INSULIN-LIKE GROWTH FACTOR BINDING PROTEINS

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Proceedings of a workshop on Insulin-like Growth Factor Binding Proteins, Vancouver BC, Canada
June 17–19, 1989

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INTRODUCTION

ON THE NOMENCLATURE OF THE IGF BINDING PROTEINS

It has been known for many years that Insulin-like Growth Factor I and II circulate in the plasma complexed to carrier or binding proteins (BP). Based on their chromatographically determined molecular size, they have been traditionally designated 150–200 K and 30–40 K IGF binding proteins. In recent years a growing number of proteins with IGF binding characteristics have been isolated from various body fluids, cell lines, and in various species. Provisional terminology based on source, species or molecular size has become increasingly confusing. Thus far three distinct IGF binding proteins have been fully characterized and their amino acid sequence determined (1–9).

Thanks to generous support from Genentech, San Francisco, CA, USA and KABI Vitrum, Stockholm, Sweden many investigators actively involved in IGF BP research met on June 17–19, 1989 in Vancouver, British Columbia, Canada. They presented recent data and exchanged their views.

We are pleased to present in these proceedings the papers and discussions. As much as possible the papers have been clustered around a specific binding protein but obviously there has been overlap and more than one IGFBP may be the subject of study.

It was the general feeling of the participants of the meeting that uniform terminology was highly desired in order to permit better communication between scientists within but also outside the rapidly expanding field of the IGF BP.

A proposal was adopted to designate the IGF binding proteins 'IGFBP' with the addition of an arabic numeral and a prefix to indicate species specificity. It should be emphasized that this designation should not be adopted until full amino acid or nucleotide sequence data are available for any new IGF binding protein.

In order to get accustomed to the new terminology a glossery of the various terminology and abbreviations that the reader will find in the papers and discussions is included in table 1.

We greatfully acknowledge Mrs S.J. Van Horne, Verbatim Words West, Ltd. Vancouver BC, Canada for very skillful transcription of the discussions and Mrs Carol F. Hintz for her help in organizing the meeting.

We hope that the proceedings will be useful for the participants of the meeting and additionally for all investigators intrigued by the still enigmatic role of the IGFBP with regard to the function and regulation of the Insulin-like Growth Factors.

Rotterdam, Munich
September 1989.

STENVERT L.S. DROP
RAYMOND L. HINTZ

Table 1. Terminology of the IGF binding proteins.

Synonym: (2, 3, 5–7)	*Proposed designation:**
Amniotic fluid binding protein (AFBP) Placental protein 12 (PP12) Alpha pregnancy associated endometrial globulin (alpha 1 PEG) Growth hormone independent binding protein Binding protein 28 (BP28) Binding protein 26 (BP26) Binding protein 25 (BP25) IBP-1	hIGFBP-1
Synonym: (1, 4, 8)	*Proposed designation:*
PP-2 BRL 3a cell line derived IGF BP MDBK cell line derived BP	hIGFBP-2 rIGFBP-2 bIGFBP-2
Synonym: (9)	*Proposed designation:*
GH dependent binding protein Acid stable subunit of the 140 K IGF complex. Binding protein 53 (BP53) Binding protein 29 (BP29)	hIGFBP-3

*h = human; r = rat; b = bovine.

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THE AMNIOTIC FLUID AND PLACENTAL DERIVED IGF BP: IGFBP-1

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Insulin-like growth factor binding proteins.
S.L.S. Drop, R.L. Hintz, editors

THE 25 KILODALTON INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN: ANALYSIS OF CHROMOSOMAL GENE STRUCTURE AND DEMONSTRATION OF PROMOTER ACTIVITY

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INTRODUCTION

The metabolic and mitogenic effects of the insulin-like growth factors (IGFs) can be modulated by a family of soluble proteins which have in common the ability to bind IGF peptides. A 25 kiloDalton (kD) human IGF binding protein (BP), BP-25, is the most thoroughly studied of these proteins; amino acid and cDNA sequences are now known (1-4). BP-25 is expressed in a tissue-specific manner (liver and secretory endometrium) and expression is developmentally regulated (fetal liver>>adult liver). BP-25 levels are also regulated by hormones; insulin appears to decrease serum BP-25 levels while progesterone increases BP-25 production by certain endometrial cells. Since many of these factors regulate BP-25 expression at the level of transcription, we (5,6) and others (7) have begun to analyze the chromosomal gene and promoter region of BP-25.

This manuscript further analyzes the BP-25 chromosomal gene and promoter. This analysis was aided by knowledge of the structure of three other IGF BPs; human BP-53 (8), human IBP-2 (J. Schwander, unpublished observations), and the rat equivalent of IBP-2 (9).

MATERIALS AND METHODS

Sequence analysis

The amino acid sequences derived from each of the four exons of BP-25 were optimally aligned with amino acid sequences from human IBP-2 and BP-53 (10), and the probability of homology among these sequences was determined by Monte Carlo analysis. Full amino acid sequences for these 3 BPs were used to construct a phylogenetic tree (11). Nucleotide sequences from the BP-25 chromosomal gene, and from the human BP-53 and rat IBP-2 cDNAs, were analyzed for the presence of CpG rich regions (12).

Promoter activity

A ~1.2 kB fragment of the BP-25 chromosomal gene, spanning from nucleotides -1205 (- signifies 5′ or upstream) to +68 relative to the mRNA

capsite (5), was inserted in both orientations into a bacterial chloramphenicol acetyltransferase (CAT) expression plasmid (modified form of pBLCAT3, kindly provided by Dr. Howard Towle); these constructs and a control plasmid containing the Herpes simplex virus tk promoter (pBLCAT2) were transfected into COS-1 cells by the calcium phosphate method, and CAT activity was assayed as described previously (13, 14).

RESULTS AND DISCUSSION

The organization of the BP-25 chromosomal gene is presented in Figure 1; this gene spans 5.2 kilobases of genomic DNA and consists of 4 exons (513, 170, 129 and 701 bp, respectively) separated by three introns (5). Exon 1 contains the entire 5′ untranslated sequence in addition to sequence encoding both the signal peptide and the first 91 amino acids of the mature protein. Exon 4 contains the entire 3′ untranslated sequence in addition to sequence encoding the final 43 amino acids of BP-25.

When amino acid sequences derived from each of the four exons of BP-25 were optimally aligned with amino acid sequences from human IBP-2 and BP-53

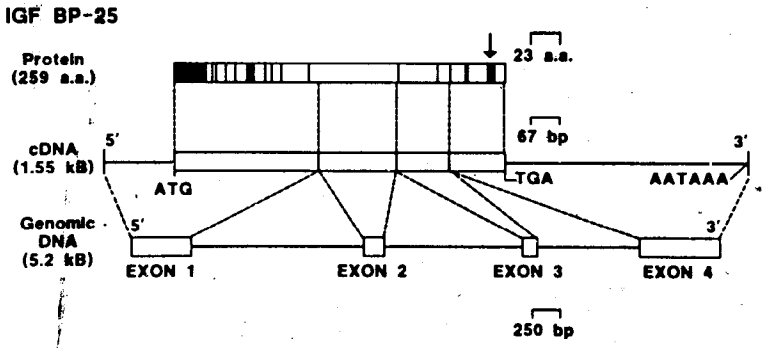

Fig. 1. Organization of the chromosomal gene for BP-25 in relation to BP-25 protein and cDNA sequences. BP-25 protein: the filled box represents the signal peptide while the open box on the right represents mature BP-25; the putative Arg-Gly-Asp cell binding domain within mature BP-25 is the thick line marked with an arrow, while cysteines are represented by the remaining vertical lines. BP-25 cDNA: the single open reading frame, beginning with the ATG translation start codon and ending with a TGA translation stop codon is represented by an open box; the 5′ and 3′ untranslated sequences are represented by solid lines. BP-25 gene: the open boxes represent the 4 exons while the introns are represented by the intervening solid lines. Regions of the BP-25 protein and cDNA sequences which are complementary to each other and to the 4 exons of the genomic sequence are indicated by the dashed lines.

(10), the sequences corresponding to exon 1 of BP-25 were the most similar. The 3 sequences were homologous due to > 45% sequence identity in all comparisons; this included conservation of all 12 cysteine residues in each sequence. The 3 sequences corresponding to BP-25 exon 4 were also homologous and included conservation of 4 cysteine residues; in this region, BP-25 sequence showed 51% identity with sequence from IBP-2, but each of these showed < 30% identity with BP-53 sequence. In contrast, when the sequence of BP-25 exons 2 and 3 was compared to corresponding sequence from BP-53 and IBP-2, little similarity was noted and, alone, these 3 sequences did not demonstrate significant homology. These observations suggest that BP-25 is more closely related to IBP-2 than BP-53; indeed, comparison of full length sequences for all 3 BPs results in a phylogenetic tree which supports this notion (Figure 2). These observations also suggest that the IGF binding domain is encoded by exons 1 and/or 4 of BP-25. Preliminary data indicate that sequence encoded by exon 1 is essential for IGF binding; when the cysteines at positions 16 or 35 of BP-25 are converted to serines by site-directed mutagenesis, the resulting BP-25 proteins can be expressed during transient transfections of COS-1 cells but their ability to bind IGF-I is abolished (DR Powell et al, unpublished observations).

In vertebrate DNA, the C of CpG dinucleotides is frequently methylated and often mutates to TpG. This could account for the depletion of CpG dinucleotides noted in vertebrate DNA. However, many genes contain regions rich in this dinucleotide, so-called CpG islands. Brinkman et al (8) demonstrated that a partial sequence of the BP-25 gene contains a 5′ CpG

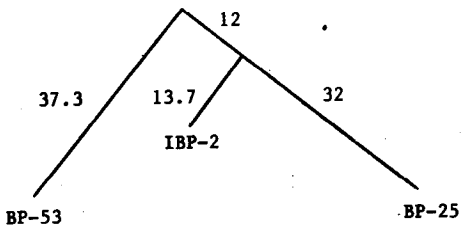

Fig. 2. Phylogenetic tree for the 3 human IGF BPs. Tree construction (11) used full-length amino acid sequences for BP-25, BP-53 and IBP-2. Branch lengths are numbers which should be proportional to true evolutionary distances.

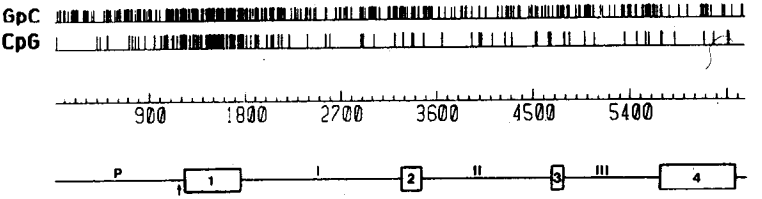

Fig. 3. Frequency of CpG and GpC dinucleotides in the BP-25 chromosomal gene. BP-25 gene organization is depicted at the bottom of the figure: exons are open boxes labeled 1-4 and introns are intervening solid lines labeled I-III; a P denotes the BP-25 promoter and upstream region, and an arrow marks the site of the mRNA capsite. The numbers above the BP-25 gene refer to the length of this sequence, in bp. At the top of the figure, the position of each GpC and CpG dinucleotide relative to the sequence of the BP-25 gene is indicated by a vertical line. A CpG island can be seen spanning the region from -90 to +580 bp relative to the mRNA capsite.

island. Figure 3 demonstrates the frequency of CpG and GpC dinucleotides in the complete sequence of the BP-25 chromosomal gene, and confirms the existence of a single 5′ CpG rich region which spans exon 1 and meets all the established criteria for a CpG island (12). The presence of a TATA box in the BP-25 promoter is consistent with the finding that all tissue-specific genes which have 5′ CpG islands also have a TATA box. Interestingly, CpG islands are also present in the 5′ regions of the cDNAs for human BP-53 (nucleotides -109 to +475 relative to the translation start site) and rat IBP-2 (nucleotodes -73 to +650 relative to the translation start site). This suggests that the promoter regions of BP-53 and of rat IBP-2 will each contain a TATA box and that the CpG island in each gene will be found to span the entire exon 1 sequence. The significance of CpG islands is unclear, but their presence in the 5′ region of all housekeeping genes and many tissue-specific genes suggests an important function. It is possible that these regions bind factors which protect the CpG dinucleotides from methylation; such factors may participate in the regulation of either transcriptional or post-transcriptional events (12).

The mRNA capsite of the BP-25 gene has been mapped either 165 bp upstream from the translation start site using mRNA from HEP G2 cells (5) or 155 bp upstream from this site using placental mRNA (7). The true capsite appears to be 165 bp upstream from the start site since the original cDNA derived from HEP G2 mRNA extends 164 bp upstream from this site (1);

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