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Review

Epigenetic regulation of the gene encoding steroidogenic factor-1

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ABSTRACT

The nuclear receptor steroidogenic factor 1 (SF-1) is expressed in a precise time and cell-specific pattern in the endocrine system. Three intronic enhancers and one upstream enhancer, which are required for controlling the restricted expression of SF-1, have been identified in the mouse gene encoding SF-1. In recent years, efforts from several laboratories have established that expression of SF-1 is controlled by DNA methylation. CpG-sites are found in the basal promoter as well as in the intronic enhancers, and the methylation status of these genomic regions nearly perfectly correlates with their transcriptional activity such that they are hypomethylated in tissues where they are active, and generally hypermethylated in tissues where they are not active. This review summarizes the present knowledge of how tissue differentially methylated regions control the transcriptional activity of the SF-1 gene, and how irregularities in the methylation pattern can contribute to disease development.

Contents

1. Introduction

The nuclear receptor steroidogenic factor 1 (SF-1/Ad4BP/NR5A1) is essential for endocrine development and function. The fundamental roles for SF-1 in the endocrine system are evident from studies on mouse models, as well as examinations of humans carrying mutations in *SF-1*. Mice with targeted disruption of *sf-1* lack adrenals and gonads, exhibit abnormalities in the ventromedial hypothalamic nucleus (VMH) and are also deficient of gonadotrope markers in the anterior pituitary (Parker et al., 2002). In humans, mutations in *SF-1* lead to a range of phenotypes linked to sexual development and reproduction, and in some cases adrenal insufficiency (Ferraz-de-Souza et al., 2010). During embryonic development, SF-1 expression is tightly controlled temporally and spatially, and in the adult, expression of SF-1 is restricted to the adrenal cortex, ovary, Leydig and Sertoli cells in the testis, gonadotropes in the pituitary and the VMH (Hoivik et al., 2010). Dr. Morohashi and his collaborators have identified one intergenic and three intragenic (intronic) enhancers that are essential for tissue and stage specific expression of SF-1 in mice (Fig. 1B). These tissue specific enhancers, which work together with basal promoters, direct expression of SF-1 to fetal Leydig cells (Fetal Leydig cell Enhancer, FLE; intergenic) (Shima et al., 2012), the fetal adrenal (Fetal Adrenal Enhancer, FAdE)(Zubair et al., 2006), the developing pituitary and adult gonadotropes (Pituitary Gonadotrope Enhancer, PGE)

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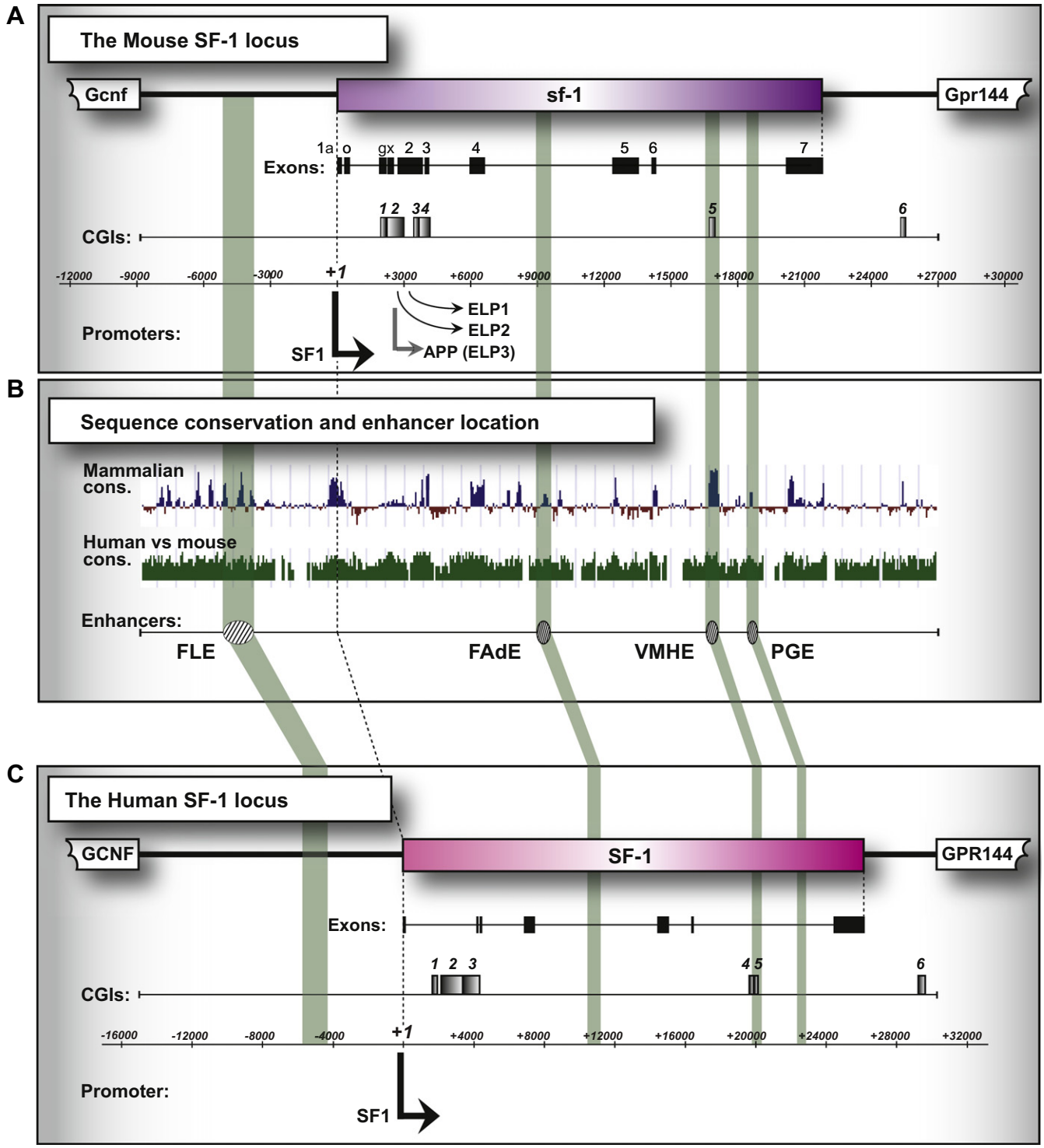

Fig. 1. Overview of the SF-1 loci in mouse and human. A and C: The mouse SF-1 (*sf-1*) and human SF-1 (*SF-1*) genes consists of 7 exons (indicated by black boxes) and are located on chromosomes 2 and 9, respectively. In both species, the SF-1 locus is flanked by the genes encoding Gcnf and Gpr144. (A) In *sf-1*, alternative promoters (indicated by arrows) give rise to SF1 and ELP1–3. Exons 1a, 1o, and 1g are non-coding. Transcripts containing Exon1 1o have not been detected (Ninomiya et al., 1995). Exon 1g containing transcripts have been identified in mice, but not in humans. With settings according to (Gardiner-Garden and Frommer, 1987), the *sf-1* locus contains six CGIs (indicated by grey boxes; CGI 1-6). Five CGIs (CGI 1-5) reside with in the coding region, and CGI 6 is located 3' of the coding region. CGIs 1–4 are clustered in the region around exons 1–3 [i.e. CGI 1;+1930/+2179, CGI 2;+2215/+3009, CGI 3;+3411/+3639 and CGI 4;+3647/+4155 relative to TSS (+1)], and CGI 5 overlaps with the VMHE (i.e. at +16751/+17013) (Hoivik et al., 2011). CGI 6 is located at +25241/+25455. (Chr 2; 38692660–38714542, mm10). (B) Sequence conservation between mammalian species (placental mammals as defined by Genome Browser (http://genome.ucsc.edu/); top conservation alignment) and mouse (mm10) and human sequences (h19) (lower conservation alignment). The positions of the enhancers are indicated in the bottom panel and by green bars across A–C. Note the conservation the tissue-specific enhancers in the conservation alignments within the enhancers, and the conserved CGI within VMHE in both species (A–C). (C) The *SF-1* locus contains six CGIs (indicated by grey boxes). Five CGIs reside wihtin the coding region (CGI 1–5) and one CGI (CGI 6) is located to the region between SF-1 and GPR144. CGIs 1–3 are clustered in the region around the first three exons [i.e. CGI 1;+1451/+1732, CGI 2;+1962/+3184, CGI 3; and +3199/+4136 relative to TSS (+1)], and CGI 4;+19444/+19697. As in the mouse gene, CGI 5 overlaps with the VMHE (at +19932/+19707). The position of CGI 6 is +29019/+29402. While mCGI 1 and hCGI 4 are not conserved between the species (threshold set to identity of 70% or higher), CGI 2, 5 and 6 are conserved, and also mCGI 3 and mCGI 4 are conserved within hCGI 3 (match identity of 79–92% over at least 100 bp region, zPicture aligment (not shown). (Chr9; 127243515–127269699, h19).