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Received 23 December 1987

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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Received 22 January 1988

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

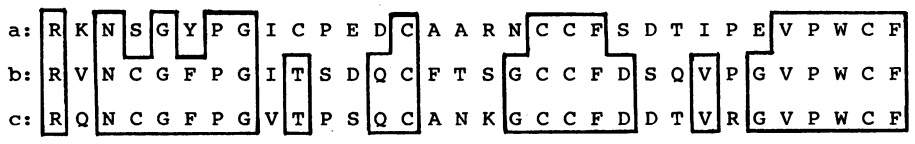

Fig. 1. Homology between PSP domain 2 (residues 65–96) (a), PSP domain 1 (residues 16–47) (b) and pS2 peptide (residues 38–69) (c)