SOMATOMEDINS

Essay
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By

Hanan Mohamed Mamdouh
(M.B., B.Ch.)

Supervisors

Dr. GIHAN KAMAL HASSAN ALY
Assistant Professor of Clinical Pathology
Faculty of Medicine
Ain Shams University

Dr. OLA HAMDY DEMERDASH
Lecturer of Clinical Pathology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
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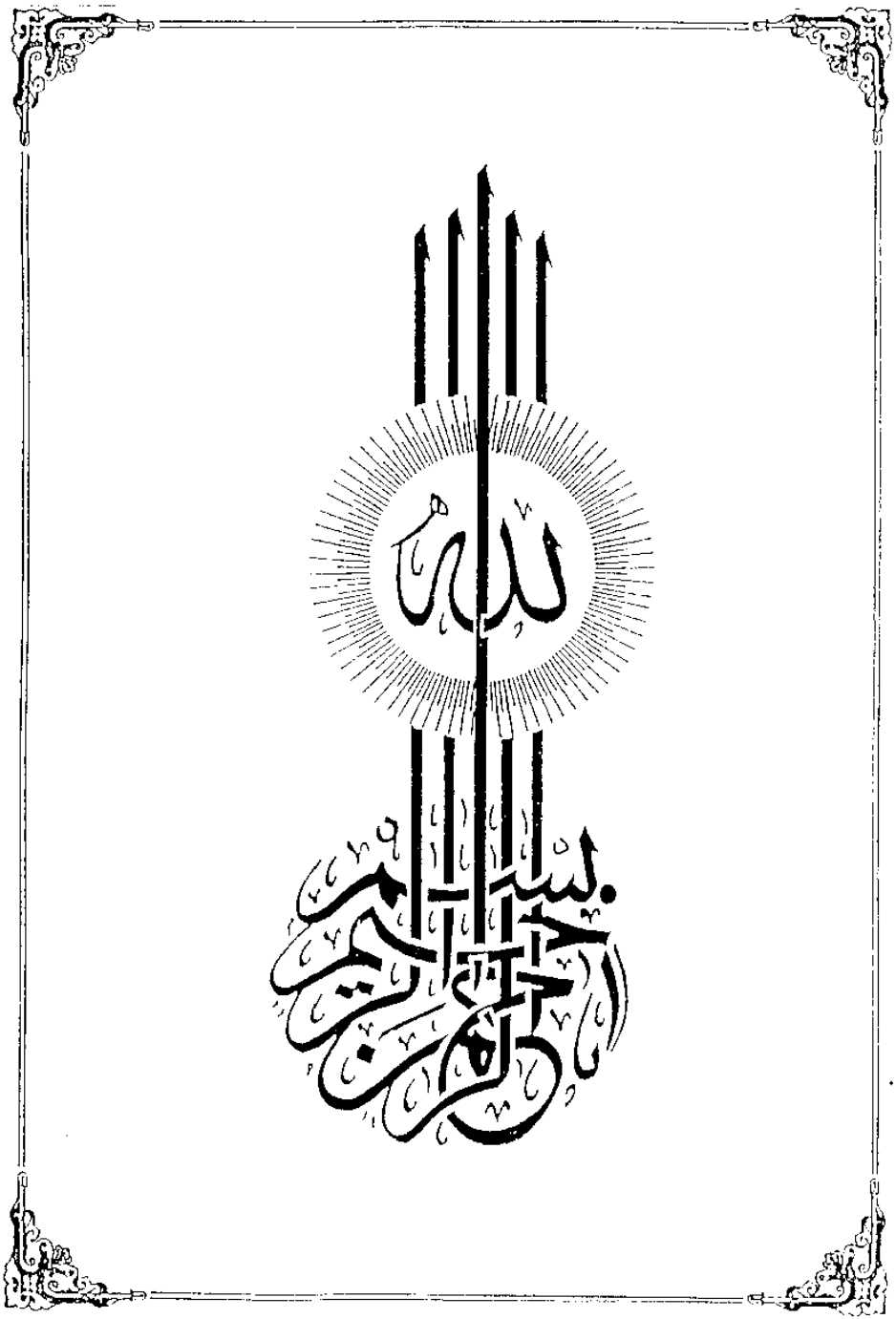
بسم الله الرحمن الرحيم

وقل ربِّ زدنی علماً

صدق الله العظيم



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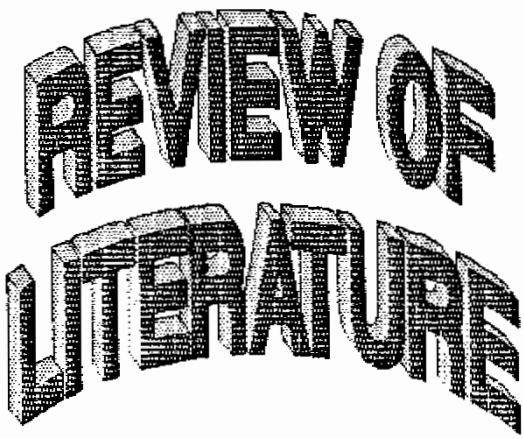
INTRODUCTION AND AIM OF THE WORK

The regulation of growth by growth hormone was first studied in the 1930's when pituitary extracts containing growth hormone became available (Silberberg, 1935). Recognizing that growth involves proliferation of cartilage at the epiphyseal plate, Kibrick et al. (1941) found that narrow epiphyseal plates in hypophysectomized rats became wider after growth hormone was given in vivo. Other workers observed that cartilage metabolism could be measured by the incorporation of radioactive sulfate into cartilage chondroitin sulfate. Cartilage from hypophysectomized rats had low sulfate uptake, which was increased by growth hormone in vivo (Murphy et al., 1956).

Salmon and Dauphaday (1957) examined the mechanism by which growth hormone stimulated growth. Hypophysectomized rat costal cartilage exposed to growth hormone in vitro had no change in sulfate uptake. Addition of serum from hypophysectomized rats also had little effect. However, serum from rats treated with growth hormone stimulated sulfate uptake. So, it was hypothesized that growth hormone stimulated skeletal growth indirectly through generation of a circulating "Sulfation factor" which acted directly to cause cartilage proliferation.

Later studies carried out by Phillips et al. (1974) and Garland et al. (1976) showed that plasma extracts with sulfation activity had wide stimulatory actions on cartilage, insulin-like actions on muscle and adipose tissue, and growth-promoting activity in Hela cells. In view of such evidence that circulating factors had a potential role in the growth and anabolism of different tissues. The operational term was then replaced by "somatomedins" in 1972 (Daughaday et al., 1972).

The aim of the present work is to give a detailed account on the somatomedin family; their historical background, genetic organization and development, structure, sites of synthesis, their binding proteins, function with special reference to regulation; their tentative clinical use and methods of assay.


REVIEW OF
LITERATURE

A. Historical Background:

Somatomedins or insulin-like growth factors (IGFs) are small polypeptides with growth promoting properties. These growth factors were discovered as three different biological activities of plasma, namely non-suppressible insulin-like activity (NSILA), sulphation factor activity (SFA) and multiplication stimulating activity (MSA). Thus, three lines of research led to the isolation and characterization of somatomedins/Insulin like growth factors (SM/IGF).

The first line arose when it became apparent that human plasma contains far more insulin-like activity than could be attributed to insulin content. This so-called non-suppressible insulin-like activity or atypical insulin was purified by a research group in Zurick (Froesch et al., 1963). Two polypeptides termed insulin-like growth factors I and II (IGF-I and IGF-II) were isolated from human plasma in 1976 (Rinderknecht and Humbel, 1976).

The second line originated from the observation that growth hormone (GH) stimulated sulphate uptake into cartilage of hypophysectomized rats in vivo, but not in vitro. Salmon and Daughaday (1957) found that in vivo growth hormone induced a sulphation factor activity in animal plasma. They proposed that the growth-promoting effect of GH

was mediated through a secondary substance. Several attempts were made for purification of the latter substance from human plasma. By using different bioassays, two groups purified the polypeptides termed somatomedin A (SMA) and somatomedin C (SMC) (Hall, 1972 and Van Wyk et al., 1975). As the idea that SFA and NSILA could be differnt expressions of the same entity, Hall and Uthne (1971) determined and found NSILA activity in the fractions containing sulphation factor activity (SFA).

The third line (MSA) is based on the growth promoting activity of serum. In this respect, MSA was found in larger amounts in medium conditioned by the rat liver cells BRL-3A, which was then used for isolation of MSA (Nissley and Rechler, 1978).

When it became apparent that the three different biological activities in plasma could be different expressions of the same chemical structure, the term somatomedin was introduced (Daughaday et al., 1972). This term, however, denoted that these substances should mediate the growth promoting actions of GH. Of the two close homologues IGF-I and IGF-II, however, only IGF-I was GH regulated. Therefore, the term somatomedins has been omitted by some investigators in preference of IGF.

B. Genetic Organization and Development-Specific Expression:

Complementary DNAs encoding human IGF-I and IGF-II have been isolated and characterized (Jansen et al., 1983; Bell et al., 1984; Jansen et al., 1985; Lebouc et al., 1986 and Rotwein, 1986). This revealed that the coding regions are flanked by regions encoding amino terminal (signal) peptides as well as carboxyl-terminal peptides, indicating that both insulin-like growth factors (IGFs) are synthesized as precursor molecules. Using the cDNAs as specific probes, the chromosomal assignment of IGF genes has been determined. The IGF-I gene maps to the long arm of chromosome 12 and the gene for IGF-II is located on the short arm of chromosome 11, only 1.4 Kb (kilobase pairs) downstream from the insulin gene (Bell et al., 1985; Holthuize et al., 1985; Hoppener et al., 1985 and Holthuize et al., 1987).

1- The IGF-I Gene:

The IGF-I gene has a discontinuous structure containing at least five exons spanning a region of more than 85 kb of genomic DNA (Rotwein et al., 1986). The exact length of the gene is unknown, since there is a gap between exons 2 and 3 of more than 59 kb. Furthermore, the 5′ end of the gene is not completely characterized yet, and the promoter is still unidentified (Holthuizen et al., 1987).

Two different cDNAs for IGF-I have been described. The IGF-I a cDNA, isolated by Jansen (1983) from an adult human liver cDNA library, is encoded by exons 1,2,3, and 5. Rotwein (1986) described a second cDNA for IGF-I also isolated from an adult liver library. This cDNA was designated IGF-Ib. It contains the sequences for the exons 1,2 and 3 as in IGF-Ia, but is followed by an alternative 3 exon, exon 4 (Fig.1).

It can be concluded that the IGF-I gene encodes both prepro IGF-I a and prepro IGF-Ib, which differ only in the amino acid sequence of the carboxyl-terminal E domain. Prepro IGF-1a contains an E-peptide of 35 amino acids whereas prepro IGF-1b has an E-peptide of 77 amino acids (Lebouc et al., 1986).

Expression of IGF-I RNA was studied by Northern blotting, using IGF-I cDNA as a probe. Adult human liver RNA hybridization shows several IGF-I specific bands. Two major RNAs of 7.6 and 1.1 kb as well as a broad zone of hybridization between 2.5 and 5.0 kb are present. In fetal liver a 7.6 kb mRNA is hardly detectable, supporting the notion that IGF-I is mainly involved in postnatal growth. It is not yet clear which of these mRNA transcripts are specific for IGF-I a or IGF-1b. On the other hand, adult rat

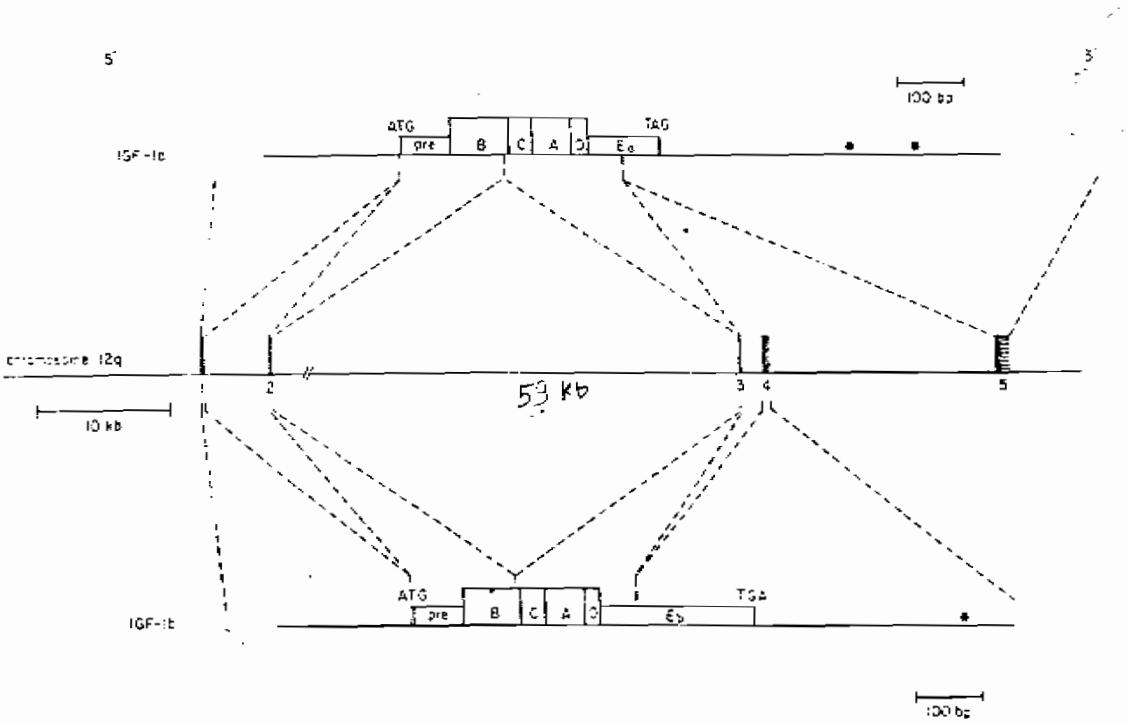


Figure (1): Schematic representation of the IGF-I gene, located on the long arm of chromosome 12 and of the two different cDNAs. IGF-Ia and IGF-Ib.
The exons are numbered 1-5.

(Quoted from Holthuizen et al., 1989).