

Msx-2 and the Regulation of Organ Size: Epidermal Thickness and Hair Length

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During organogenesis, the issue of size regulation is as important as shape and differentiation. We propose that the regulation of the dimensions of the epithelium and its appendages (length, width, thickness) are based on regulation of cell numbers in specific sites, reflecting the input and output of cells in that region. This process is in turn regulated by the flow from the domain of proliferating cells to the domain of postmitotic differentiated cells. When the homeobox gene *Msx-2* is over-expressed in transgenic mice under the control of the CMV promoter,

the epidermis is thickened with hyperproliferation and hyperkeratosis. Hairs are shorter and the matrix region is shrunken. We suggest that *Msx-2* may be one of the regulators involved in the control of organ size, and the above phenotypes are the manifestations of an increased cellular flow from proliferation domain to differentiation domain in the tissue. **Key words:** *dysplasia/hair follicle/hyper-keratosis/Msx/organogenesis, skin development. Journal of Investigative Dermatology Symposium Proceedings 4:278-281, 1999*

ORGAN SIZE, CELL NUMBER, AND MOLECULAR REGULATORS

The control of size is central to the formation of an organ. During organogenesis, induction determines the site where the organ forms, morphogenesis determines the shape of the organ, and differentiation makes the final structure. Before the final differentiation takes place, however, the organ will grow to a certain size. Among different but related species, organs can be of similar shapes but different sizes (e.g., mice *versus* rats, or different kinds of dogs). In the same organism, skin appendages, as one organ, can have a large spectrum of sizes (e.g., tail feathers *versus* down feathers, and scalp hair *versus* villus hair). Limb skeletons also come with different lengths and widths. Because the size of cells comprising any given organ are roughly the same, the size of the organ is mainly determined by the number of cells it contains. We can assume that the size of an organ in a particular region reflects the input of cells minus the output of cells. The input of cells can come from cell proliferation and cell immigration. The output of cells can come from apoptosis and cell emigration. How the organ "senses" its size and stops growth remains a mystery. The issue of how the size of an organ is regulated has just begun to be appreciated (Raff, 1996).

In the case of skin and skin appendage development, the major regulatory component appears to be the cell proliferation, and this

is what we will focus on. Although there has been great progress in understanding the mechanisms underlying cell proliferation (reviewed in Murray, 1995), how this is related to organ size has not been explored. We propose that the number of cells in the organ that the precursor cells, in this case transient amplifying (TA) cells (Watt, 1998), can build up depends on the number of divisions that take place during a certain time period. Because the duration of the cell cycle not including G0 or G1 is relatively constant, the size of the organ becomes a function of the time interval that cells are allowed to divide (Fig 1).

There are different modes of growth. In deregulated new growth such as in tumors, new cells are added at any time to any place, and the enlargement can occur in all dimensions. In regulated new growth, new cells can either be added to the tip as the growth point, as is the case for limb buds, or to the proximal end as is the case in the hair and feather. During the phase of organ growth, as cells in the proliferation domain divide, some transit to differentiation status, therefore reducing the pool of TA cells. We propose a model in which there are positive and negative regulators that control the cellular flow from the proliferation domain to differentiation domain (Fig 1). A similar orderly progression has been shown in the elongation of long bones using the IHH (Indian hedgehog)-patched-PTHrP-PTHrP receptor pathway (Vortkamp *et al*, 1996), and in retina development using the Notch-delta pathway (Henrique *et al*, 1997). Here we explore the role of the *Msx-2* related pathway.

MSX-2 IS A REGULATOR OF GROWTH CONTROL

The *Msx* genes are transcriptional factors (Davidson, 1995) that are related to the *Drosophila* *Msh* gene family (Walldorf *et al*, 1989). In vertebrate development, there are three homologs: *Msx-1*, *-2*, and *-3*. *Msx-1* and *-2* are found expressed in many sites of epithelial-mesenchymal interactions, including the calvaria, limb bud, tooth bud, feather placode, hair follicles, mammary glands, etc. What is their function in these apparently diverse organs?

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Abbreviations: BMP, bone morphogenetic protein; CMV, cytomegalovirus; FGF, fibroblast growth factor; ID, inhibitor of differentiation; IHH, indian hedgehog; Lef, lymphoid enhancer factor; *Msx*, muscle segment homeobox homolog; PTHrP, parathyroid hormone related protein; TA, transient amplifying.

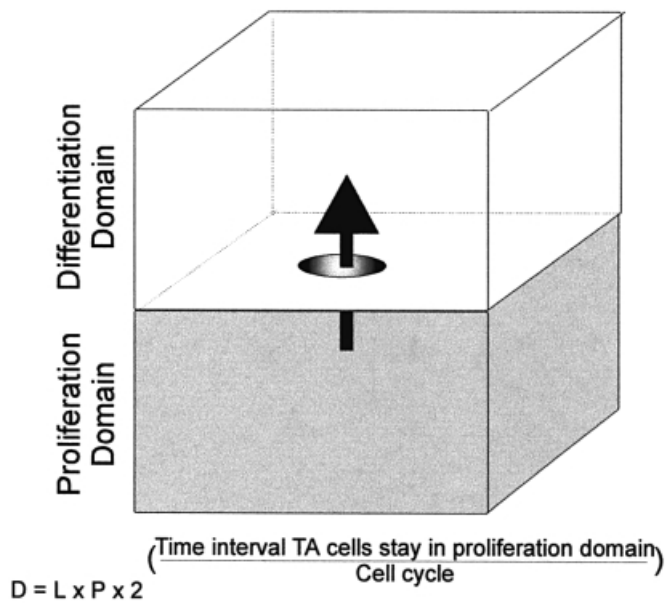


Figure 1. Schematic diagram showing a prototype of the proliferation and differentiation domains of an organ. Cell proliferation takes place in the proliferation domain (gray) and then cells move from the proliferation domain to the differentiation domain (white). The rate of transition is regulated by a hypothetical opening (graded black to white opening) located at the interface of the two domains. The flow can be modulated by positive and negative regulators. Gray ellipses, TA cells. The number of cell divisions that takes place is the time interval that hair precursor cells stay in the proliferation domain divided by the time required for one cell cycle. D, the length along a particular dimension; L, the length of a mature epithelial cell; P, the number of TA cells. The application of this model to the stratified epithelium of skin and hair follicles is shown in **Fig 2**. Similar analyses can be applied to intestinal villi (crypt region as the proliferation domain), long bone (growth plate as the proliferation domain), neural tissues (neuro-epithelium as the proliferation domain), mammary glands, etc.

In a broad sense, *Msx-1* and *-2* seem to be involved in growth control. For example, in craniofacial development, a Pro 148→His mutation of the human *Msx-2* gene was found to correlate with Boston-type craniosynostosis (Jabs *et al*, 1993). In this case, the premature closure of the sutures limited the growth of the skull and caused a small cranium cavity. This condition was mimicked in transgenic mice expressing a mutant or normal mouse *Msx-2* gene (Liu *et al*, 1995). The mechanism is believed to be caused by premature differentiation of osteoblast precursors. In the case of *Msx-1*, targeted disruption of *Msx-1* in mouse mutants show abnormalities in the craniofacial bones and small and missing teeth (Satokata and Maas, 1994).

In the limb bud, *Msx-1* and *-2* are expressed in the apical ectodermal ridge (AER) and the mesenchyme beneath it. Their expression are FGF dependent and are proposed to be important for regulating the function of the progress zone (Muneoka and Sassoon, 1992). By comparing regions of *Msx-2* expression with cellular behavior, *Msx-2* positive cells show less proliferation than adjacent progress zone cells, and also are correlated with regions of programmed cell death that sculpture out the shape of the limb bud. *Msx-2* was ectopically expressed using the RCAS retroviral vector in the posterior limb bud mesenchyme. The results were restricted outgrowth and formation of the skeletal elements, showing phenotypes of truncated limbs with reduced width (Ferrari *et al*, 1998). The authors consider the mechanism to be the imbalance in cell proliferation and programmed cell death caused by abnormally high levels of *Msx-2* activity.

At the level of cultured cells, *Msx-1*, *-2* are also involved in growth control. A nonbiased study was conducted to search for genes that can reverse the v-Ki-ras transformed NIH 3T3 cell

phenotypes. Interestingly, a carboxy-terminal fragment of *Msx-2* was isolated that has this ability. Expression of endogenous *Msx-2* is also upregulated in NIH3T3 cells transfected with v-Ki-ras (Takahashi *et al*, 1996). In myogenic cells, forced expression of *Msx-1*, but not *Msx-2*, blocked myogenic differentiation and caused a transformed phenotype (Song *et al*, 1992).

These data suggest that *Msx-1* and *Msx-2* play a key role in regulating cell proliferation, differentiation, and/or programmed cell death. Although the detailed molecular mechanism remains to be determined, here we study the significance in the regulation of organ size using developing skin and skin appendages. Here we also present a working model to show how the cellular flow between the proliferation domain and the differentiation domain can modulate the final size of an organ or a region of an organ (**Fig 1**). The flow is represented by a hypothetical opening in the barrier located between the proliferation and differentiation domain (black to white graded opening). Different molecular regulators can increase or decrease the flow. We propose that *Msx-2* is one of the molecules that increase the flow.

MSX-2, HAIR LENGTH, AND EPIDERMAL THICKNESS

Skin appendages, including hairs and feathers, are of different lengths in different parts of the body. This is most apparent in the feather. In peacock, the tail feathers can be longer than 1 m and grow at a rate of 8 mm per day, in contrast to the flight feather that grows at about 4 mm per day. In the human, the scalp hair can also be longer than 1 m, whereas the villus hairs on the face are only a few millimeters long. What factors may regulate the length of skin appendages? In skin development, proliferation seems to play a much more major role compared with cell migration or apoptosis. With focus on the proliferation/differentiation, starting from a fixed number of TA cells (*p*), the length along a particular dimension (*D*) is dependent on the length of a mature epithelial cell (*L*) times the number of cell divisions that occur, or the time interval that hair precursor cells stay in the proliferation domain divided by the time required for one cell cycle. There are two stages relevant to this discussion: development and hair cycle. We will first focus on development.

Msx-1 and *-2* are found to be expressed in developing skin in the feather placode (Noveen *et al*, 1995), mouse hair follicle epithelia (Reginelli *et al*, 1995), and human skin epithelia (Stelnicki *et al*, 1997). To study the effect of high levels of *Msx-2* expression on skin development, we produced transgenic mice with *Msx-2* driven by a CMV promoter (Jiang *et al*, 1999). Over-expression of *Msx-2* in skin *in vivo* caused epidermal dysplasia, hyperkeratosis, desquamation, and flakiness. Transgenic mice also showed abnormal hair growth. Hair follicles were misshapen and reduced in size, particularly in the proximal end. The matrix region was shrunken, and keratinization appeared earlier compared with the control. Beyond the matrix region, in the more distal region, the hair cortex and medulla appeared more normal. Hairs were shorter in the beginning, although they eventually caught up in 2 wk.

How do we explain these results? The hair follicles appeared narrower in width and shorter. The matrix epithelia, or the proliferation domain of hair follicles, were shrunken. Keratinization appeared to start earlier. This suggests that increased *Msx-2* activity caused precocious maturation of hair precursor cells; by depleting the pool of transient amplifying cells in the matrix, hairs were shorter in the newborn stage (**Fig 2A**). Other redundant pathways may act to compensate and the length of hairs eventually recovered. This is consistent with the findings in calvaria and limb, in which the increase of *Msx-2* activity leads to a smaller cranium cavity and truncated limb skeleton.

The skin consists of multiple layers of epithelial cells. Cells proliferate in the basal layer and move up as they differentiate. The cells interact to regulate these morphogenetic processes. In *Msx-2* transgenic mice the epidermis was thickened. Proliferating cells remained in the single basal layer, and the suprabasal layer was thickened and hyper-keratotic. The expression of DCC and integrin

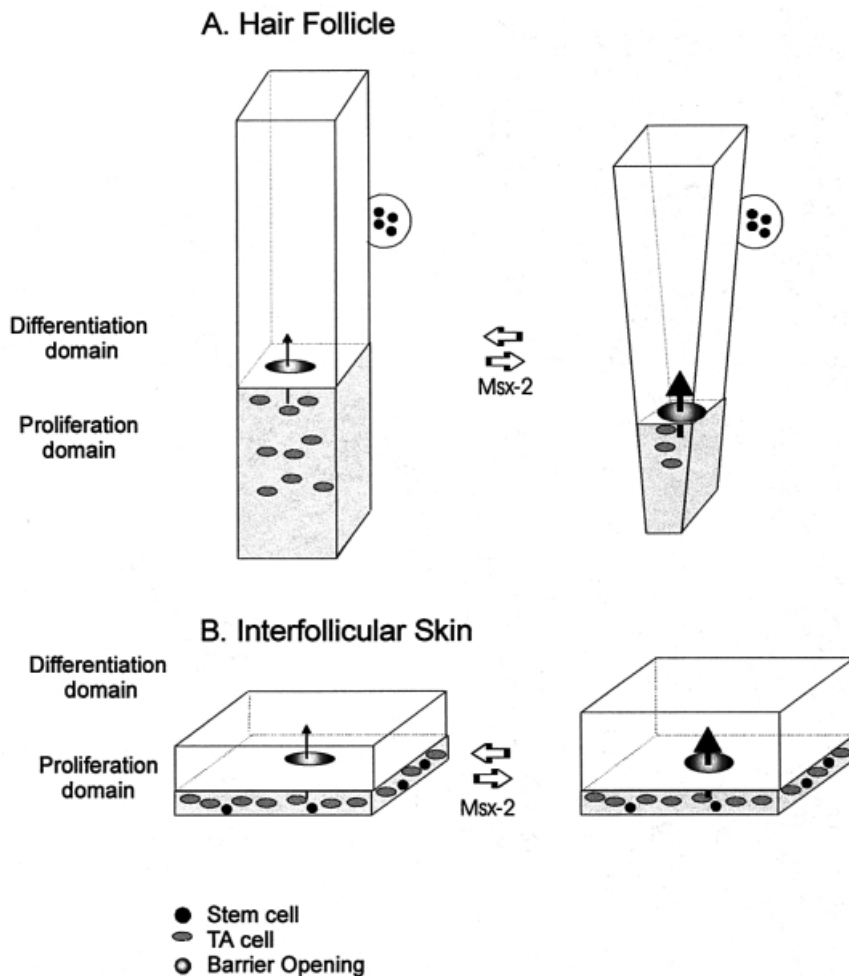


Figure 2. Proliferation and differentiation domains in the hair follicle and epidermis. Based on the prototype of Fig 1, we propose the following working hypothesis for what happens in the skin of *Msx-2* over-expressing transgenic mice. The size of the opening (depicted as a graded black to white opening) located at the interface of the two domains reflects the rate of cellular flow between the proliferation domain and the differentiation domain. Small ellipses, TA cells; filled circles, stem cells. (A) Hair follicles. In the hair, the self-renewing stem cells (black) are out of the follicle in the bulge and cannot generate transient amplifying cells (gray) continuously. The increased flow from the proliferation domain to the differentiation domain produced by *Msx-2* treatment decreases the number of transient amplifying cells, resulting in a shrunken hair matrix region. (B) Epidermis. In the epidermis, the stem cells are in the basal layer and can readily replenish the transient amplifying cells. So the increased flow is able to sustain the size of the proliferation domain and the stratified epithelium thickens.

$\beta 1$ normally found in the basal keratinocytes was reduced in the basal cell population. Above the basal layer, there was an increased layer of cells expressing both basal and suprabasal keratins, suggesting that the identity of cells between the proliferation and differentiation domains was perturbed. We suspect that the mechanism is an accelerated maturation of basal keratinocytes (Fig 2B).

With *Msx-2* over-expression, why does the epidermis become thicker but hair follicles become smaller? One of the possible explanations is the availability of stem cells. In the hair, stem cells are located within the bulge region (Cotsarelis *et al*, 1990), and a small limited number are released to the matrix to become the TA cells in the initiation of each hair cycle. Thus the number of TA cells within the follicle is limiting. Premature transition of proliferating cells to the differentiation domain depletes the TA cell pool and leaves a shrunken matrix and shorter hair (Fig 2A). In contrast, the basal layer of the epidermis contains both stem cells and transient amplifying cells (Watt, 1998). Whereas *Msx-2* also causes enhanced transit of TA cells into the differentiation domain, these cells can be readily compensated by adjacent stem cells, therefore the increased cellular flow leads to thickened and hyperkeratotic epidermis (Fig 2B).

OTHER RELATED MOLECULAR REGULATORS

What molecules may modulate *Msx* expression? *Msx* expression has been shown to be regulated by various molecules, including fibroblast growth factors (FGF), *Bmps*, $TGF\beta$, dorsalin, *Dlx*, syndecan, tenascin, and inhibitor of differentiation (ID) (Evans and O'Brien, 1993; Noveen *et al*, 1995; Sharpe, 1995; Thesleff *et al*, 1995; Thomas *et al*, 1995; Tureckova *et al*, 1995; Weiss *et al*, 1995; Ganan *et al*, 1998). Some of these may be among the physiologic

molecular candidates to regulate epidermal thickness and hair length.

Among these, FGF and their receptors appear to play a role in skin appendage formation during embryonic development. In embryonic chicken skin, FGF and FGFR are specifically expressed in feather germs (Noji *et al*, 1993). FGF induce new feather buds from developing chicken skin (Song *et al*, 1996; Widelitz *et al*, 1996). FGF transcripts are also found in the hair follicles of adult mice (reviewed in Widelitz *et al*, 1997). Transgenic mouse skin expressing FGF-7 driven by a K14 promoter suppressed hair follicle formation (Guo *et al*, 1993), whereas expression of a dominant-negative FGF-7 in transgenic mice produced a wavy shaft resembling that in the rough mutant mouse (Guo *et al*, 1996). Transgenic mice expressing a dominant-negative FGFR driven by the K10 promoter show disrupted and thickened epidermis (Werner *et al*, 1993). How these phenotypes may involve the *Msx* pathway remains to be studied.

We have stated that the duration of the hair cycle can also influence the length of hairs. Because anagen is the time proliferating cells are added to the hair filament, prolonging the time of anagen can increase the length of hairs. This seems to be the case for Angora mice (Sundberg *et al*, 1997). It was shown that the *Angora* gene has a mutated FGF-5 and FGF-5 knockout mice showed elongated hair phenotypes (Hebert *et al*, 1994). The molecular control of the hair cycle is still under investigation (Stenn *et al*, 1998), and how FGF-5 acts with other gene networks (Chuong and Noveen, 1999) to control the duration of anagen is not clear. We do know that *Msx-2* is also involved in the hair cycle, but the investigation is still ongoing (Wu *et al*, unpublished data).

Msx has been reported to regulate BMP expression (Chen and Zhao, 1998; Ferrari *et al*, 1998) or to be regulated by BMP (Zou and Niswander, 1996; Marazzi *et al*, 1997) in different developmental systems. In tooth formation, BMP4 was shown to be both upstream and downstream of Msx-1 (Chen and Maas, 1998). Inhibition of the BMP pathway by Noggin could alter the shape of teeth by morphologically transforming incisors to molars (Tucker *et al*, 1998). Thus these signaling pathways may act together to modulate the shape and size of epithelial appendage organs.

Msx may also affect the molecular pathway involving the Lymphoid enhancer factor, Lef-1 (Kratochwil *et al*, 1996). Lef-1 could be a mediator for Wnt signaling transduced by β -catenin (which then binds Lef-1 and enters the nucleus to change gene expression) and may be downstream to Msx-1 in the tooth induction pathway. Over-expression of Lef-1 causes hairs to grow out from the gum region, a sign of activating the induction of all epithelial appendages (Zhou *et al*, 1995). Along this line, a stable form of β -catenin controlled by the K14 promoter was shown to induce *de novo* hair follicle morphogenesis as well as hair tumors (Gat *et al*, 1998).

CONCLUSIONS

In summary, the shape and size of epithelial appendage organs are controlled by the net addition of cell numbers in a temporal and spatial specific manner. This is controlled by several cellular processes, including proliferation, immigration, death, emigration, and differentiation. The time that cells spend in the proliferation domain is regulated by many molecular pathways. We think Msx-1 and Msx-2 are among the major regulators influencing the transition to the differentiation domain. Together with other molecules that modulate Msx activities, these gene networks (Chuong and Noveen, 1999) act to translate cellular processes (e.g., cell cycle, cytodifferentiation) into morphogenetic processes (e.g., organ size, shape). Analyzing these developmental pathways, and linking the molecular pathways to morpho-regulation during organogenesis (Edelman, 1992), is an important future goal.

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