Pancreatic Stone Protein/Regenerating Protein Family in Pancreatic and Gastrointestinal Diseases

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Abstract

Pancreatic stone protein (PSP; reported in 1979), pancreatitis-associated protein (PAP; 1984) and regenerating protein (Reg I; 1988) were discovered independently in the fields of the exocrine (pancreatitis) and endocrine (diabetes) pancreas. Subsequent analysis revealed that PSP and Reg I are identical and PAP belongs to the same protein family. PSP/Reg I and PAP share a selective and specific trypsin cleavage site and result in insoluble fibrils (PTP, PATP). Search for a functional role of PSP had led to the idea that it might serve as an inhibitor in pancreatic stone formation and PSP was renamed lithostathine. Inhibitory effects of lithostathine in stone formation have been questioned. Evidence so far obtained can support a lithogenic role rather than a lithostatic role of PSP. PAP and its isoforms have been investigated mainly regarding responses to inflammation and stress. Reg I and its isoforms have been examined on regeneration, growth and mitogenesis in gastrointestinal neoplastic diseases as well as diabetes. Evidence obtained can be applied in the prediction of prognosis and therapy for inflammatory and neoplastic diseases.

Key words: pancreatic stone protein, regenerating protein, lithostathine, pancreatitis-associated protein, pancreatic and GI diseases

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Introduction

Pancreatic stone protein (PSP), also known as lithostathine, and regenerating protein (Reg I) have been found independently in the field of pancreatitis and diabetes, although the two proteins have been subsequently proved identical. In an attempt to characterize proteins trapped in pancreatic stones from chronic calcifying pancreatitis, De Caro et al identified a 14 kDa protein that was named pancreatic stone protein (PSP) in 1979 (1).

Approaches to the protein were pursued in the 1980s independent from the French group. Gross et al reported the presence of protein fibrillar precipitates at neutral pH in bovine pancreas (2). They termed that protein pancreatic thread protein (PTP). A protein with similar characteristics in humans was later described by the same group (3).

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Structural Aspects

PSP has been argued to play a crucial role of intraductal pancreatic stone formation in chronic pancreatitis. PSP, initially characterized as a glycosylated acidic phosphoprotein of a 14 kDa, was found to be the major constituent of human pancreatic stones by the group of Sarles (1, 13). They assumed that this protein was a potent inhibitor of calcium carbonate precipitation in pancreatic juice.

Four molecular forms of the protein, PSP S2-5 (secretory form, 14-19 kDa) are synthesized in the pancreatic acinar cells as a single polypeptide and secreted into the duodenum along the same secretory pathway as the exocrine enzymes. PSP isolated from pancreatic stones and PSP S1 (133 amino acids) derived from PSP S2-5 (144 amino acids) through the tryptic cleavage of the Arg11-Ile 12 bond in the N-terminal part (undecapeptide) of PSP S2-5. PSP and PSP S1-5 are from the same source and the difference is seemingly in their polypeptide chain length. Cloning and sequencing PSP mRNA confirmed that the protein is encoded by a single transcript and the amino acid sequence of the encoded protein is identical to the previously determined for the PSP S2-5 polypeptide (13-21). The polymorphism of PSP S2-5 is suggested to be caused by posttranslational maturation of a single polypeptide. The presence of PSP S1 also suggests thezymogen activation in the pancreatic juice or pancreas (22).

The secretory forms of PSP/lithostathine ( ※ S2-5 comprise 144 amino acids. Trypsin hydrolysis of the Arg11-Ile 12 bond generates a polypeptide of 133 amino acids, called PSP/lithostathine S1. This form of the protein has been independently isolated from acid extracts of normal human pancreas and its secretion in the form of 7-10 nm long single threads by Gross et al; it was named pancreatic thread protein (PTP), because of its fibril formation (3). The N-terminal undecapeptide is deduced to normally impede fiber formation but not aggregation (23). Purified PSP/lithostathine has been also shown to form similar fibrils after tryptic cleavage in vitro (23). Pancreatitis-associated protein (PAP), a secretory acute-phase protein of the pancreatic acinar cell and its secretion, shows strong sequence homology to PSP/Reg and PTP. Graf et al demonstrated formation of a spontaneously precipitating peptide after the tryptic cleavage at Arg11-Ile12 bond of recombinant rat PAP and called it pancreatitis-associated thread protein (PATP) like PTP (7, 24). These findings suggest that PSP/lithostathine/Reg and PAP I and PAP III isoforms consist of a family of highly regulated soluble secretory stress proteins, which convert into a family of insoluble helical thread proteins (7). Human Reg protein, pancreatic stone protein and pancreatic thread protein are just different names for a single protein existing in several molecular forms but derived from a single Reg gene, since the functional Reg is a single copy gene and primary amino acid sequence of PSP and PTP is identical with that of the protein encoded in the human Reg gene (25-27). Rouquier et al also observed a complete sequence identity between the rat PSP mRNA and rat Reg mRNA (28).

PAP is an additional secretory protein which appears in pancreatic juice and pancreas after induction of pancreatitis by either cerulein or taurocholate in rat (5, 29) and after acute pancreatitis in grafted pancreas in human (6). In search for homology between PAP and other pancreatic proteins, a significant degree of similarity was observed only with Reg protein, which is identical to PSP. Amino acid sequences of PAP and PSP were 63% similar. This high similarity suggests PSP/Reg and PAP genes might originate from a common ancestor gene (30).

(※The usage of either PSP or lithostathine was followed by that in the cited paper.)

Functional and Pathophysiological Aspects

Inhibitor or promoter of pancreatic stone formation?

One of the earliest pancreatic lesions in chronic pancreatitis is thought to be the deposition of protein plugs in the pancreatic ductules (31). If concentration-dependent precipitation in pancreatic juice is a basic cause of protein plug formation, a candidate protein must increase in its concentration. PSP could not be a candidate protein for stone formation, because PSP hyperconcentration in pancreatic juice has not been consistently reported. However, the ability to produce insoluble aggregates or fibrils in pancreatic juice seems more important than hyperconcentration in the initiation of precipitation of a protein (23). In this respect PSP can be a potent candidate for protein plug and subsequent growth to pancreatic stone.

Though PSP was initially found to be a major constituent of human pancreatic stones by Sarles’ group (1), supersaturation of calcium carbonate in pancreatic juice and its major constituent of the stone led them to the assumption that an inhibitor of calcium carbonate crystal growth had to be present in the juice. Such an inhibitor must interfere with crystall nucleation or growth (1, 13-20), and can also explain why some patients develop pancreatic stones but how the normal population is protected against it (31). They, therefore, renamed pancreatic stone protein as lithostathine (32), with reference to the capacity of the protein to inhibit calcium carbonate crystal growth, not to the tendency to form insoluble fibrils and precipitates. Subsequent biochemical in vitro experiments (33, 34) and clinical studies on PSP in pancreatic juice (35-38) seemed to support their assumption.

Decreased secretion of PSP was expected in pancreatic juice of chronic pancreatitis, but the PSP levels reported were controversial. The PSP levels in pancreatic juice were significantly decreased in chronic calcifying pancreatitis when the PSP assay was carried out using radial immunodiffusion (35), enzyme-linked immunosassay with monospecific polyclonal antibodies to the secretory forms of PSP.
(S2-5) (36), immunoblotting with antibody against synthetic peptide of the N-terminal end of lithostathine S2-5 (37), or using non-immunological method of fast protein liquid chromatography for lithostathine S2-5 (38). Conflicting results, no significant difference between chronic pancreatitis and controls were reported by Schmiegel et al using fluorometric immunoassay (39), by Provansal-Cheylan et al using radioimmunoassay with monoclonal antibodies against PSP S1 extracted from pancreatic stones (36), and by Hayakawa et al using immunoassay with monoclonal antibody recognizing PSP S1 and S2-5 at equal effectiveness (40). These discrepant results could be explained partly by different specificities of the anti-PSP used in the PSP assays (35-37, 39, 40).

If premature activation of trypsinogen to trypsin occurs, soluble PSP S2-5 is subsequently converted to insoluble PSP S1 in the pancreatic secretion. PSP levels determined by an assay specific to PSP S2-5 may be reduced in chronic pancreatitis, even when the total amount of PSP S1 and S2-5 remain unchanged. The premature activation occurred more frequently than we expected since the intraductal activation of trypsinogen prior to recurrent attacks of pancreatitis has been reported (41, 42).

Bimmler et al confirmed that purified rat lithostathine displays calcium carbonate crystal inhibitor activity in vitro experiments. However, control proteins such as bovine trypsinogen and human serum albumin and ions such as phosphate appear to be equally active. They, thus concluded that the inhibitor activity is doubtful to be a specific functional property of this protein in pancreatic stone formation (43, 44). De Reggi et al also ascribed the inhibitory activities of lithostathine in pancreatic stone formation to nonspecific effects from inorganic compounds in the pancreatic juice, such as NaCl and phosphate or coexisting proteins, such as albumin and trypsinogen (45). The tendency of the C-terminal peptide of PSP/lithostathine to precipitate has been observed by several independent investigators (3, 7, 18, 22-24, 46, 47) and its predominant presence in pancreatic stones has been reported repeatedly (1, 15, 46, 48, 49, 50, 51). Both Bimmler’s and De Reggi’s groups, thus, questioned whether or not the name lithostathine should be used until the details of the function of the protein is more clearly elucidated.

Protein analysis of intraductal precipitates and calculi is important to clarify the mechanism of stone formation and the role of PSP in chronic pancreatitis. Investigation of the organ matrix of the pancreatic stones revealed the presence of PSP as a major protein component (1, 46, 48, 49, 51). A wide variety of contents of proteins and structures of the pancreatic stones suggests that the mechanisms and protein components involved in the stone formation are multifactorial and that PSP is not a sole protein involved in the stone formation (1, 46, 48, 49, 52-56).

Stent occlusion

Endoscopic drainage, especially stent placement, of the pancreatic duct has greatly advanced pain control in chronic pancreatitis. Good clinical results, however, are hampered by rapid occlusion. Analysis of protein components of clogging materials in pancreatic stents proved PSP/lithostathine, albumin and trypsin as major protein components (57-59). Details of the mechanism in pancreatic stent occlusion still remain uncertain, but stents with larger side holes may less frequently become clogged (60). PSP/lithostathine seems to promote, not inhibit, the stent occlusion.

Bacterial aggregation

In search of a functional role of PAP/Reg III, Iovanna et al demonstrated bacterial aggregation by the addition of PAP/Reg III to bacterial cell cultures of E. coli (30). Based on the sequence homology of PSP/lithostathine/Reg and PAP/Reg III, they also revealed bacterial aggregation of E. coli by PSP/lithostathine/Reg purified from human pancreatic juice (61). Trypsin cleavage of the proteins is required for proteoglycan binding and bacterial aggregation (62, 63). Fine structure of the protein plugs indicated involvement of bacteria and acidic glycoprotein in fine reticular substance suggestive of fibril formation of PSP/lithostathine/Reg and PAP/Reg III (53, 64). Marotta et al also reported antibacterial activity in human pancreatic juice (65). However, details of the mechanism of bacterial aggregation and antibacterial activity still remain unclear (66).

Anti-inflammatory activity and prognostic indicator

PAP was first observed in rat pancreatic juice 6 hours after induction of experimental pancreatitis with taurocholate or cerulein, reached maximum in the acute phase, and disappeared during recovery (5). The protein was synthesized on the rough endoplasmic reticulum and stored in zymogen granules before being secreted, similar to other pancreatic secretory proteins. PSP/Reg I and PAP/Reg III are members of the pancreatic Reg family of proteins and share common characteristics in structure and function. The absence of PAP in normal pancreas and its extensive induction observed during the early phase of the disease suggest that PAP could be a stress protein or acute phase protein induced upon cell insult. Orelle et al reported elevation of serum PAP in acute (19/19 patients) and chronic (7/10) pancreatitis (67). Iovanna et al demonstrated that monitoring serum PAP in acute pancreatitis patients provides prognostic information (68). Pezzilli et al determined serum amylase, lipase and CRP in addition to serum PAP in 58 patients with acute pancreatitis and 20 with nonpancreatic acute abdomen on admission and during subsequent days of their study. They concluded that the clinical value of serum PAP in acute pancreatitis is quite limited and PAP is not a useful marker for evaluating the severity of the disease (69). Polanc et al also reported that serum PAP was increased in 70% of patients with acute pancreatitis on admission and gave good correlation to APACHEII and CRP. However, they evaluated that the diagnostic specificity of serum PAP is low, because patients, who develop local complications in acute pancreatitis, can-
not be excluded by normal serum PAP levels on admission to the hospital (70). Duarte-Rojo et al evaluated the clinical usefulness of four serum markers, PAP, CRP, interleukin-6, and interleukin-10 in comparison to Ranson’s score as a prognostic marker (71). They concluded that analysis of time frames improved the accuracy of all markers. Serum PAP tends to elevate in progression to acute pancreatitis, but the diagnostic sensitivity and specificity, and the mechanism of increase of PAP in diseases need further studies (72, 73).

Zenilman et al simultaneously determined two different proteins of the Reg family (PSP/Reg I and PAP/Reg III) in sera of experimental acute pancreatitis in the rat and concluded that serum level of PAP/Reg III was a sensitive marker of pancreatic injury, but PSP/Reg I was not (74). Although simultaneous comparison of serum levels of the two proteins has not been reported, serum levels of PSP have been studied in pancreatic diseases. Bluth et al failed to present significant increase of serum Reg I levels during taurocholate-induced acute experimental pancreatitis in rat, though tissue Reg I protein and Reg I receptor increased in the pancreas (75).

In contrast to PSP in human pancreatic secretions, serum PSP levels in pancreatic disease have been reported to be higher in pancreatic diseases than controls by Schmiegel et al (39) and Hayakawa et al (76). Frequencies of serum PSP elevation in both studies were similar to each other in acute (80% and 79%) in the studies of Schmiegel et al and Hayakawa et al, respectively), chronic (60% and 44%) pancreatitis and pancreatic cancer (36% and 42%). The frequencies of serum PAP elevation in acute pancreatitis on admission were 79% in the study of Pezzilli et al (69) and 70% in that of Polanec et al (70). Sensitivities of serum PSP and PAP seem to be similar in human acute pancreatitis.

Elevation of serum PSP tended to be greater in severe acute pancreatitis than in mild pancreatitis. In chronic pancreatitis there was no significant difference in serum PSP levels between calcified and noncalcified pancreatitis. Location of the tumor in pancreatic cancer did not affect serum PSP levels between head and body-tail cancer (76).

Among nonpancreatic diseases chronic renal failure under hemodialysis presented significantly higher serum PSP than other disease groups except for acute pancreatitis. Serum PSP levels in other nonpancreatic diseases did not differ from that of the controls. Frequencies of increased serum PSP were 79% in acute pancreatitis, 44% in chronic pancreatitis and 42% in pancreatic cancer, 100% in chronic renal failure, 33% in gastric cancer, 11% in peptic ulcer, 18% in gallstone, 19% in liver cirrhosis, and 17% in diabetes mellitus (76). Some of the patients with myocardial infarction, cardiac failure, perforation of the GI tract, or ileus in ICU seem to present increased PSP in serum and urine (77).

Verdier et al reported renal lathiothamine in urine, kidney stones, and cells of the proximal renal tubules (78). Tatemichi et al confirmed that urine PSP was eluted at the position corresponding to PSP S2-5 on cation exchange chromatography and was converted to PSP S1 by trypsin digestion (77). Sobajima et al reported that urinary PSP excretion was increased from the initial stage of diabetic nephropathy and the increase became more marked as nephropathy progressed. They suggested that increased PSP excretion might reflect renal tubular dysfunction (79). Total serum PSP level tends to increase in severe acute pancreatitis than in mild acute pancreatitis (76, 80). Serum PSP exists in two molecular forms, PSP S2-5 and PSP S1, in patients with acute pancreatitis. Nakae et al (80) revealed that elevation of serum PSP S1 was greater in severe acute pancreatitis than in mild pancreatitis and the PSP S1 elevation could reflect activation of trypsinogen and subsequent digestion of PSP S2-5 to PSP S1 by trypsin in the pancreas. Satomura et al also reported elevation of serum PSP in pancreatic disease, other digestive diseases including cancer and chronic renal failure, and correlation of serum PSP and elastase-1 in chronic pancreatitis and pancreatic cancer (81).

The release mechanism of PSP is unknown. A mechanism similar to that for the release of pancreatic enzyme may be partly at work, because a significant correlation was present between serum PSP and trypsin (76), or elastase-1 (81). Elevation of serum PSP in patients after ERCP was noted, even when evidence of pancreatitis was absent (76). Reflux of pancreatic secretion as well as acinar cell damage may contribute to the elevation of serum PSP. PSP measurements in various materials may offer new diagnostic or pathophysiological information different from those obtained from conventional markers. However, further studies are required including tissue origin of PSP, because serum PSP levels did not fall below the normal lower limit in patients after total pancreatectomy (76). Serum PSP was transiently increased after stress such as anesthesia in animals without pancreatic injury (82) and critical diseased in the ICU patients (77). Pro- and anti-inflammatory cytokines might induce expression of PSP/Reg/PAP family (11, 29, 71, 72, 83). Pancreatic stellate cells (PSC) play a central role in fibrogenesis associated with acute and chronic pancreatitis. Assuming a protective role of PSP/reg protein, a secretory stress protein, from its dramatic upregulation during acute and chronic pancreatitis, Li et al investigated soluble collagen, fibronectin, TIMP-1 and -2 in PSC supernatants after addition of the PSP/reg protein. The findings obtained suggest that PSP/reg might have a protective function in repair phase of acute and chronic pancreatitis by promoting resolution of fibrosis (84).

**Islet regeneration and diabetes**

Regenerating islets can be induced by the administration of poly (ADP-ribose) synthetase inhibitors to 90% depancreatized rats. Amelioration of the surgical diabetes obtained was observed with the morphological evidence of marked enlargement and regeneration of B cells in the islets. Administration of recombinant rat Reg protein showed similar effects to the surgical diabetes (85). The result indicated that Reg protein was a growth factor for pancreatic B cells and also could be used as another therapeutic approach for diabetes mellitus (85, 86). However, tumor-promoting activity
of Reg protein should be considered for its therapeutic effect on diabetes (87).

Chronic pancreatitis is a progressive or recurrent inflammation of the pancreas, resulting in exocrine and/or endocrine insufficiency. Management of pain, steatorrhea, pancreatic stone formation, and diabetes are important for long-term prognosis of the patients. The pancreatic acinar cells play an important role in development and maintenance of B cells in the pancreatic islets. Loss of the endocrine function, especially of B cell in the islets progresses in parallel to the decrease of exocrine function in chronic pancreatitis in clinical (88-91) and experimental (92, 93) studies. Reg/PSP is an acinar product and could modulate the islet function in chronic pancreatitis with acinar depletion as well as in primary diabetes (93).

The role of PSP/Reg in pancreatic stone formation is still not clear, either promotor or inhibitor. Tropical calcific pancreatitis (TCP) is an idiopathic, juvenile, nonalcoholic form of chronic pancreatitis with a unique geographical distribution, while fibro-calcular pancreatic diabetes (FCPD) is a condition, characterized by the development of diabetes secondary to TCP. A genetic etiology for TCP and FCPD has been suggested from its familial aggregation and geographical distribution (94-96). However, comprehensive screening for Reg IA gene rules out association with TCP and FCPD (97, 98).

Shervani et al screened sera from type 1 and type 2 diabetes subjects for anti-Reg autoantibodies in search for correlations in the general characteristics of the subjects with the presence of anti-Reg autoimmunity and confirmed the attenuation of Reg-induced B cell proliferation by the autoantibodies (99). Thus, autoimmunity to Reg may be associated with the development/acceleration of diabetes in some patients. Reg proteins may be a target of an autoimmune response in type 1 diabetes with consequent production of autoantibodies and failure of regeneration. Astorri et al reported that increased serum Reg IA protein in type 1 and type 2 diabetes and anti-Reg IA antibodies in type 1 diabetes. These findings may promote Reg IA protein and autoantibody as new tools in evaluating and monitoring B-cell regeneration and autoimmunity (100). Liu et al suggested Reg II as an autoantigen on B-cells that elicits T-cell attack in type 1 diabetes (101). Hou et al investigated therapeutic potentials by intramuscular delivery of a naked DNA plasmid encoding proinsulin and pancreatic Reg III protein on streptozotocin-induced type 1 diabetes mice and speculated that it might serve as a promising candidate for the gene therapy of type 1 diabetes (102).

Mitogenesis and cancer

Watanabe et al examined expression of the human Reg gene in various normal and tumor tissues in human (25). They reported that the human Reg gene was expressed in the pancreas, and at lower levels, in the gastric mucosa and the kidney. To date, was no detectable Reg mRNA has been found in the liver, spleen, brain, thyroid gland, submandibu-
cosa at the transition zone of colorectal cancer (CRC) and occasionally within the tumor itself. There was no correlation with histologic grade or 5-year patient survival and it may be a sensitive marker for mucosa at risk for development of neoplasia (118). Reg IA immunostaining pattern is significantly different between non-neoplastic and neoplastic lesions and immunohistochemical analysis of Reg IA expression is useful for the differential diagnosis of non-neoplastic and neoplastic lesions in long-standing ulcerative colitis-associated neoplasia (119).

There is no significant correlation between the expression of Reg and PAP genes and tumor stage, tumor sites, age or sex of the patients with colorectal cancer. However, in patients with non-metastatic disease who underwent ostensibly curative surgery, the expression of Reg alone and co-expression of Reg with PAP had a highly significantly adverse effect on survival (120). Astrosini et al pointed out overexpression of Reg IA in colorectal cancer with peritoneal carcinomatosis and its potential for a prognostic marker (121). Expression of Reg IA, IB, III, and HIP/PAP is negatively correlated with depth of invasion of CRCs. Reg IB and HIP/PAP could be considered reliable markers of favorable prognosis of CRC patients (122).

Reg IV is the most recently discovered member of the family and shares structural and functional features with other members of the family (123). Based on the primary structures of the Reg proteins, the members of the family have been grouped into four subclasses, Reg I, II, III and IV (124). Reg IV is different from Reg I in its tissue expression profiling. In normal colonic mucosa there is no expression of Reg I (25, 117, 118). On the contrary, Reg IV is relatively specific for the GI tract including normal, benign and malignant tissues (125).

Reg IV may play an important role in the initiation of colorectal adenoma differentiation. The discovery of Reg IV may be useful for early diagnosis of colorectal adenoma formation (126, 127). Reg IV expression is upregulated in adjacent non-cancerous mucosa and adenomas, then it is decreased in CRCs. The overexpression may be an early event in CRC carcinogenesis. Reg IV may be a useful marker for intestinal type mucinous carcinoma and a good candidate as a molecular therapeutic target for CRCs (128).

Harada et al demonstrated that the expression of Reg I protein was significantly dependent on the histologic differentiation of intrahepatic cholangiocarcinoma (ICC) and on the grade of biliary dysplasia (precursor lesion of ICC) in hepatolithiasis. They suggested that neoexpression of Reg I is a good marker for biliary mucosa at risk for development of ICC, probably via a cell-proliferative effect (129). Reg IA and PAP mRNA levels were measured in hepatocellular carcinoma (HCC) by Yuan et al PAP expression designated a subset of low-grade, low-stage HCC with frequent betacatenin mutation and hence a more favorable prognosis, whereas further genetic or epigenetic alterations, such as p53 mutation and Reg IA expression, lead to more advanced HCCs (130). Tamura et al reported that Reg IV expression is more frequently observed in well to moderately differentiated compared to poorly differentiated adenocarcinomas and it is significantly correlated with expression of caudal-related homeobox transcription factor (a candidate for involvement in the induction of intestinal metaplasia). They suggested that Reg IV is involved in gallbladder carcinoma carcinogenesis through intestinal metaplasia and is associated with relatively favorable prognosis in patients after surgery (131).

Reg IA protein functions as a growth factor for gastrointestinal cancer cells, and its mRNA expression is associated with a poor prognosis in patients with cancer. Yamauchi et al confirmed that PPARgamma-agonist thiazolidinediones (TZDs) inhibit cell proliferation and Reg IA protein/mRNA expression in gastrointestinal cancer cells through a PPARgamma-dependent pathway. TZDs can be a candidate for novel anti-cancer drugs for patients with gastrointestinal cancer expressing both Reg IA and PPARgamma (132). Bishnupuri et al demonstrated that recombinant human Reg IV protein protected normal intestinal crypt cells from irradiation (IR)-induced apoptosis and overexpression of Reg IV in human colorectal cancer (CRC) cells was associated with increased resistant to IR-induced apoptosis. They tested a hypothesis that antagonism of Reg IV signaling would be a useful tool to increase CRC cell susceptibility to IR-induced apoptosis. Two complementary approaches of Reg IV antagonism using specific monoclonal antibodies and small interfering RNAs were examined in models of human CRC. Both approaches resulted in significantly reduced proliferation and increased apoptosis (133). Immunohistochemical analysis revealed that Reg IA expression was higher in pancreatic cancer cell with diabetes than in those without diabetes. Reg IA may act as one of the tumor promoter and contribute to the aggressive nature of pancreatic cancer, especially in those with diabetes (134).

Takayama et al reported that serum Reg IV was higher in patients with pancreatic cancer and those with chronic pancreatitis. However, no correlation was shown between Reg IV and CA19-9. Immunohistochemical analysis demonstrated a correlation between serum Reg IV and Reg IV expression in pancreatic cancer (135).

Eguchi et al observed that the patients with higher serum Reg IV levels presented an unfavorable histologic response to chemoradiotherapy, and experienced local recurrence postoperatively. They suggested that overexpression of Reg IV can be used as a clinical predictive biomarker (136).

Reg genes are up-regulated in a variety of GI malignancies and have been associated with a more aggressive tumor phenotype. Antagonism of Reg signaling or combination of Reg proteins with other anti-cancer therapies can be more effective tools for treatment of GI malignancies.

Future Prospects

PSP, PAP and Reg were found in the pancreas by independent research groups during investigation of the patho-
physiology of chronic pancreatitis (PSP), acute pancreatitis (PAP) and diabetes (Reg), respectively. Subsequent analysis of the three proteins revealed that PSP and Reg are identical and the three proteins and their isoforms belong to the same family of proteins, although the functional roles of the proteins have not been fully elucidated. Focuses of research interests of the proteins depend on the circumstances of the discovery of the respective protein. More research efforts should be directed toward the functions of regeneration, mitogenesis, carcinogenesis, anti-inflammation and anti-apoptosis of Reg, PAP and their isoforms. We can expect more elaborate markers of prognosis and effective therapeutic tools for inflammatory and neoplastic diseases in the future.

The authors state that they have no Conflict of Interest (COI).

References


120. Macadam RC, Sarela AI, Farmery SM, Robinson PA, Markham AF, Guillou PJ. Death from early colorectal cancer is predicted by the presence of transcripts of the REG gene family. Br J Cancer 83: 188-195, 2000.


