REVIEW

POU-domain transcription factors: pou-er-ful developmental regulators

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Genetic analyses have suggested that complex networks of interacting developmental regulators expressed in overlapping temporal and spatial patterns ultimately lead to activation of regulatory genes that specify organ development and cell phenotypes (for review, see Nüsslein-Volhard and Wieschaus 1980; Sternberg and Horvitz 1984; Akam 1987; Gehring 1987; Ingham 1988; Scott et al. 1989; Olson 1990). Many of these developmental loci encode sequence-specific DNA-binding proteins, presumably transcription factors, that share specific DNA-binding motifs conserved throughout evolution. This paper reviews the characterization of a gene family that contains a novel DNA-binding motif—the POU domain—which appears to exert critical developmental actions, providing insights into the mechanisms by which distinct cellular phenotypes emerge during organogenesis. This review will also summarize the known POU-domain factors, the unique features of their interactions with cognate DNA-binding sites, and the recent evidence of their specific developmental and transcriptional functions.

The highly conserved POU domain was initially recognized after the simultaneous cloning of three mammalian transcription factors and a *Caenorhabditis elegans* developmental regulator. Many additional POU-domain proteins have been identified subsequently and they are expressed in distinct temporal and spatial patterns during development. Developmental mutants resulting from disruption of two POU-domain genes have provided direct evidence that POU-domain transcription factors exert critical functions in the proliferation of specific cell types, as well as in the activation of specific programs of gene expression that define specific cell phenotypes within an organ. Several POU-domain regulators appear in early embryogenesis, a time at which no homeo domain proteins have yet been identified, which implies roles for them in the early developmental regulation of gene transcription. A striking feature of the, where no POU-domain gene family is that most of these genes are expressed in the mammalian forebrain, where no classic homeo domain proteins have yet been identified. These findings are consistent with functions for POU-domain proteins in the development of this evolutionarily recent brain structure.

What, then, are likely to be the roles of the POU domain that may confer specific advantages in regulating organogenesis? Analysis of several POU-domain-specific proteins has defined roles for the POU domain in high-affinity, site-specific DNA sequence recognition and in protein–protein interactions. POU-domain proteins interact with cognate DNA recognition elements in a fundamentally different fashion from the classic homeo domain proteins, in that both portions of the bipartite POU domain apparently contact DNA, thereby constituting a functionally distinct class of regulatory proteins. POU-domain proteins exert either positive or negative transcriptional effects by binding to recognition elements as monomers or as homodimers formed as a consequence of DNA-dependent cooperative interactions. The POU domain may expand the potential diversity of transcriptional effects, because specific members of the POU-domain gene family can form heterodimeric complexes; one consequence of this is actually to prevent DNA binding and transcriptional activation of specific target genes. Finally, the POU domain may exert unique functions with regard to stimulation of DNA replication.

Identification of a large family of POU-domain transcription factors

The constantly expanding family of POU-domain genes was initially identified through analyses of cell-specific and general transcription factors. Analysis of an anterior pituitary-specific transcription factor that bound to related *cis*-active motifs in the rat prolactin (Prl) and growth hormone (GH) genes and the B-cell-specific and ubiquitous octamer-binding proteins permitted the identification and cloning of cDNAs that encode the transcription factors Pit-1 (GHF-1), Oct-2 (OTF-2), and the universal octamer-binding protein Oct-1 (OTF-1, NFIII) (Bodner et al. 1988; Clerc et al. 1988; Finney et al. 1988; Ingraham et al. 1988; Ko et al. 1988; Müller et al. 1988; Scheidereit et al. 1988; Sturm et al. 1988). Pit-1 and Oct-2 serve as transcription factors, activating expression of appropriate fusion genes in heterologous cell types (e.g., Ingraham et al. 1988, 1990; Müller et al. 1988; Gerster et al. 1990; Müller-Immerglück et al. 1990; Tanaka and Herr 1990). These three mammalian proteins and *unc-86*, the gene encoding a regulator of cell fate in *C. elegans* (Chalfie et al. 1981), were found to share an extensively

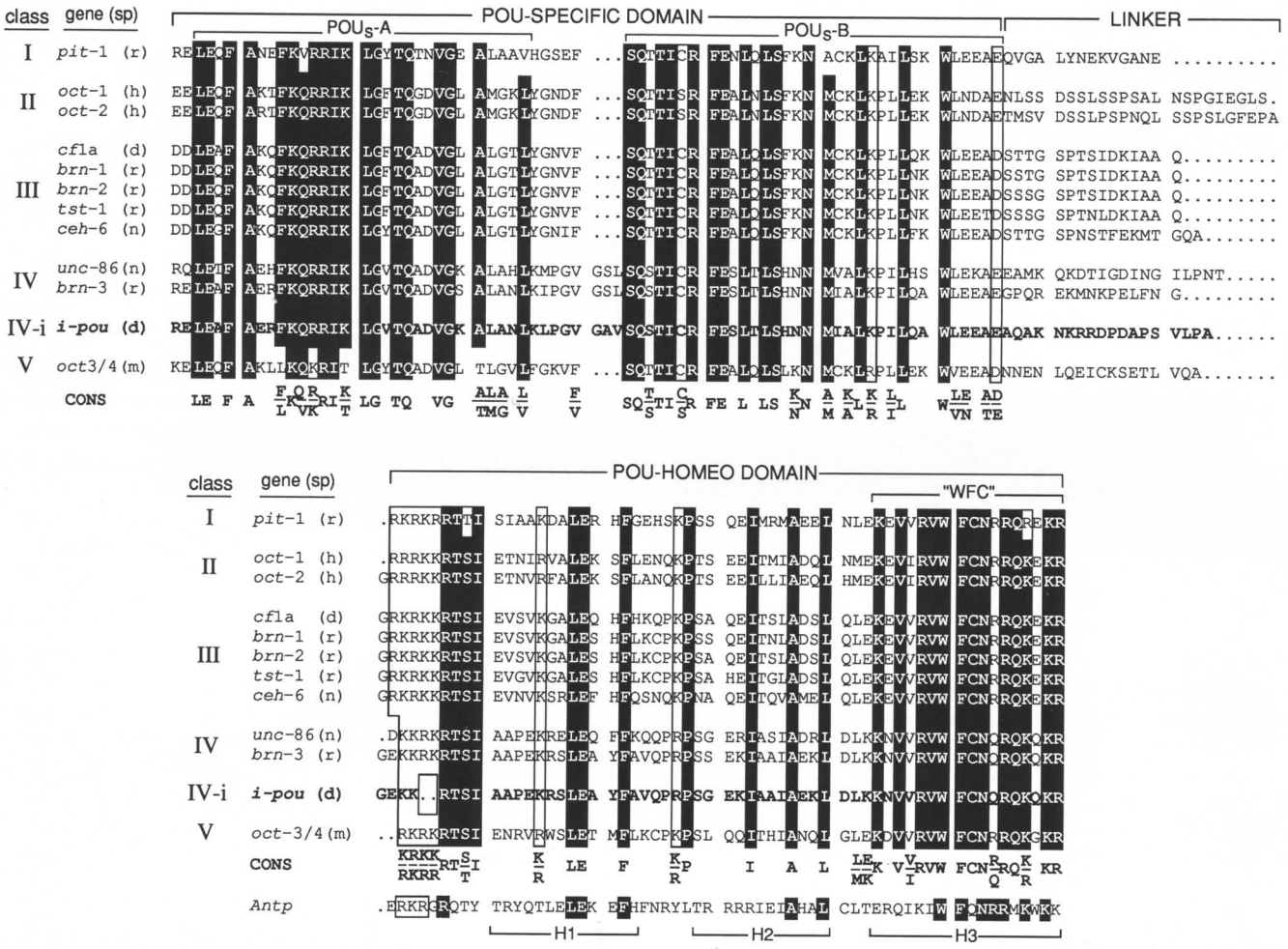

Figure 1. Comparison of the POU-domain sequence of a family of related POU-domain proteins. Homologies are indicated by black highlighting. The homeo domain of *Antennapedia (Antp)* is shown with positions of three helical domains, indicated as H1, H2, and H3. Species from which factors were cloned are rat (r), *C. elegans* (n), mouse (m), and human (h). The $^{R}/_{K}$ RI $^{K}/_{T}$ LG sequence in the *pit*-1 gene is the 3′ terminus of an exon. The helical domains of the POU homeo domain and the basic residues at the amino terminus of this domain are encoded by separate exons. Alternative names for identified family members are Pit-1 (GHF-1); Oct-1 (OTF-1); Oct-2 (OTF-2; NFIII), cf1a (D-POU-1); and Tst-1 (SCIP; Oct-6). (Cons) Consensus sequence.

conserved domain of ~150 amino acids called the POU domain (Herr et al. 1988). As summarized in Figure 1, numerous additional POU-domain genes in mammals, *Drosophila*, and *C. elegans* have been identified (Burglin et al. 1989; He et al. 1989; Johnson and Hirsh 1990; Monuki et al. 1990; Okamoto et al. 1990; Rosner et al. 1990; Schöler et al. 1990a; Suzuki et al. 1990). Post-transcriptional events generate further heterogeneity of POU-domain proteins, as exemplified in the case of alternative Oct-2 transcripts (e.g., Schreiber et al. 1988; Hatzopoulos et al. 1990).

Structure of the POU domain

The structural features of the POU domain will be reviewed because this region appears to confer several unique features. The POU domain varies from 147 to 156 amino acids in length and contains two major regions of very high homology—the POU-specific (POU_S) and POU-homeo domain (POU_{HD}) (Fig. 1). The precise length of the POU_S domain (69–71 or 76–78 amino acids) depends on the arbitrary assignment of the amino-terminal boundary. The arbitrary assignment of the amino-terminal boundary of the POU_S shown in Figure 1, which does not correspond to an intron–exon junction, includes all functionally critical information. Two distinct regions of particularly high homology, referred to as the POU_S-A region and the POU_S-B region, are noted (see Fig. 1). A poorly conserved spacer region, 14–25 amino acids long, separates the POU_S domain from the 60-amino-acid POU_{HD}, highly conserved among POU-domain proteins and unambiguously related to the classic homeo domains found in *Drosophila* (Scott et al. 1989). The POU_{HD} is predicted to contain three helices (Fig. 2), which correspond to those now established in the case of the classic homeo domain (Otting et al. 1988, 1990; Kiss-

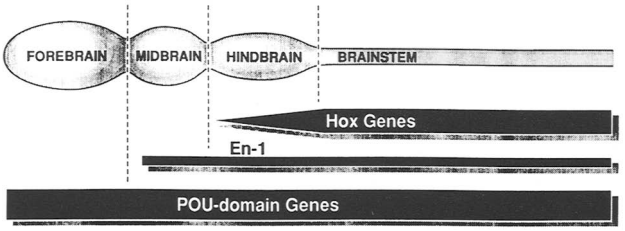

Figure 2. POU-domain proteins are expressed in the mammalian forebrain, in contrast to Hox genes, which are expressed in the hindbrain. Engrailed (en) homologs are detected in the midbrain.

inger et al. 1990), with the third "recognition" helix containing RVWFCN residues in all known members of the POU-domain gene family. On the basis of precedents in the homeo domain gene family, it is conceivable that the cysteine residue may not be invariant in the POU-domain gene family. Both amino- and carboxy-terminal boundaries of the POU_{HD} and the amino terminus of the POU_S domain contain clusters of basic amino acid residues, critical for their function as transcription factors (see below).

On the basis of the primary sequence throughout the POU domain, including the basic amino acid cluster at the amino terminus of the POU_{HD} and patterns of highest conservation in the linker region separating the POU_S and POU_{HD} domains, the POU-domain proteins may be classified into five groups (POU-I to POU-V) (Fig. 1). Although the spacer region of Oct-1 has been shown to be functionally capable of accommodating additional residues for in vitro binding (Sturm and Herr 1988), the conservation of the spacer in different classes of POU-domain proteins suggests a functional role. Outside the POU domain, there is enormous divergence between all known family members. However, in concert with many other families of transcription factors, many members of the POU-domain gene family contain regions rich in specific amino acids, including serine/threonine-rich (Pit-1, Oct-1, and Oct-2), glutamine-rich (Brn-2, Oct-1, Oct-2), and glycine/alanine-rich (Tst-1/SCIP(suppressed cAMP-inducible POU)/Oct-6) domains.

POU-domain protein *trans*-activation regions

POU-domain proteins appear to function as positive or negative transcriptions factors with the major transcriptional activating domain(s) of known members of this family located outside of the POU domain (Theill et al. 1989; Ingraham et al. 1990; Müller-Immerglück et al. 1990; Tanaka and Herr 1990). The serine/threonine-rich regions of Oct-1 (OTF-1) and Oct-2 (OTF-2) transfer transcriptional function (Tanaka and Herr 1990), and a comparable serine/threonine-rich region serves as the major activation domain of the Pit-1 (GHF-1) protein (Theill et al. 1989; Ingraham et al. 1990). The alternative *trans*-activation domains for Oct-2 may depend on the response element tested (Müller-Immerglück et al. 1990). While Pit-1, Oct-2, and Brn-2 are positive transcriptional activators (Ingraham et al. 1988; Müller et al. 1988; He et al. 1989; Tanaka and Herr 1990), the widely expressed Oct-1 protein has been reported to activate transcription of only a distinct class of promoters (e.g., Tanaka et al. 1988), presumably dependent on the position and nature of the *cis*-active recognition elements. The Tst-1/SCIP/Oct-6 protein appears to have the capacity to regulate specific gene transcription both positively and negatively (He et al. 1991; Monuki et al. 1990; Suzuki et al. 1990), depending on the promoter analyzed (Po, a member of the immunoglobulin superfamily), or the octamer element, perhaps a sequence of the glycine/alanine-rich regions.

POU-domain proteins are expressed in early embryogenesis and during forebrain development

Analysis of the ontogeny of the POU-domain gene family has revealed that specific POU-domain proteins are expressed selectively throughout the course of mammalian development. The discovery that several POU-domain genes are expressed in germ-line cells and early embryogenesis suggests functions in early development. One POU-domain protein, referred to as Oct-3/4 (Okamoto et al. 1990; Rosner et al. 1990; Schöler et al. 1990), is expressed in the female germ line and embryonic ectoderm until gastrulation and is restricted to primordial germ cells by embryonic day 8.5. The *Tst-1/SCIP/Oct-6* gene product (He et al. 1989; Monuki et al. 1990; Suzuki et al. 1990) also appears early in development in the inner cell mass of mouse embryos, but subsequently is expressed in specific neurons and testes, and after birth in a temporally restricted fashion in myelinating glia (Schöler et al. 1989; Monuki et al. 1990; Suzuki et al. 1990; He et al. 1991). Oct-3/4 and Tst-1/SCIP/Oct-6 are expressed in embryonic cell lines. Additional members of this family also appear to be expressed at these early times in development. Whereas a maternally derived classic homeo domain protein, *bicoid*, as well as dorsal, is crucial in *Drosophila* for establishing gradients that establish the developmental cascade of spatially specific transcription factor activation (Anderson 1987; Akam et al. 1987; Ingham et al. 1988), there are as yet no known mammalian maternally expressed homeo domain gene products.

From an apparently homogeneous population of neuroendothelial cells, brain development involves an intricate program of gene expression that leads to the establishment of a vast diversity of neuronal phenotypes and a precise, complex pattern of connections between them. The evidence that novel POU-domain proteins are expressed with distinct spatial and temporal patterns during establishment of the nervous system has raised the intriguing possibility that these proteins exert specific roles in specifying neuronal phenotypes. Hybridization histochemistry has revealed that all known POU-domain transcripts, except Oct-3/4, are expressed in all levels of the neural tube during at least some period of development. All transcripts are expressed in the ventricular (proliferative) zone of the neuroepithelium,

which gives rise to the central nervous system (He et al. 1989), with subsequent restriction to specific neurons. For example, the *Brn*-3 gene transcript exhibits a highly restricted pattern that includes sensory ganglion cells, which are derived from the neural crest (He et al. 1989). In contrast, *Brn*-1 and *Brn*-2 transcripts (see Fig. 1) are expressed in almost all regions of the cerebrum (layers II–V) and cerebellum (Purkinje cells), and their expression is correlated with all stages of establishment of cortical lamination. The *Tst*-1/*SCIP*/*Oct*-6 gene is expressed in the cerebral (layers V–VI) and cerebellar (granule cells) cortices and in many nuclei, but is also transiently expressed in myelinating glia (He et al. 1989; Monuki et al. 1990). The patterns of anatomical restriction in the developing nervous system tend to reflect the adult loci of expression, but the extent of restriction varies dramatically. Some transcripts, such as *pit*-1, are entirely restricted out of the central nervous system. Intriguingly, in contrast to classic homeo domain proteins, POU-domain proteins are widely expressed in the developing and mature forebrain and midbrain, suggesting that they may function in the development of neuronal phenotypes in this recently evolved brain region (see Fig. 2).

Neuronally expressed POU-domain gene products exert transcriptional effects in the central nervous system. *Brn*-2 expressed in the paraventricular nucleus of the hypothalamus, in cells expressing neuropeptides such as corticotropic releasing hormone (CRH), can bind to and activate the promoter of the CRH gene (X. He et al., unpubl.). *Tst*-1/*SCIP*/*Oct*-6, transiently expressed in glia in the proliferative phase preceding myelination, is potentially regulated by cAMP (Monuki et al. 1990). It is capable of binding to and negatively regulating a gene encoding a member of the immunoglobulin superfamily (Po), expressed in glia at this time (Monuki et al. 1990; He et al. 1991). In *Drosophila*, a POU-domain factor, highly homologous to the other mammalian members of the POU III class, cf1a (Johnson and Hirsch 1989), is expressed in neuronal and epidermal tissues and can bind to and *trans*-activate a neuronal regulatory site within the dopa decarboxylase gene (Johnson and Hirsh 1990; Treacy et al. 1991).

Developmental functions of POU-domain transcription factors

The analysis of two genetic defects in POU-domain transcription units has provided direct evidence of the function of these proteins in activating the gene programs required for appearance and proliferation of specific cell phenotypes.

C. elegans *development*

Genetic analysis of *C. elegans* development revealed that a POU-domain gene, *unc-86*, is required for the commitments in several neuroblast lineages. Mutations in the *unc-86* locus prevent mother cells from differentiating into daughter cells, with retention of maternal phenotype (Chalfie et al. 1981; Finney et al. 1988). Three affected lineages are shown in Figure 3A. In each case, the daughter cells continue to exhibit the phenotype of mother cells, and, therefore, specific types of neurons fail to appear. In the lineages shown, failure to express *unc-86* may lead either to inappropriate cell death or to appearance of neurons failing to serve specific functions. Recent analyses (Finney and Ruvkin 1990) have revealed expression of unc-86 protein occurring several minutes after cell division in the nuclei of cells corresponding to those affected by the *unc-86* mutations, consistent with the proposed role of unc-86 in modulating the pattern of gene expression that distinguishes daughter cells from mother cells. The molecular basis for asymmetric activation of unc-86 in only one of two daughter cells remains unknown, although it is apparently not dependent upon cell–cell interactions. Interestingly, the unc-86 protein is also expressed in a number of neuronal types, not linked by any known common marker, which do not disappear with genetic mutants of the *unc-86* locus (Ruvkun and Finney 1991). It has been suggested that unc-86 directs the patterns of gene expression in these cells, modulating their mature phenotype.

The *unc-86* mutant has also provided insight into combinatorial codes required to establish specific phenotypes. Thus, a homeo domain gene, *mec-3*, which is important in establishing specific neuronal phenotypes (Chalfie et al. 1989), depends on *unc-86* function for its expression. However, the distribution of the encoded proteins within the nervous system indicates that expression of *unc-86* is itself not sufficient to activate *mec-3*.

Mammalian development

A mammalian mutant in the *pit*-1 locus provides insight into the molecular mechanisms that establish specific cell types within an organ. Expression of Pit-1 is normally confined to three cell types in the anterior pituitary gland, defined on the basis of the trophic factor elaborated. These are referred to as thyrotrophs (express thyroid-stimulating hormone-β [TSH-β)], lactotrophs (express Prl), and somatotrophs (express GH) (Simmons et al. 1990). Pit-1 transcripts and protein are initially expressed in the rat anterior pituitary gland on embryonic day 15 preceding the initial appearance of Prl and GH transcripts on embryonic days 16–17 (Dollé et al. 1990; Simmons et al. 1990). However, *pit*-1 gene expression is initially observed in thyrotrophs, considerably later than the initial appearance of TSH-β gene expression (Simmons et al. 1990) (see Fig. 3B). Pit-1 has been independently demonstrated (e.g., Ingraham et al. 1988; Mangalam et al. 1989; Fox et al. 1990; Sharp and Cao 1990) to be capable of binding with high affinity and of *trans*-activating both the Prl and GH promoters, except for a report suggesting that Pit-1/GH-1 is capable only of selectively binding and activating the GH promoter (Castrillo et al. 1989).

One form of genetically transmitted dwarfism in mice,

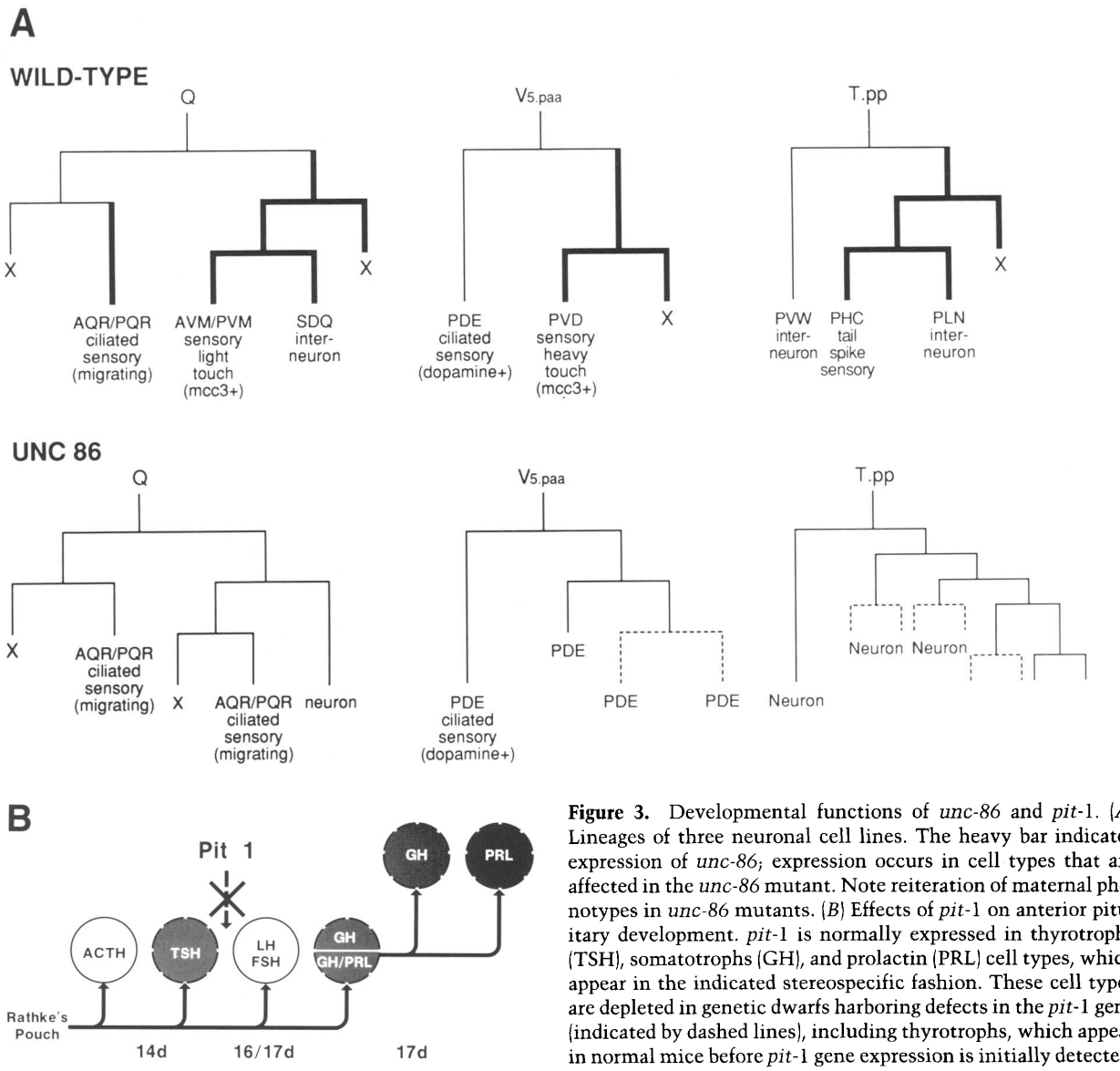

Figure 3. Developmental functions of *unc-86* and *pit*-1. (*A*) Lineages of three neuronal cell lines. The heavy bar indicates expression of *unc-86*; expression occurs in cell types that are affected in the *unc-86* mutant. Note reiteration of maternal phenotypes in *unc-86* mutants. (*B*) Effects of *pit*-1 on anterior pituitary development. *pit*-1 is normally expressed in thyrotrophs (TSH), somatotrophs (GH), and prolactin (PRL) cell types, which appear in the indicated stereospecific fashion. These cell types are depleted in genetic dwarfs harboring defects in the *pit*-1 gene (indicated by dashed lines), including thyrotrophs, which appear in normal mice before *pit*-1 gene expression is initially detected.

characterized as two allelic recessive mutations on chromosome 16 (Snell 1929; Eicher and Beamer 1980), permitted definition of the developmental roles of Pit-1. These genetic dwarf mice produce no detectable GH, Prl, or TSH, and mature somatotroph, lactotroph, and thyrotroph cell types are depleted in these dwarfs (Roux et al. 1982; Wilson and Wyatt 1986). Both allelic mutations involve disruptions in the *pit*-1 gene; the Jackson dwarf results in a disruption of the *pit*-1 gene, while the Snell dwarf mutation involved a G → T transversion that converts the tryptophan residue in the WFC homology in the POU_{HD} to a cysteine residue, generating a mutant protein that fails to bind to recognition elements (Li et al. 1990). Thus, Pit-1 is required for the specification of three of the five cell types in the anterior pituitary gland, including the somatotroph and lactotroph phenotypes (Fig. 3B). However, the ultimate selective and qualitative expression of Prl and GH genes in their respective cell types (Lira et al. 1988; Crenshaw et al. 1989) probably requires additional activating and restrictive mechanisms.

The hypoplastic nature of the genetic dwarf pituitary provides direct evidence that cell proliferation and survival of specific cell types are important components of the program specified during normal development by Pit-1, reflecting either direct or indirect roles of Pit-1 in DNA replication. These data are consistent with the indication that Oct-1 and, potentially, other POU-domain proteins are strongly suggested to exert important functions in DNA replication. In available adenovirus in vitro replication assays, the POU domain of either Oct-1 (OTF-1, NFIII) or Oct-2 (OTF-2) was capable of enhancing in vitro DNA replication (Verrijzer et al. 1990a), while mutant proteins lacking the POU_S domain were actually inhibitory in this replication assay.

These data indicate that combinatorial codes for both

unc-86 and Pit-1 appear to be required for the quantitative and qualitative pattern of target gene expression. Thus, differential expression of the Pit-1-dependent Prl and GH target genes in distinct cell types, and unc-86-dependent expression of *mec*-3 in specific neurons in *C. elegans*, must both reflect the actions of additional activating and restricting factors. In the thyrotroph cell type, which appears prior to detectable *pit*-1 gene expression, Pit-1 could potentially be required for survival or proliferation of this cell type and may exert functions comparable to those suggested for *unc-86* in preventing programmed cell death. These data link POU-domain transcription factors to the proliferation of specific cell types, and progression and commitment events in organogenesis.

It is likely that other POU-domain proteins exert similar developmental functions. Because the octamer motif has been associated with lymphoid-specific immunoglobulin gene expression (Singh et al. 1986; Dreyfus et al. 1987; Wirth et al. 1987; Scheidereit et al. 1988), it is likely that Oct-2, in concert with other functions, also exerts determining functions in B-cell development and activation of immunoglobulin gene expression. *Oct*-3/4 maps to mouse chromosome 17 near or within the major histocompatibility complex (Schöler et al. 1990b), perhaps within loci that are associated with early embryonic lethal phenotypes.

Functions of the POU domain

The unique patterns of neuronal expression of the large family of POU-domain regulators make it particularly interesting to understand fully the functional properties conferred by the POU domain. Mutagenesis studies involving Pit-1 and Oct-1 suggest that both the POU_S and POU_{HD} are combinatorially required to permit high-affinity, site-specific binding. In the case of Pit-1, although the POU_{HD} is sufficient for binding to a distinct set of A/T-rich DNA sequences with a relaxed specificity, the POU_S domain is required for high-affinity, site-specific binding, increasing affinity up to 1000-fold for physiologic Pit-1 response elements (Ingraham et al. 1990). The POU_S domain is similarly critical for high-affinity binding of Oct-1 to its recognition elements (Sturm and Herr 1988; Verrijzer et al. 1990b). Additionally, each of the three basic amino acid clusters at the amino terminus of the POU_S domain and both amino and carboxyl termini of the POU_{HD} serve critical functions in high-affinity DNA binding by POU-domain proteins, as mutations in any of these regions abolished high-affinity binding (Sturm and Herr 1988; Ingraham et al. 1990; Treacy et al. 1991). Creating POU-domain chimeras between Oct-1 and Pit-1 POU_S and POU_{HD} revealed that both domains exert critical functions in discriminating octamer- and Pit-1-binding sites (Ingraham et al. 1990). The invariant cysteine residue sequence in the POU_{HD} "recognition helix" is apparently not absolutely required for high-affinity site-specific recognition, because mutation of this amino acid residue fails to affect Pit-1 binding (Elsholtz et al. 1990; Ingraham et al. 1990). A comparable amino acid residue in classic homeo domain proteins has been suggested to dictate site-specific binding for several DNA sites (Hanes and Brent 1989; Treisman et al. 1989). Disruption of the predicted first helix (helix A; Fig. 4) in the POU_S domain or helix 3 (WFC) in the POU_{HD} abolishes DNA binding; however, disrupting the other putative helical structures in the POU_S and POU_{HD} does not affect binding (Fig. 4). This appears to be in contrast to the proposed hydrophobic helical interactions between helix 1 and helix 2 of the engrailed homeo domain protein that are required to present the minor groove contacts important for binding (Kissinger et al. 1990; Otting et al. 1990). This analysis of the α-helical domains and conserved structures and the contacts of the POU domain on cognate sites suggests that POU-domain proteins interact with their DNA recognition sites differently from homeo domain proteins, with both the POU_S and the POU_{HD} contacting DNA. This formulation awaits high-resolution structural analysis.

Although the DNA-binding sites of classic homeo domain proteins generally are A/T-rich sequences, the best-described sites for POU-domain proteins for Oct-2, Oct-1, and Pit-1 are variants of $(A/T)_{4-5}$TTTGCAT or

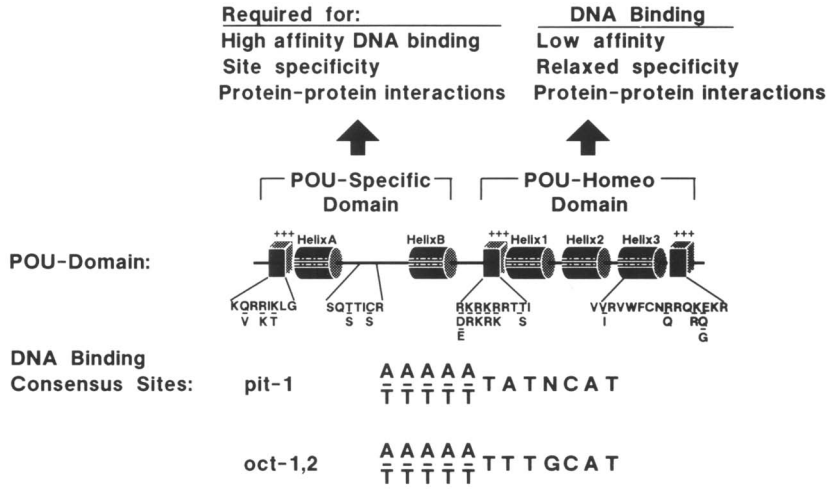

Figure 4. Schematic representation of the POU domain, indicating predicted helical domains, and the most highly conserved sequences. The known functions of POU_S and POU_{HD} are listed above. These proteins bind to heterogeneous sites containing A/T-rich sequences; consensus sequences for Pit-1 and Oct-1 are shown below.

$(A/T)_{4-5}$TATNCAT, respectively (Wirth et al. 1987; Nelson et al. 1988; Elsholtz et al. 1990). Although additional data are clearly required, it has been suggested that POU_S and POU_{HD} interact with both the TATNCA and A/T-rich sequences in the binding site (Ingraham et al. 1990; Kristie et al. 1990; Verrijzer et al. 1990b). In this regard, it is interesting that the Pit-1 homeo domain can itself bind with relatively high affinity to certain recognition sites for the *Drosophila* homeo domain regulators (Ingraham et al. 1990), while the full POU domain fails to bind effectively to these sites. It is tempting to speculate that one advantage of this large, apparently asymmetric, recognition element is that post-translational regulation could impose differential binding, conformation, and functional effects on different subsets of *cis*-active elements, dependent upon sequences outside the canonical TATNCAT core-binding motif. For other sites, the POU_S domain may not be critical for binding, as exemplified by Pit-1 binding on the engrailed site (Ingraham et al. 1990) and Oct-1 binding to the TAATGARAT sequence (Verrijzer et al. 1990b). These data together imply that the POU domain is functionally and structurally distinct from the homeo domain and that a subset of POU-domain-binding sites will be distinct from those containing the TATNCAT motif. For example, Tst-1 *cis*-active elements contain, instead, ATTA motifs (He et al. 1991). On the basis of all available data, it is suggested that the POU-domain-binding site is an asymmetric element spanning 12–15 bp, with the POU_S domain contacting TATNCA sequences and the POU homeo domain also contacting, in variable conformations, A/T-rich sequences 5′ of the TATNCA core. Precise orientation of the POU_S and POU_{HD} on binding sites requires further experimentation.

POU-domain protein—protein interactions

The POU domain permits protein–protein interactions that may be critical for function. Pit-1, Oct-1, and Oct-2 have been described to behave as apparent monomers in solution (LeBowitz et al. 1989; Poellinger and Roeder 1989; Ingraham et al. 1990) and can bind as monomers to their cognate DNA recognition elements. Cooperative binding interactions are exhibited by Oct-2 on an octamer element adjacent to a heptamer element on a natural binding site, and many of the Pit-1-binding sites in the rat Prl and GH promoters permit DNA-dependent Pit-1 dimer formation via cooperative binding interactions. (LeBowitz et al. 1989; Poellinger et al. 1989; Ingraham et al. 1990). Cooperative interactions between Oct-2 proteins increase transcriptional activity (Poellinger et al. 1989). Many Pit-1-binding sites might be considered to contain direct repeats or palindromic arrangements of the TATNCA(T) core motif, but it would appear that on certain sites Pit-1 binds preferentially and with high affinity as a monomer. On the basis of the precedents of Oct-2 and Pit-1, it is suggested that specific cooperative binding may be a feature of many POU-domain proteins; however, these dimers apparently occur only on a subset of binding sites. Because the highly conserved RRIKLG sequence in the POU_S-A region represents the 3′ boundary of an exon in the *pit*-1 gene (Li et al. 1990), it is tempting to speculate that the POU_S-A and POU_S-B regions may subserve differential functions with respect to protein–protein interactions and high-affinity, sequence-specific DNA binding. In addition to the ability to confer DNA-dependent protein–protein interactions, the POU domain may be important in formation of heterodimers on DNA and in solution between family members such as Oct-1 and Pit-1 that are often coexpressed in a single cell type (He et al. 1989; Voss et al. 1991), comparable to the functionally important heterodimers between members of other gene families (e.g., Rauscher et al. 1988; Glass et al. 1989; Murré et al. 1989a,b). Consistent with this possibility, DNA-independent interactions between specific POU-domain proteins have been observed in mammals and *Drosophila* (Treacy et al. 1991; Voss et al. 1991), alternatively promoting or inhibiting the binding of specific positive POU-domain regulators. I-POU (inhibitory-POU, see Fig. 1) specifically interacts with cf1a, inhibiting its ability to bind and activate a specific neural promoter (Treacy et al. 1991). Because the relative levels of positive and inhibitory POU-domain proteins vary during development within specific neuronal and endocrine cell types, these types of protein–protein interactions may serve to impose sharp temporal and spatial boundaries, on the basis of stoichiometry of different POU-domain proteins.

Functional protein–protein interactions are also conferred by specific sequences in the POU_{HD}, established by the intriguing ability of Oct-1 to bind to the herpes virus αTIF/VP16 gene product, dependent on specific residues in helix 2 or the POU_{HD} (McKnight et al. 1987; Gerster and Roeder 1988; O'Hare and Goding 1988; Stern et al. 1989). αTIF/VP16 has been shown to interact with host Oct-1 protein in activation of viral early genes (O'Hare and Goding 1988; Preston et al. 1988). This apparently involves the formation of a complex with a third protein (Kristie et al. 1989; Gerster et al. 1990). The mutation of the three critical residues in the POU_{HD} helix 2 to those present in Oct-2 significantly decreases the αTIF/VP16 binding (Stern et al. 1989). Mammalian homologs of αTIF/VP16 have yet to be established. In the context of specific promoters, perhaps due to actions of additional factors, the isolated POU domain can serve to activate transcription weakly in the absence of additional information (Gerster et al. 1990; Ingraham et al. 1990; Müller-Immerglück et al. 1990). On the basis of these data, both the POU_S and the POU_{HD} together appear to permit specific DNA-dependent and DNA-independent protein–protein interactions that may be functionally crucial in both binding and *trans*-activation. Moreover, it appears that both regions modify the specificity and the affinity of these proteins for their cognate recognition elements.

Activation and regulation of POU-domain genes

Activation of POU-domain proteins is linked to actions of morphogens and classic signal transduction pathways.

On the basis of precedents in *Drosophila* for other classes of developmental regulators (Akam et al. 1987; Scott et al. 1989), the molecular mechanisms of activation and maturation of POU-domain proteins are likely to involve the actions of numerous other classes of transcriptional regulators. *Oct*-3/4, expressed early in development and in embryonic stem cells, is markedly inhibited by retinoic acid, which induces phenotypic alteration along several pathways (Jones-Villeneuve et al. 1983; Strickland and Mahdavi 1988). These events can also be mimicked by introduction of the c-*jun* gene (deGroot et al. 1990). The finding that *Oct*-3/4 and *Tst*-1/*SCIP*/*Oct*-6 are strongly and negatively regulated by retinoic acid provides a correlation between expression of these POU-domain proteins and early developmental commitment events (Schöler et al. 1989; Okamoto et al. 1990; Suzuki et al. 1990).

The cloning of the *pit*-1 gene has permitted an initial assessment of the regulatory mechanisms responsible for its initial activation and regulation (Chen et al. 1990; McCormick et al. 1990). Two Pit-1 binding and regulatory elements were identified in the *pit*-1 gene, flanking the cap site. The 5′ sequence was a positive regulatory element, conferring Pit-1-dependent gene expression, while the 3′ element was an inhibitory element, attenuating expression by 10-fold (Chen et al. 1990). These data are consistent with an autoregulatory loop that seems to function in maintaining *pit*-1 gene expression, effecting, in a sense, a memory of cell commitment. The very low levels of *pit*-1 transcript and protein in the *dw* genetic dwarfs are consistent with the model that *pit*-1 transcriptional autoregulation exerts an important function in maintenance of *pit*-1 gene expression (Li et al. 1990). Functional elements in the *pit*-1 promoter that bind CREB (Chen et al. 1990; McCormick et al. 1990), could serve developmental regulatory functions. In this regard, it is intriguing that the *Tst*-1/*SCIP*/*Oct*-6 gene is transiently expressed during a phase of rapid cell division preceding the myelinating phases of Schwann cell differentiation stimulated by cAMP (Monuki et al. 1990).

Conclusions

The large family of POU-domain proteins appears to exert critical functions as developmental *trans*-activators of genes that define specific cell phenotypes and in the proliferation of these cell types within an organ. Unexpectedly, the majority of known mammalian POU-domain genes are expressed in distinct spatial and temporal patterns in the forebrain, an area that does not express classic homeo domain genes. POU-domain proteins may exert functions in development of neurons in this recently evolved portion of the central nervous system by mechanisms comparable to those exerted by Unc-86 and Pit-1 in sensory neuron and anterior pituitary cell development, respectively.

The unique DNA-binding properties of the POU domain, and the additional protein–protein interactions permitted by both the POU_S and POU_{HD} sequences, may provide additional, critical advantages to forebrain development via both homodimeric and heterodimeric protein–protein interactions that could refine both the specificity and regulatory consequences of members of this class of transcription factor. The heterogeneous binding sites for POU-domain factors do not appear to be palindromic and are likely to exhibit differential functional responses to post-translationally modified POU-domain proteins, potentially permitting even more complex combinatorial patterns of positive and negative gene regulation. It now becomes of significant interest to elucidate potential POU-domain–protein interactions, to identify the physiological target genes, and to elucidate the precise roles of the large family of POU-domain proteins in development of specific organs, particularly the central nervous system.

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