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Review

The function of TRPS1 in the development and differentiation of bone, kidney, and hair follicles

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Summary. *TRPS1* is a gene involved in Tricho-rhino-phalangeal syndrome (TRPS), an autosomal dominant skeletal disorder. *TRPS1* encodes a GATA-type transcription factor that has nine zinc-finger motifs. A variety of mutations in *TRPS1* including deletions and insertions, have been found in patients with TRPS type I and III. The functions of each domain of TRPS1 have been clarified from study of these mutations. Further studies on the localization and the function of TRPS1 have been performed using *TRPS1*$^{\Delta gt}$ and *Trps1*-deficient mice, which allow examination of the development and differentiation of all tissues with *Trps1* expression. These studies suggest that TRPS1 exhibits a variety of functions in cartilage, kidneys, and hair follicles. In the growth plate cartilage, TRPS1 regulates the differentiation, proliferation, and apoptosis of chondrocytes through interaction of several signaling molecules. In addition, TRPS1 has a function downstream of BMP7, which regulates the mesenchymal-epithelial transition when nephrons are formed in renal development. Furthermore, TRPS1 suppresses the epithelial-mesenchymal transition and renal fibrosis induced by unilateral ureteral obstruction by decreasing Arkadia expression. Finally, *TRPS1* is expressed in the dermal papillae and the mesenchymal cells surrounding the hair pegs, and the loss of TRPS1 largely influences the development of hair follicles. The molecular mechanisms of the function of TRPS1 in cartilage, kidneys, and hair follicles are discussed in this review.

Key words: TRPS1, BMP7, Development, Differentiation, Chondrocytes, Kidney, Hair follicles

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Introduction

The *TRPS1* gene has been reported to be responsible for Tricho-rhino-phalangeal syndrome (TRPS) type I (Momeni et al., 2000). TRPS type I [MIM 190350] and type III [MIM 190351] (TRPS I or TRPS III) are autosomal dominant skeletal disorders characterized by short stature and craniofacial anomalies such as a bulbous tip of the nose, a flat and long philtrum, protruding ears and sparse scalp hair (Giedion et al., 1973; Niikawa and Kamei, 1986). TRPS III is more severe than TRPS I in that it involves additional brachydactyly (Nagai et al., 1994; Itin et al., 1996). The *TRPS1* gene is approximately 260.5 kb in length and consists of 7 exons (Momeni et al., 2000). The third exon contains a Kozak consensus ATG translation start site and the first C_2H_2-type zinc finger domain. The seventh exon encodes an Ikaros-type zinc finger domain and a TAA stop codon (Chang et al., 2002). It encodes a 1281-amino-acid (aa) zinc-finger transcription factor that has a calculated molecular mass of 160 kDa and contains an unusual combination of nine predicted zinc finger domains, including seven classical C_2H_2-type domains, which are related to those found in the transcription factor TFIIIA of *Xenopus laevis*, one GATA C_4-type domain and two Ikaros C_2H_2-type zinc fingers (Fig. 1A) (Georgopoulos et al., 1992; Momeni et al., 2000). The GATA zinc-finger is flanked by two basic nuclear localization signals (NLS1: LRRRRG, 886–891 aa, and NLS2: RRRTRKR, 946–952 aa), and it has been demonstrated that only the second motif functions as a NLS in TRPS1 (Kaiser et al., 2004), which indicates that TRPS1 functions as a nuclear zinc finger protein.

Genotype analysis of patients with TRPS has identified many different mutations in the *TRPS1* gene. TRPS I is associated with deletions and nonsense mutations in the N-terminal half of one allele of *TRPS1*. Mutations in the NLS prevent the translocation of TRPS1 into the nucleus, which results in a reduction in

the TRPS1 concentration in the nucleus (Fig. 1Bc) (Momeni et al., 2000). In addition, TRPS III has a more severe phenotype than TRPS I and is associated with missense mutations in the GATA binding domain or the Ikaros-type zinc finger domain, which create alleles encoding a dominant antagonist of the wild-type TRPS1 protein, resulting in a dominant-negative effect (Fig. 1Bd) (Momeni et al., 2000; Ludecke et al., 2001; Kaiser et al., 2004).

Using a loss-of-function approach, the function of the last three zinc-finger motifs (motifs 7–9) has been determined. Motifs 8 and 9 (1217–1237 and 1245–1267 aa), which have a high degree of similarity to the Ikaros-type zinc-finger, are involved in the formation of homo- or heterodimers and in the repression effect of TRPS1 (Ludecke et al., 2001; Malik et al., 2001; Kaiser et al., 2004; Asou et al., 2007). Mutations in these motifs also cause haploinsufficiency (Fig. 1Bc). The seventh zinc-finger motif (896–920 aa, C_2C_2-type) binds to DNA sequences harboring a (T/A)GATA(A/G) sequence or an inverse GATA consensus sequence. An intact GATA zinc-finger is indispensable for the transcription repression activity of TRPS1 (Chang et al., 2002). TRPS1 has been reported to function as a transcription factor that represses the activity of the GATA4 transcription factor in vitro (Chang et al., 2002). However, on the basis of the analysis of *TRPS1*$^{\Delta gt}$ mice, the notion that TRPS1 may directly antagonize GATA transcription activators *in vivo* seems unlikely (Malik et al., 2002).

TRPS1 is expressed in a tissue-specific manner and acts as a critical regulator of organ development. In mouse embryos, *Trps1* mRNA is detected prior to E7.5, with peak levels at around E11.5, and expression during mid-gestation (embryonic days 12.5–14.5) is detected in the facial region and pharyngeal arches, including the joints of the limbs, the maxilla, mandible, snout, prospective phalanges, and hair follicles (Malik et al., 2001; Suemoto et al., 2007; Nishioka et al., 2008; Piscopo et al., 2009). In the visceral tissues, Trps1 expression is detected in the mesenchyme of the developing lung, gut, kidney, and mesonephric duct (Kunath et al., 2002; Gai et al., 2009). In humans, the tissue distribution of *TRPS1* mRNA is found to be high in the prostate, testis, ovary, kidney, lung, and mammary gland (van den Bemd et al., 2003).

Growth retardation is a feature frequently found in patients with TRPS I, who are commonly short in stature (Naselli et al., 1998). Skeletal abnormalities include brachyphalangeal dysostosis (digital abnormalities of proximal interphalangeal joints, clinobrachydactyly of hands and feet) and cone-shaped epiphyses (CSE) at the base of the proximal and mid-phalanges (Giedion, 1967, 1998; Dunbar et al., 1995). Other rare features, such as chest and spinal abnormalities, can be found as well (Felman and Frias, 1977; Sugiura, 1978). CSEs or hip changes are variable, whereas the facial appearance of all patients with TRPS I is similar (Giedion et al., 1973; Naselli et al., 1998).

Trps1$^{\Delta gt}$ and *Trps1*-null mice die within 24 hours due to respiratory failure (Malik et al., 2002; Suemoto et al., 2007) and display severe hair abnormalities, a short and flat snout, growth retardation, reduced calcification and primary ossification, low bone density, and fragile rib cartilage; these characteristics are similar to those found in humans with TRPS I. In addition to the superficial overlap between the clinical findings in human TRPS I patients and the phenotypes in *Trps1*-null

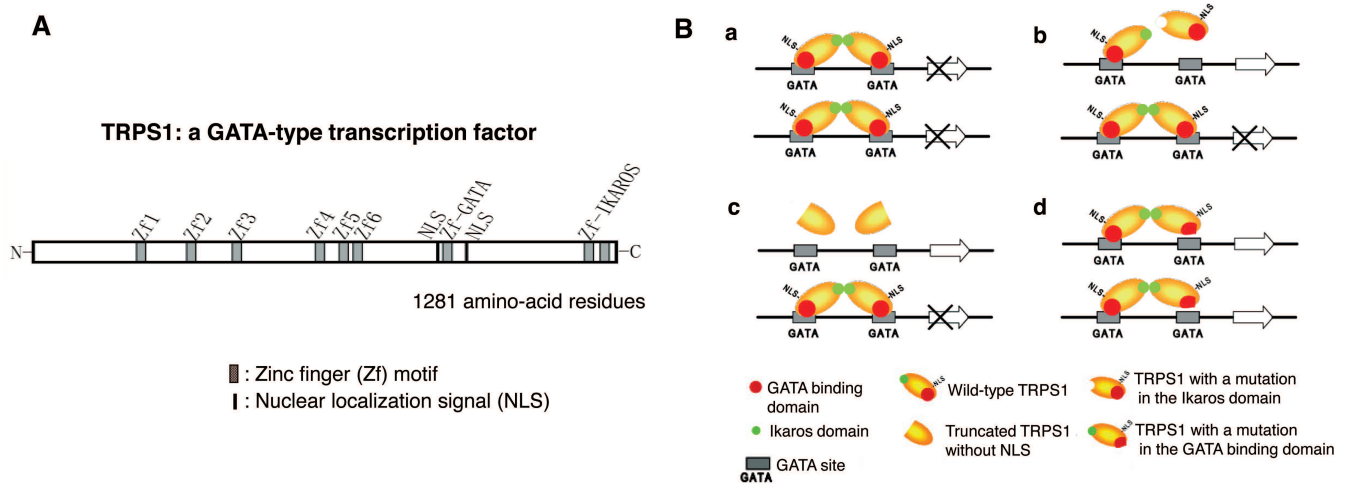

Fig. 1. Schematic representation of the structure of the TRPS1 protein **(A)** and the probable mechanisms by which the mutated Trps1 proteins exert the repressor effect on the transcription of target genes **(B)**. Wild-type TRPS1 forms homodimers to bind the GATA sites and represses the transcription of the target genes **(a)**. Mutations in the Ikaros domain of one allele of TRPS1 prevent homodimer formation **(b).** Deletions of the N-terminal half of TRPS1 prevent the protein from translocating into the nucleus **(c)**. Missense mutations in the GATA binding domain create alleles that function as dominant antagonists of the wild-type TRPS1 protein **(d)**. Arrows with a cross indicate the repression of transcription of the target genes of TRPS1.

mice, *Trps1*-null mice revealed unexpected abnormalities in kidney development (Gai et al., 2009).

In this review, we highlight the current understanding of the function of Trps1 in cartilage and kidney development, focusing on cell differentiation and the epithelial-mesenchymal transition. In addition, we will briefly touch on aspects of Trps1 function in the hair follicles.

Trps1 contributes to bone formation and mineralization

Endochondral ossification is a multi-step process that starts with mesenchymal condensation. This process begins with the migration of mesenchymal cells to the site of future skeletogenesis, where they aggregate into compact nodules. The mesenchymal cells within the region of condensation differentiate through a series of intermediate phenotypes (proliferative and prehypertrophic chondrocytes) before they mature into the differentiated hypertrophic chondrocytes and ultimately undergo apoptosis. Chondrocyte differentiation in the cartilaginous anlagen is accompanied by molecular and morphological changes in the surrounding perichondrial cells. These mesenchymal cells sustain their undifferentiated status until the chondrocytes within the anlagen begin to become hypertrophic (St-Jacques et al., 1999; Kronenberg, 2003; Long et al., 2004).

Trps1 expression is found in the developing cartilage anlagen, including that of the facial bones, bones of the inner ear, ribs, vertebrae and the long bones (Kunath et al., 2002). A detailed analysis of the long bones of embryonic mice showed that Trps1 is highly expressed in the mesenchymal condensations in the anlagen of future endochondral bones at E12.5 (Napierala et al., 2008). On E14.5, Trps1 is expressed throughout the growth plate, with strong immunostaining in the proliferating region with an anti-Trps1 antibody. After the establishment of endochondral ossification, Trps1 expression is further confined to prehypertrophic chondrocytes and the perichondrium (Itoh et al., 2008; Napierala et al., 2008; Nishioka et al., 2008).

Further analysis of different regions within the cartilage shows various aspects of Trps1 function in the regulation of endochondral ossification and mineralization. Histomorphometric analyses have demonstrated that the proliferating zone and the prehypertrophic zone were significantly longer in Trps1-mutant mice than in WT littermates (Suemoto et al., 2007; Napierala et al., 2008; Nishioka et al., 2008; Wuelling et al., 2009). These enlarged zones indicate an increased proliferation/apoptosis ratio of columnar cells, or a disturbed differentiation of proliferating cells into hypertrophic cells. By analyzing the proliferating and apoptotic cells in the growth plates of *Trps1*-null mice, Suemoto et al. demonstrated that Trps1 regulates proliferation and apoptosis of chondrocytes by directly suppressing Stat3 signaling. Later, it was demonstrated that Trps1 is required to maintain the normal organization of chondrocytes in parallel with Indian hedgehog (Ihh) signaling and that the lack of Trps1 leads to the overexpression of PTHrP, which in turn delays chondrocyte differentiation (Fig. 2, 1) (Nishioka et al., 2008, Wuelling et al., 2009). Meanwhile, an analysis of the Fgfr3- and Ihh-positive zone showed an increased length of prehypertrophic chondrocytes in Trps1-mutant mice, indicating disturbed differentiation of proliferating cells into hypertrophic chondrocytes (Fig. 2, 3) (Napierala et al., 2008; Wuelling et al., 2009). In addition to the elongation of the growth plate, Trps1-mutant mice experienced abnormal mineralization of the perichondrium. Further studies demonstrated that these abnormalities are due to the disturbed interactions between Trps1, Runx2, and Gli3, causing an increased Ihh signaling, which in turn inhibits chondrocyte differentiation and accelerates perichondrial mineralization (Fig. 2, 5) (Napierala et al., 2008; Wuelling et al., 2009). On the other hand, in differentiating osteoblasts, Trps1 expression negatively modulates the mineralized bone matrix formation by directly repressing the promoter region of osteocalcin (Piscopo et al., 2009). These data suggest that Trps1 plays a role in osteoblast differentiation and in chondrogenesis.

In summary, as shown in Fig. 2, Trps1 executes multiple functions in proliferating chondrocytes, expanding the region of resting chondrocytes (Wuelling et al., 2009), regulating proliferation and apoptosis

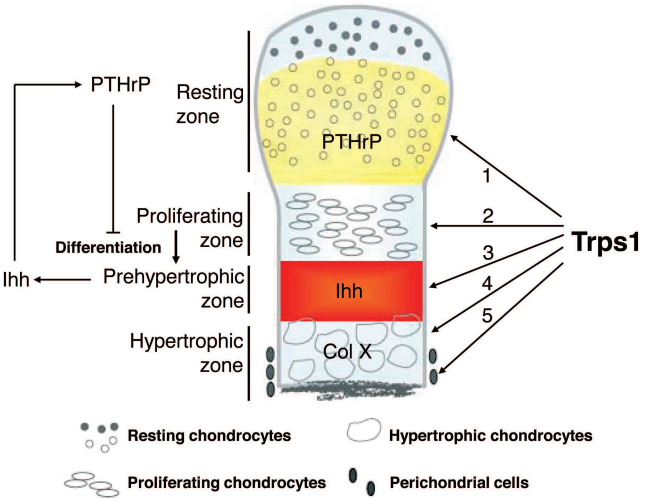

Fig. 2. Trps1 regulates chondrocyte differentiation in different regions of epiphyseal cartilage in parallel with Ihh/PTHrP signaling. **1:** Trps1 maintains resting chondrocytes in which PTHrP is expressed. PTHrP signals are transmitted to the growth plate to inhibit differentiation to hypertrophic chondrocytes. **2:** Trps1 promotes chondrocyte proliferation through the regulation of PTHrP. **3:** In the prehypertrophic zone, Trps1 induces the differentiation of chondrocytes through Ihh signaling. **4:** Trps1 regulates hypertrophic chondrocytes to induce apoptosis by suppressing Stat3. **5:** Trps1 regulates perichondrial mineralization through an interaction with Runx2.

(Suemoto et al., 2007; Nishioka et al., 2008), promoting the differentiation of proliferative chondrocytes into hypertrophic chondrocytes (Wuelling et al., 2009), and regulating mineralization and the formation of matrix (Napierala et al., 2008). These reports suggest that Trps1 has specific functions in different zones of epiphyseal cartilage by interacting with different subsets of transcription factors (e.g., Runx2 and Gli3) or suppressing different target genes (e.g., Stat3 and PTHrP).

Trps1 is critical for normal kidney development and the epithelial-mesenchymal transition

Renal tubular epithelial cells originate via a program of reciprocal interaction of two distinct tissues: the ureteric bud and metanephric mesenchyme (Saxen and Sariola, 1987). Briefly, signals from the ureteric buds promote the survival of nephrogenic mesenchymal cells and induce them to condense and undergo the mesenchymal-epithelial transition (MET), leading to renal tubular formation. Concomitantly, signals from the mesenchymal cells stimulate the growth and branching of the ureteric buds that ultimately form the collecting duct system.

During nephrogenesis, Trps1 is present in the epithelial cells of the ureteric buds and in the induced mesenchymal cells that undergo the MET. In mouse embryonic kidneys, Trps1 is first expressed in the protruding ureteric buds at E10.5. Fig. 3A shows Trps1 expression in ureteric buds at E11.5. After the invasion of the ureteric buds into the metanephric mesenchyme at

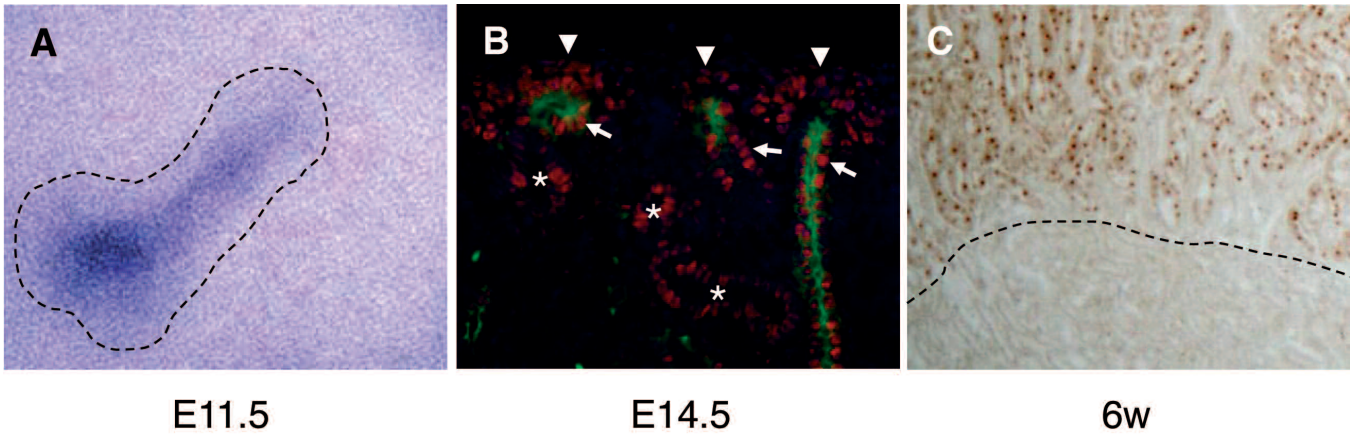

Fig. 3. Trps1 expression in embryonic kidneys and adult mouse kidneys. **A.** Trps1 is expressed in the protruding ureteric buds at E11.5 as demonstrated by LacZ staining. Broken lines indicate the margin of a ureteric bud. **B.** at E14.5, Trps1 is strongly positive (red) in the ureteric buds and in the condensed (cap) mesenchyme and renal vesicles. Arrowheads and asterisks indicate cap mesenchyme and renal vesicles, respectively. Arrows indicate the ureteric buds (green). **C.** immunohistochemistry of Trps1 in 6 week-old mouse kidney. Trps1 is specifically localized to the nuclei of proximal tubule epithelial cells. Broken lines indicate the border of the cortex and the medulla of the kidney.

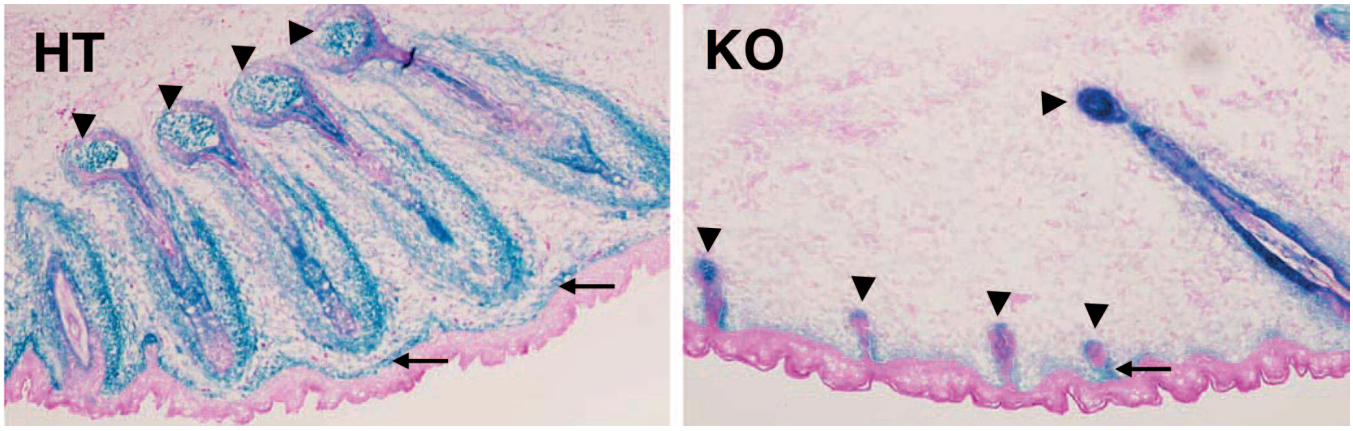

Fig. 4. LacZ staining of vibrissae in heterozygous (HT) and homozygous (KO) *Trps1*-null newborn mice. *Trps1* expression is restricted to the nuclei of the mesenchyme-derived papillae cells (arrow heads) and the mesenchymal cells surrounding the hair pegs and underlying the epidermis (arrows). Note that the development of the hair follicle is affected in KO mice, although the number of hair follicles is the same as in HT mice.

E12.5, the ureteric buds release signals to induce and condense the mesenchymal cells and express Trps1. At E14.5, Trps1 immunostaining is strongly positive in the ureteric bud cells and in the condensed mesenchyme and renal vesicles that will form the mature renal tubules (Fig. 3B) (Kunath et al., 2002; Gai et al., 2009). Finally, Trps1 is restricted in the proximal tubular epithelial cells of adult mice (Fig. 3C) (Gai et al., 2010).

Comparison of kidneys between wild-type and Trps1-null newborn mice revealed that the *Trps1*-null mice have fewer tubules and glomeruli, expanded renal interstitium, and numerous uninduced metanephric mesenchymal cells, which resulted in fewer nephrons. In addition, in vivo and in vitro studies have demonstrated that a lack of Trps1 disrupts the transition from mesenchymal cells to epithelial cells and that Trps1 expression is regulated by Bmp7 *via* the p38 MAP kinase pathway (Gai et al., 2009). Moreover, the branching of ureteric buds is elongated in Trps1 KO kidneys compared with wild-type kidneys (Gai et al., 2009).

Given the fundamental role of Trps1 in directing differentiation, maintaining the epithelial state of renal tubular epithelial cells, and in activity downstream of Bmp7, we hypothesized that the loss of Trps1 could be involved in the pathogenesis of the epithelial-mesenchymal transition (EMT) during renal fibrosis. In renal fibrosis induced by unilateral ureteral obstruction (UUO), the mRNA and protein levels of Trps1 were reduced in both wild-type and Trps1-haploinsufficient mice, but Trps1-haploinsufficient mice had more severe tubulointerstitial fibrosis than wild-type mice. Furthermore, Trps1 haploinsufficiency enhances TGF-ß1-induced EMT and tubulointerstitial fibrosis by decreasing the amount of Smad7 through Arkadia/ubiquitin-mediated degradation (Gai et al. 2010).

Collectively, Trps1 is essential to the mesenchymal-epithelial transition and ureteric bud branching during nephrogenesis, and Trps1 haploinsufficiency promotes the epithelial-mesenchymal transition in the process of renal fibrosis. Whether Trps1 haploinsufficiency may promote EMT in patients with TRPS suffering from chronic kidney disease or whether over-expression of Trps1 may inhibit TGF-$ß_1$-induced EMT needs to be further studied.

Trps1 in hair follicles

In developing hair follicles, Trps1 expression is first found in the mesenchyme of the anlagen at E12.5. In the undifferentiated epithelium at E14.0, Trps1 expression appears transiently as diffuse, spotty staining in the dorsal epidermis. During the hair germ stage at E15.5, Trps1 expression is observed in the nuclei of the cells in the dermal condensate, with some diffuse staining still present in the epidermis. By the peg and bulbous peg stages at E16.5 and E17.5, Trps1 expression becomes restricted to the nuclei of cells of the mesenchyme-derived dermal papillae and the mesenchymal cells surrounding the hair pegs and underlying the epidermis (Fig. 4) (Kunath et al., 2002; Fantauzzo et al., 2008). Notably, Trps1 expression in the mesenchyme surrounding the hair follicle and underlying the epidermis is specific to morphogenesis and is not observed during postnatal hair follicle cycling. Given the fact that hair follicle morphogenesis occurs as the result of an extensive and collaborative interaction between epithelial and mesenchymal skin components (Oliver and Jahoda, 1988; Hardy, 1992; Paus, 1998; Millar, 2002), we could speculate that Trps1 may be involved in the interactions between epithelial and mesenchymal cells during hair follicle morphogenesis and that it may be regulated by Bmp7. The molecular mechanism by which the loss of Trps1 affects hair follicle development still remains unknown (Fig. 4).

Conclusions

Several reports have demonstrated that Trps1 is localized to the mesenchyme of a variety of tissues during murine embryogenesis (e.g., cartilage, kidney, hair follicles, gut, and lung) (Fantauzzo et al., 2008; Napierala et al., 2008; Gai et al., 2009). Additionally, Trps1 has been demonstrated to regulate the mesenchymal cells undergoing proliferation and differentiation in cartilage and in the kidney (Suemoto et al., 2007; Itoh et al., 2008; Napierala et al., 2008; Nishioka et al., 2008; Gai et al., 2009; Wuelling et al., 2009). It has been proposed that Trps1 may function in the development of hair follicles, the gut and the lungs, as well as in the development of prostate and breast cancers (van den Bemd et al., 2003; Chang et al., 2004, 2007; Savinainen et al., 2004; Radvanyi et al., 2005). The roles of Trps1 in the differentiation of mesenchymal cells have been added to the growing body of evidence implicating the GATA family of transcription factors as key regulators of cell specification and maintenance. A future goal relevant to understanding the detailed functions of Trps1 in various cell types should be to identify the downstream targets that mediate the effects of Trps1, and the cofactors that interact with it. Two major questions need to be answered regarding Trps1: 1) How does Trps1 control cell differentiation? 2) Could the cofactors and downstream targets differentiate different species of cells? Several essential experiments for a comprehensive analysis should be done to answer these questions.

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