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Differential expression of LIM domain-only (LMO) genes in the developing mouse inner ear

Min Deng [a], Ling Pan [a], Xiaoling Xie [a], Lin Gan [a,b,c,*]

[a] *Center for Aging and Developmental Biology, University of Rochester, Rochester, NY 14642, USA*
[b] *Department of Ophthalmology, University of Rochester, Rochester, NY 14642, USA*
[c] *Department of Neurobiology and Anatomy, University of Rochester, Rochester, NY 14642, USA*

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Abstract

The vertebrate inner ear, a complex sensory organ with vestibular and auditory functions, is derived from a single ectoderm structure called the otic placode. Currently, the molecular mechanisms governing the differentiation and specification of the otic epithelium are poorly understood. We present here a detailed expression study of *LMO1–4* in the developing mouse inner ear using a combination of in situ hybridization and immunohistochemistry. *LMO1* is specifically expressed in the vestibular and cochlear hair cells as well as the vestibular ganglia of the developing inner ear. *LMO2* expression is detected in the periotic mesenchyme of the developing mouse cochlea from E12.5 to E14.5. The expression of *LMO3* expression is first observed in the cochlea at E13.5 and becomes confined to the lesser epithelial ridge (LER) from E14.5 to E17.5. *LMO3* is also expressed in some of the vestibular ganglion cells. *LMO4* is initially expressed in the dorsolateral portion of the otic vesicle and its expression persists in the semicircular canals, macula, crista, and the spiral ganglia throughout embryogenesis. Thus, the regionalized expression patterns of *LMO1–4* are closely associated with the morphogenesis of the inner ear.

Keywords: LIM; LIM domain-only; LMO; LMO1; LMO2; LMO3; LMO4; Inner ear development; Transcription factor

1. Results and discussion

The nuclear LMO protein family consists of four transcription regulatory factors, LMO1–4, and are shown to play myriad roles in cell fate specification, differentiation, and cytoskeletal organization (Bach, 2000; Dawid et al., 1998). Structurally, LMO proteins contain two tandem zinc finger LIM domains for protein–protein interaction but lack the DNA-binding and other functional domains (Dawid et al., 1998; Rabbitts, 1998; Sugihara et al., 1998). They likely act to promote the formation of multimeric transcription regulatory complexes with bridging factors such as basic helix–loop–helix (bHLH) and GATA proteins (Rabbitts, 1998). Additionally, they could function antagonistically toward LIM homeodomain (LIM-HD) proteins by competing for binding to the essential cofactor Ldb/NLI (LIM-domain-binding protein) (Bach, 2000; Jurata et al., 2000). Functionally, LMO1 and LMO2 have been shown to act as oncoproteins in lymphocytes (Sanchez-Garcia and Rabbitts, 1993). During hematopoietic development, LMO2 functions as a linker to recruit hematopoietic transcription factors such as SCL(TAL1)/E2A and GATA1 as well as the cofactor Ldb1 to form the higher-order protein complexes (Wadman et al., 1997). LMO4 has also been shown to participate in a novel multiprotein complex comprising BRCA1 and CtIP in breast epithelial cells (Sum et al., 2002). In addition, LMO4 interacts with other proteins, including the transcription factors Deformed Epidermal Autoregulatory Factor-1 (Deaf-1) (Sugihara et al., 1998), Grainyhead-like epithelial transactivator (GET-1) (Kudryavtseva et al., 2003), the bHLH protein HEN1 (Manetopoulos et al.,

* Corresponding author. Tel.: +1 585 273 1510; fax: +1 585 276 1947.
E-mail address: lin_gan@urmc.rochester.edu (L. Gan).

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2003) and Smad8, a protein involved in the BMP pathway (Colland et al., 2004). Targeted gene disruption experiments in mice have shown that while the null mutation of LMO1 or LMO3 alone results in no discernible phenotype, the compound mutant of LMO1 and LMO3 die within 24 h of birth with no apparent anatomical defects (Tse et al., 2004). Homozygotes for LMO2 targeted null mutation exhibit a lack of yolk sac erythropoiesis and die around E10.5 (Warren et al., 1994). Null mutation of LMO4 leads to perinatal lethality due to a severe neural tube defect which occurs in the form of anencephaly or exencephaly (Hahm et al., 2004; Lee et al., 2005;

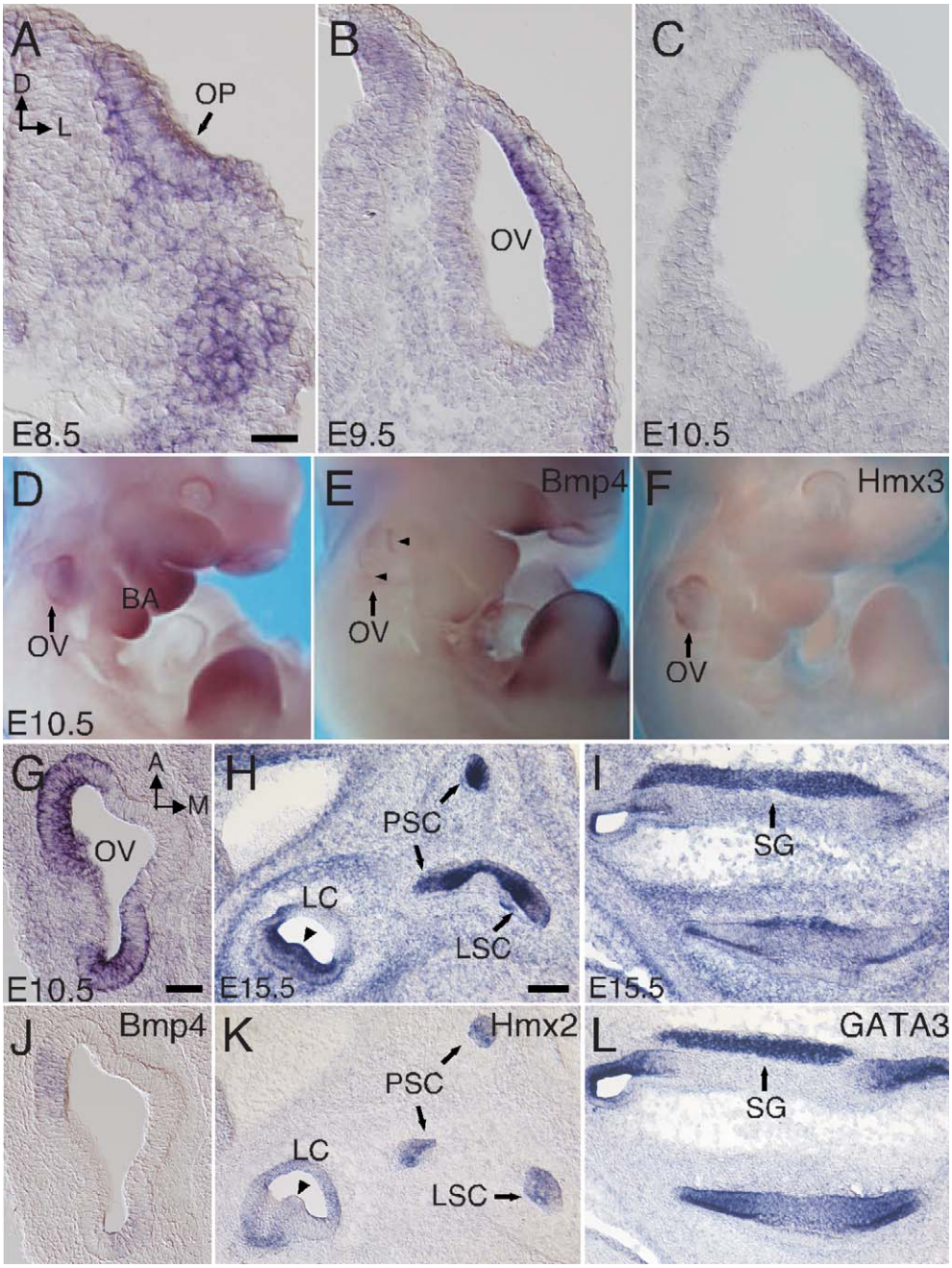

Fig. 1. Expression of *LMO4* in the developing mouse inner ear. *LMO4* expression begins in the otic placode at E8.5 (A, transverse section). At E9.5 (B, transverse section), *LMO4* is expressed in the lateral part of the otocyst. Transverse section (C) and whole-mount (D–F) in situ hybridization of E10.5 embryos with probes indicated. Arrowheads show Bmp4 expression domain. At E10.5, *LMO4* is expressed in the dorsolateral portion of the otic vesicle. (G and J) At E10.5, in situ hybridization of coronal adjacent section revealed that *LMO4* expression overlaps with *Bmp4* in the presumptive crista. *LMO4* mRNA is also weakly expressed in the adjacent ectoderm (C and G) and in the branchial arches (D). Compared with Hmx2 (K) and GATA3 (L) expression, in situ hybridization of adjacent transverse sections at E15.5 shows that *LMO4* is expressed in crista (H, arrowhead), semicircular ducts (H, arrows), and spiral ganglion cells (I). Abbreviations for this and other figures are: A, anterior; D, dorsal; L, lateral; M, medial; BA, branchial arches; LC, lateral crista; LSC, lateral semicircular canal; OP, otic placode; OV, otic vesicle; PSC, posterior semicircular canal; SG, spiral ganglion. Scale bar equals 50 μm.