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Expression of the transcription factor Zfp191 during embryonic development in the mouse

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Abstract

The human zinc finger protein 191 (ZNF191) is a Krüppel-like protein and can specifically interact with the widespread TCAT motif which constitutes the HUMTH01 microsatellite in the *tyrosine hydroxylase* (*TH*) gene (encoding the rate-limiting enzyme in the synthesis of catecholamines). Allelic variations of HUMTH01 are known to have a quantitative silencing effect on *TH* gene expression and to correlate with quantitative and qualitative changes in the binding by ZNF191. This factor has been isolated from bone marrow and promyelocytic leukemia cell lines indicating that *ZNF191* also plays a role in hematopoiesis. Thus, *ZNF191* could participate in the regulation of several genes implicated in different functions. Moreover, mice that are deficient in *Zfp191*, the murine homologue of *ZNF191*, have been shown to be severely retarded in development and to die approximately at embryonic day 7.5. In order to gain further insight into its biological functions, we have analysed the localisation of *Zfp191* throughout mouse development. Expression was detected early during embryogenesis in ectodermal, endodermal, mesodermal and extra-embryonic tissues. In particular, *Zfp191* was observed in the developing central nervous system. Interestingly, its expression levels were prominent in areas of proliferation such as the subventricular zone. *Zfp191* expression pattern during development can account for the phenotypic features of $Zfp191^{-/-}$ embryos.
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1. Results and discussion

A predominant part of the human genome consists of repetitive sequences of various types encompassing large segmental duplications, interspersed transposon-derived repeats and tandem repeats (International Human Genome Sequencing consortium, 2001) including microsatellites. These sequences have long been considered to be neutral elements devoid of biological effect and junk DNA sequences. However, several studies have shown that they do have a role in genome organization such as the formation of heterochromatic compartments (Csink and Henikoff, 1998; Horvath et al., 2001) and in transcription (Bell et al., 1982; Hamada et al., 1984; Aoki et al., 1997). For example, the TCAT motif, which constitutes the HUMTH01 microsatellite, is present in the first intron of the human gene encoding *tyrosine hydroxylase* (*TH*) (Polymeropoulos et al., 1991) and exhibits the characteristic features of a transcriptional enhancer element (Meloni et al., 1998). This motif is specifically recognized by nuclear factors one of which has been cloned by one-hybrid-system from a brain cDNA library (Albanese et al., 2001) and identified as the human zinc finger protein ZNF191 (also known as ZNF24). ZNF191 has been previously isolated from bone

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marrow and promyelocytic leukemia cell lines indicating that *ZNF191* also has a role in hematopoiesis (Han et al., 1999). In addition, tissue mRNA analysis has shown that the *ZNF191* gene is expressed in a variety of human organs (Han et al., 1999; Albanese et al., 2001). Altogether these observations suggest that the function of *ZNF191* participates in the regulation of several genes implicated in different functions. Studies on the localisation of this factor, which is greatly facilitated in animal models, will allow further insight into its biological functions.

ZNF191 shows 94% identity to its mouse homologue zinc finger protein Zfp191 (also called ZF-12), which is the highest rate of homology among the human-mouse SCAN family member orthologue pairs (Edelstein and Collins, 2005). Zfp191 was originally isolated from a cDNA subtraction library between cDNAs from a chondrocytic cell line and mRNAs from a mesenchymal precursor cell line (Prost et al., 1999). *Zfp191* mRNA was detected in rib cartilage as well as in various other embryonic and adult organs by RT-PCR and Northern blot hybridization. *Zfp191* transcripts were detected in heart, brain, liver, skeletal muscle, kidney and testis. Thus, it has been proposed that *Zfp191* could play a role not only in cartilage differentiation but also in basic cellular processes (Prost et al., 1999). The biological function of *Zfp191* is still unclear despite the generation of transgenic mice expressing the human zinc finger protein ZNF191 (Li et al., 2004), as well as mice that are deficient in *Zfp191* (Li et al., 2006). In the former context, overexpression of ZNF191 caused no obvious pathological changes. In contrast, $Zfp191^{-/-}$ embryos have been shown to be severely retarded in development and die approximately at embryonic day E7.5, which suggests that *Zfp191* plays a fundamental role in early development. However, the precise role of *Zfp191* during development has not been investigated. The better understanding of the phenotypic consequences of the loss of Zfp191 function requires the establishment of a detailed spatial and temporal expression pattern which has not yet been conducted. Here, we describe the expression profile of *Zfp191* during mouse embryonic development using section *in situ* hybridization analysis.

Zfp191 was not expressed in embryonic stem cells (data not shown) while it was detected at E6.5 by *in situ* hybridization (Fig. 1C and D). In early stages (E6.5, E7.5) *Zfp191* expression was ubiquitous: it was detected in the primitive ectoderm and mesoderm and a weaker signal was observed in the endoderm, probably due to a lower cell density of this structure (Fig. 1C–H). At E8.5, *Zfp191* expression was also ubiquitous and a stronger signal was detected in the neuroectoderm, which could be related to higher cell density in this tissue than in surrounding tissues (Fig. 1I). From E9.5, *Zfp191* was more specifically expressed in several tissues derived from ectoderm, endoderm and mesoderm, and histological examination revealed a number of regions where *Zfp191* transcription was active in the developing embryo (Table 1).

1.1. Expression of *Zfp191* in the central nervous system

1.1.1. Expression in areas associated with neural progenitors

From E8.5 to E11.5 (Figs. 1I and 2A–F), *Zfp191* mRNA expression was detected in all prospective regions of the central nervous system without antero-posterior and dorso-ventral regionalisation. This expression was associated with the proliferative cell marker BrdU (Fig. 2A–B). At all studied stages *Zfp191* was expressed in the entire proliferative ventricular zone (VZ) of the lateral ventricle in the telencephalon, of the third ventricle in the diencephalon, and of the fourth ventricle in the hindbrain (Fig. 2A–F, H–I and K–M). However, this expres-

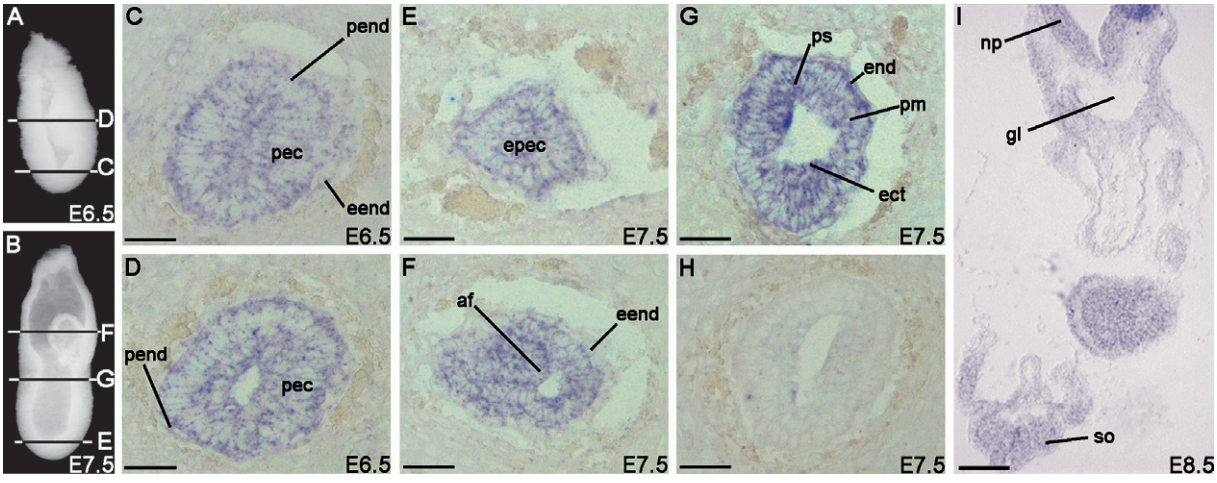

Fig. 1. Expression of *Zfp191* mRNA during early mouse development. Transverse sections of embryos at embryonic day E6.5 (C and D) (14 μm), E7.5 (E–H) (14 μm) and E8.5 (I) (14 μm). (A and B) Position of the sections within E6.5 and E7.5 embryos. At E6.5, E7.5 and E8.5, *Zfp191* expression is detected ubiquitously in the embryo. (H) Sense strand control probe is negative on E7.5 equivalent transversal section. Pend, primitive endoderm; pec, primitive ectoderm; eend, primitive extra-embryonic endoderm; epec, embryonic pole of egg cylinder; af, amniotic fold; ps, primitive streak; end, endoderm; ect, ectoderm; pm, primitive mesoderm; np, neuropore; gl, gut lumen; so, somite. Scale bar represents 25 μm for (C–H) and 300 μm for (I).

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