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Exocrine Meets Endocrine: Pancreatic Stone Protein and Regenerating Protein—Two Sides of the Same Coin

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Background. **Regenerating protein (*reg*) and pancreatic stone protein (PSP) have been discovered independently in the fields of diabetes and pancreatitis.**

Materials and methods. **These proteins are identical; however, because of the gap between the endocrine and exocrine field, there was never a consensus and the nomenclature has not been rectified. Since the time of the initial discovery, more isoforms have been unified. Historically, PSP was discovered long before *reg*, yet, in many areas outside of the pancreatitis research field, *reg* is being used.**

Results. **For PSP/*reg*, a role in proliferation and regeneration of islet cells has been postulated. A hitherto insufficiently understood phenomenon is the massive up-regulation of PSP/*reg* in pancreatic tissue and juice under conditions of stress. Similarly, PAP (pancreatitis-associated protein)/*reg III* has been attributed various functional roles. Structurally, the ability to form fibrils after tryptic cleavage is a striking common features of both proteins. However, this biochemical transformation is in itself not enough to gain functional insight. Thus, physiological and genetic approaches are required to further characterize the role of these proteins in the pancreas. Recently, more evidence has been presented in support of the theory that PSP/*reg* plays a key role in islet neogenesis/regeneration.**

Conclusions. **In this review we discuss the debate on the localization and functional roles of PSP/*reg* and PAP/*regIII*. Therefore, we have summarized hypotheses and experimental results supporting such hypotheses.**

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INTRODUCTION

In an effort to characterize proteins trapped in pancreatic stones, in 1979 De Caro identified a 14 kDa protein that was termed pancreatic stone protein (PSP) [1]. Subsequent analysis in several species revealed that this polypeptide was a tryptic fragment of a slightly larger pancreatic secretory protein [2–4]. The term 'pancreatic stone protein' was forthwith reserved for this secreted form while the fragment, based on its insolubility and fibril forming capacity, was named pancreatic thread protein (PTP) [5]. In 1988, a cDNA coding for a 16 kDa protein was identified from islets of 90% depancreatized animals; this protein was named regenerating protein (*reg*) based on its occurrence in regenerating islets and on its absence in controls [6]. Sequence comparison later revealed that *reg* and PSP are identical [7].

The circumstances of the discovery of *reg* [6] led to the concept that it promoted regeneration of islets by induction of cellular proliferation. The search for a functional role of PSP, on the other hand, had led to the idea that it might serve as an inhibitor of pancreatic stone formation; based on experiments testing calcite crystal growth inhibition, PSP was renamed lithostathine [8]. However, the relevance of these experiments was questioned in the years to come [9, 10].

A second set of molecules—pancreatitis-associated protein (PAP) and its various isoforms—belong to the same family of proteins. PAP was first observed in rats with acute pancreatitis and then in human pancreatic grafts after transplantation [11, 12]. PAP turned out to be up-regulated several hundred fold in animals with

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TABLE 1

Summary of the Terminology Used for PSP, *reg* Protein, and PAP

	Pancreas: Reg	Pancreas: PSP & PAP	Other organs	Isoforms	Literature
Rat	Reg I	PSP, Pancreatic thread protein, Lithostathine	Duodenum stomach	1	[1, 6]
	Reg III (1, 2, 3)	PAP (I, II, III)	small bowel (PAP I, III)	3	[5, 11, 65]
			small bowel (Reg IV)	1	[17]
Mouse	Reg I	PSP		1	[14]
	Reg II			1	[14]
	Reg III (α,β,γ,δ)	PAP	Reg II (Schwann cells, motoneurons)	4	[4, 6, 25, 66]
			Reg IV ?	1	
	INGAP related protein		Duodenum, stomach	1	[16]
Human	Reg I (α, β)	PSP (α, β)		2	[4]
	Reg III	PAP	Hepatocellular carcinoma (HIP/PAP)	2	[5, 8, 12, 67]
Hamster	INGAP (Islet neogenesis-associated protein)				[15]

edematous or necrotizing pancreatitis. PAP and PSP/*reg* share a selective and specific trypsin cleavage site 11 amino acids from the amino terminus, resulting in insoluble fibrils after cleavage. The latter demonstrate high resistance to further cleavage by trypsin or other proteases [13]. Such fibrils have been generated from human, bovine, and rat PSP/*reg* and PAP.

In the mouse, an additional protein with homology to PSP/*reg* and PAP was detected and termed *reg II*. To avoid further confusion, Unno *et al.* endeavored to clarify the nomenclature of these proteins [14].

A further protein, the so-called islet neogenesis-associated protein INGAP, found during islet neogenesis in cellophane-wrapped hamster pancreas, was cloned and sequenced by Rafaeloff *et al.,* and turned out to be another member of the *reg* protein family [15]. A similar protein, INGAP-related protein (INGAPrP), is abundantly expressed in normal pancreas [16].

Finally, a protein predominantly expressed in the small intestine was described by Hartupee and colleagues who, using the *reg* nomenclature, called it *reg IV* [17].

However, the functional roles of these proteins—be it their integral or their cleaved forms—have not been sufficiently clarified up to date.

The discovery of a functional involvement of *reg* in injured motoneurons did not foster clarification, as in these experiments *reg II* was reportedly used, which according to Unno's terminology would have been *reg III*. Altogether, the situation remains confusing and the gap between the functional studies performed in the endocrine field *versus* those in the exocrine field could not be bridged. In Table 1, a compilation of the complex terminology is given to create some transparency. The dendrogram in Fig. 1 depicts the molecular relationship based on sequence comparison and alignment.

STRUCTURAL FEATURES

PSP/*reg* are 16 kDa polypeptides with a signal sequence for export. The overall sequence and the distribution of the cysteines imply that the proteins belong

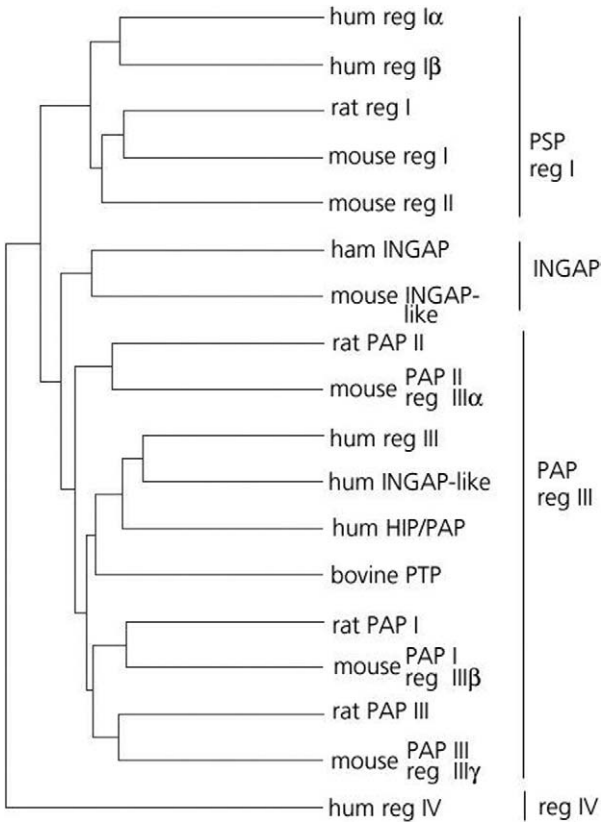

FIG. 1. Dendrogram representing the 'molecular relationship' between the various members of the secretory stress proteins. The isoforms from human, mouse, and rats were compared by the pile-up software from the Genetics computer group (GCG, WI).