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Organization and expression of the developmentally regulated H1° histone gene in vertebrates

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ABSTRACT The H1 class of histones comprises several main-type, S-phase dependent isoforms and, in addition, a sperm-specific H1t and a peculiar subtype, H1°, which is confined to highly differentiated cells. In contrast to main type histone genes, the H1° gene expression does not strictly depend on DNA replication. Also in contrast to the other H1 subtype genes, the mammalian H1° gene is not included in a histone gene cluster and its mRNA differs in structure, size and mode of processing from other histone mRNAs. The regulation of expression of the H1° gene varies from main type H1 genes in several respects. This is manifested in the promoter structure which contains sequence elements that are also found in main type H1 promoters, but also shows regulatory motifs which appear to be involved in a developmental regulation of the H1° gene, such as a retinoic acid receptor binding site, which has been described in the mammalian H1° gene promoter.

KEY WORDS: *chromatin, histones, transcription, promoter, differentiation*

Introduction

The H1 class of histone proteins exerts its functions at several levels of chromatin organization (van Holde, 1989). H1 proteins interact with the DNA which links the core particles of the chromatin subunits, the nucleosomes. These core particles consist of two sets of the four histone classes H2A, H2B, H3 and H4, and this protein octamer interacts with 146 base pairs of DNA. Binding of H1 at the entry/exit site of the nucleosomal core DNA seals two rounds of DNA at the histone octamer surface and thus forms an intermediate particle, the chromatosome (Simpson, 1978). The remaining linker DNA, which connects these particles to the next chromatosome, completes the repeated chromatin subunit structure, i.e. the nucleosome. Sealing two rounds of DNA at the core particle surface and linking chromatin subunits are not the only functions of H1 histones. They are an absolute prerequisite for the formation of the next level of chromatin organization in forming the 30 nm fiber of supranucleosomal chromatin (Thoma *et al.*, 1979).

Nuclear functions such as DNA replication, transcription and repair are exerted at the chromatin level. Thus, the local chromatin organization contributes to the regulation of genetic activity, H1 histones participate in transcriptional control (Schlissel and Brown, 1984; Wolffe, 1989; Croston *et al.*, 1991; Paranjape *et al.*, 1994) and may influence the accessibility of the chromosomal DNA at gene control regions. The existence of several non-allelic variants of H1 histones may thus provide a means to modulate the contributions of H1 histones to supranucleosomal chromatin structures and to local gene control.

The mammalian H1 histone complement comprises five main type H1 histones plus the spermatogenesis specific H1t and the H1° subtype. This latter H1 isoform was discovered by Panyim and Chalkley (1969a,b) as a new histone confined to non-proliferating mammalian cells. Zlatanova (1980) has shown that synthesis of H1° is not inhibited upon blocking DNA replication by treatment with hydroxyurea. Later it was shown that H1° synthesis can be induced in several tumor cells using inhibitors of DNA replication (Hall *et al.*, 1985; Hall and Cole, 1986).

Gjerset *et al.* (1982) have demonstrated that the synthesis of H1° in rodents is developmentally and hormonally controlled. In the meantime, this has been demonstrated in several cell types. Since H1° replaces main type H1 histones upon chromatin remodeling, it is frequently referred to as a *replacement histone variant* (Smith *et al.*, 1984). This review attempts to describe the different experimental approaches and systems, which have been used to describe the control mechanisms which may regulate the expression of this class of histone genes. Emphasis will be put on mammalian systems, but data about amphibian or avian H1° homologs will be included.

The replacement H1 histone class of proteins

H1° histones have been described in several mammalian species (Panyim and Chalkley, 1969a,b). Emphasis has been put mostly on H1° analysis in mouse, rat and man. Non-mammalian homologs of H1° are the amphibian H1° (Rutledge *et al.*, 1981; Risley and Eckhardt, 1981; Shimada *et al.*, 1981; Moorman and de Boer, 1985) and the avian subtype H5 (Appels

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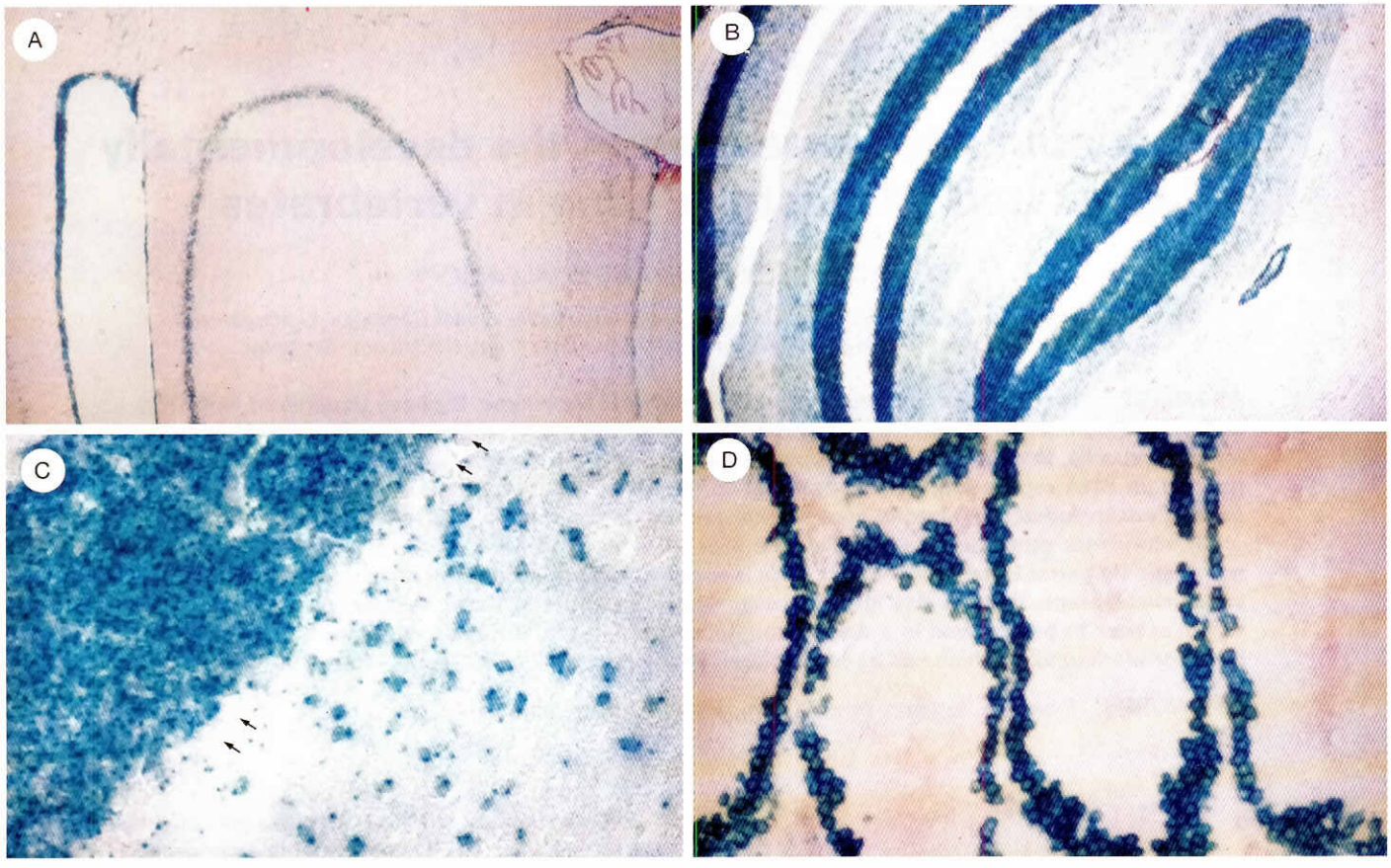

Fig. 1. Expression of a transgene carrying the histone H1° regulatory region, ligated to the ß-galactosidase reporter gene. *Expression in hippocampus* **(A)** *and cerebellum* **(B)** *showing a strong expression in the granular layer but no expression in the molecular layer or in the Purkinje cells (arrows,* **C***).* **(D)** *Expression of the transgene in spermatogonia, but not in spermatids or in Leydig cells (magnification: 250x in A,B,D; 400x in C). Taken from García-Iglesias et al., 1993). Reproduced with the kind permission of Springer-Verlag.*

and Wells, 1972). H5 is confined to the nuclei of avian erythrocytes. It replaces main type H1 histones during erythropoiesis.

The class of replacement H1 histones varies structurally from main type H1 histones. They are generally shorter and comprise around 190 amino acid residues versus main type H1 species, which are generally longer than 210 amino acids. Like main type H1, the replacement variants consist of three domains, but just parts of the central domain are conserved in comparison with the other H1 species. All H1 proteins are highly enriched in lysine residues (hence their initial definition as *lysine rich histones*). H5, which is structurally very similar to mammalian H1°, differs from this replacement H1 species just in its high content of arginine, which replaces a high proportion of the lysine residues found in the C-terminal domain of H1° (Doenecke and Tönjes, 1984, 1986).

The similarity between the primary structures of different members of the H1 replacement histone protein family is manifested in their immunological cross-reactivity (for review, see Zlatanova, 1990). An antibody which was raised against the central domain of chicken H5 reacted with mammalian H1°, but not with main type H1 (Allan *et al.*, 1982). Using this antibody, Smith *et al.* (1984) showed reactivity with H1° from various tissues of mouse, hamster, rat, calf, pig and rabbit. Neary *et al.* (1985) demonstrated that the serological homologies between H1° and H5 are not restricted to the central globular region, but include the C-terminal domain.

The structure of the globular region of chicken H5 has recently been studied by X-ray crystallography (Ramakrishnan *et al.*, 1993). This analysis revealed a striking similarity with the DNA binding motif of the HNF-3/fork head transcription factor (Clark *et al.*, 1993). This result implies that DNA binding of H5 and of these transcription factors follow the same principle. This similarity may be functionally significant, since both transcription factors and histones of the H5/H1° family may be involved in a remodeling of chromatin upon regulating gene activity.

The structural homology between H5 and H1° was the basis for the first isolation of a mammalian H1° gene. Using a duck H5 gene (Doenecke and Tönjes, 1984) as a hybridization probe, the human H1° gene was isolated from a genomic library (Doenecke and Tönjes, 1986; Kress *et al.*, 1986) and allowed the subsequent isolation of the mouse H1° cDNA from a library which had been prepared with RNA from a retinoic acid treated murine F9 teratocarcinoma cell line (Alonso *et al.*, 1988).

The genes encoding H1° and H5 histone proteins

Genes or cDNAs encoding H1 replacement proteins and the respective promoter structures have been described in man

(Doenecke and Tönjes, 1986), mouse (Alonso *et al.*, 1988; Breuer *et al.*, 1989; Cheng and Skoultchi, 1989), rat (Castiglia *et al.*, 1993; Girardot *et al.*, 1994), *Xenopus laevis* (Rutledge *et al.*, 1988; Khochbin and Wolffe, 1993), chicken (Krieg *et al.*, 1983; Ruiz-Carrillo *et al.*, 1983) and duck (Doenecke and Tönjes, 1984). Just one copy of an H1° gene was found in the human and murine genomes, respectively (Alonso *et al.*, 1988; Doenecke *et al.*, unpublished), whereas two different H1° subtype cDNAs were found in a *X. laevis* cDNA library (Rutledge *et al.*, 1988).

The chromosomal localization of the H1 histone complement was studied in detail in the human genome. Albig *et al.* (1993) demonstrated that all H1 genes except the H1° gene are located on the short arm of chromosome 6. In contrast, the human H1° gene maps to the long arm of chromosome 22. Interestingly, a corresponding chromosomal site was determined by Brannan *et al.* (1992) for the murine H1° gene in the context of establishing an interspecific linkage map of mouse chromosome 15, which is in part syntenic with the human chromosome 22. In both cases, no other histone genes map to these chromosomes. We thus may conclude that the separation of H1° and other H1 histone genes, which are organized in clusters together with core histone genes, took place before the evolutionary separation leading to these rodent and primate species.

H1° and H5 mRNAs vary from main type H1 histone mRNA

S-phase dependent histone gene transcription results in mRNA molecules which are non polyadenylated and all show a terminal stem-and-loop element, which is a prerequisite for a proper processing of the primary transcript (Birnstiel *et al.*, 1985; Schümperli, 1988; Liu *et al.*, 1989). Both the H1° and H5 mRNAs differ from this organization. The H1° mRNA (Kress *et al.*, 1986, Alonso *et al.*, 1988; Cheng and Skoultchi, 1989) and the H5 mRNA (Molgaard *et al.*, 1980; Krieg *et al.*, 1983; Doenecke and Tönjes, 1984) are polyadenylated, but only the H1° mRNA has the polyadenylation signal AAUAAA near its 3' prime end (Kress *et al.*, 1986). The H5 mRNA shows two dyad symmetry elements, which are highly conserved in duck and chicken H5 species (Krieg *et al.*, 1983; Doenecke and Tönjes, 1984). Another difference compared with main type histone mRNAs is the exceeding length of the H1° mRNA, which is 2.3 kb in human and 2.1 kb in mouse H1° mRNA. This is mainly due to a very long 3' non-coding region (1.3 kb in human H1°, Kress *et al.*, 1986), whereas the coding region spans less than 0.6 kb.

In contrast to the human H1° mRNA, the murine mRNA occurs in two lengths of 2.1 and 1.8 kb (Alonso *et al.*, 1988).The functional meaning of this occurrence of two mRNA types is still unknown, but Brocard *et al.* (1994) could recently show that these two mRNA species are derived from the same gene and are produced by alternative 3' end processing and polyadenylation.

Patterns of H1° gene expression in adult and developing tissues

H1° was initially described as a typical chromatin constituent of non-proliferating, terminally differentiated cells (Panyim and Chalkley, 1969a,b). In a survey of several calf, rat and mouse tissues, proliferating cells such as thymus showed no H1°, but H1° was extractable from tissues with little cell division such as endometrium, liver, kidney or lung. Similarly, Gabrielli *et al.* (1985) have demonstrated the contribution of H1° to the chromatin of human lung and liver.

The pattern of main type H1 subtypes and H1° in adult tissues is the result of developmental processes. This has been particularly studied during the brain development of rat (Pina *et al.*, 1984, 1987; Stambolova *et al.*, 1984; Pina and Suau, 1987; Dominguez *et al.*, 1992) and mouse (Gjerset *et al.*, 1982; Perkins and Young, 1987) indicating that the accumulation of H1° differs in glial and neuronal cells and that the general H1 pattern changes during postnatal development. Pina *et al.* (1987) have shown that the period of H1° accumulation coincides with the stage of terminal brain cortex differentiation, while changing patterns of H1a-e start at birth.

A totally different approach towards establishing tissue-specific patterns of H1° gene expression was taken by Garcia-Iglesias *et al.* (1993). In their study, the H1° promoter region (see below) was ligated to the ß-galactosidase region and the expression of the indicator gene was monitored in transgenic mice (Fig. 1). It was found in brain (hippocampus, cerebellum), in kidney (convoluted tubules, glomeruli) and in testis, where spermatogonia were the only germ cells which expressed the ß-galactosidase gene. Liver cells were only weakly stained, but in that

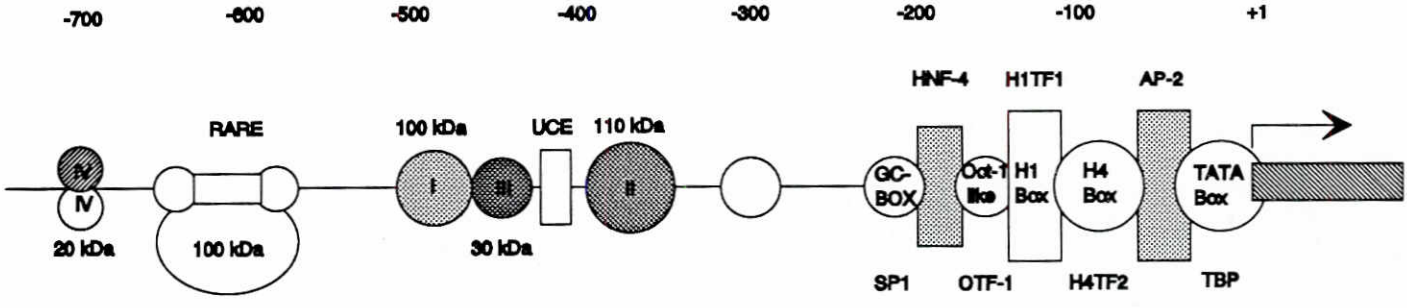

Fig. 2. Schematic representation of potential recognition sites for factors binding to the proximal 800 bp of the mouse H1° promoter. *RARE: retinoic acid responsive element. Shaded areas represent sequence elements of unknown function where protein binding (approximate molecular mass in kDa) has been observed in vitro. Other sequence motifs (TATA box, AP-2 binding site, H4 box, H1 box, Oct-like element, GC-rich element) represent regulatory sequence elements which have also been observed in other promoters. The UCE element is a sequence which has been observed in the murine, human and amphibian H1° promoters. Numbers above the factors indicate the approximate distance (in bp) upstream of the transcription start point (+1).*

approach it should be kept in mind that the promoter fragment used may depend in some tissues on upstream sequence elements which were not part of the promoter used for these constructs.

The contribution of H1° to the H1 complement of mammalian liver cells is around 20%. This level is reached gradually, beginning with very low levels soon after birth (LaRue *et al.*, 1983). Liver regeneration after partial hepatectomy is a model system which illustrates this relation between the proliferation rate of a cell and its H1° content, since it has been demonstrated that the level of H1° decreases after hepatectomy and increases again when regeneration comes to an end (Gjerset *et al.*, 1982; Fedoseeva *et al.*, 1983). Khochbin *et al.* (1991) have studied the H1° mRNA and protein concentrations after partial hepatectomy of the rat. Interestingly, it turned out that H1° mRNA was synthesized immediately after hepatectomy at the same rate as H3 histone mRNA (as an indicator of DNA replication). This indicated that the accumulation of H1° mRNA and protein was uncoupled under these conditions. Further examples for this uncoupling were discovered in tumor cell line systems (Rousseau *et al.*, 1991, 1992).

In vivo patterns of H1° expression during development were studied in *Xenopus laevis* by immunocytochemical methods. After establishing H1° patterns in various tissues of *Xenopus laevis* (Moorman *et al.*, 1984, 1986; Moorman and de Boer, 1985), Moorman *et al.* (1987) demonstrated a differential H1° gene expression in time and position during specific stages of development. It turned out that the distribution of H1° protein changed during tadpole development and differed in the derivatives of each embryonic germ layer. Thus, changes in the pattern of H1 histones apparently parallel these developmental processes and may provide a basis for an analysis of the role of varied H1 subtypes in gene regulation.

Induction of H1° in tumor cell lines

A very broad spectrum of murine, human and other cell lines has been used for the analysis of the regulation of expression of the H1° gene (for reviews, see Doenecke *et al.*, 1994; Zlatanova and Doenecke, 1994). Of particular interest in the context of this review is the fact that several cell lines can be induced towards a more differentiated phenotype. Studies on the induction of Friend virus transformed murine erythroleukemia cells towards erythroid differentiation led to the isolation of an apparently new H1 subtype termed IP_{25} (Keppel *et al.*, 1977), which later turned out to be H1°. This induction was also observed by Candido *et al.* (1978), who detected IP_{25} in several vertebrate tumor cell lines after addition of sodium butyrate. Similarly, D'Anna *et al.* (1980) described a novel H1 protein after addition of sodium butyrate to Chinese hamster ovary (CHO) cells and termed this protein BEP (butyrate enhanced protein), which again turned out to be H1°.

Discussing the inducibility of H1° in tumor cell lines, these may be classified into three categories. First, cell lines exist, which don't have any H1° protein and cannot be induced to synthesize either H1° mRNA or protein. The promyelocytic leukemia cell line HL60 is an example for this type of cells (Hochhuth and Doenecke, 1992). This line can be induced towards granulocyte or macrophage development (Koeffler, 1983), but no H1° can be induced. The second type of cells is represented by the human hepatoma cell line HepG2, which constitutively expresses the H1° mRNA and protein at a high level, and its synthesis is independent of the rate of cell proliferation (Hochhuth and Doenecke, 1990). The third group comprises such cell lines which express the H1° gene at a low level and can be induced towards an accumulation of H1° mRNA and protein. This group may be subdivided in a group of cells which cannot be induced towards differentiation, but accumulate H1° during growth arrest, and a second kind of cell lines which can be induced towards differentiation and thereby show a decreased rate of proliferation and increased levels of H1° mRNA and protein. Examples for the first group are HeLa cells which can be induced by sodium butyrate to synthesize H1° mRNA (Kress *et al.*, 1986; Hall *et al.*, 1985); examples for the second group are murine erythroleukemia cells which can be induced towards a more differentiated phenotype and H1° synthesis with dimethyl sulfoxide or butyrate (Keppel *et al.*, 1977) or hexamethylene bisacetamide (Chen *et al.*, 1982; Rousseau *et al.*, 1991). Butyrate as an inducer of H1° has also been used in murine B16 melanoma cells (Chabanas *et al.*, 1985, Rousseau *et al.*, 1992) and in amphibian A6 cells (Khochbin and Wolffe, 1993). This will be discussed below in the context of gene regulation and promoter function.

Hormonal control of H1° gene expression has been demonstrated by Gjerset et al. (1982) in mouse and rat tissues that depend on hormonal stimuli for maintenance and activity. A suitable model for hormonal effects controlling cell differentiation is the murine teratocarcinoma cell line F9, which can be induced by retinoic acid to parietal endoderm (Strickland *et al.*, 1980; Hogan *et al.*, 1983). We have shown that this step of differentiation is accompanied by an induction of H1° gene expression (Alonso *et al.*, 1988). This allowed us to isolate the murine H1° cDNA from a library constructed with RNA from retinoic acid-induced F9 cells and was the basis for a detailed analysis of the murine H1° gene regulation.

H1° promoter structure and gene regulation

The promoters of H1° genes have been analyzed in detail in three species, i.e. the murine (Breuer *et al.*, 1989, 1993; Mader *et al.*, 1984), human (Bouterfa *et al.*, 1993) and amphibian (Khochbin and Lawrence, 1994; Girardot *et al.*, 1994) H1° promoter functions were analyzed in the respective cell systems.

About 1800 nucleotides upstream of the ATG initiation codon of the human H1° gene were sequenced and the proximal 600 nucleotides were compared with the murine and amphibian promoter sequences (Bouterfa *et al.*, 1993). Several sequence motifs were conserved in all three promoter species (Fig. 2). A TATA box was found in all three promoters about 25 nucleotides upstream of the transcription start site. It is followed further upstream (in that order) by a AP2 consensus site (Imagawa *et al.*, 1987) and a sequence motif, which has been found before as a conserved region in H4 histone gene promoters (Dailey *et al.*, 1988). This H4TF2 binding site is located between -60 and -47 relative to the transcription start site. A GC-rich element is found around positions -100 and again around -160. In the region between -130 and -110 a highly conserved element includes the heptanucleotide AAACACA, which previously has been found in all H1 gene promoters except the H5 gene promoter. The exis-

tence of this H1 box (Coles and Wells, 1985; Dalton and Wells, 1988; LaBella *et al.,* 1989) within the H1° promoter initially was unexpected since factors binding to this element are involved in the S-phase regulation of H1 histone genes, whereas H1° gene expression was considered as S phase-independent (Dalton and Wells, 1988). In the meantime, however, evidence accumulated that H1° mRNA in Friend cells accumulates during the S phase (Grunwald *et al.,* 1991) and that the H1° gene transcription during liver regeneration occurs at the same rate as the synthesis of replication dependent histone mRNA (Khochbin *et al.,* 1991). In addition to the highly conserved sequence elements, variations of established motifs may be identified, such as a heptanucleotide ATTTGCT which resembles the Oct-1-binding motif ATTTGCAT (Fletcher *et al.,* 1987) and a nonanucleotide GGAAAGGTC which is similar to the GGCAAGGTT motif in the HNF-4 binding site (Sladek *et al.,* 1990).

The murine and human H1° promoters both contain a conserved element around position -530 relative to the cap site. This element has the characteristics of a retinoic acid receptor binding site with a tandem repeat of the sequence PuGGTCA, separated by eight base pairs. In addition to this hormone binding site which is found in the human and murine H1° promoters (not in *Xenopus*), the human H1° promoter has a second potential receptor binding element of this type at about -1500 which is not tandemly, but invertedly repeated and may be a thyroid hormone response element (Bouterfa *et al.,* 1993).

Functional studies with the human H1° promoter have concentrated on the differential regulation of the H1° gene in different human tumor cells. The results of assays with reporter gene constructs, footprint methods and electrophoretic mobility shifts indicated that the usage of individual promoter portions varied, when different tumor cells and cell extracts (HeLa, HepG2, HL-60) were analyzed (Bouterfa *et al.,* 1993).

A 1300 base pair fragment of the murine H1° promoter seems to contain all signals needed for a differentiation-specific transcription of the gene. When this 1300 base pair promoter fragment was cloned in front of the β-galactosidase coding region and the resultant recombinants were transfected into mouse ES cells, it was possible to demonstrate a specific transcription of the gene in the endodermal layer after differentiating the ES cells to embryoid bodies (Alonso *et al.,* 1991). This transcription seems to be specific, since injection of the same recombinants into *Xenopus laevis* oocytes and analysis of the transcripts in developing embryos shows a rather unspecific transcription pattern suggesting that *Xenopus* does not contain factors needed for a tissue-specific transcription of the H1° histone (Steinbeisser *et al.,* 1989).

Recently, Girardot *et al.* (1994) have cloned the rat H1° promoter using PCR techniques. This promoter was tested in experiments dealing with the correlation between core histone hyperacetylation and H1° induction, since both effects are inducible by sodium butyrate (Candido *et al.,* 1978). Using an inhibitor of histone hyperacetylation (Trichostatin A), the authors demonstrated that hyperacetylation has a dominant effect on the expression of the H1° gene, which is stimulated with no direct correlation to a specific stage of the cell cycle (Girardot *et al.,* 1994).

As mentioned above, the mammalian H1° promoters share several sequence elements with the *Xenopus laevis* H1° promoter. This amphibian promoter has been cloned and functionally analyzed by Khochbin and Wolffe (1993). It contains the same TATA-, H4TF2-, GC rich- and H1 box-elements as the mammalian promoters. In addition, a sequence element at about -450 was identified as highly conserved compared with the human and murine promoters. The authors studied the butyrate mediated enhancement of H1° gene transcription in transfection experiments with *Xenopus* A6 cells and by *in vitro* transcription assays with extracts from these cells. It turned out that the H1 box- and H4TF2 elements are involved in the differentiation specific H1° histone gene expression in cooperation with the aforementioned upstream conserved element around position -450 relative to the cap site. This was further investigated in a reconstituted *in vitro* transcription system in the presence of H1 histones (Khochbin and Lawrence, 1994), and it was concluded that the upstream conserved element cooperates with the proximal sequence motifs in maintaining the basal histone H1° gene expression.

Conclusions

The contribution of H1 histones to the formation of higher order structures and to the control of transcription in addition to the multiplicity of H1 isoforms suggest that variations in patterns of H1 histones modulate chromatin organization and local transcriptional activity. H1° *in vivo* is confined to highly differentiated cells in several cell systems, but its changing pattern during amphibian development and its dependence on hormonal stimuli suggest that H1° also plays a role within the chromatin structure of developing cells and tissues. *In vivo* models of development, cell culture systems which allow to study defined steps of cell differentiation, the detailed analysis of the mammalian and amphibian promoters and the analysis of chromatin structures at the sites of H1° binding should help to understand the role of H1° in development and differentiation.

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