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A surprising sequence homology

A few years ago we isolated a new peptide from porcine pancreatic extracts (Jørgensen *et al.*, 1982*b*). An initial characterization revealed that the peptide had some peculiar characteristics, e.g. seven disulphide bridges were present in the peptide consisting of only 106 amino acid residues. Further studies showed that the peptide was probably related to the exocrine function of the pancreas (Thim *et al.*, 1982), and a pharmacological screening indicated that the peptide had a spasmolytic effect (Jørgensen *et al.*, 1982*a*). Although we were not completely certain that this effect was actually the physiological function, we decided to name the peptide Pancreatic Spasmolytic Polypeptide (PSP). Following the amino acid sequence determination of PSP, the Dayhoff protein sequence database (National Biomedical Research Foundation, Georgetown, Washington, DC, U.S.A.) was searched (Thim *et al.*, 1985). This search did not pick up any proteins with significant homology to PSP (Thim *et al.*, 1985).

Recently, we received a new, updated version of the database (version 13, updated 30 June 1987), and to our surprise a search picked up a significantly high alignment score between PSP and a pS2 peptide. The amino acid sequence of the pS2 peptide had been derived from an mRNA which is induced by oestrogen in the human breast cancer cell line MCF-7 (Jakowlew *et al.*, 1984; Prud'homme *et al.*, 1985). The nucleotide sequence of a pS2 full-length cDNA predicted a peptide of 84 amino acid residues, out of which 26 or 21 residues represented a putative signal peptide corresponding to a mature pS2 peptide of 58 or 63 residues (Jakowlew *et al.*, 1984). PSP contains two homologous domains (Thim *et al.*, 1985) and both of these show a high degree of homology to the mature pS2 peptide (Fig. 1).

The implications of this high degree of homology cannot be established at present. However, it is our hope that the identified structural similarity may contribute to the elucidation of the physiological functions of the two peptides.

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Homology of human pancreatic stone protein with animal lectins

The main protein constituent of human pancreatic stones has been shown to be derived from a glycoprotein precursor that accounts for about 10% of the secretory proteins of human pancreatic juice (Multigner *et al.*, 1985; Montalto *et al.*, 1986). In pancreatitis, premature zymogen activation leads to proteolysis of this precursor within the pancreas, yielding form(s) of stone protein that are practically insoluble at neutral pH. It has been suggested that precipitation of degraded forms of stone protein may be responsible for initiating the formation of pancreatic stones in chronic calcifying pancreatitis (Figarella, 1988). The normal physiological function of this secretory protein, however, is unclear. De Caro *et al.* (1984) have proposed that stone protein may act as a stabilizer of supersaturated pancreatic secretion by inhibiting the growth of calcium carbonate crystals. This view, however, was challenged recently (Figarella, 1988) since the inhibitor of crystal nucleation was shown to be distinct from stone protein.

Recently the complete amino acid sequence of human pancreatic stone protein has been published (Montalto *et al.*, 1986; Rouimi *et al.*, 1987; De Caro *et al.*, 1987). Computer-based surveys of protein sequences failed to detect homology of this protein with any other sequence except with bovine pancreatic thread protein (Gross *et al.*, 1985), the bovine equivalent of human pancreatic stone protein.

We have recently developed a sensitive procedure that can detect homologies not recognized by conventional programs of sequence comparison (Patthy, 1987*a*). In this procedure, similarity to a consensus sequence characteristic of a protein family is used to decide whether a new sequence has the features typical of that family. Using

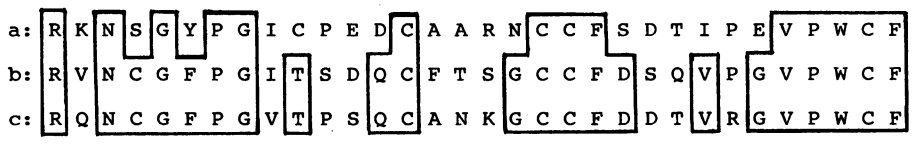

Fig. 1. Homology between PSP domain 2 (residues 65–96) (a), PSP domain 1 (residues 16–47) (b) and pS2 peptide (residues 38–69) (c)

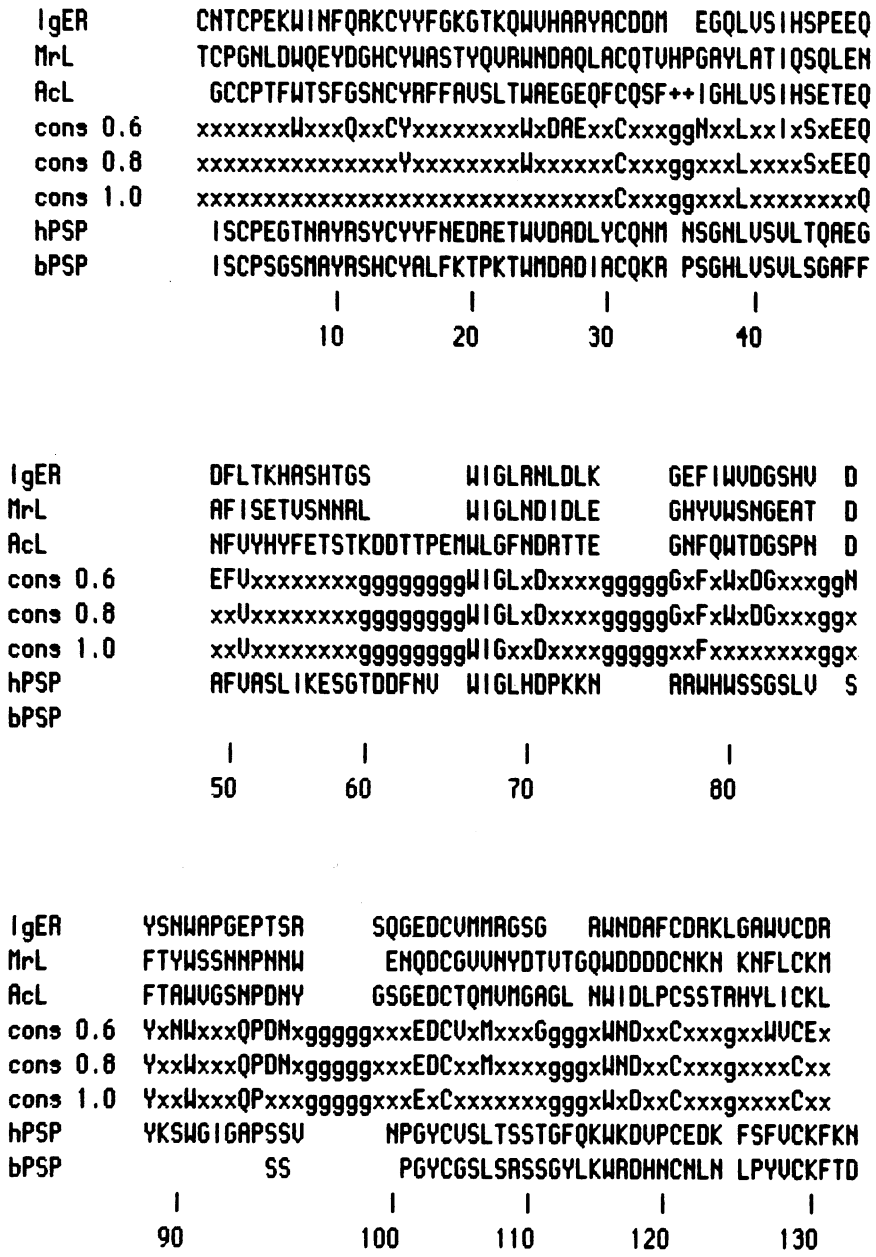

Fig. 1. Homology of human and bovine pancreatic stone protein (hPSP, bPSP) with animal lectins

The consensus sequences of animal lectins were determined with $k = 0.5$ and $f = 0.6$, 0.8 and 1.0 as described in the text. Note that the residues characteristic of lectins are conserved in hPSP and bPSP. For comparison the sequences of some of the lectins referred to in the text are also included in the Figure: immunoglobulin E receptor (IgER), lectin of the acorn barnacle, *Megabalanus rosa* (MrL), lectin of the sea urchin, *Anthocidaris crassispina* (AcL). [For typographical reasons, longer insertions in the sequences (+) are not shown.] The numbering refers to the sequence of human pancreatic stone protein; in consensus sequences x marks variable residues and g indicates regions tolerant of deletions and insertions.

consensus sequences constructed for animal lectins (Patthy, 1987*b*), we have found that bovine and human pancreatic stone proteins (bPSP and hPSP) are homologous with the globular domains of these proteins (Fig 1); of the 19 residues conserved in all lectin sequences 16 are also conserved in hPSP including the four cysteines and the three tryptophans. When the sequence of hPSP is compared with individual lectin sequences the percentage identity was found to range between 18 and 32%, hPSP being most similar to IgE receptor (Ludin *et al.*, 1987). The significance of this sequence similarity is underlined by the fact that hPSP displays the features characteristic of the lectin-fold: the residues typical of lectins are conserved, the gaps in the alignment occur in regions (g) known to be tolerant of deletions–insertions (Fig. 1).

On the basis of homology it is proposed that the folding of hPSP is similar to that of the other lectins and the cysteines form disulphide bonds in a pattern homologous to that determined for MrL, the lectin of the acorn barnacle, *Megabalanus rosa* (Muramoto & Kamiya, 1986) and AcL, the lectin of the sea urchin, *Anthocidaris crassispina* (Giga *et al.*, 1987). Homology would thus predict disulphide bonds between Cys-3 and

Cys-14, Cys-31 and Cys-129 and Cys-104 and Cys-121. In harmony with this prediction, a disulphide bond does indeed connect Cys-3 to Cys-14 (Rouimi *et al.*, 1987); the disulphide bond pattern of the remaining four cysteines has not yet been established. In the case of bPSP the middle part of the molecule (residues 49–98, cf. Fig. 1) has been removed by proteolysis and the *N*-terminal region (residues 1–48, A chain) is linked to the *C*-terminal region (residues 98–133, B-chain) via disulphide bond(s) (Gross *et al.*, 1985). This observation is consistent with the proposed disulphide pattern: the two chains are linked by the disulphide bond connecting Cys-31 and Cys-129.

The homology of pancreatic stone protein with lectins raises the possibility that PSP may also serve to bind carbohydrates or carbohydrate moieties of proteins, an assumption that may be tested in future investigations.

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