the Msc genes during the induction of these organs are found in association with epithelial-mesenchymal interactions ([34–36], and for review see [9]), suggesting that these genes may play a role in embryonic inductive events. In vitro studies showed that the Msc-1 gene plays an important role in regulating the growth and differentiation potential of cells [9].

Induction is caused by interaction(s) between two tissues. Following induction, the differentiation fate of target tissue is altered.
During the formation of skin appendages, epithelium and mesenchyme are inducers and targets of each other. To study the molecules involved in this process, we have been using embryonic chicken skin as a model because of the distinct feather pattern, availability of skin explant cultures, and large flexibility for manipulation [12, 37]. In this study, we examined expression of Mx genes in developing chicken skin from stage 31 to 37. We found that both Mxl-1 and Mxl-2 are closely associated with epithelial cells undergoing growth and that reagents that inhibit skin-appendage growth also suppress Mxl-1 and Mxl-2 expression.

**MATERIALS AND METHODS**

**Embryos** White leghorn fertilized chicken eggs were obtained from K and R Farm (Westminster, CA) and Chino valley ranchers (Clino, CA). Eggs were incubated at 37°C for 6.5 to 10 d and embryos were staged according to Hamburger and Hamilton [38].

**Skin Explant Cultures** Dorsal skins between the lower neck and tail were removed from 7–10-day old White Leghorn chicken embryos in Hanks’ balanced saline solution and laid down on culture inserts (Falcon). Culture inserts were placed in six-well dishes (Falcon), containing 2 ml/well of Dulbecco’s modified Eagle’s medium supplemented with 0.1% gentamicin. For activation of adenylyl cyclase the media was additionally supplemented with 20 μM forskolin. The cultures were incubated at 37°C at an atmosphere of 5% CO₂ and 95% air for 2 to 6 d. Subsequently the skin explants were prepared for in situ hybridization and immunostaining.

**35S In Situ Hybridization of Frozen Sections** Chicken Mxl-1 and Mxl-2 clones pGHOX7C [39] and pGHOX8A [27] were kindly provided by Dr. Upholt (University of Connecticut). To generate antisense probes, the plasmids were digested with EcoRI and transcribed in a standard transcription reaction using 35S-UTP and SP6 RNA polymerase. To generate sense probes the above clones were digested with XbaI and transcribed with T7 RNA polymerase. In situ hybridizations were performed according to Schreiber et al [40] with minor modifications. Briefly, unfixed frozen tissue blocks were sliced in a cryostat, fixed with 4%
paraformaldehyde, and treated with 0.1 M triethanolamine and 0.25% acetic anhydride. The tissue sections were then hybridized to radioactive probes (approximately 0.15 ng probe/μl hybridization buffer) for 5–6 h at 50°C. Subsequently, the tissues were treated with 20 μg/ml RNase A in 0.5 M salt solution for 45 min at 37°C. The sections were then washed in 0.1 X SSC/20 mM dithiothreitol at 65°C for 2 h. In situ signals were visualized by exposing Kodak X-OMAT-AR film to slides for 1–3 d. Following that, slides were dipped in Emulsion (Kodak NTB2) and emulsions were developed after 5–10 d and observed under a bright-field dark-field microscope (Olympus BH2).

Nonradioactive In situ Hybridization Whole mount in situ hybridization protocols were based on Sasaki and Hogan [41] with minor modifications. Following fixation and bleaching, tissues were hybridized overnight at 70°C with 2 μg/ml of probe. These tissues were subsequently incubated with anti-digoxigenin Fab conjugated to alkaline phosphatase (Boehringer Mannheim). Color was developed by addition of alkaline phosphatase substrate NBT/BCIP (Promega).

Similar procedures were performed on paraffin sections. Tissues were fixed with Bouin’s fixative, processed as described in Chuong et al. [15], and deparaffinized. Following rehydration, slides were immediately treated with Proteinase K. The rest of the procedure was carried out following the protocol of Sasaki and Hogan [41]. Hybridization was carried out using lower stringency conditions in comparison to the whole mount. For the probes used here, the hybridization was carried out at approximately 48°C in a humidified chamber.

Immunocytochemistry Tissues were fixed in Bouin’s fixative, embedded in paraffin, and sectioned. Antibodies were visualized by Alk-phosphatase-conjugated secondary antibodies. These procedures have been used frequently by us [15,42].

BrdU Labeling and Detection with Whole Mount Immunostaining Embryonic skins were labeled with 50 μM/ml of BrdU for 1–2 h in a tissue-culture incubator. Specimens were fixed in 100% ethanol for 2 h. Fixed tissues were washed in phosphate-buffered saline for 1 h. DNA from the skins were denatured by incubating with 2 N HCl at 37°C for 1 h and neutralized by incubation in 0.1 M sodium borate, pH 8.5. The BrdU-labeled DNA was tagged by overnight incubation at 4°C with 6 μg/ml anti-BrdU antibody diluted in phosphate-buffered saline containing 0.1% bovine serum albumin. The skins were washed three times in phosphate-buffered saline for 1 h each and incubated with anti-mouse IgG antibody conjugated with peroxidase (Vector) for 5 h. The skins were washed in phosphate-buffered saline for 2 h and peroxidase detection was performed according to the avidin-biotin peroxidase complex substrate kit (Vector).

RESULT

In this study we investigated the roles of two homeobox genes, Msx-1 and Msx-2, during skin-appendage development. We began by examining the expression of their transcripts with in situ hybridization. The overview of Msx expression during chicken skin development can be seen in Fig 1.

Msx-1 Is Expressed in the Placode of Skin Appendages To have an overview, we first examined Msx-1 expression in embryonic day-8 chicken dorsal skin by whole mount in situ hybridization (Fig 1A,C). The Msx-1 transcript can be seen to be present in the feather bud, not the interbud regions. At higher magnification, Msx-1 can be seen on the bud epithelium, with weak staining in the mesenchyme. To further identify cells expressing Msx genes, we prepared sections from different stages of embryonic development for in situ hybridization. Msx-1 RNA first appears specifically in the placode epithelia at E7 (Fig 2A). In the more developed placode (right side of Fig 2A) and in E8 buds, Msx-1 can be seen

Figure 3. The expression of Msx-2 in developing feather buds revealed by in situ hybridization of frozen sections. Bright-field view. Longitudinal sections of dorsal chicken skin at different stages of development were hybridized to an 35S-labeled Msx-2 antisense RNA probe. A,B,C,D: skin from stages 31 (E7), 33 (E8), 35 (E9), and 36 (E10), respectively. E, control using a Msx-2 sense probe on E8 skin. a, anterior of feather bud, p, posterior of the feather bud. Long arrows point to the limit of Msx-2 expression. Two short arrows point to the border of bud epithelial domain. The bud with an asterisk in B is enlarged and shown in Fig 4C. Bar, 500 μm.
asymmetrically expressed in the anterior feather bud epithelium (Fig 2B). Weak staining in the feather mesenchyme can be seen at this stage (Fig 2B). At E9, Msx-1 expression extends to the posterior epithelium and loses the asymmetry (Fig 2C). At E10, feather buds elongate rapidly. At this stage, Msx-1 is expressed all over the bud epithelium but not in the mesenchyme area (Fig 2D). Note that in all the examined stages, Msx-1 is completely absent from the interbud regions. Muscle in the body wall beneath the dermis can be seen to be positive for Msx-1 (Fig 2E). Control hybridizations using Msx-1 sense probe are negative (Figs 1E and 2E).

Mmx-2 Has an Overlapping but Different Expression Pattern than Msx-1 In the whole mount in situ hybridization, Mmx-2 is also expressed specifically in the buds. The expression is very similar to Msx-1, although more staining is detected in the feather mesoderm (Fig 1B, D). Hybridization to sections of E7 skin show that Mmmx-2 expression also appears in the placode epithelium in a periodic fashion. A subtle difference is that Mmx-2 appears to be more concentrated in the middle of the placode (Fig 3A), versus the more anterior staining found for Mssx-1 (Fig 2A). When feather buds protrude out of the ectoderm surface, Mmx-2 can be seen to be enriched in the anterior and distal bud epithelia (Fig 3B), whereas the Mssx-1 gene is only expressed in the anterior region (Fig 2B). At E9, Mmmx-2 also can be seen in the distal half of the elongating bud epithelium. At this stage, Mmmx-2 is also expressed to a moderate amount in the distal bud mesoderm (Fig 3C). At E10, the Mmmx-2 expression covers most of the feather bud epithelium and the mesenchymal expression is gone (Fig 3D). Note the interbud epithelium is always negative during these stages. Control hybridizations using a Mssx-2 sense probe are negative (Fig 1F and 3E).

Expression of Mmx Genes Is Most Similar to that of Tenascin The expression of Mmx genes in the early placode is very similar to tenascin-C expression at this stage [14, 42]. Therefore we compared their expression patterns (Fig 4). At the placode stage, tenascin-C protein has a similar periodic expression pattern that coincides with Mmmx 2 expression. In the early bud stage, tenascin-C is mainly found in the anterior and distal bud epithelia as well as the anterior mesenchyme. Mmmx-2 is also expressed on the anterior and distal bud epithelia. Some expression of Mmmx-2 in the mesenchyme can also be seen (Fig 4B). Thus the expression of Mmmx-2 and tenascin, particularly in the early epithelia, are very similar. Whether there is a regulatory relationship among them remains to be seen.

Expression of Mmx Genes in Feather Follicles As development continues, the elongated feather buds begin to invaginate into dermis to form feather follicles. In the feather follicle, as in the hair follicle, proliferating epithelial cells are located in the base of the follicle in a structure known as the “collar” (equivalent to hair “matrix”). Mmx genes are highly expressed in these regions (Fig 5A, solid arrow). In the proximal feather filament, the Mmmx-2 gene is negative (Fig 5A, blank arrow). In the distal feather filament, the Mmmx-2 gene becomes positive again in the barb ridge epithelium, but is negative in the marginal plate epithelium (Fig 5B). We have shown that in feather filaments NCAM is positive on the marginal plate, but negative on the barb ridge epithelia [13] and this is shown here for comparison (Fig 5C). In the mature feather follicle, both Mmmx-1
and Msx-2 genes are expressed in the collar epithelia (Fig 6), but are absent from the dermal papilla. In the feather filament again Msx genes are seen in the barb ridge epithelia where cell proliferation continues.

**Suppression of Msx Gene Expression Is Correlated with Arrest of Elongation of Feather Buds** We used BrdU labeling and whole mount staining to view the proliferation in the explant (Fig 7). Before skin-appendage induction, BrdU-labeled cells are homogeneously distributed (stage 1). Following induction, there is a concentrated distribution of BrdU-positive cells under the feather germ (stage 2). This is followed immediately by the formation of dermal condensations that are devoid of proliferating cells (stage 3) for about 24 h [44]. Cells then resume mitosis and the round buds are enriched for actively proliferating cells (stage 4). When feather buds elongate, centers of active proliferation gradually shift to the proximal end (stage 5) [45]. At a later stage, new proliferation centers form in the barb ridge zones (stage 6). These results form the basis for analyzing the distribution of growing cells in developing feather buds.

We have tested several potential regulators of Msx genes in skin development. Among the various reagents tested, we observed that forskolin, an activator of the enzyme adenyl cyclase, or dibutyryl cyclic adenosine monophosphate (dBcAMP), an activator of protein kinase A, can inhibit the elongation of feather buds. The forskolin- treated feather buds remained as round stumps even after 6 d of

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**Figure 5. Expression of Msx-2 in later feather buds.** A,B, 35S in situ hybridization with dark-field illumination. A, invaginating feather buds (solid arrow) that are beneath the skin surface (white broken lines) and proximal feather filaments (blank arrow) that are above the skin surface. B, distal feather filament marginal plates (small arrow) that are Msx-2 negative and barb plates (regions between marginal plates) that are Msx-2 positive. C, immuno-alkaline phosphatase staining with antibodies to NCAM. Black is positive. NCAM is positive on the marginal plates and negative on the barb plates, and is shown here for comparison. See Fig 9 for terminology. Bar, A, 250 μm; B, 100 μm.

**Figure 6. Expression of Msx genes in feather follicles.** Digoxigenin in situ hybridization on sections of mature feather follicles using probes to Msx-1 (A) and Msx-2 (B). C, sections at a more distal level that cuts across the feather filament were hybridized against Msx-2. Arrows point to marginal plates (for explanation see Fig 9). cl, collar (equivalent to the matrix region of hair follicle); dp, dermal papilla; ff, feather filament. Bar, 100 μm.
forskolin-treated Msx-suppressed skin is very similar to the antibody-treated tenasin-suppressed skin [42].

This and other previous work have demonstrated the complexity and subtlety of the molecular heterogeneity in the seemingly similar placode/bud epithelia. It was shown that tenasin is found in the anterior, NCAM in the distal, and fibroblast growth factor type 2 receptor in the posterior portion of the feather bud epithelium (the anterior end is the side that forms an obtuse angle with the skin and the plane where the rachis will form) [42, 49]. We now observe that Mxs-2 is expressed in the anterior and distal portions of feather bud epithelia. Mxs-1 is in the more anterior portion, and the expression stops before the distal portion. The functional significance of the molecular complexity caused by these staggered patterns is not known. The findings here set the stage for future tests with gene delivery experiments.

In several stages, regions expressing Mxs genes are regions where active cell proliferation takes place. In developing limb buds, Mxs genes are expressed in the distal apical ectodermal ridge and in the progress zone [31, 50–52]. The distal elongating feather buds that express Mxs genes may be functionally equivalent to those in limb buds. When elongated feather buds invaginate to form feather follicles, active cell proliferation shifts down to the follicle base and forms the collar epithelium (equivalent to the matrix zone of hair). The expression of both Mxs-1 and Mxs-2 is also shifted down to the collar region. In the distal feather filament, the cylindrical epithelium starts to fold and form alternating barb-plate and marginal-plate epithelia. Active cell proliferation resumes in the barb-plate epithelia that will become the feather branch proper, whereas the marginal plate epithelia will die [53]. Mxs genes are expressed in the barb plate but not the marginal plate. Thus, the expression of Mxs genes and active cell proliferation are correlated in three different stages.

The expression patterns of Hox genes (Hox A-D clusters) in skin have been reported [18–20]. One of the unique features is that the expression pattern of some Hox gene (C6, C8, and D4) were shown to be body-position specific [15, 16]. Thus we hypothesized that the unique combination of Hox genes expressed in different skin domains constitutes the “skin Hox codes”, which may determine specific characteristics, such as skin-appendage phenotypes, in that region [17]. In contrast, in this study, we did not observe body-position-specific expression patterns for Mxs-1 and Mxs-2.

Regions examined include skin from the head, anterior and posterior body, and wing. This is consistent with the current understanding of homeobox genes in other organs: Hox genes (A-D clusters) are involved in pattern formation whereas Mxs genes are involved in growth and regeneration (reviewed in [1] and [54]).

Potential Roles of Mxs Genes in the Development and Regeneration of Skin Appendages From studies in limbs, it has been suggested that Mxs genes may keep cells in a “dedifferentiated” state, including proliferative, non-differentiating cells that are responsive to regulatory signals [8]. Results from in vitro experiments are consistent with this notion. When Mxs-1 was transfected into myoblasts, it inhibited the expression of myogenic genes and differentiation of the cells into myotubes. The transfected cells also formed tumors in nude mice [9]. In addition, digits amputated at the level where mesoderm expresses Mxs-1 can still regenerate, whereas amputation at the level not expressing Mxs-1 cannot regenerate [8]. Finally, a mutated Mxs-2 gene in which a proline in the homeodomain was mutated to histidine showed abnormal function, and led to the precocious ossification of osteo blasts and resulted in the early closure of the skull suture [55].

In skin development, the expression of Mxs-1 and Mxs-2 occurs in an overlapping but non-identical fashion. Mxs proteins are transcription factors with high homology in their homeodomain and may bind the same DNA element(s). It was suggested that Mxs-1 and Mxs-2 may be antagonistic or agonistic to each other in their action, depending on different contexts [54]. Alternatively, the co-expression may be required for certain specific functions. Indeed the regulation of the two Mxs genes are related. Alignment

culture (Fig 8A,E). In the control cultures, both Mxs-1 and Mxs-2 were expressed in a pattern that was similar to our in vivo observation, in regions of active growth (Fig 8B,C). In contrast, in the forskolin-treated skin, the expression of Mxs-1 is almost completely gone (Fig 8F). The Mxs-2 transcript is also reduced and, most interestingly, the remaining level of expression was similar in the bud and interbud regions (Fig 8G), suggesting loss of the spatial specificity by activation of protein kinase A. Cell proliferation was analyzed in these specimens. Control feather buds exhibited a high percentage of proliferating cells in all of the elongated buds. In the round buds of forskolin-treated skin, BrdU-positive cells are fewer and distributed in an empty ring, characteristic of the dermal condensation stage (Fig 8D,H and compare with Fig 7). Thus the loss of Mxs expression is correlated with the loss of growth potential of feather buds.

DISCUSSION

Comparison of Mxs Expression and Other Genes in Developing Skin A schematic representation of feather development with a summary of Mxs gene expression is shown in Fig 9. Before induction, all ectoderm is Mxs negative. At the time of induction, Mxs genes appear specifically in the placode epithelium. The expression of Mxs genes in the placode, when there is still no apparent morphologic changes in placode epithelia, suggests that Mxs genes are among the very early molecules required during skin-appendage induction. The other molecules expressed so early in this region are tenasin [42, 46] and BMP-4 [47]. In tooth development BMP-4 has been shown to induce Mxs-2 expression [48]. The expression of Mxs genes and tenasin in the early feather placode are so similar that the regulation of tenasin by Mxs genes is likely. This is consistent with the finding that the morphology of
Figure 8. **Forskolin, an activator of adenylyl cyclase, suppresses the expression of Msx-1 and Msx-2.** A, E8 chicken dorsal skin explant grown at 37°C in Dulbecco’s modified Eagle’s medium for 6 d. E, same as A but the skin was grown in the presence of 20 μM forskolin for 6 d. Forskolin-untreated (B, C) and treated (F, G) skin explants were sectioned and hybridized with Msx-1 (B, F) and Msx-2 probes (C, G). Note that after forskolin treatment, the presence of Msx-1 is nearly completely gone. Msx-2 is reduced and the remaining transcripts appear in both bud and interbud domains (arrows). Forskolin-untreated (D) and treated (H) skin explants were labeled with BrdU as described in Fig 7. Note the high percentage of BrdU-labeling cells in the control versus the low labeling in forskolin-treated skin. Fsk, forskolin. Bar, A–C and E–G, 500 μm; D and H, 100 μm.
of the 5' flanking regions of the human Msx-1 gene [56] and Msx-2
gene [57] indicated that several stretches of DNA sequences that
may serve as responsive elements have been conserved.

In our attempt to find specific regulators for Msx expression in
skin, we found that forskolin, an agonist for adenylyl cyclase
that leads to the activation of protein kinase A, is a very effective
suppressor of Msx-1. Forskolin also reduces Msx-2 gene expression
but to a lesser extent. One of the targets of PKA is the cAMP
responsive element binding protein (CREB). CREB is phosphoryl-
ated by protein kinase A to become P-CREB, which can then
modulate transcription of genes containing CRE in their 5'-flanking
regions [58, 59]. To see if Msx genes are regulated by CREB, we
searched for CRE with the consensus sequence CGTCA [60] in the
5'-flanking regions of different Msx genes. This element was found
in a location upstream of the transcription start site and downstream
from a putative CAT box in the 5'-flanking region of the mouse
Mss-2 gene. An element with a similar sequence (CGTCG) was
also found at the corresponding location in the human Mss-2 gene.
Tests to see if these elements are authentic CREs are in progress.

The study on Mss-1 and Mss-2 genes in skin shows that
epithelial domains undergoing further growth to become skin
appendages are Mss positive, whereas domains remaining inactive
are Mss negative. This implies that Mss genes may be required to
make epithelial cells "competent" to respond to signals that instruct
them to form a skin appendage. If this is true, epithelia with missing
or overexpressed Mss genes will have an abnormal ability to
develop or regenerate skin appendages. At the present time we are
testing this hypothesis using retroviruses that ectopically express
mutant and normal Mss genes. In the future, when we can further
understand the regulation and the roles of Mss genes in skin
appendage formation, we may be able to modulate hair growth in
alopecia patients or in burn-wounded skin.

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