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Cloning and expression analysis of YY1AP-related protein in the rat brain

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Summary. YY1AP-related protein (YARP) is a structural homolog of YY1AP, a transcriptional coactivator of the multifunctional transcription factor YY1. We cloned a rat YARP cDNA that encoded a 2256 amino acid protein with 93% homology to the human counterpart. Northern blots revealed significant expression of the YARP gene in the rat brain. In situ hybridization demonstrated its expression in neurons throughout the brain, including pyramidal cells in the cerebral cortex and hippocampus and granule cells in the dentate gyrus. YARP was coexpressed with YY1 in these same neuronal cells. However, there was no evidence of YARP expression in glia. In the developing rat brain, the level of YARP mRNA (~10 kb) peaked at embryonic day 18 and promptly declined thereafter to reach the steady-state level found in adulthood, by 14 days after birth. These results suggest that YARP functions at a late stage of neurogenesis during perinatal development of the rat brain, as well as in mature neurons.

Keywords: YY1-associated protein – YARP – Dingo – GON4L – Transcriptional coactivator – Neuron

Abbreviations: GAPDH, glyceraldehyde-3-phosphate dehydrogenase; RT, reverse transcription; YY1AP, YY1-associated protein; YARP, YY1AP-related protein (alias Dingo or GON4L)

Introduction

The ubiquitous transcription factor YY1 is a multifunctional zinc finger protein that can either activate or repress gene transcription and regulates the expression of several genes associated with basic cellular processes, such as cell-cycle control and programmed cell death (Shi et al., 1997; Thomas and Seto, 1999). Thus, YY1 plays a fundamental role in normal biological processes, including embryogenesis, differentiation and cellular proliferation and potentially in cancer biology, viral infections and immune responses (Gordon et al., 2006; Wang et al., 2006). It has been shown that YY1 can activate the transcription of c-myc (Riggs et al., 1993) and p53 (Furlong et al., 1996), and repress promoters of interferon-β (Weill et al., 2003), c-fos and skeletal α-actin (Gualberto et al., 1992; Natesan and Gilman, 1993). Whether YY1 acts as an activator or repressor on a gene depends on the promoter sequences surrounding the YY1-binding sites and interactions with other regulatory proteins, including p300/CREB-binding protein (CBP) and histone deacetylases HDACs 1–3 (Shi et al., 1997; Thomas and Seto, 1999; Gordon et al., 2006; Wang et al., 2006). YY1 can also interact with TBP, TAFs, TFIIB, Sp1, ATF/CREB, Rb, p53, Mdm2, poly(ADP-ribose)polymerase-1 and NF-κB (Gordon et al., 2006).

YY1AP is a recently identified coactivator of YY1 which can physically interact with YY1 and enhance the transcriptional activation of a YY1 responsive promoter (Wang et al., 2004). YY1AP is ubiquitously expressed in human tissues and colocalized with YY1 in the nucleus in cell cultures (Wang et al., 2004). YY1AP is a novel member of the structurally diverse YY1-binding proteins described above. However, in a previous study, we cloned a cDNA for a YY1AP-related protein, termed YARP (alias Dingo or GON4L; DDBJ accession no. NM_001037533), from the human neuroblastoma cell line SK-N-SH (Ohtomo et al., 2007). The cloned cDNA encoded a 2240 amino acid protein that contains a domain with 97% homology to an entire YY1AP sequence of 739 amino acids, in which two YY1-binding domains and a transactivation domain demonstrated in YY1AP (Wang et al., 2004) are highly conserved. In the YARP structure, various functional motifs are also predicted, including nuclear localization signals and domains associated with protein–protein interactions, DNA-binding and chromatin assembly, found outside the "YY1AP-homology" domain (Ohtomo et al., 2007). Therefore, YARP is suggested to be multifunctional and to play not only a role analogous to YY1AP, but also

its own specific roles in DNA-utilizing processes such as transcription.

In order to gain an insight into the physiological roles of YARP, we cloned cDNA for the rat YARP ortholog and defined its expression profile in rats, with special reference to the brain, by northern blotting and in situ hybridization.

Materials and methods

Animals and sample preparation

Male F344 rats (8 weeks old) were used, except in experiments of developmental changes in the YARP gene expression using Wistar rats. RNA was extracted from rat tissues using Isogen reagent and a poly(A)$^+$ isolation kit (Nippon Gene, Tokyo, Japan). Brain homogenates were prepared at a concentration of 10% (w/v) in 0.25 M sucrose containing 1 mM EDTA, 10 mM Tris–HCl (pH 7.5) and protease inhibitor cocktail, Complete (Roche), using a Potter-Elvehjem glass homogenizer with a Teflon pestle. Protein concentration was determined using a Bio-Rad DC protein assay kit with bovine serum albumin as the standard.

cDNA cloning

The NCBI BLAST program was used to search for cDNAs with similarity to the human YARP cDNA clone. One of the matched sequences (DDBJ accession no. AK122531) was amplified by RT-PCR, and the rapid amplification of cDNA ends (RACE system ver. 2.0, Invitrogen) was performed to obtain a longer sequence. Finally, a YARP cDNA was amplified by RT-PCR with 5′-GATGGTAACCGAGCAGGTGC-3′ and 5′-GTCGGGA CCTGATACATGACAT-3′ as PCR primers, after oligo(dT)$_{18}$-primed RT of poly(A)$^+$ RNA prepared from rat brain. The cDNA was cloned into pCR-XL-TOPO (Invitrogen), resulting in a plasmid pCR-TOPO-rYARP. RT reactions were incubated at 42 °C for 90 min with Superscript III RNase H$^-$ reverse transcriptase (Invitrogen). PCR was performed with LA Taq-GC Buffer (Takara Bio, Tokyo, Japan) and cycling conditions were 98 °C for 30 sec, followed by 35 cycles of 94 °C for 15 sec and 68 °C for 10 min. The nucleotide sequence of the cDNA has been submitted to the DDBJ (accession no. AB195689).

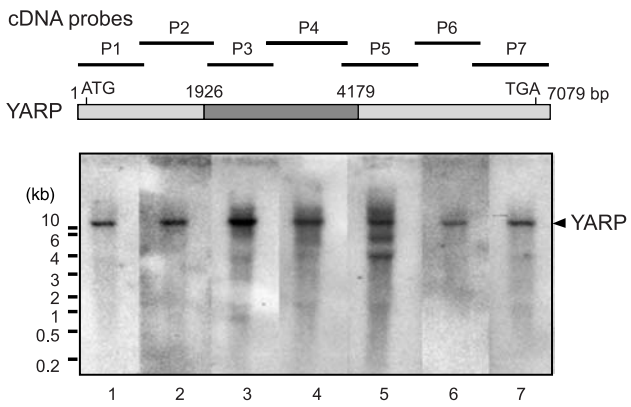

Fig. 1. Northern blots of rat YARP. Poly(A)$^+$ RNA (2 μg/lane) prepared from whole rat brain was probed with rat YARP cDNA fragments corresponding to the nucleotides 1–990 (*P1*), 909–2038 (*P2*), 1942–2848 (*P3*), 2803–4044 (*P4*), 3954–5097 (*P5*), 5047–6031 (*P6*) and 5928–7079 (*P7*) in *1–7*, respectively. An arrowhead indicates the position of hybridized RNA for YARP (~10 kb). The positions of size markers are indicated on the left. The cDNA sequence of rat YARP is schematically represented above the blots, along with the cDNA probes used. The region highly conserved between YARP and YY1AP is shown as a dark gray bar

Northern blotting

Northern blotting was performed as described previously (Ohtomo et al., 2007). RNA was separated on formaldehyde-agarose gels and transferred onto HybondN$^+$nylon membranes (Amersham Biosciences) using Turboblotter rapid downward transfer system (Schleicher & Schuell). Approximately 1 kbp-fragments of the YARP cDNA, which were amplified by PCR and designated P1–P7 (for the precise sequences, see the legend of Fig. 1), were labeled with [α-^{32}P] dCTP and used as probes. The hybridization signal was detected with the bioimaging analyzer BAS 2000 II (Fuji Photo Film, Tokyo, Japan).

Antibody and western blotting

Rabbit antibody (αYH875) against a synthetic polypeptide corresponding to human YARP amino acids 875–893 and western blotting were as described previously (Ohtomo et al., 2007). The amino acid sequence of the antigen polypeptide is identical to rat YARP amino acids 883–901, except for the asparagine at 886 and valine at 888 that are replaced by aspartate and isoleucine, respectively, in human YARP. On western blots, the antibody αYH875 was confirmed to recognize a rat YARP polypeptide (amino acids 610–1009) expressed in bacteria as a glutathione S-transferase fusion protein (data not shown).

In situ hybridization

In situ hybridization was performed as described previously (Kuramochi et al., 2002). Briefly, cDNA fragments of rat YARP (nucleotides 4093–4645) and YY1 (nucleotides 79–1110; DDBJ accession no. AY442180) (Nishiyama et al., 2003) were subcloned into pBluescript II SK(+) (Stratagene) and used as the template for in vitro transcription. For digoxigenin-labeling of antisense and sense cRNAs, the plasmid DNA (1 μg) was linearized by *Eco*RI or *Bam*HI, respectively and incubated with T3 or T7 RNA polymerase (50 U) at 37 °C for 6 h in the presence of 0.35 mM digoxigenin-labeled UTP (Roche). Thereafter, the DNA template was removed by treating with DNase. Paraffin-embedded serial sections (3-μm thick) were processed from rat tissues. After deparaffinization, the sections were hybridized with the digoxigenin-labeled cRNA at 42 °C overnight, and finally treated with a 1:500-fold dilution of alkaline phosphatase-conjugated anti-digoxigenin antibody (Roche). The enzyme activity was visualized as blue staining. For a negative control, the antisense probe was replaced by the corresponding sense probe. The sections were counterstained with methylgreen.

Results and discussion

Cloning of rat YARP cDNA

As schematically represented in Fig. 1, the cloned cDNA for rat YARP was 7079 bp in length, not including the poly(A) tail, and contained 99 bp of 5′-untranslated region (UTR) and an open reading frame (ORF) encoding 2256 amino acids with a calculated molecular mass of 248 kDa, followed by the stop codon TGA. This was followed in turn by a 209-bp 3′-UTR which contained a consensus polyadenylation signal (TATAAA) located 22 bp upstream of the poly(A) tail. Since an in-frame stop codon (TGA) was located 66 bp upstream of the presumed start

codon, the cDNA clone was found to completely cover the translated region. Pairwise sequence comparison using the BLAST 2 program revealed a 74% identity and a 93% homology between the amino acid sequences of the rat and human YARP, indicating that the YARP gene is highly conserved amongst species. In the recently updated version of the NCBI DNA database, YARP-related sequences were integrated as the ''reference sequence'' and named GON4L (alias Dingo). The nucleotide sequence of the rat YARP cDNA was almost identical to that of rat Dingo (DDBJ accession no. NM_001024797), although our clone was 167 and 495 bp shorter at 5′ ends and 3′ ends, respectively.

Analysis of YARP transcripts

Existence of YARP mRNA was demonstrated by northern blotting, with rat brain poly(A)$^+$ RNA, together with a series of cDNA fragments (P1–P7) that covered the entire YARP sequence, as probes. As shown in Fig. 1, all these probes hybridized to a common sized RNA of ∼10 kb consistent with the human YARP mRNA (Ohtomo et al., 2007). No other bands were detected on these blots. In the case of human YARP, its splice variants YARP2 and YARP3 are also expressed (Ohtomo et al., 2007). However, no similar variants were detected in the rat brain. Moreover, even YY1AP mRNA was not identified. Our attempts to find their expression by RT-PCR and DNA database searches were unsuccessful (data not shown). Therefore, of the YY1AP-homologs including YY1AP itself, YARP (∼10 kb mRNA) is the sole form that is significantly expressed in the rat brain. The P5 probe additionally hybridized to ∼5 kb and ∼4 kb RNAs (lane 5); however, these appeared not to encode the YY1AP-homology domain that would have been detected by the probes P3 and P4. Thus, further analysis was not performed in regard to these bands.

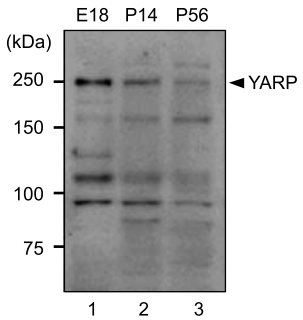

Fig. 2. Western blots of YARP protein. Brain homogenates (40 μg/lane) prepared from rats aged E18, P14 and P56 were probed with an anti-YARP antibody (αYH875) on the blots, in *1–3*, respectively. An arrowhead indicates the position of band for YARP. Positions of molecular mass markers are indicated on the left

Detection of YARP protein

To detect rat YARP protein, western blotting was performed with brain homogenates prepared from rats aged embryonic day (E) 18 and postnatal days (P) 14 and 56 (Fig. 2). In all brain homogenates, ∼250 kDa protein was recognized by an anti-YARP antibody, αYH875 (Ohtomo et al., 2007). Although the antibody cross-reacted with several other proteins, the molecular mass of 250 kDa is consistent with the molecular weight of 248,000 calculated from the amino acid sequence deduced from the rat YARP cDNA. Moreover, the much higher level of this protein seen at E18, compared with P56, is compatible with developmental changes in YARP mRNA level in the brain (see Fig. 8). Thus, it is suggested that rat YARP gene is expressed as ∼250 kDa protein in the brain.

Genomic organization of rat YARP gene

A rat genome BLAST analysis using the NCBI Map Viewer program revealed that the rat YARP gene is comprised of at least 32 exons, spans ∼75 kb, and is mapped to the chromosome 2 (2q34). In humans, the YARP (1q22) and YY1AP (1q21.3) genes are located on chromosome 1 at a distance of ∼70 kb from each other, and are suggested to be products of the gene duplication occurring

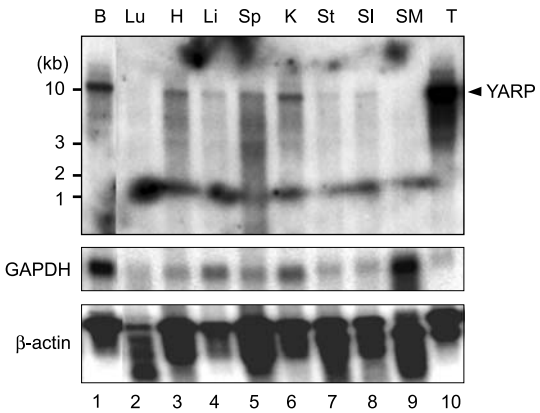

Fig. 3. YARP mRNA levels in rat tissues. Poly(A)$^+$ RNAs (2 μg/lane) prepared from the brain (*B*), lung (*Lu*), heart (*H*), liver (*Li*), spleen (*Sp*), kidney (*K*), stomach (*St*), small intestine (*SI*), skeletal muscle (*SM*) and testis (*T*) were hybridized with the rat YARP cDNA probe P4 described in the legend for Fig. 1, in *1–10*, respectively. An arrowhead indicates the position of hybridized RNA for YARP. Positions of size markers are indicated on the left. Blots probed with GAPDH and β-actin cDNAs as loading control are also shown

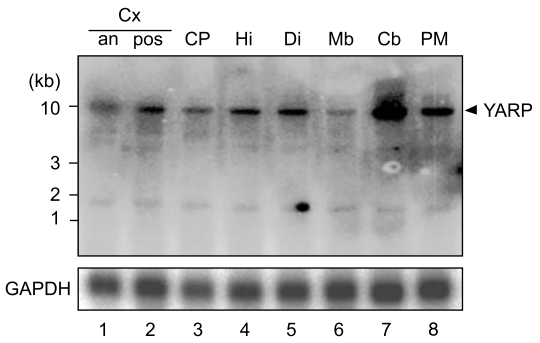

Fig. 4. Regional difference of YARP mRNA levels in the rat brain. The brain was separated into eight regional blocks: cerebral cortex (*Cx*) – anterior (*an*) and posterior (*pos*) parts, striatum (*CP*), hippocampus (*Hi*), diencephalon (*Di*), midbrain (*Mb*), cerebellum (*Cb*) and pons/medulla oblongata (*PM*). The poly(A)$^+$ RNA (2 µg/lane) was prepared and hybridized with a rat YARP cDNA probe (nucleotides 2510–4092) in *1–8*, respectively. An arrowhead indicates the position of hybridized RNA for YARP. Positions of size markers are indicated on the left. Blots probed with a GAPDH cDNA as loading control are also shown

during human genome evolution (Ohtomo et al., 2007). A structure similar to the human YY1AP gene could possibly be localized near the YARP gene, to chromosome 2 of rats. However, no corresponding transcripts were detected (Figs. 1, 3, 4, 8), raising the possibility that the rat YY1AP gene became a pseudogene after the duplication occurred.

YARP gene expression in rat tissues

Next, we examined the expression of the YARP gene in various rat tissues (Fig. 3). In all the tissues examined, a YARP mRNA of ~10 kb was detected, except in the lung and skeletal muscle, in which no hybridization signals were detectable. The highest level of the YARP mRNA was demonstrated to be in the testis, and a significant level of expression was confirmed in the brain. In the brain, YARP mRNA was detected in all regions, with the highest level found in the cerebellum (Fig. 4). The expression level was also significant in the pons/medulla oblongata, the posterior region of the cerebral cortex, the hippocampus and the diencephalons. In all the tissues and brain regions examined, the YARP mRNA was seen only as a ~10 kb mRNA.

In situ hybridization in rat brain and testis

In situ hybridization revealed that the YARP gene is expressed in neurons within the brain (Figs. 5, 6). Hybridization signals were found all over the brain and clear staining was observed in certain types of neurons, including mitral cells of the olfactory bulb (Fig. 5A), pyramidal cells of the cerebral cortex (B) and CA1–CA3 regions of the hippocampus (D, E), granule cells within the dentate

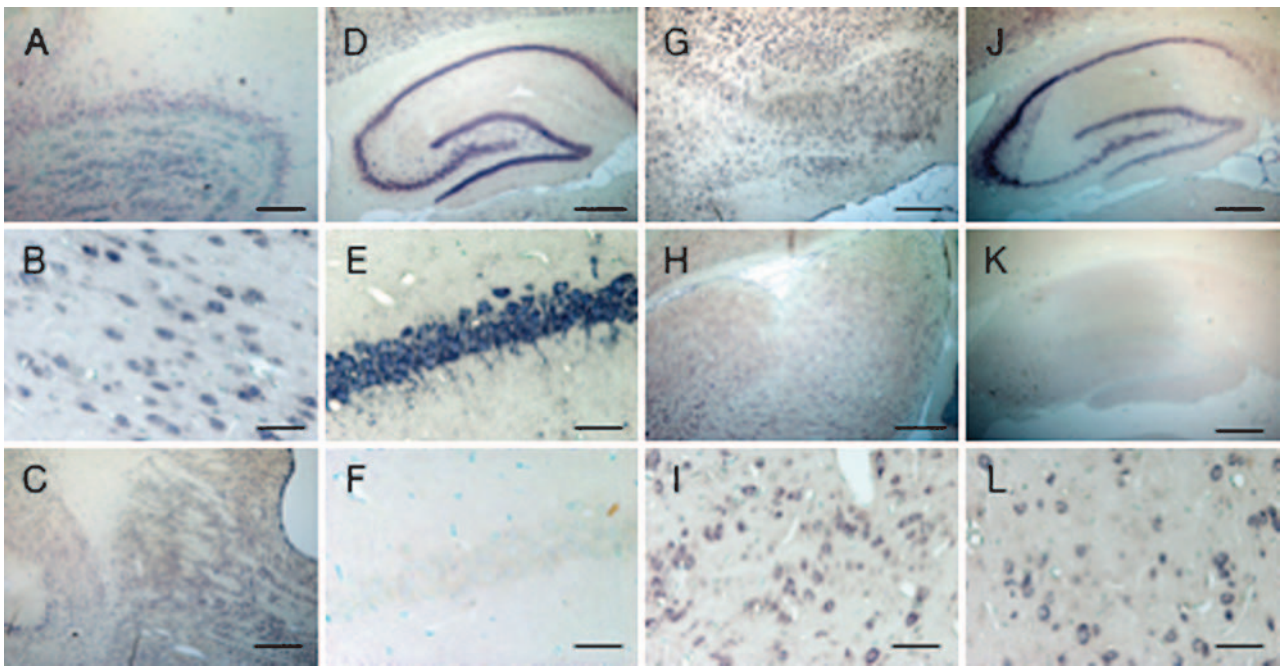

Fig. 5. In situ hybridization of YARP and YY1 in the rat brain. Sagittal brain sections were probed with YARP (**A–I**) or YY1 (**J–L**) cRNAs. The hybridization signal is shown in blue and counterstained in green. **A** Olfactory bulb; **B** cerebral cortex; **C** striatum; **D–F**, **J**, **K** hippocampus; **G** diencephalon; **H**, **I**, **L** midbrain. **F**, **K** Negative control of hybridization using the corresponding sense probes. Scale bars: 500 µm in **C**, **D**, **G**, **H**, **J** and **K**, 200 µm in **A**, and 50 µm in **B**, **E**, **F**, **I** and **L**

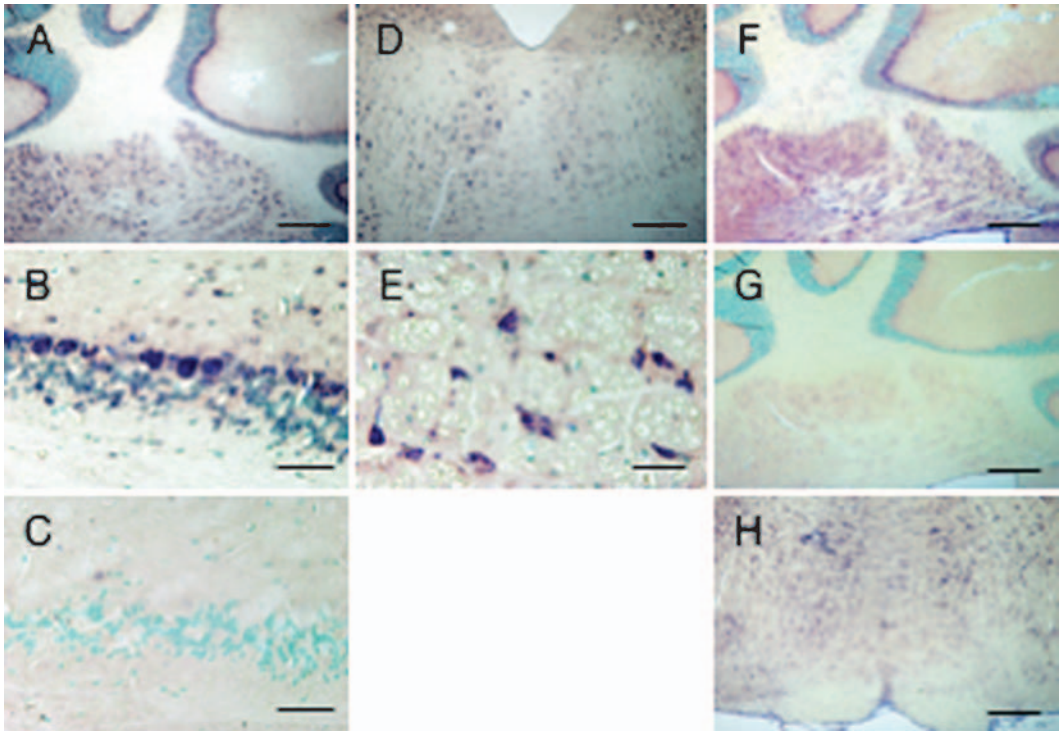

Fig. 6. In situ hybridization of YARP and YY1 in the rat brain. Coronal brain sections were probed with YARP (**A**–**E**) or YY1 (**F**–**H**) cRNAs. The hybridization signal is shown in blue and counterstained in green. **A**–**C**, **F**, **G** Cerebellum; **D**, **E**, **H** pons and medulla oblongata. **C**, **G** Negative control of hybridization using the corresponding sense probes. Scale bars: 500 μm in **A**, **D**, **F**–**H**, and 50 μm in **B**, **C** and **E**

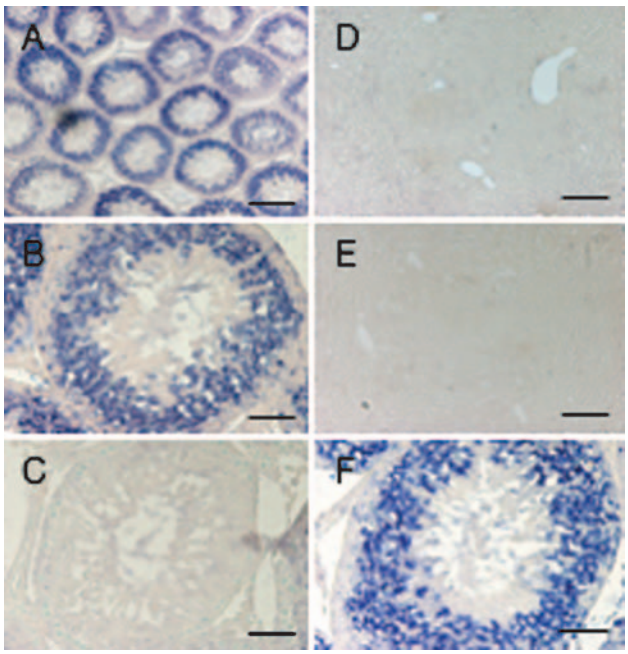

Fig. 7. In situ hybridization of YARP and YY1 in rat testis and liver. The testis and liver sections were probed with YARP (**A**–**E**) or YY1 (**F**) cRNAs. The hybridization signal is shown in blue and counterstained in green. **A**–**C**, **F** Testis; **D**, **E** liver. **C**, **E** Negative control of hybridization using the corresponding sense probe. Scale bars: 200 μm in **A**, **D** and **E**, and 50 μm in **B**, **C** and **F**

gyrus (D), and Purkinje cells of the cerebellum (Fig. 6A, B). Large nerve cells were also clearly stained in the striatum, diencephalons, midbrain, pons and medulla oblongata. However, no evidence was found of YARP expression in glial cells. When the expression of YY1 was similarly examined, its hybridization signals were also found in neurons all through the brain and overlapped with those of YARP, indicating that the YARP and YY1 genes are coexpressed in the same neuronal cells within the brain (Figs. 5J–L, 6F–H). In the testis, YARP and YY1 genes were expressed in the spermatogenic cells, especially spermatocytes within the seminiferous tubules, but not in spermatogonia (Fig. 7A, B, F). In these experiments, the sense cRNA probes generated no signal (Figs. 5–7). Almost no staining was observed for YARP in the liver (Fig. 7D), being consistent with the weak expression of YARP in this tissue as demonstrated by northern blotting (Fig. 3). These results ensure the specificity of the hybridization signals detected on the tissue sections.

Developmental changes in YARP gene expression in the brain

In the developing rat brain, the YARP gene was highly expressed during the late embryonic days (Fig. 8). In the

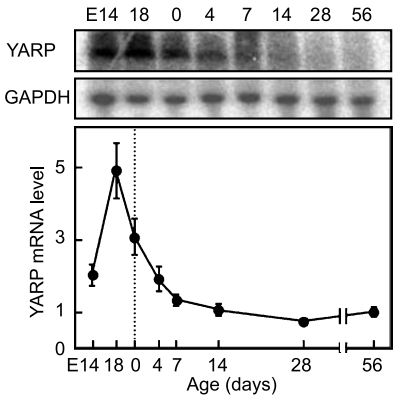

Fig. 8. YARP mRNA levels in the developing rat brain. The brain was excised from rats at the time points indicated and the portion excluding the hindbrain (cerebellum, pons and medulla oblongata) was used, except at E14, where the whole brain was used. Total RNA (40 μg/lane) was extracted and hybridized with a rat YARP cDNA probe P4 described in the legend for Fig. 1. Results are normalized with those of GAPDH and expressed as relative values (mean ± SEM, $n = 4$), taking the value at P56 as 1. For E14, three brain samples were pooled and used, and the result from three independent experiments is plotted. Blots probed with the YARP and GAPDH cDNAs are also shown

time period examined, from E14 through P56, the level of YARP mRNA (~10 kb) in the brain was highest at E18 and promptly declined thereafter to reach the steady-state level seen in adulthood (P56), by P14. The YARP mRNA was detected at E14 with a 2-fold higher level than that found at P56, increased to a 5-fold higher level at E18 and decreased to the nearly adult levels at P7.

Possible roles of YARP in the brain

The generation of neural cell types within the brain occurs in a temporally distinct yet overlapping manner. Neurons are generated first, followed by astrocytes and then oligodendrocytes (Sauvageot and Stiles, 2002). In rats, neurogenesis begins in the ventricular zone at E12, peaks at E14 and recedes by E17 (Parnavelas, 1999). Then, cells originating from the subventricular zone at E17 to P14 are destined predominately for glial lineages, with the peak of astrocyte formation occurring between P0 and P2, and the height of oligodendrocyte formation happening at P14 (Parnavelas, 1999; Levison et al., 1993; Zerlin et al., 1995). This sequential development of neurons and glia from progenitor cells is governed by interactions between growth factor signals and downstream transcription factors. For neurogenesis, high expression of the proneural transcription factor Ngn1, peaking at E14, actively promotes neuronal fate determination via its association with the transcriptional coactivators CBP/p300, with a concurrent inhibition of astrocytic differentiation (Sauvageot and Stiles, 2002; Sun et al., 2001).

In light of these points, the timing of YARP gene expression suggests a role for YARP in neurogenesis during rat brain development (Fig. 8). However, YARP gene expression peaks at E18 and is still high at birth (P0). It therefore appears that YARP is not involved in cell fate determination of neural precursors, but rather plays a role, directly or indirectly downstream of the proneural genes, in establishing cells committed to the neuronal lineage. This is in line with the findings of our previous study which showed the induction of YARP gene expression in the neuroblastoma cell line SK-N-SH, during dibutyryl cAMP-induced neural differentiation (Ohtomo et al., 2007). Thus, our results suggest that YARP functions at a late stage of neurogenesis during pre- or peri-natal development of the brain.

It is also possible that YARP plays a similar function in adulthood, as neurogenesis has been shown to persist in the mature brain (Kempermann et al., 2004) and is modulated by both physiological stimuli (Kuhn et al., 1996; van Praag et al., 1999; Gould et al., 1999) and pathophysiological conditions (Parent et al., 1997; Kokaia and Lindvally, 2003; Nixon and Crews, 2004). However, the YARP gene is expressed in most neurons throughout the brain (Figs. 4–6), whereas adult neurogenesis is confined to the subgranular zone of the hippocampus and the subventricular zone of the lateral ventricles (Kempermann et al., 2004; Kokaia and Lindvally, 2003). Therefore, YARP may have another role. The persistent expression of the YARP gene in the adult rat brain may support phenotypes conferred to neurons following terminal differentiation, as well as those appearing in nascent neurons retained in adulthood. In addition, a number of genes which play important roles in mature neurons have been demonstrated to be regulated by YY1 (Korhonen et al., 1997, 2005), such as dynamin (Yoo et al., 2001), dopamine β-hydroxylase (Seo et al., 1996) and β-site amyloid precursor protein-cleaving enzyme 1 (Nowak et al., 2006), besides those described above (Shi et al., 1997; Thomas and Seto, 1999; Gordon et al., 2006; Wang et al., 2006). Some of these mechanisms may involve YARP as a binding partner to YY1.

In summary, we suggest a role for the YARP gene in the mammalian brain by defining its expression profile in rats. Several questions may be posed; for instance, how does YARP act in human cells where YY1AP is coexpressed, unlike in rats? Do they antagonize or synergize each other's functions via interaction with YY1? Further studies

are required to clarify the molecular and functional properties of the YARP gene product.

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