Int. J. Dev. Biol. 52: 1119-1122 (2008)
doi: 10.1387/ijdb.082700rm

THE INTERNATIONAL JOURNAL OF DEVELOPMENTAL BIOLOGY
www.intjdevbiol.com

Expression of the novel gene *Ened* during mouse and *Xenopus* embryonic development

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ABSTRACT We have recently identified *1110032E23Rik* as a down-regulated target gene in Fgf receptor-signalling-deficient mouse embryoid bodies. Here, we present the expression pattern of this novel gene, designated *Ened* (Expressed in Nerve and Epithelium during Development), in mouse and *Xenopus laevis* embryos. Murine *Ened* transcripts were first seen at E9.5 in the heart and the gastrointestinal tract. At later stages of gestation, expression could be found in the floor plate, peripheral nervous system, lens epithelium, skin, midline dorsal aorta, lung, kidney and testis. In *Xenopus*, the expression of the *Ened* orthologue displayed common RNA distribution in several ectodermal and mesodermal tissues, but also distinct expression in locations including the brain, notochord and blood islands. We suggest that *Ened* might be a novel target gene of the Fgfr signalling pathway during embryonic development, and that its expression could be modulated by the basement membrane component laminin-111.

KEY WORDS: *Ened, embryonic development, epithelium, Fgf/Fgfr signalling, peripheral nerve*

Fibroblast growth factors (Fgfs) and their receptors (Fgfrs) have been shown to play important roles in the regulation of cellular proliferation and of subsequent differentiation and tissue patterning during vertebrate embryogenesis (Böttcher and Niehrs, 2005). Embryoid bodies (EBs) are aggregates of *in vitro*-cultured embryonic stem cells and an established model to study the role of Fgfs in epithelial morphogenesis (Weitzer, 2006). It has previously been demonstrated that EBs, in which endogenous Fgfr signalling was attenuated by the over-expression of dominant-negative Fgfr2 (dnFgfr2), failed to produce the first epithelial layer of the EBs, *i.e.* the endoderm. In addition, expression of the network-forming basement membrane proteins laminin-111 and collagen type IV was abrogated in Fgfr signalling-deficient EBs, and as a consequence ectoderm differentiation failed (Li *et al.*, 2001). In a recent study, we conducted an extensive microarray-based gene expression analysis of dnFgfr2-transfected EBs and presented a catalogue of genes whose expression was significantly influenced by deficient Fgfr signalling. Among the strongly down-regulated targets, a number of not yet annotated genes were identified, including the hitherto uncharacterized gene *1110032E23Rik* (Meszaros *et al.*, 2007). As confirmed by RT-PCR analysis, the expression level of this gene was reduced in dnFgfr2 EBs, indicating that this novel gene might be a target of the Fgfr signalling pathway (Meszaros *et al.*, 2007). In the current study, we investigated the gene expression of *1110032E23Rik* during mouse and *Xenopus laevis* embryonic development. Based on its expression characteristics in mouse embryos, we have named this novel gene *Ened* (Expressed in Nerve and Epithelium during Development).

Results and Discussion

Mouse *Ened* is localized to chromosome 3E3 (NCBI Map Viewer). A full-length cDNA clone encompassing 3528 nucleotides was obtained from RZPD (Germany; I.M.A.G.E. consortium clone IMAGE:6827227) and sequenced (GenBank Accession No. EU797522). Mouse *Ened* encodes a hypothetical protein

Abbreviations used in this paper: EB, embryoid body; Ened, expressed in nerve and epithelium during development; Fgf, fibroblast growth factor; Fgfr, fibroblast growth factor receptor; dnFgfr2, dominant-negative fibroblast growth factor receptor 2.

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Electronic Supplementary Material for this article, consisting of 1 additional figure, is available online at: http://dx.doi.org/10.1387/ijdb.082700rm

Accepted: 24 June 2008. *Published online:* 14 August 2008; *Edited by:* Christine Mummery.

0214-6282/2008/$35.00

of 517 amino acids with a calculated molecular weight of 58.3 kDa. No obvious protein motifs were found. A putative transmembrane helix was detected at the N-terminus of the mouse Ened protein, spanning from amino acids 38-56. A Blast search revealed orthologous full-length *Ened* sequences in human, horse, opossum, and chicken with an overall amino acid identity of 83% to human and horse, 72% to opossum and 61% to chicken (Supplementary Fig. S1A). The putative transmembrane domain is largely conserved between these species (Supplementary Fig. S1A, open box). In addition, we identified an orthologous EST sequence of the *Ened* gene in *Xenopus laevis*. A C-terminally truncated cDNA clone purchased from RZPD (I.M.A.G.E. consortium clone IMAGE:8070075) contained a 1.5 kb insert that was sequenced (GenBank Accession No. EU746496). Alignment of the translated protein sequences of mouse and *Xenopus* Ened indicated homologous sequences between the two species (Supplementary Fig. S1B). These results suggest that the Ened protein is conserved in several vertebrate species.

The expression pattern of *Ened* was elucidated by non-radioactive and radioactive *in situ* hybridization on mid-gestation stage

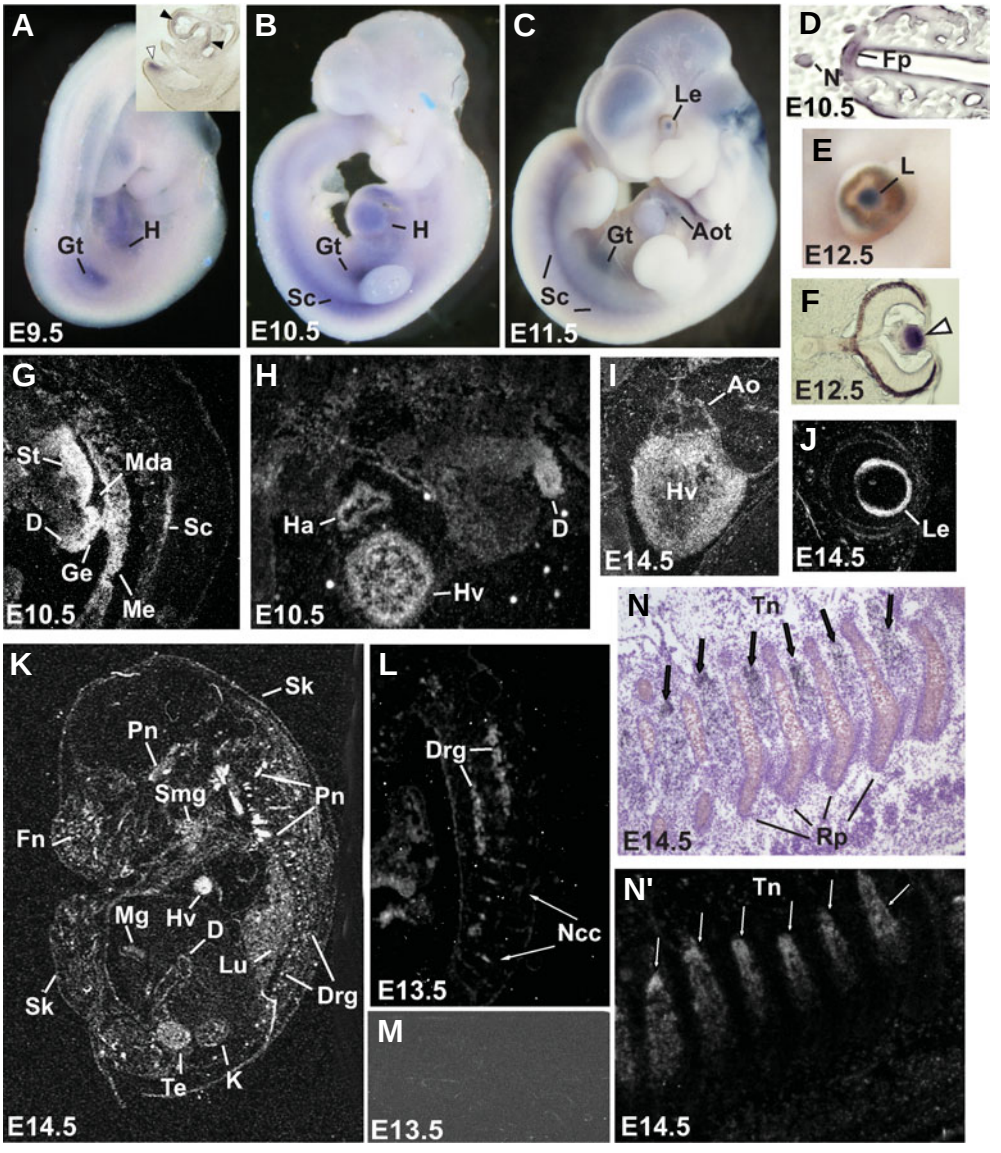

Fig. 1. *Ened* expression in mouse embryos from E9.5 to E14.5. *Lateral views of whole-mount* in situ *hybridized mouse embryos at E9.5 to E11.5 (A,B,C). In mouse embryos hybridized with anti-sense riboprobe,* **(A)** *distinct expression can be observed in the heart and gastrointestinal tract at E9.5. The inset shows sagittal section of E9.5 embryo with signals in the wall of the heart (filled arrowheads) and gastrointestinal tract (open arrowhead).* **(B)** *At E10.5* Ened *expression appeared in the sympathetic chain in addition to the heart and gastrointestinal tract.* **(C)** *At E11.5* Ened *expression emerged in the lens epithelium in addition to the heart, aortic outflow tract, gastrointestinal tract and the sympathetic chain.* **(D)** *Magnified view of transversally cut whole-mount hybridized E10.5 embryo showing expression in the floor plate and notochord.* **(E)** *Magnified view of the eye of whole-mount hybridized embryo at E12.5 depicting* Ened *expression in the lens.* **(F)** *Transversal section of E12.5 eye from (E), indicating robust staining in the lens epithelium (arrowhead).* **(G)** *Radioactive* in situ *hybridization on sagittal section of E10.5 embryo, depicting signals in the stomach, midline dorsal aorta, duodenum, mesentery, in the genital eminence of the urogenital ridge and in the sympathetic chain.* **(H)** *Enhanced view of the thoracic region of E10.5 embryo showing labelling in the walls of heart atrium and ventricle and in the duodenum.* **(I)** *Magnified view of the heart at E14.5 showing signals in the ventricle and aorta.* **(J)** *Magnified view of the eye on sagittal section of radioactive* in situ *hybridized mouse embryo at E14.5 depicting strong labelling in the lens epithelium.* **(K)** *Sagittal section of radioactive* in situ *hybridized E14.5 mouse embryo displaying* Ened *expression in the peripheral nerves of the head and spine, in the skin, in the epithelial lining of the submandibular gland, heart, midgut, duodenum, lung, kidney and testis.* **(L)** *Magnified view of the trunk area of radioactive* in situ *hybridized E13.5 embryo displaying expression in the dorsal root ganglions and the migrating neural crest cells between the somites (arrows).* **(M)** *Sagittal section of E13.5 embryo hybridized with radioactive sense probe as control.* **(N)** *Light microscopy view of the thoracic area at E14.5 revealing labelled thoracic nerve cells (silver grain dots) between the rib primordial (black arrows).* **(N')** *Dark field capture of the same area showing signals exclusively in the thoracic nerves (white arrows). Ao, aorta; Aot, aortic outflow tract; D, duodenum; Drg, dorsal root ganglions; Fp, floor plate; Fn, facial nerve; Ge, genital eminence; Gt, gastrointestinal tract; H, heart; Ha, heart atrium; Hv, heart ventricle; K, kidney; L, Le, lens epithelium; Lu, lung; Mda, midline dorsal aorta; Me, mesentery; Mg, midgut; N, notochord; Ncc, neural crest cells; Pn, peripheral nerve; Rp, rib primordial; Sc, sympathetic chain; Sk, skin; Smg, submandibular gland; Te, testis; Tn, thoracic nerve.*

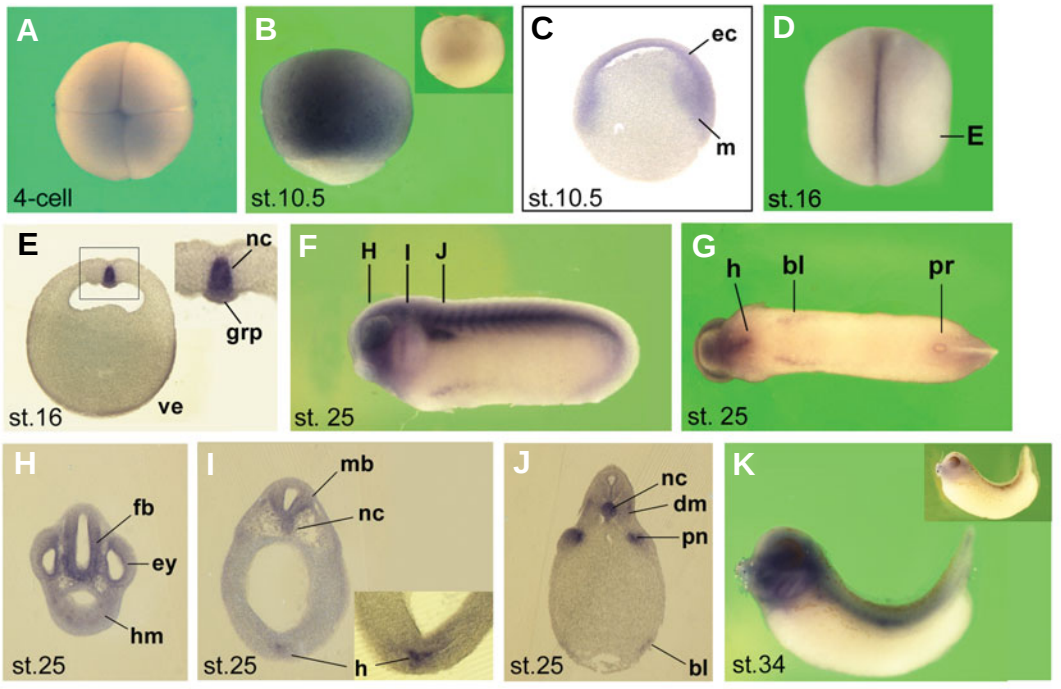

Fig. 2. Gene expression of *Xenopus Ened*. *Whole-mount* in situ *hybridization with an* Ened *antisense riboprobe. Insets in panels (B,K) depict embryos hybridized with* Ened *sense RNA as control. Embryos are shown in animal view* **(A)**, *lateral view* **(B,F,K)**, *dorsal view* **(D)**, *ventral view* **(G)**, *and as transversal sections* **(C,E, H-J)**. *bl, blood islands; dm, dermomyotome; ec, ectoderm; ey, eye; fb, forebrain; grp, gastrocoel roof plate; h, heart; hm, head mesenchyme; m, mesoderm; mb, midbrain; nc; notochord; pn, pronephros; pr, proctodeum; ve, ventral epidermis.*

mouse embryos from E9.5 to E14.5 (Fig. 1). Expression of *Ened* was initially detected at E9.5 in the heart and midgut (Fig. 1A). At E10.5, *Ened* expression was apparent in the atrium and ventricle of the heart, mesenteric lining of the gut, stomach, duodenum, genital eminence, midline dorsal aorta, and sympathetic chain (Fig. 1B,G,H). Further expression domains were found in the notochord and floor plate of the neural tube (Fig. 1D). From E11.5 onwards, *Ened* expression appeared in the lens epithelium (Fig. 1C,E,F,J). In E14.5 embryos, in addition to the observed expression in the lens epithelium (Fig. 1J), heart (Fig. 1I) and gastrointestinal tract (Fig. 1K), *Ened* expression emerged in the submandibular gland, lung, kidney, testis, and skin (Fig. 1K). Moreover, additionally to the epithelial expression domains, *Ened* signals were detected in the developing peripheral nervous system, including the sympathetic chain from E10.5 (Fig. 1B,C,G), dorsal root ganglia from E13.5 (Fig. 1K,L), and in facial, head and spinal nerves, as well as migrating neural crest cells between the somites (Fig. 1K,L). Moreover expression was evident in the thoracic nerves emerging between the rib primordia (Fig. 1N,N'). Together, mouse *Ened* expression exhibited a dynamic expression pattern in many epithelial tissues and nerves.

Next, we studied the gene expression of the *Ened* orthologue in early *Xenopus laevis* embryos (Fig. 2). By whole-mount *in situ* hybridization, we detected low levels of maternal *Ened* mRNA at the 4-cell stage (Fig. 2A). At the onset of gastrulation (stage 10.5), transcripts were uniformly expressed in the animal cap and marginal zone (Fig. 2B,C). During neurulation, distinct expression was observed in the notochord and underlying gastrocoel roof plate, as well as in the ventral epidermis (Fig. 2D,E). In tailbud embryos, expression of *Ened* was maintained in the notochord (Fig. 2F,I,J), and additional transcripts appeared in the anterior brain, eyes and head mesenchyme (Fig. 2F,H). Signals were also found in the heart, dermomyotome, pronephros (kidney), and lateral blood islands (Fig. 2F,G,J), as well as in the proctodeum (Fig. 2G). Expression persisted in head tissues, heart and notochord at late tailbud stage (Fig. 2K). In sum, the mouse and *Xenopus Ened* genes share several expression domains, including the eye, heart, notochord, gastrointestinal tract, kidney, and skin.

Intriguingly, we observed expression of *Ened* at sites with known Fgf/Fgfr signalling activity and in tissues that are rich in basement membranes. Previous studies have shown that Fgf8 is expressed in and crucial for the formation of the heart field (Reifers *et al.*, 2000; Alsan and Schultheiss, 2002; Ilagan *et al.*, 2006), and that Fgf10 cooperates with Fgfr2 in cardiac morphogenesis (Marguerie *et al.*, 2006). Also, *Ened* expression could be detected in the notochord, which is a prominent site of Fgf4 expression (Isaacs *et al.*, 1995), and is surrounded by the basement membrane component laminin (Fey and Hausen, 1990). We also detected the expression of *Ened* in other epithelial tissues such as submandibular gland, midgut and stomach, lung, kidney, testis, skin, and lens epithelium. Fgf/Fgfr signalling has been shown to be essential for the development of these tissues (Orr-Urtreger *et al.*, 1993; Cancilla *et al.*, 2000; Warburton *et al.*, 2000; Steinberg *et al.*, 2005; Katoh and Katoh, 2006; Robinson, 2006; Bates, 2007). In *Xenopus*, Fgf8 expression has been detected in the developing kidney (Christen and Slack, 1997) and Fgf signalling was shown to be required for the condensation of pronephric primordium from intermediate mesoderm and the epithelialization of mesenchyme into pronephric nephrons (Urban *et al.*, 2006). Also, the requirement of both the basement membrane component laminin α1 chain and Fgf/Fgfr signalling in branching morphogenesis of the lung, submandibular gland and kidney during embryonic development has been described (Ekblom *et al.*, 1998; Arman *et al.*, 1999; Qiao *et al.*, 2001; Steinberg *et al.*, 2005). The finding that *Ened* is expressed in epithelial tissues suggests that it could be a downstream effector of Fgf/Fgfr signalling and/or it might be regulated by basement membrane components such as laminin-111. Addition of Matrigel (containing large amounts of laminin-111) to differentiating dnFgfr2 EBs rescued ectoderm development (Li *et al.*, 2001). Interestingly, *Ened* expression increased in mutant EBs treated with Matrigel (unpublished data) suggesting that laminin-111 influences Ened

expression.

In summary, we have elucidated the expression of the novel gene *Ened* during both mouse and *Xenopus* development. Our results indicate that *Ened* shares several expression domains, including the eye, heart, notochord, gastrointestinal tract, kidney, and skin. We speculate that *Ened* might be affected or targeted by Fgf/Fgfr signalling during embryogenesis because of its expression pattern at known Fgf/Fgfr signalling sites. On the other hand, *Ened* expression could also be directly regulated by basement membrane components such as laminin-111.

These theorems will be further elucidated by functional studies during both mouse and *Xenopus* development.

Experimental Procedures

The open reading frame (ORF) finder tool (http://www.ncbi.nlm.nih.gov/projects/gorf/) confirmed that the mouse *Ened* full-length cDNA clone contained the predicted ORF sequence of 1554 nucleotides spanning from nucleotides 76-1629. The cDNA clone of *Ened* orthologue in *Xenopus laevis* was control digested with NotI/EcoRV that indicated an insert size of 1.5 kb. The clone was sequenced and the obtained 1181 nucleotide long sequence was deposited to GenBank. Translation of the nucleotide sequences was performed using Transeq software (http://www.ebi.ac.uk/emboss/transeq/) and analysis of the transmembrane sequence was with TMpred software (http://www.ch.embnet.org). Multiple alignment of the amino acid sequences was carried out with MultAlin software (http://bioinfo.genopole-toulouse.prd.fr/multalin/multalin.html).

Whole-mount and radioactive *in situ* hybridization (Phylogeny, Inc. Columbus, USA) were carried out as described previously (Sorokin *et al.*, 1997; Pera *et al.*, 2001; Pizard *et al.*, 2004). Digoxigenin- and ^{35}S-UTP-labeled sense and antisense riboprobes were generated by amplifying a 564 bp fragment of the ORF corresponding to nucleotides 926 to 1490 that were linearized with NotI and EcoRI and transcribed with T7 and T3 RNA polymerase, respectively. For *in situ* hybridization in *Xenopus laevis* embryos, digoxigenin-labeled sense and antisense riboprobes were generated from the cDNA clone for *Xenopus Ened* in pExpress1 by linearizing with NotI and EcoRI, and transcribing with Sp6 and T7 RNA polymerase, respectively. Following whole-mount *in situ* hybridization, embryos were embedded in Albumine/Gelatine and sectioned.

Acknowledgements

Supported by the Swedish Cancer Society (to M.D.) and the Swedish Research Council (to M.D. and E.M.P).

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