



VITO-2, a new SID domain protein, is expressed in the myogenic lineage during early mouse embryonic development

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ABSTRACT

MCAT elements and its cognate binding partners, the transcription enhancer factors (TEFs) play important roles in the regulation of expression of several muscle-specific genes. The biological effects of TEFs strongly depend on different co-factors, which might act as co-activators or anti-repressors to enable transcriptional activation of target genes by TEFs. Previously, we have cloned and characterized VITO-1, which acts as a skeletal muscle-specific transcriptional co-activator of TEFs. Here we describe the cloning and expression profile of a related gene, VITO-2 (also termed Vgl-3), which shares a high homology with VITO-1 in the SID domain responsible for interaction with TEFs. During early embryonic and fetal development VITO-2 is mainly expressed in the myogenic lineage with an onset of expression in the myotomes of somites VI at E9.5 slightly later than VITO-1. At later developmental stages VITO-2 is predominantly found in the nervous system. In adult mice VITO-2 was detected in different tissues, including skeletal muscle, heart, kidney, liver and brain, where it was found in cortical and cerebellar neurons as well as in Purkinje cells. The expression of VITO-2 in the mesoderm was repressed by the notch/delta pathway and activated by Myf-5 since Dll-1 mutant showed an aberrant expression of VITO-2 but not VITO-1 in the tail bud and in the caudal neural tube at E10.5 while Myf-5 mutant mice lack expression of VITO-1 and VITO-2 in somites until E10.5.

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1. Results and discussion

1.1. VITO-2 is a new member of the SID containing-family of proteins

Transcriptional control of expression of skeletal muscle-specific genes is mediated by different *cis*-acting elements, which bind different classes of transcription factors. Certain groups of DNA binding proteins such as the MyoD family of transcription factors (Braun et al., 1992a, 1990; Weintraub et al., 1991) that activate muscle-specific genes show an exclusive or preferential expression

in skeletal muscle cells. Alternatively, some transcription factors that control muscles specific genes are characterized by a more widespread or even ubiquitous expression pattern thereby raising a certain conceptual problem, which asks for additional levels of regulation. We have recently identified a transcriptional co-factor, VITO-1 that is expressed in the somitic myotome from E8.75 mouse embryos onwards and later on in skeletal muscle and thus might convey tissue specific activity to the widely active TEF transcription factor family, which bind to MCAT motifs that are present in multiple skeletal and cardiac muscle-specific genes (Günther et al., 2004; Mielcarek et al., 2002). In zebrafish two putative homologues of VITO-1 (vgl-2a and vgl-2b) have been described. Vgl-2b shows a similar expression pattern as VITO-1 in somites of zebrafish embryos but also an expression in the notochord, which is not found for VITO-1 during mouse embryogenesis (Mann et al., 2007). VITO-1 also shares a similarity to the *Drosophila* vestigial protein in the SID (40%), which interacts with the *Drosophila*

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homologue of TEFs, scalloped (Sd) (Andrianopoulos and Timberlake, 1994; Campbell et al., 1992). In mammals numerous other potential interaction partners of TEFs have been described including YAP65 (Vassilev et al., 2001), TAZ (Mahoney et al., 2005), members of the p160 family (Belandia and Parker, 2000) and mammalian homologues of *Drosophila* vestigial including VITO-1 (Gunther et al., 2004; Maeda et al., 2002; Mielcarek et al., 2002; Vaudin et al., 1999). A recent yeast two hybrid screen did also identify Vgl-3, which is identical to VITO-2, as a potential interaction partner of Tef-1 although a thorough analysis has not been performed (Kitagawa, 2007).

To identify new members of the SID containing-family of proteins we performed an extensive in silico screening of available mouse EST databases at www.ncbi.nih.gov using the SID as bait.

The SID contains 85 amino acids although only a region of 23 amino acids is strongly conserved among all SID proteins (grey box in Fig. 1). Two EST clones from the mouse were identified (Accession Nos. BE285904 and BC042696), which showed an identity of 16 out of 23 (= 69.56%) and 32 out of 85 amino acids (= 37.64%) within the core and the complete SID domain, respectively, compared to *Drosophila* vestigial. The new gene showed a strong similarity to VITO-1 (96.47% similarity within the complete SID) and was hence named VITO-2. A full-length cDNA of VITO-2 is represented as EST clone BC042696, RIKEN cDNA 1700110N18 and comprises 2.1 kb. Further screening of human EST databases yielded a human homologue of VITO-2, which showed as similarity of 83.21% at the amino acid level (238 out of 286) to the mouse protein. Analysis of the genomic sequences of mouse and human VITO-2 based on the

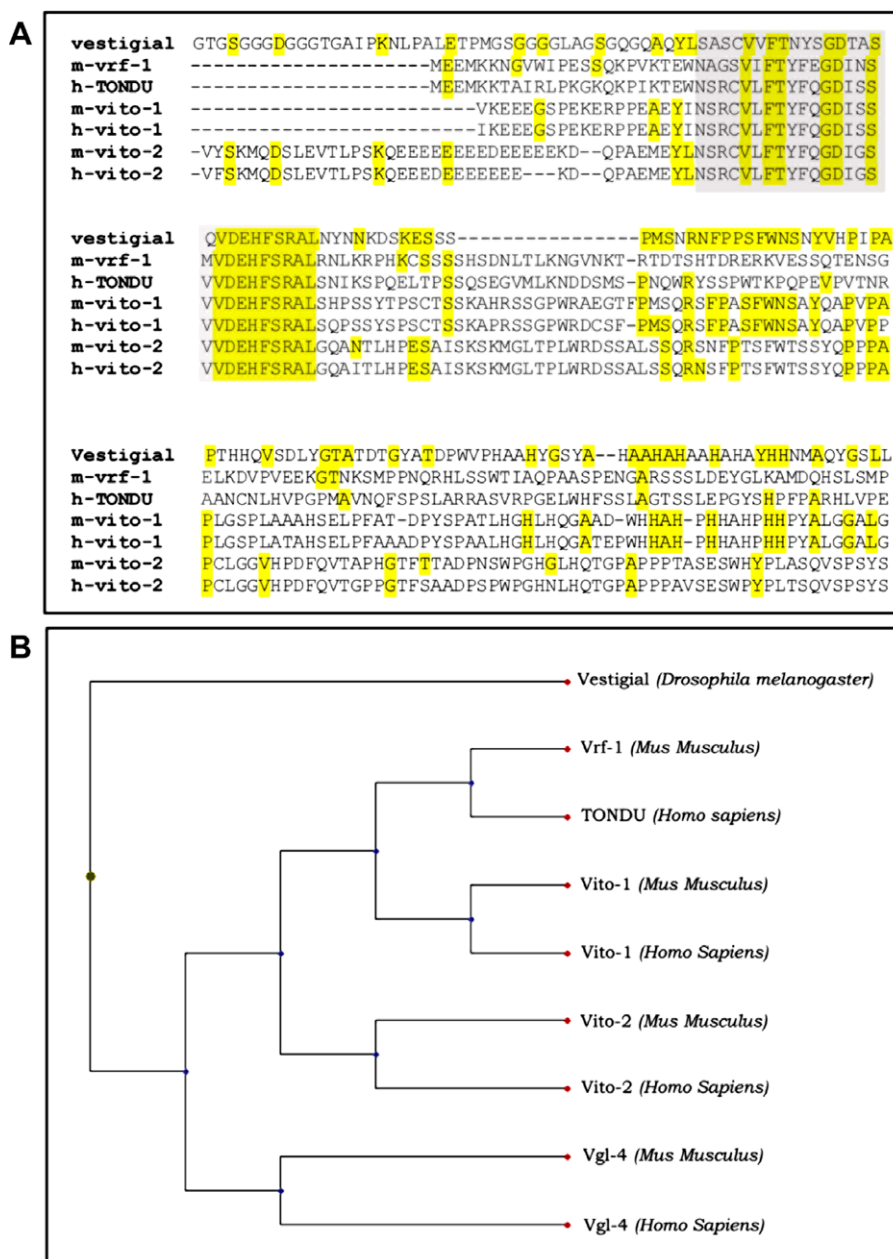


Fig. 1. VITO-1 is closely related to VITO-1 and Vrf-1/TONDU. (A) Alignment of the amino acids sequences of *Drosophila* vestigial, human TONDU, mouse vestigial related factor 1 (mvr or Vgl-1), mouse and human VITO-1/2 around the scalloped interaction domain (SID). Residues matching the vestigial sequence are indicated in yellow. The complete SID is boxed in light grey. The core SID is boxed in a darker grey. The core part of the SID domain of vestigial shows a high consensus between all VITO family genes members. (B) A phylogenetic tree of all known members of VITO family proteins and the *Drosophila* vestigial revealing a close relationship between VITO-1 and Vrf-1/TONDU and between VITO-1 and VITO-2.

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