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STRUCTURAL–FUNCTIONAL GENOMICS. NEW TECHNOLOGIES

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The *oct* Genes and Oct Proteins

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Abstract—The review considers the functions and properties of Oct proteins, which belong to the POU family of transcription factors, and the roles of the POU and other domains in DNA recognition and interaction with other proteins of the transcription initiation complex. The structure and expression regulation of the *oct* genes are described with special emphasis on alternative transcription initiation from different promoters and alternative splicing, which result in several protein subforms.

Key words: POU proteins, POU genes, transcription factors, expression regulation, alternative promoters, alternative splicing

INTRODUCTION

Oct proteins belong to a broad family of nuclear proteins possessing the DNA-binding POU domain, which was first revealed in transcription factors PIT-1, Oct-1, and Oct-2 [1]. The POU domain consists of two highly conserved subdomains, which are joined together by a structurally variable flexible linker. The N-terminal one was termed POU-specific subdomain (POUs), and the C-terminal one, POU homeodomain (POUh), to denote its high homology to homeoproteins [1]. Transcription factors Oct-1 and Oct-2 were identified, purified, and functionally characterized in the late 1980s [2–4]. Among all double-stranded DNA sites recognized by the POU domain, these proteins most efficiently bind octamer ATGCAAAT, which was first found in the promoters of immunoglobulin genes [5] and then in promoters and enhancers of numerous other genes [6–8]. Oct proteins activate transcription by various mechanisms, which may also employ other transcription factors [6–8] or coactivator proteins [6]. On recent evidence, the POU domain of Oct-1 directly contacts the TATA-binding protein (TBP), which is essential for its interaction with a remote enhancer [9]. The multiplicity of functions played by Oct proteins is due to the context of the recognition sequence, contacts with other proteins, and structural features of the Oct protein itself, which contains not only the POU domain, but also other functionally important regions. Thus a Gln-rich region located in the N-terminal part of Oct-1 participates in activating the promoters of many genes [10], with the exception of the snRNA genes. The C-terminal region contains an Ala-rich domain, which may contribute to the silencer activity of Oct-1 [11]. Here we consider the properties of Oct proteins, their interaction with DNA, and the structure and expression regulation of the *oct* genes.

Oct PROTEINS

Commonly, Oct-1, Oct-2, and Oct-3/4 are classed as Oct proteins. In some cases, POU proteins known under other names are assigned to this group [12]. Oct proteins vary in tissue and cell locations: Oct-1 occurs in nuclei of all eukaryotic cells; Oct-2 is synthesized in cells of the immune and nervous systems; while Oct-3/4 are produced in oocytes, germ cells, and in totipotent and pluripotent cells during embryo development [12].

The POU domain plays the central role in DNA recognition [13]. A complex of the POU domain with octamer ATGCAAAT and the adjacent sequences was subjected to X-ray analysis [14]. The following findings are most important. The third α-helix of POUs contacts the left part of the octamer, while the third α-helix of POUh interacts with its AT-rich right part (Fig. 1). Contacts are formed in the DNA major groove in both cases. The interaction of the subdomains with DNA is cooperative [13, 14]. Other regions of the POU domain form only single contacts with DNA. In total, the DNA–protein interaction involves approximately 30 hydrogen bonds and van der Waals contacts.

The roles of individual amino acid residues were studied by mutation analysis. Mutations were introduced both in the protein and in the recognition sequence. Highly conserved Asn-51 proved to contact a particular adenine (ATGCAA<u>A</u>T) in the major groove of the recognition site [15]. Any substitution of this residue decreased the affinity for the octamer no less than two orders of magnitude, and impaired the interaction specificity. Conserved Val-47, which is in the third recognizing helix of POUh, was replaced consecutively by 19 other amino acid residues, and the

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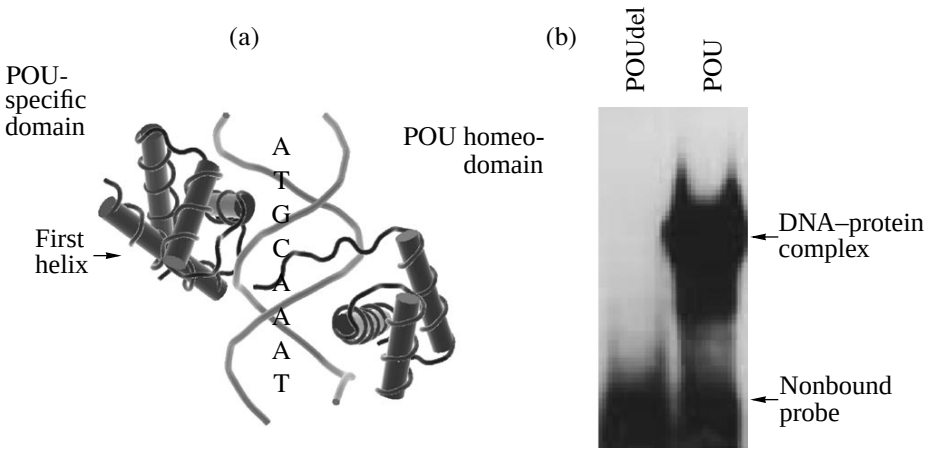


Fig. 1. Complexation of the POU domain with the DNA octamer: (a) complex structure inferred from the X-ray data [14] and (b) comparison of the DNA binding efficiency for the POU and POUdel domains by the gel retardation assay [18].

resulting mutant proteins were tested for affinity and specificity of interaction with the octamer having all possible nucleotides in position 8 (ATGCAAANGA) [16]. Similar experiments were carried out with homeospecific site ATAANGA. All mutants have lower affinity for the oct site as compared with the native protein. However, the highest affinity for the homeospecific site was characteristic of the Val47Ile mutant, which agrees with the presence of Ile, rather than Val, in the corresponding position of all homeoproteins examined. The involvement of both POUs and POUh in recognizing the oct site was shown to compensate, at least partly, for the effects of point mutations [16]. We found that Cys-50 contacts two thymines located beyond the octamer in synthetic oligonucleotide CATACGTTTATTCC, which was crystallized together with a POU protein [17]. The finding fails to elucidate the functional role of Cys-50, because the thymines "recognized" in this experiment are not conserved (otherwise, POU protein would most likely recognize the decamer ending with TT, rather than the octamer). To study the role of Cys-50, we constructed mutant proteins with all possible substitutions in position 50 of POUh and oligonucleotides with substitutions at the right flank of the octamer (ATGCAAATNN). The wild-type POUh was shown to recognize the octamer with the highest affinity and specificity. Mutations impaired the interaction: all mutant proteins had lower affinity for the native octamer, but some had higher affinity for the homeosite or the decamer. With Cys-50, the interaction between the POU domain and the octamer was most specific and least dependent on the octamer-flanking nucleotides.

We constructed an *oct-1* mRNA lacking 174 nt in the POUs-coding region [18]. The deletion affected the first helix of POUs in the POUdel mutant (Figs. 1b, 2). The corresponding cDNA was expressed in *Escherichia coli*, and POUdel was isolated and purified. The native POU domain and POUdel were compared with respect to the binding with a labeled probe containing the oct site. In contrast to the native POU domain, POUdel did not bind the oct-containing probe. To correctly interpret this result, it should be noted that the α-helix is a dipole and that its absence impairs the macrointeractions within the POU domain. Another important note is that several highly conserved amino acid residues are eliminated by the deletion. Thus Arg-20 is hydrogen-bonded with the DNA sugar-phosphate backbone and with Glu-51 in the POU domain bound to the oct site [14]. On X-ray evidence, Leu-9, Phe-12, Phe-16, and Leu-23 form numerous van der Waals contacts within the POU domain; the contacts are probably important for the correct folding of the domain. Hence, the structure of POUs, its cooperative interaction with POUh, and the ability to recognize DNA are altered in POUdel.

The oct site is the optimal target of Oct proteins in DNA. Experiments with arbitrarily modified nucleotide sequences showed that POU proteins recognize not only the canonical octamer, but also noncanonical regions, most of which contained the TAATNN homeospecific site [19]. Some of such sites were separated by a spacer of 3–4 nt [7].

If Oct proteins recognize the noncanonical sites *in vivo*, such sites would be present in promoters and enhancers of some genes to provide for their expression regulation. The nucleotide sequences recognized by Oct proteins in regulatory regions of various genes are shown in the table. To recognize some of these, Oct must interact with accessory proteins or other transcription factors.

Complexation with other proteins extends the functions of the POU domain and the set of its target sequences. The interaction of Oct-1 and Oct-2 with accessory protein OCA-B (OBF-1, Bob-1) was stud-

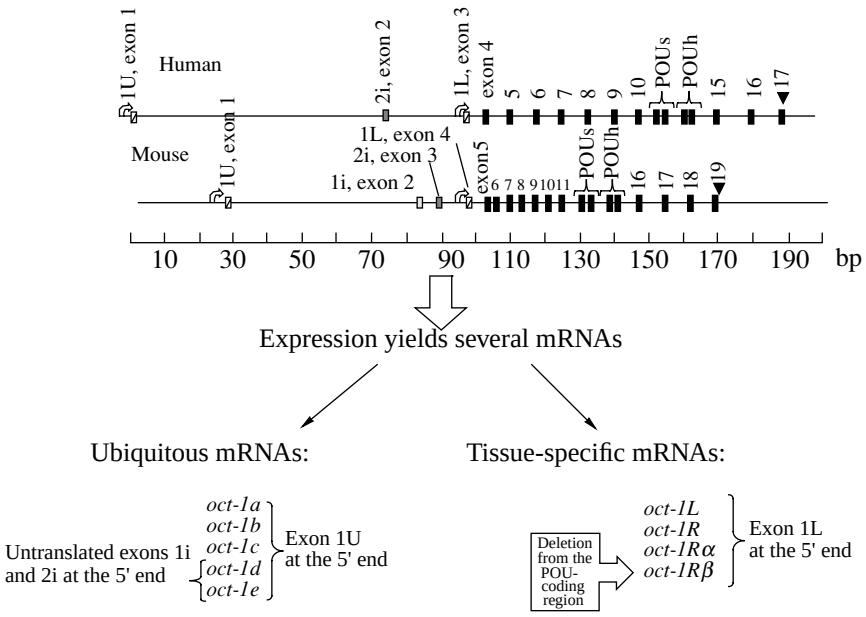


Fig. 2. The structures of human and mouse *oct-1*. Bars, exons; bent arrows, transcription start sites; triangles, 3' ends of the genes. Ubiquitous and tissue-specific *oct-1* mRNAs resulting from alternative transcription initiation and alternative splicing are shown at the bottom; their structural features are indicated.

ied in most detail [20]. Produced in lymphoid cells, OCA-B binds with the POU domain and contacts the central adenine (ATGCAAAT) of the octamer in complex with DNA [20, 21]. Another accessory protein, VP16, is essential for transcription of the herpes virus genome. VP16 forms a multicomponent complex with the POU domain of Oct-1, other virus proteins, and sequence ATGCTAATGATA [21]. These proteins recognize not only different DNA sites, but also different regions of the POU domain and, consequently, may simultaneously interact with a POU protein [21].

DNA sites recognized by the POU domains of Oct-1 and Oct-2

Nucleotide sequence	K_d, 10^{-9}	Reference
ATGCAAAT	4.5	[7, 19]
ATGTAAAT	4.9	"
ATGCAAAA	6.1	"
TGCATAAT	17.1	"
ACGATAAT	22.2	"
TGCAtat TAAG	10.3	"
TGCAtacCAAg	18.0	"
TGCAtatcTAAT	23.3	"
ATGCTAATGARAT	–	[6]
TAATGARAT	–	[6]
*AG**TTGCAAAT**	–	[33]

* The consensus sequence recognized by C/ERB is underlined, and the octamer consensus boldfaced.

The mouse and human Oct-1 proteins are highly homologous. Human and mouse POUh differ only in four residues located in the first and second helices. However, human Oct-1 forms a stable complex with VP16, whereas the mouse protein has extremely low affinity for this coactivator [22]. Comparison of the POUh sequence for human and mouse Oct-1 and Oct-2 revealed high homology between mouse Oct-1 and human Oct-2, which does not interact with VP16. Hence it is possible to speculate that introduction of the corresponding mutations would prevent human Oct-1 from interaction with VP16 and thereby attenuate the effect of the herpes virus on the cell. It should be remembered, however, that the functional consequences of any mutation cannot be fully predicted.

As shown recently, Oct-1 and Oct-2 may bind to DNA both as a dimer and as monomers [23–25]. The dimer is formed on interaction with palindromic sequences containing the octamer or its close analog. These are the palindromic Oct recognition element (PORE) ATTTGAAATGCAAAT and a sequence known as More PORE (MORE, ATGCATATGCAT).

Only PORE forms a ternary complex with an Oct protein and cofactor OBF-1, which expedites the interaction. There is evidence that PORE-like palindromic sequences are primary targets in generation of the ternary complexes of OBF-1, Oct, and DNA. The POU domain of Oct proved to be arranged along the helix axis of a palindromic DNA region, as also characteristic of the POU domain of PIT-1 [26].

It was shown that POU proteins may interact with transcription-complex proteins TBP [9] and TAF [7]. DNA bending at the contact between the POU domain and TBP brings distant DNA regions close together [7], which is necessary for generation of a functional transcription initiation complex. In addition, Oct-1 is essential for transcription initiation on the snRNA genes [27, 28]. In this case, the POU domain of Oct-1 binds to the enhancer of the snRNA gene and simultaneously contacts the snRNA activating protein (SNAP) complex. This contact involves SNAP190, which is structurally similar to OBF-1. Other SNAPs interact with TBP. The interaction is accompanied by DNA bending, which is essential for bringing the enhancer close to the promoter. This chain of events results in transcription initiation on the snRNA gene.

Along with the POU domain, other domains of Oct proteins participate in interactions with coactivators and transcription factors [29, 30]. The N-terminal regions of Oct-1 and Oct-2 each contain a Gln-rich region, which participates in activating the promoters of various, but not snRNA, genes. The C-terminal portion of Oct-1 contains what is known as Ala domain, which is involved in gene silencing [31]. The silencer domain of Oct-1 recognizes extended A/T regions and binds to these to form a silencer complex. The DNA sequences binding with the Ala domain are tightly associated with the nuclear matrix in matrix attachment regions (MARs). Several sites binding with the Ala domain of Oct-1 were found in the 5' region of the human thyrotropin β-subunit gene [31].

Presumably, multifunctional Oct-1 is involved not only in transcription initiation, but also in suppressing gene activity and assembling chromatin loops. The assumption is based on the fact that Oct-1 is contained in the nuclear matrix along with several other nuclear proteins such as histone H1, topoisomerase II, and HMG-I/Y [32].

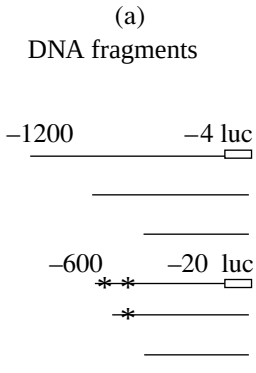
THE *oct* GENES

In the human genome, the *OTF-1* locus, which contains *oct-1*, is in region cen-q32 of chromosome 1. The size of *OTF-1* was estimated and 16 *oct-1* exons were identified and localized in the first relevant work [34]. By now, genome sequencing showed that *OTF-1* is about 200 kb and harbors at least 21 *oct-1* exons. The structure of mouse *oct-1* was also established (Fig. 2).

More recently, new data were obtained for expression regulation and the exon–intron structure of *oct-1*. An *oct-1* cDNA cloned from myeloma NS/0 cells [35] proved to differ in structure of the 5' end from the *oct-1* cDNA cloned from nonlymphoid cells [34]. The first mRNA variant found in lymphoid cells and tissues contains exon 1L (L, lymphocyte) coding for 10 amino acid residues at the 5' end. The other mRNA variant has 5' exon 1U coding for 21 residues. The mRNAs with exon 1U were observed both in lymphoid and nonlymphoid cells [36, 37]. No mRNA contains both exons 1L and 1U. Thus, new tissue-specific *oct-1* mRNAs, *oct-1L* and *oct-1R* each containing exon L at the 5' end, were revealed in lymphoid cells of the bone marrow, lymph nodes, the spleen, and the thymus and in cell lines corresponding to various differentiation stages of B and T cells. Among all POU-protein-coding genes, *oct-1* and *oct-2* show especially high functional and structural homology. As sequence comparisons showed, human *oct-1* is highly similar to mouse *oct-2* [34]. Interestingly, exon 1U of human *oct-1* has no homology to the first exon of mouse *oct-2*, whereas exon 1L and the first exon of *oct-2* are similar in size and homologous in sequence [37].

A natural question is whether expression of the ubiquitous and tissue-specific *oct-1* mRNAs is regulated by tissue-specific transcription initiation or by tissue-specific splicing. To study this, regions adjacent to exons 1L and 1U were cloned from the human and mouse genomes and sequenced [38–40]. The 1U region proved to be enriched in GC, while the 1L region, in AT. Consistently, the former contains more than 25 GC-rich *cis* elements recognized by factor Sp1, while the 1L region of mouse [38, 39] and human [40] *oct-1* harbors a similar number of NTAATNN homeospecific sites and two ATGCAAT octamers.

Genes involved in intricate cell processes are often regulated at several expression levels. Alternative transcription from at least two promoters is one of the regulatory mechanisms. At present, many genes are known to be regulated this way (see [41] for review). Alternative promoters contribute to the fine temporal or tissue-specific expression regulation. One of the promoters is usually constitutive and directs gene expression in numerous tissues and cells, ensuring synthesis of housekeeping or ubiquitous proteins. Another promoter is tissue-specific and responsible for protein synthesis in particular tissues at particular stages of cell differentiation or organism development. To study the role of regions 1U and 1L in regulating *oct-1* transcription, a series of reporter constructs was obtained with the polymerase chain reaction and cloned in a vector containing or lacking the SV40 enhancer [40]. The gene fragments under study had one and the same 3' terminus and differed in size of the 5' region (Fig. 3). In transfected nonlymphoid HEK293 cells, the promoter activity of the 1U region was substantially higher than that of the 1L region. Interestingly, the region 5' of the 1U promoter proved to contain a silencer, which was not suppressed by the enhancer. It should be noted that the SV40 enhancer slightly increased the 1U promoter activity in nonlymphoid cells. Other results were obtained in lymphoid Raji cells transfected with the same constructs. In this case, the 1L promoter activity increased several times



(b) Luciferase activity

	HEK293		Raji	
	enh$^-$	enh$^+$	enh$^-$	enh$^+$
U1	++	++	+	+++
U2	++	++	+	+++
U3	++++	++++	+++	+++
L1	+	+	+	++
L2	+	+	+	++++
L3	+	+	+	+++

Fig. 3. Transcriptional regulation of human *oct-1* with two promoters. (a) Reporter constructs contained the luciferase (*luc*) gene under the control of various fragments flanking exon 1U or 1L in the 5' region of human *oct-1*. Positions of the octamers are shown with asterisks. (b) The reporter constructs were cloned in a vector with (enh+) or without (enh–) the SV40 enhancer, the products used to transfect HEK293 and Raji cells, and cell lysates tested for relative luciferase activity.

in the presence of the enhancer, and was appreciably higher than that of the 1U promoter (Fig. 3). Maximal activity was observed for the 1L region containing the proximal octamer. A silencer containing the other, distal octamer was upstream of the promoter. The enhancer only partly suppressed the 1L silencer and completely inhibited the 1U silencer in Raji cells. These findings indicate that *oct-1* transcription is directed by two promoters, which are each preceded by a silencer. Transcription from the 1L promoter is tissue-specific and depends on an external enhancer [40].

Alternative splicing yields many mRNA subforms in eukaryotes. This is characteristic of many genes located on different chromosomes. Mean number of different mRNAs corresponding to one gene is 2.6 for human chromosome 22 and 3.2 for human chromosome 19 [42]. Like other proteins, transcription factors may occur in several isoforms, which result from alternative mRNA splicing and differ not only structurally, but also functionally. The interaction of these related proteins with DNA depends on the context of their recognition sequence and on other nuclear proteins (coactivators and transcription factors). The isoforms of a protein act similarly or each have a unique function varying with tissue or developmental stage.

Likewise, Oct-1 has several isoforms: some are synthesized in all tissues and cell lines, while some others are tissue-specific (Fig. 2). We recently found the *oct-1d* and *oct-1e* mRNAs, which contain 5'-untranslated exons [18]. These are between exons 1U and 1L in mouse *oct-1*. As known for many genes, 5'-untranslated exons suppress translation when containing short open reading frames upstream of the major one or assuming a particular secondary structure to hinder translation initiation [43, 44]. Hence 5' exons 1i and 2i may be assumed to affect translation of the *oct-1* mRNA. A sequence homologous to exon 1i of mouse *oct-1* proved to be absent from the human genome, suggesting a difference in posttranscriptional regulation of *oct-1* expression.

The tissue-specific Oct-1 isoforms associated with early cell differentiation are of particular interest. These are produced in the bone-marrow population of immature B cells [45]. The *oct-1L* mRNA persists at a high level in cells of the spleen and lymph nodes. High content of this mRNA is also characteristic of myeloma NS/0 cells, which correspond to terminally differentiated B cells. In minor amounts, the *oct-1L* mRNA is synthesized in thymocytes and in T-cell lymphoma EL-4. The *oct-1R* subform was not detected in the thymus or in T cells [37, 45]. Produced in lymphoid cells of the B lineage, Oct-1L and Oct-1R may participate or even play an essential role in the immune response and in the regulation of immunoglobulin gene expression. The mechanisms regulating the tissue-specific expression of the immunoglobulin genes are still incompletely understood. It was long believed that Oct-2, which is synthesized predominantly in B cells and neurons, acts tissue-specifically to activate the promoters of the light and heavy immunoglobulin chain genes. However, recent studies showed that knockout in *oct-2* of somatic cells does not impair transcription of the immunoglobulin genes [46, 47]. According to a new model, Oct-1 participates in immunoglobulin gene expression along with Oct-2 [48, 49]. These transcription factors are only partly interchangeable, because synthesis of IgG1, IgG3, Ig2B, and soluble IgM is disturbed in *oct*-2$^{-/-}$ mice. B cells develop normally until the stage of membrane IgM synthesis even in the absence of both Oct-2 and OBF-1; transcription of the immunoglobulin genes is virtually unaffected in this case. These findings indicate that the role of Oct-1 in transcription regulation of the immunoglobulin genes is still far from completely understood, and implicate and additional, unidentified cofactor in their control [49]. With the exception of IgM, synthesis of all immunoglobulin isotypes involves class switching by site-specific recombination, which utilizes the ATTT switching elements located upstream of the heavy chain genes (all but those of IgA). Nuclear Oct-1, HoxC4, and heterodimer Ku70/Ku86 bind to these elements to suppress switching [50].

When this review had already been prepared, purification and functional characterization were reported for OCA-S, a multicomponent Oct-1 coactivator essential for transcription of the histone H2B gene in the S phase of the cell cycle [51]. Purified OCA-S (300 kDa) proved to consist of seven protein subunits, including five identical to known enzymes. Thus one subunit was undistinguishable from glyceraldehyde-3-phosphate dehydrogenase. The interaction of this

enzyme with the POU domain of Oct-1 depends on the redox potential of the cell. *In vitro*, NAD^+ substantially increases the interaction, whereas NADH suppresses it. Possibly, the Oct-1–OCA-S system contributes to the association of the redox potential with histone gene expression and DNA replication. Yet OCA-S contains four other enzymes, the roles of which are still obscure. These may extend the effects of Oct-1 far beyond the currently known range. Interestingly, OCA-B (OBF-1), another Oct-1 coactivator, does not depend on the redox potential of the cell. On recent evidence, cell metabolism is tightly associated with gene expression regulation in the eukaryotic cell (see [52]). The association seems far more sophisticated as compared with the classical schemes advanced by Jacob and Monod many years ago.

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