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Identification of a Core Motif That Is Recognized by Three Members of the HMG Class of Transcriptional Regulators: IRE-ABP, SRY, and TCF-1α

M. Alexander-Bridges, Louis Ercolani, X.F. Kong, and Nargis Nasrin

Howard Hughes Medical Institute, Diabetes Unit and Medical Services, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114

Abstract Insulin induces glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene transcription in part by regulating one or more proteins that bind a cis-acting element, IRE-A. We have recently cloned a protein, IRE-ABP, that binds the IRE-A element. IRE-ABP is a member of the HMG class of transcriptional regulators and is 67% identical within its HMG box domain to the candidate gene for the testis-determining factor, SRY. IRE-ABP and SRY share binding specificity for the IRE-A motif. This sequence is also highly conserved with a core motif, 5′-Py-cttttg(a/t)-3′, contained in T-cell specific genes that have high affinity for TCF-1α, another member of the HMG class of transcriptional regulators. Thus, diverse members of the HMG family interact with similar nucleotide sequences to regulate expression of genes that initiate and maintain the differentiated phenotype. We have found this core motif in the upstream region of many genes that are positively and negatively regulated by insulin. These observations suggest that IRE-ABP or a related family member may coordinate the expression of these genes. The HMG family of proteins has diverse functions ranging from the regulation of differentiation and mating type in yeast to the regulation of tissue- and species-specific gene expression in mammals. Insulin regulates GAPDH gene transcription in a tissue-specific manner. We propose that members of the IRE-ABP family play an important role in controlling tissue specificity of the insulin response.

Key words: insulin, gene transcription, GAPDH, hormone regulation, differentiation-dependent gene expression

MODELS OF INSULIN-REGULATED GENE TRANSCRIPTION

Insulin initiates diverse alterations in cell metabolism and growth. Many enzymes that mediate insulin's effect on glucose utilization and storage in lipogenic tissues are regulated coordinately. Insulin stimulates the expression of genes that modulate glucose uptake, utilization, and storage and simultaneously inhibits the expression of gluconeogenic enzymes and hormones that catalyze the breakdown of energy stores. The molecular mechanism by which these affects are achieved is unknown.

As a model system for study of insulin's inductive effect on transcription of metabolic genes, we use the gene that encodes a glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH). In lipogenic tissues this gene is markedly stimulated by insulin. Insulin increases GAPDH mRNA ten-fold in cultured 3T3-L1 adipocytes [Alexander et al., 1985, 1988]. Similar increases in GAPDH mRNA occur in the fat and liver of rats fasted and refed a high-carbohydrate, low-fat diet, a manipulation that boosts insulin secretion [Nasrin et al., 1990]. These effects are also seen in the fat of diabetic rats treated with insulin [Alexander et al., 1990]. These responses are not seen in preadipocytes [Alexander et al., 1985] or muscle. This pattern of tissue specific regulation has also been observed with insulin-sensitive glucose transporters [Kahn et al., 1989, 1991]. These observations imply that tissue-specific hormonal regulation of GAPDH gene expression requires differentiation-dependent expression of distal components in the pathway of insulin signal transduction that are missing in preadipocytes and muscle.

We have previously shown in 3T3 adipocytes and H35 hepatoma cells that insulin stimulates transcription of the GAPDH gene through two upstream cis-acting elements located between −488 and −269 [Nasrin et al., 1990]. An insulin response element, the IRE-A, located between nucleotides −480 and −435, specifically inter-

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acts with an insulin-induced DNA binding protein [Nasrin et al., 1990]. The activity of this binding protein increases by four-fold in differentiated 3T3 adipocytes treated with insulin for 1 h. Furthermore, binding activity is induced with differentiation of 3T3 adipocytes [Alexander et al., 1990] and in the liver of refed rats, an important in vivo correlate to our tissue culture models [Nasrin et al., 1990]. These observations support the hypothesis that this nuclear binding protein is an essential component in transduction of the insulin signal in metabolically active tissues.

Other systems in which insulin regulates gene transcription by means of cis-acting sequences have been defined. Like GAPDH [Alexander et al., 1990], amylase gene expression declines dramatically in streptozotocin-treated rats and is restored by insulin treatment of diabetic rats [Osborn et al., 1987]. At least one sequence that mediates the induction of amylase by insulin, the insulin-dependent element (IDE), has been localized to nucleotides −167 to −138 [Keller et al., 1990]. There are several areas of homology between the upstream region of the amylase gene and the domain of IRE-A (−480 to −435) that makes contact with protein, CTTTCCCGCCTCTCAGCC. In particular, the 3′ region of the IRE-A, CTCTCAGCC, is similar to a sequence, CTCTCACGC, located within the amylase IDE.

Concurrent with its stimulation of enzymes that regulate glucose uptake and utilization, insulin inhibits the synthesis of hormones and enzymes involved in gluconeogenesis and lipolysis. For example, the counterregulatory effect of insulin on catabolic processes is mediated in part by inhibition of glucagon gene expression and secretion. Philippe et al. [1991] have mapped the sequences that mediate the negative effect of insulin on glucagon gene transcription to domain A, CACGCCTG, of an enhancer in the glucagon gene [Knepel et al., 1990]. The core sequence proposed in this work (G/C)GCCT(G/C) resembles the 5′ domain of the IRE-A, CCCGCCTC [Nasrin et al., 1990]. Numerous homologies have been noted between the 5′ most contact points of the IRE-A, CCCGCCTC, and other insulin-sensitive genes but the significance of these homologies is unclear.

The sequences that mediate the effect of insulin on negatively regulated genes such as growth hormone [Yamashita and Melmed, 1986; Prager et al., 1990], and phosphoenolpyruvate carboxykinase (GTP), PEPCK [Forest et al., 1990; Magnuson et al., 1987; O'Brien et al., 1990] have also been defined. Prager et al. have detected an insulin-stimulated DNA binding protein that binds a 26 nucleotide DNA motif in the growth hormone gene. The effect of insulin on expression of this protein depends on protein synthesis. Within the 26 nucleotide motif used to perform the binding assay lies a sequence, ATGGCCTGCGG, with 8/11 base identity to a repeated sequence in the amylase gene, ATGGCCTCAGA [Prager et al., 1990]. These repeats are located upstream of the amylase, IDE. Nevertheless, this motif is similar to the core motif (G/C)GCCT(G/C) found in glucagon and GAPDH, and may yet prove to be regulated when directly tested. An element that mediates a component of the inhibitory effect of insulin and phorbol esters on PEPCK has been defined. This element, referred to as the insulin-responsive sequence, IRS (TGGTGTTTTG) shares 6/10 base identity with the amylase IDE (GTTTATTTTG), but not with GAPDH, growth hormone, or the glucagon gene [O'Brien et al., 1991]. In toto, the fact that no consensus sequence for insulin action on gene transcription has evolved to date may indicate that distinct proteins mediate the effect of insulin on gene transcription. Nevertheless, the fact that homologies exist between genes that are subject to positive and negative regulation by insulin suggests that the effects of this hormone on certain genes may be mediated through similar sequences.

In this Prospect we propose that a sequence recognized by IRE-ABP that is present in genes subject to positive and negative regulation by insulin may play a role in mediating the tissue-specific effect of insulin on transcription of a diverse group of genes in lipogenic tissues.

THE IRE-A MOTIF HAS A 5′ AND 3′ DOMAIN

We have previously shown that the IRE-A motif has a minimal size of approximately 27 nucleotides, AACTTTCCCGCCTCTCAGCCTTTGAAAG [Nasrin et al., 1990]. In an effort to precisely define a motif for the IRE-A binding protein we mapped the contact points for the interaction of this protein with the IRE-A motif by use of the methylation interference assay. A large domain, CTTTCCCGCCTCTCAGCC, was contacted by this protein. Mutations within the footprinting domain inhibited the ability of syn-

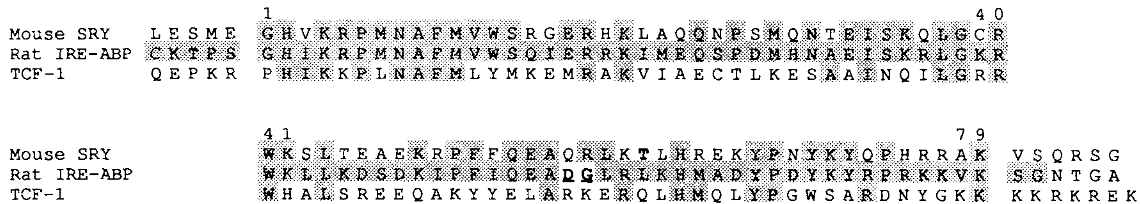

Fig. 1. Comparison of the HMG domains of mouse SRY [Gubbay, 1990], rat IRE-ABP, and TCF-1α [Waterman et al., 1991].

thetic oligonucleotides to compete on a gel shift assay.

CLONING A PROTEIN THAT BINDS THE 3′ DOMAIN OF IRE-A

The wild type IRE-A motif was used to isolate a clone from a rat adipocyte library using the Singh-Sharp Southwestern screening approach [Singh et al., 1988; Staudt et al., 1988]. The cloned cDNA encodes a protein that binds IRE-A DNA with sequence specificity that overlaps that of adipocyte IRP-A nuclear extract protein [Nasrin et al., 1991]. Studies are in progress to determine whether this protein mediates the effect of insulin alone or in association with another polypeptide.

The primary sequence of IRE-ABP contains a novel DNA binding motif referred to as an HMG box [Jantzen et al., 1990]. Jantzen et al. first described the cloning of hUBF, a sequence-specific DNA binding protein that contains four regions of homology to a family of nuclear proteins that associate non-specifically with chromatin called the high mobility group (HMG) proteins. This domain has subsequently been identified in several sequence-specific transcriptional regulators, including SRY, TCF-1, and TCF-1α.

Interestingly, the HMG box domain of IRE-ABP is 68% identical to the testis-determining factor, SRY [Gubbay et al., 1990; Sinclair et al., 1990]. Because of the similarity between the IRE-ABP and SRY in the HMG box region (see Fig. 1), we determined whether SRY binds the IRE-A motif. Interestingly, the HMG box domain of SRY and IRE-ABP protect the 3′ domain of the IRE-A motif (CTCTCAGCCTT-TGAAAG·······) from digestion by DNAse I. Thus, although we have observed that the affinity of SRY and the SRY-like genes for IRE-A DNA is reduced relative to IRE-ABP, we conclude that the SRY-like genes interact with a similar spectrum of sequences.

Of interest, the sequence in IRE-A that contacts the IRE-ABP protein and SRY is highly homologous to a sequence, 5′-Py-ctttg(a/t)-3′, previously proposed by Katherine Jones's laboratory as a consensus motif for T-cell specific genes [Waterman and Jones, 1990; Waterman et al., 1991]. These genes bind with high affinity to another HMG protein, TCF-1α. They include TCRα, TCRδ, CD4, HIV-1, and $p56^{lck}$. TCF-1, a unique T-cell specific factor that regulates expression of CD3ε binds a similar sequence [van de Wetering et al., 1991]. TCF-1α, also known as LEF-1 [Travis et al., 1991], activates transcription through the T-cell receptor Cα enhancer in a context dependent manner. R. Grosschedl's laboratory has shown that LEF-1 makes contact with the sequence CCTTTGAA in the TCRα gene [Travis et al., 1991]. Mutations in this domain eliminate binding and transcriptional activation by TCF-1α. The identical sequence is present in IRE-A and mutations in this motif impair binding of the adipocyte complex to DNA. Thus, the adipocyte nuclear extract protein requires this sequence as well. We conclude that diverse members of the HMG family of proteins modulate gene transcription through a spectrum of sequences that contain this core motif.

PROSPECTS

Identification of a core motif for the HMG family in an insulin-regulated element provides clues regarding the identity of important physiological targets of the IRE-ABP and the SRY-like family of transcriptional regulators and their roles in regulation of gene transcription. The observation that SRY and IRE-ABP are closely related raises the question whether these proteins carry out similar functions. Parallels may exist between their role in initiating differentiation of embryonic tissues and maintaining alterations in cell phenotype in specific tissues, their

GENE	ACCESSION #	YCTTTGWA	LOCATION	TWCAAAGR	LOCATION
GAPDH	J02678	CCTTTGAA	2930	TTGAAAGA	690
Glucokinase	M24943	CCTTTGTC	1345	AGCAAAGA	490
Aldolase B	X02283	ACTTTGAT	840	TACAAAGA	725
L-type pyruvate kinase	X05684	CCTTTGAT	2980	TACAAAGG	11730
Rat pyruvate kinase	M17088	CCTTTGAT	1210	TGCAAAGA	690
Glycerol-3 phosphate dehydrogenase	J02678	CCTTTGAA	2930	TACAAAGG	1110
Glycerophosphate dehydrogenase	M13366	CCTTTGAA	15	TACAAAGC	6620
Murine pancreatic amylase 2.2y	M15965	CCTTTGTC	490	TACAAATT	240
Albumin gene	M11844	CCTTTGCA	2560	TACAAAGG	1070
Serum albumin	M12523	TCTTTGAA	7090	TACAAAGA	1660
Glutamine synthetase	J03820	TGTTTGAA	290	GACAAAGG	675
Adipocyte serine protease	M13386	GATTTGAA	730	GACAAAGA	1650
Adipocyte P2 gene (mouse)	M13261	CCTTTGTG	310	TACAAAAT	300
Adipocyte lipid binding protein	M13385	GCTTTGAA	1450	AACAAAGA	80
Adenine phosphoribosyltransferase	M11310	CCTTTGAT	80	CACAAAGC	1480
G protein αi_2 subunit	M57287	ACTTTGAC	770	TACAAATA	845
C-sis proto-oncogene	Y00326	GCTTTGAA	1460	TACAAAAA	2840
Cytoplasmic beta-actin	X00351	CCTTTGCC	285	CGCAAAGA	2700
Tissue plasminogen activator	K03021	TCTTTGAA	1990	TACAAAGA	3030
Prolactin gene	X00368	TGTTTGAA	800	TACAAAGA	7600
Human glucagon gene	X05385	CCTTTGAT	2995	ACCAAAGA	210
Human growth hormone	J00148	CCTTTGAC	740		
Phosphoenolpyruvate carboxykinase	Ref. 4	CCTTTGGC	745		
c-fos	K00650	CCTTTGAT	2995		
N-myc	M3241	ACTTTGAA	3495		

Fig. 2. Potential targets of the IRE-ABP. Genes that carry the core motif 5′-Py-ctttg(a/t)-3′ on either strand are shown. The accession number and approximate location of the motif are reported in Genbank format [Beale et al., 1985].

role in regulating metabolism and growth in adult tissues, and the mechanism(s) by which they are regulated by extracellular signals.

Identification of the Targets of the HMG Family of Proteins

For TCF-1α, many potential targets are known [Waterman and Jones, 1990; Waterman et al., 1991]. They include proteins involved in signal transduction, and tissue-specific functions. The observation that the core sequence recognized by this protein is also recognized by SRY and IRE-ABP makes it possible to predict the genes that mediate the effect of insulin by IRE-A and initiate differentiation by SRY. We have carried out extensive searches of Genbank and of personal files of insulin-sensitive genes and found that the core motif is present in the non-coding region of insulin-sensitive, nutritionally regulated, and growth factor responsive genes (Fig. 2). We have preliminary evidence that some of these sequences gel shift with our cloned IRE-ABP. Of interest, several glycolytic hormones that are coordinately regulated with GAPDH in 3T3 adipocytes such as aldolase and in liver such as glucokinase carry the sequence. The amylase gene, which is dramatically regulated with induction of diabetes, carries the core motif near its promoter. The sequence is also found in genes that are regulated in a negative direction by insulin. For example, the site identified in the PEPCK gene coincides with a previously described accessory factor AF1 [O'Brien et al., 1990]. This factor modulates the glucocorticoid response of PEPCK. It will be interesting to determine whether IRE-ABP plays a role in mediating the inhibitory effect of insulin on glucocorticoid-stimulated PEPCK gene expression through this site.

Defining the Role of the HMG Family in Differentiation and Tissue-Specific Gene Expression

The SRY-like family of proteins is implicated in initiating differentiation and in regulating tissue-specific gene expression. SRY was cloned

and identified as the testis-determining gene on the basis of genetic data. Several patients with an XY genotype who failed to develop the male phenotype have mutations in the HMG box domain of SRY [Berta et al., 1990; Jager et al., 1990]. Certain transgenic mice with an XX genotype that express the cloned SRY gene develop the male phenotype. Thus, this locus is thought to be responsible for initiation of testis formation in the developing embryo. SRY transcripts are detected in the genital ridge at a specific time during embryogenesis, 10.5 to 11.5 days post coitus [Koopman et al., 1990]. In the adult male, expression is limited to the testis. If SRY encodes the testis-determining factor, it is near the apex of a developmental program that requires the recruitment of growth factors, receptors, metabolic machinery, and the activation of transcription factors. It is particularly interesting therefore to find that the IRE-A motif is present in the non-coding region of many genes that are expressed in the developing and mature testis. The genes that are regulated by TCF-1α during T-lymphocyte activation are described above. EGF receptors, apoferritin, transferrin, amino acid aminotransferases, and glycolytic enzymes such as aldolase, glycerophosphate dehydrogenase, and pyruvate kinase all contain IRE-A–like sequences. Insulin has been shown to be a prerequisite for normal growth and secretion of androgen binding protein and transferrin in cultured Sertoli cells [Rich et al., 1983; Karl and Griswold, 1980]. These cells metabolize glucose to lactate at a very high rate [Robinson and Fritz, 1981], suggesting the need for hormonal control of the glycolytic cycle [Jutte et al., 1982]. In addition, several oncogenes involved in regulation of gene transcription and cell growth, c-fos [Stumpo and Blackshear, 1988], the early growth response gene, Egr-1 [Sukhatme et al., 1987; Taub et al., 1987; Stumpo et al., 1991], and c-myc [Taub et al., 1987], contain sequences that are conserved within the 5′ and 3′ domains of IRE-A. Of course direct biochemical studies will be necessary to understand the significance of these homologies.

The possibility that the IRE-ABP protein may, like SRY, play a role in differentiation is intriguing but remains to be shown. We speculate that this protein plays a role in determining tissue specificity of the hormone response for the following reasons. IRE-ABP mRNA is specifically expressed in tissues with lipogenic potential, in particular adipose tissue and liver. IRE-ABP is also present in Sertoli cells, another tissue in which glycolysis proceeds at a high rate. In contrast, IRE-ABP mRNA is not detectable in muscle where insulin has a much less dramatic effect on expression of glucose transporters and GAPDH gene expression [Kahn et al., 1989, 1991]. Thus the pattern of expression of this trans-acting factor may explain the tissue specificity of the hormone response.

How Is Promoter and Tissue Specificity Regulated Within the HMG Family?

Our current understanding of the mechanisms by which family members with similar sequence specificity can achieve promoter selectivity is derived in large part from study of homeodomain proteins [Hoey and Levine, 1988; Keleher et al., 1988; Herskowitz, 1989; Stern et al., 1989] and other HMG proteins [Bell et al., 1989, 1990]. Protein-protein interactions that alter the affinity of a protein for a given site, its sequence specificity, and promoter specificity have all been described. Family members with similar specificity for a core sequence can vary in affinity due to differences in the nucleotides immediately surrounding the minimal motif that provide a proper context for interaction of protein with DNA [Deutsch et al., 1990]. Functional diversity can be achieved by altering the context of a complete transcriptional unit with respect to other enhancers. For example, the effect of TCF-1 α on transcription depends on the combined effect of nearby cis-acting elements that bind a cAMP responsive protein and the tissue-specific trans-acting factor c-ets [Ho et al., 1989, 1990a, 1990b]. In the absence of the cAMP responsive enhancer this transcriptional unit acts as a repressor [Ho et al., 1990b]. Such protein-protein interactions could explain how positive and negative regulation of gene expression is achieved through the same element.

Regulation of HMG proteins through direct interaction with tissue- or species-specific accessory proteins is another mechanism by which functional diversity can be achieved through a given site. For example, hUBF directs transcription of ribosomal RNA genes in a species-specific manner by interacting with an accessory protein, hSL [Bell et al., 1989, 1990]. HUBF can bind and protect the human ribosomal RNA promoter, but interaction between hUBF and SL1 is required for transcriptional activation to occur through these sequences. Mouse and hu-

man SL1 have distinct DNA binding properties that confer promoter selectivity and species-specific transcription to hUBF. Thus, the accessory protein hSL, not hUBF, is the essential determinant of species-specific transcription.

These observations suggest that a single HMG protein could achieve functional diversity by interacting with one or more accessory proteins to regulate distinct promoters or regulate the same promoter in opposite directions. Thus, coordinate activation or inhibition of a group of regulatory enzymes could occur through the core motif described herein. The accessory proteins could respond to distinct signals that modulate the activity of HMG proteins via phospho-dephospho interconversions at various stages in the cell cycle and during differentiation. This possibility would be amenable to regulation by diverse extracellular signals and allow a specific response in distinct tissues.

Finally SRY and IRE-ABP belong to a large gene family which alone may explain the pleiotropic effect of insulin on gene expression. If multiple forms of IRE-ABP exist, functional diversity could be achieved through one of several mechanisms. Family members may have different affinities for a given recognition sequence or interact with distinct regulatory proteins. Different forms of the IRE-ABP family or its accessory proteins could be expressed during growth, after differentiation, and in different metabolic states. Clearly these mechanisms could easily explain negative or positive regulation through the same core sequence.

Regulation of HMG Proteins by Growth Factors

If like IRE-ABP, the SRY-like genes are distal components in the signal transduction pathway of a peptide hormone on gene expression, one might expect that post-translational modifications play a role in regulating the activity or expression of these genes during development and in mature cells. In this regard, the binding activity of HMG-1 is regulated by phosphorylation of the growth cycle regulated kinase CDC2 [Reeves et al., 1991]. Understanding the mechanism by which insulin and other growth factors activate these proteins will require characterization of the binding, dimerization, transcription, and regulatory domains of the HMG proteins.

In summary, cloning of IRE-ABP has opened many avenues of investigation. 1. The observation that diverse members of the HMG family of proteins bind a core motif should facilitate the identification of other target genes for IRE-ABP and/or SRY. Studies are underway to define the binding specificity of IRE-ABP–like family members. We expect that IRE-ABP will coordinately regulate numerous insulin-sensitive genes to alter the flux of metabolites into glycogen and fat. 2. Identification of IRE-ABP as an SRY-like gene raises the question whether IRE-ABP plays a role in the regulation of differentiation-dependent gene expression and the maintenance of the differentiated state. Conversely, the demonstration that SRY and IRE-ABP can protect a core sequence in a glycolytic gene suggests that factors with a primary role in regulating differentiation, such as SRY and TCF-1α, may activate a diverse spectrum of genes to regulate anabolic processes during differentiation (and in the mature cell). 3. The observation that there are multiple forms of the SRY and IRE-ABP gene products provides a potential explanation for the pleiotropic actions of insulin on various cell types and for coordinate regulation of negatively and positively regulated genes by insulin. 4. Once the binding, transcriptional, and phosphorylation domains of IRE-ABP are identified an effort can be made to understand how these activities are modulated by growth factors and hormones.

We expect the identification of a binding motif for the IRE-ABP/SRY-like family of transcriptional regulators to facilitate studies of the role of this family in regulating cell metabolism and phenotype.

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