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Review

Stress kinases and heat shock proteins in the pancreas: possible roles in normal function and disease

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Abstract: Mitogen-activated protein kinases (MAPKs) and heat shock proteins (Hsps) are ubiquitous proteins that function in both normal and stress-related pathophysiological states of the cell. Recent advances in the study of such Hsps and their interaction with signaling kinase cascades, including the cloning of new members, has helped to define their physiological roles in various tissues. In the pancreas, three major MAPKs, ERKs, JNKs, and p38, have been demonstrated. While intracellular signals involved in the ERK cascade have been most extensively investigated, only a few upstream regulators and downstream effector proteins of the JNKs and p38 MAPK are known in the pancreas. Similarly, a number of Hsps have been identified in pancreas, including Hsp27, Hsp60, and Hsp70. Although the activation of various MAPKs and the induction of Hsp expression have clearly been demonstrated following experimental exposure of rodent pancreas to stress conditions, it remains to be determined whether Hsps have a protective or detrimental effect during acute pancreatitis or at the onset of pancreatic carcinoma. This review will summarize current knowledge of the regulation and function of stress-activated kinases and stress proteins in the pancreas.

Key words: pancreas, MAPK, Hsp, stress kinase

Introduction

Mitogen-activated protein kinases (MAPKs) are serine-threonine directed protein kinases that were originally identified as mitogen-activated. Now they are known to be activated by a variety of different stimuli, ranging from cytokines, growth factors, neurotransmitters, and hormones to cell adherence and different kinds of stress.[1] These kinases are expressed in a wide variety of eukaryotic cells. While in yeast and nematodes much is known about the biological functions of various MAPK cascades, in differentiated mammalian cells only little is presently known. This is not only due to the difficulty of altering gene function in differentiated cells, but also to cell-type dependent variations in their function. Thus, the role of a particular kinase cascade in pancreatic acinar cells, for example, has to be studied in those specific cells. In addition, specificity of MAPK responses is also determined by the specific stimuli to which a tissue or cell type might respond. MAPKs are known to regulate a number of cellular processes, including gene transcription, protein translation, metabolism, and cytoskeletal organization. As such, the MAPKs have been shown to be involved in control of cell growth, differentiation, survival, apoptosis, and cytokine production.

As known so far, MAPK cascades are universally composed of three protein kinases acting in series: a MAPK that is activated by a MAPK kinase (MKK) which is, in turn, activated by a MAPKK kinase (MKKK).[2] A common feature of the MAPKs is that they are activated by dual phosphorylation of tyrosine and threonine residues present in a T-X-Y sequence motif. At the initiating end of each cascade, MKKKs receive information from cell surface receptors or interact with small guanosine triphosphate (GTP)-binding proteins of the Ras superfamily.[3] These include Ras and members of the Rho GTPase family, comprised of Rho, Rac, and Cdc42, and all are generally active when liganded with GTP.[4] Large families of guanine nucleotide exchange factors (GEFs) catalyze the release of GDP and conversion to the GTP-bound "on" state of the small G-proteins. Similarly, GTPase-activating proteins (GAPs) deactivate the small G-proteins by accel-

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erating the intrinsic rate of hydrolysis of bound GTP to guanosine diphosphate (GDP).[5]

Activated MAPKs can then further regulate downstream kinases or carry the information to the nucleus or cytoskeleton by translocating within the cell.[6,7] Following nuclear translocation, MAPKs phosphorylate and modulate a variety of transcription factors.[8] Furthermore, MAPKs or their downstream targets, including the small heat shock protein 27 (Hsp27), participate in the regulation of structure and function of the cytoskeleton. Currently, there have been 14 MKKKs, 7 MKKs, and 12 MAPKs identified in mammalian cells. There are five independent MAPK cascades known, which are designated $MAPK^{erk1/2}$, $MAPK^{p38}$, $MAPK^{jnk}$, $MAPK^{erk3/4}$, and $MAPK^{erk5}$.[9] Because little is known about $MAPK^{erk3/4}$ and $MAPK^{erk5}$, this review will focus on the three original kinase cascades.

The ERK1/2 cascade

The first MAPK cascade identified in vertebrates was a growth factor signaling pathway leading to the activation of ERK1 and ERK2, also known as p42 and p44 MAPK, based on their molecular mass.[10] The name ERK for Extracellular Regulated Kinase is derived from the fact that a variety of extracellular signals activates these kinases, including agonists acting on tyrosine kinase and G-protein-coupled receptors. ERK1/2 are activated by mitogens in all cells and appear to be essential for mitogenic signaling (see[11] for recent review). Prolonged activation and nuclear retention is required for transcription of cyclin D1,[11] suggesting a role for the ERKs in regulating entry into the cell cycle. Outside the nucleus, ERKs may also contribute to proliferative responses; in activated cells half of the ERKs are bound to the cytoskeleton.[7]

ERKs are activated in a multistep process. In the original mitogen-activated pathway, a growth factor receptor with a tyrosine kinase domain autophosphorylates itself to provide docking sites for adaptor proteins such as Grb2 (Growth factor receptor-bound protein 2) and Shc (Src homology / collagen related). These adapter proteins promote the recruitment of GEFs for Ras, such as SOS (named for its drosophila homolog Son of Sevenless), which facilitate the exchange of GDP for GTP bound to Ras. Activated Ras then activates MAPKKKs, represented by the Raf family members cRaf-1, A-Raf, and B-Raf, by recruiting them to the plasma membrane, where they also become phosphorylated. Activated Raf kinases then phosphorylate the MAPKKs MEK1 and MEK2 (MEK for MAP kinase or ERK Kinase) on serine residues, thereby activating them. Activated MEK1/2 catalyzes the dual phosphorylation of ERK1/2, which either translocate to the nucleus where they phosphorylate transcription factors, including Elk-1 and c-Myc, or phosphorylate other MAPK activated protein kinases such as MAPKAPK-1 (also known as $p90^{RSK}$), and Mnk1/2 (MAPK signal-integrating kinase) (see Fig. 1). RSKs phosphorylate transcription factors and histone H3, while Mnk1/2 has been shown to phosphorylate the translation initiation factor eIF4E. ERK1/2 activation can be blocked by use of the MEK inhibitor PD 98059. ERK activation is terminated by a dual specific phosphatase such as MAPK phosphatase-1 (Mkp-1).

Stress activated kinases (JNK and p38) and their regulation

Subsequently, two additional MAPK cascades were identified in mammalian cells, leading to activation of JNKs, named for their activity as Jun Kinases,[12–14] and p38 MAPKs, named for the molecular mass of the parent molecule.[15–17] In contrast to the ERKs, which are most potently activated by hormones and growth factors, the JNKs and p38 are most potently activated by proinflammatory cytokines and environmental stresses such as UV irradiation and osmotic shock.[8,18] Thus, JNKs and p38 are also known as SAPKs (for Stress-Activated Protein Kinases). JNK/SAPKs may also play a role in mitogenic signaling, but their major role is thought to be in regulating apoptosis. However, this regulation appears to be cell type-specific; in some cells activation of JNKs protects against apoptosis, while in other cells apoptosis is promoted by this pathway.[11,19,20]

The JNK cascade is composed of JNK1, JNK2, and JNK3 as MAPKs, which are activated by dual phosphorylation by the MAPKKs MKK4 and MKK7.[21,22] A variety of MAPKKKs, including the MEK kinases MEKK1-5, the mixed lipid kinases MLK2/3, and other kinases including ASK1, TAK, and Tpl2,[23–28] activate these MKKs. Known activators of these MAPKKKs are the small GTPases Rac, PAK, and Cdc42. Ultimately, JNKs phosphorylate transcription factors such as c-jun, c-fos, and serum response factor accessory protein-1 (Sap-1) (see Fig. 1). Interestingly, distinct JNK isoforms show different substrate specificity and thereby may differentially modulate gene expression. JNKs also prevent degradation of several nuclear factors by selectively blocking their ubiquitination.[20]

For p38 MAPK, four different isoforms are known and designated α, β, γ, and δ,[9] and their identified MAPKKs are MKK3, MKK4, and MKK6.[26,27,29–33] The known upstream MAPKKKs are ASK1, TAK, MLK2, and MEKK1[34] and at the level of G-proteins, Cdc42 is a known activator of MAPKKKs in this cascade. In mammalian cells, few downstream targets of p38 MAPKs are

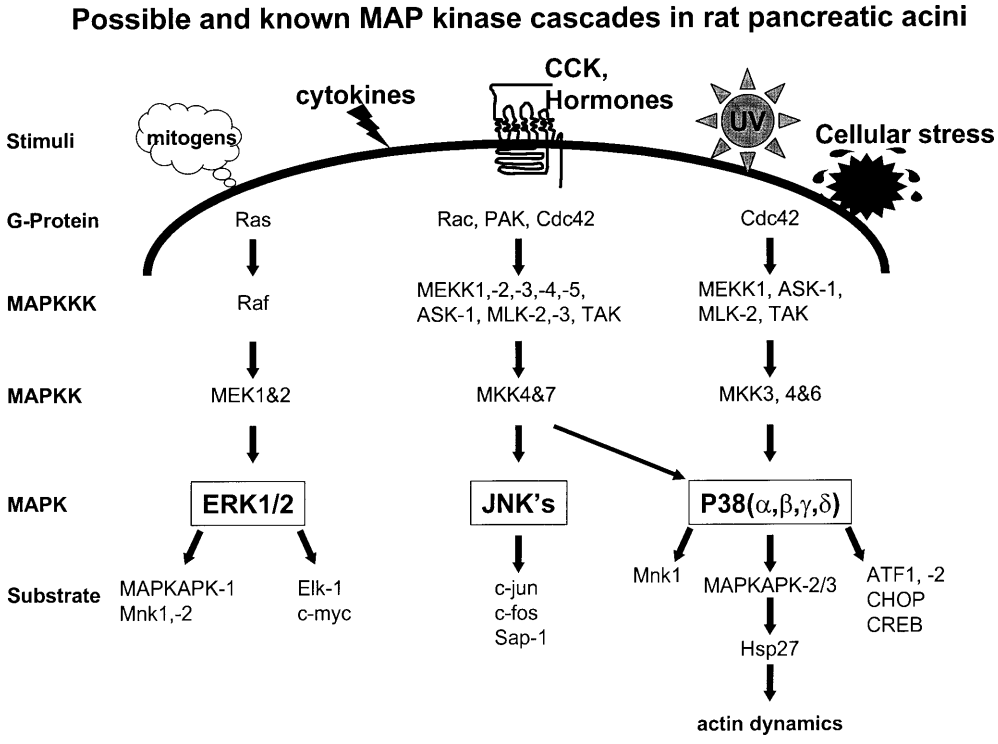

Fig. 1. Schematic representation of three mitogen-activated protein kinase (*MAPK*) signaling cascades. A variety of cell surface receptors transduces signals through G-proteins, which in turn activate a three-module kinase cascade. Each MAPK transmits signals to the nucleus, by translocation to the nucleus, and/or phosphorylates transcription factors. In addition, MAPKs also activate additional kinases. Activation of these cascades helps to coordinate the expression and regulation of different genetic programs. See text for details, including explanation of acronyms

known. Identified substrates for the p38 MAPKs are the transcription factors CHOP, ATF-1, ATF-2, and CREB (see references in[33]). In addition, p38 MAPKs can trigger the activation of other kinases such as Mnk1/2 and MAPKAPK-2, and-3, the latter two of which regulate cytoskeletal changes through phosphorylation of Hsp27.[35–37]

Heat shock and other stress proteins

In addition to stress kinases, there are a large number of stress-induced proteins, some of which also undergo regulatory phosphorylation. Cells and tissues are challenged constantly by exposure to extreme conditions that cause acute and chronic stress. Prolonged exposure to stress interferes with efficient operations of the cell and can negatively affect the biochemical properties of proteins. In adverse environments, proteins unfold, misfold, or aggregate. Upon heat shock, the elevated synthesis of molecular chaperones and proteases acts to repair protein damage and assists in the recovery of the cell.[38] Adaptation to stress leads to elevated expression of heat shock genes such that molecular chaperones are rapidly synthesized and deployed to prevent protein misfolding. Stress-induced transcription requires activation of a heat shock factor (HSF) that binds to the heat shock promoter element (HSE). So far, multiple HSFs have been found to regulate the heat shock response (for details see[38]).

There are many members of the Hsp family as well as several other families of stress inducible proteins. Hsps are defined physiologically by their ability to be induced by heat shock and, in molecular terms, by the presence of a functional heat-shock element in their promoter.[39] Heat shock proteins are named after their molecular weight, and include Hsp90, Hsp70, Hsp60, Hsp20, and Hsp8.5, and some are localized as cytosolic proteins (see also Table 1). Hsp70 is involved in the folding of newly synthesized proteins in the cytosol. Immunoglobulin heavy chain-binding protein (BiP), also named glucose regulated protein 78 (Grp78), a member of the Hsp70 family, is localized in the lumen of the endoplasmic reticulum (ER) and is involved in the transport of newly synthesized proteins across the ER membrane.[40] It is also well established that induction of Hsps in response to stress correlates with increased resistance to subsequent cellular damage. It has been demonstrated that this protective effect is, in part, the result of inhibition of apoptosis (for details see[41]). Altered programmed cell death has been associated with pathological processes such as cancer, infections, and chronic inflammation. However, Hsps are also present in significant amounts in unstressed cells, where they accomplish essential functions such as chaperone activities that have been shown for members of the families of Hsp90, Hsp70,

Table 1. Heat shock protein (Hsp) families, their known members and function

Family	Protein	Function
Hsp20	Hsp27	Cellular resistance to hydrogen peroxide, ultraviolet radiation, chemotherapeutic drugs. Resistance of actin polymers to cytochalasin. Tolerance of hyperthermia. Increased expression during pancreatitis.
	αB-crystallin	αB-Subunit is induced by heat shock and osmotic stress, and re-locates to the nucleus after stress. Also known as Hsp20. Cellular tolerance of hyperthermia, ischemia. Resistance to hydrogen peroxide and tumor necrosis factor.
Hsp60	Hsp60	Tolerance of hyperthermia and ischemia.
	Hsp65	Tumor regression.
Hsp70	Hsp70	Tolerance of hyperthermia and ischemia. Regulation of heat shock response.
	Hsc70	Tolerance of hyperthermia.
	Hsp72	Protection against heat-induced nuclear protein aggregation, hypoxia, and thermal radiosensitization.
	Grp78	Transport of newly synthesized proteins across the ER.
Hsp90	Hsp90	Tolerance of hyperthermia and ischemia. Cell proliferation and cell cycle control. Glucocorticoid and other steroid receptor function.

Grp, glucose-regulated protein; ER, endoplasmic reticulum; Hsc70, constitutive form of Hsp70

Hsp60, and Hsp20.[42] In addition, there are specific functions; for example, Hsp90 forms a complex with steroid receptors and dissociates upon ligand binding.

A characteristic feature of all small heat-shock proteins described so far, including Hsp27 and αB crystallin, is their oligomerization to large intracellular aggregates (400- to 800-kDa or even larger). Hsp27 has been shown to act as a molecular chaperone, probably when existing as large aggregates, and it facilitates the refolding of partially denatured proteins into active conformations in vitro.[43,44] In addition, Hsp27 can also act as a phosphorylation-regulated F-actin barbed end-capping protein capable of inhibiting actin polymerization.[45] Monomers or small oligomers mediate this latter action. The oligomeric size of Hsp27 is regulated by phosphorylation. Phosphorylation of Hsp27, by activation of p38 MAP kinase and MAPKAP kinase-2/3, stabilizes the microfilaments in cells against oxidative and other stresses. This action is thought to be a specific function of small oligomers, or possibly even monomers of Hsp27.[46]

Kinase cascades and heat shock proteins in the pancreas

The ERK1/2 pathway in pancreatic acini

Pancreatic secretagogues were first shown to induce the tyrosine phosphorylation of and increase the kinase activity of ERK1/2 in isolated rat pancreatic acini as well as in in-vivo pancreas.[47,48] These studies showed that cholecystokinin (CCK), carbachol, bombesin, and active phorbol ester all activated ERK1/2, while secretin and vasoactive intestinal polypeptide (VIP) did not. Maximal activation of ERK1/2 occurred within 2–10 min, both in vivo and in vitro. In several cell types, cAMP has been shown to inhibit activation of ERKs by feedback phosphorylation, but in acini this effect was not seen. Subsequently, it was shown that CCK also activated MEK1 and MEK2,[49] Raf,[50] and the binding of GTP to the small G-protein Ras,[49] indicating the existence of a complete kinase cascade. In addition, it was shown that CCK also leads to the activation of the downstream kinase MAPKAPK-1.[51] Immunoblotting revealed three different forms of Raf in pancreatic acinar cells, Raf-A, Raf-B, and c-Raf-1, and two forms of MEK, MEK1 and MEK2, all of which were found to be regulated by CCK.[50] CCK and epidermal growth factor (EGF) were observed to activate ERK1/2 by different mechanisms. CCK and active phorbol ester stimulated Raf activity in a protein kinase C (PKC)-dependent manner, whereas EGF's effect was significantly smaller and PKC-independent. By contrast, EGF significantly increased the steady state level of GTP-bound Ras, while CCK had no effect.[50] In another study, EGF, and to a lesser extent CCK, stimulated the tyrosyl phosphorylation of Shc and formation of a Shc-Grb2-Sos complex in rat pancreatic acinar cells, thereby providing a potential link between G_q-coupled CCK receptor stimulation and Ras activation in these cells,[52] although, as mentioned above, the steady state level of GTP-Ras did not change.[50] In pancreatic-derived AR42J cells, which possess primarily cholecystokinin B receptors, similar results were obtained, showing that gastrin activates ERKs.[53] Furthermore, in these cells it was also shown that gastrin increased tyrosyl phosphorylation of Shc and its association with the Grb2-Sos complex.[53] More recently, it was shown that carbachol and EGF induced tyrosyl phosphorylation of Shc and its associa-

tion with Grb2-Sos in isolated gastric canine parietal cells.[54] Thus, while a potential mechanism for Ras activation in acini exists, the role of Ras in CCK-induced ERK activation is not totally clear.

It is also of interest that up to 90% of pancreatic cancers possess a mutated and permanently activated form of Ras. Nicke et al.[55] used an in-vitro adenoviral-mediated gene transfer system to express a dominant-negative mutant Ras (Ras^{N17}) in isolated rat pancreatic acini. Interestingly, expression of the dominant-negative Ras^{N17} blocked the ability of CCK to stimulate acinar cell JNK activity and DNA synthesis, but had no effect on the activation of ERK1/2. Conversely, EGF-mediated ERK activation was blocked. For more detail on this MAPK cascade in acinar cells see a previous review.[56]

The JNK cascade

JNKs are activated similarly to the ERKs by dual phosphorylation on tyrosine and threonine residues and have been thought to be activated primarily by stress or cytokines. Only few reports exist concerning the regulation of JNKs in the pancreas. CCK, carbachol, and bombesin have been shown to activate two isoforms of JNK (p46 and p55) both in isolated acini and in the intact rat pancreas.[47,57] VIP showed no activation of JNKs, similar to the findings with ERKs. Interestingly, in isolated acini, higher levels of basal JNK activity are observed compared with in vivo levels, which might indicate JNK activation in vitro caused by mechanical stress during preparation of the acini. However, the activation of JNKs requires much higher concentrations of agonist than does the activation of ERKs, and is slower in in-vitro experiments. It is also of interest that increasing intracellular Ca^{2+} levels, brought about by the use of cyclopiazonic acid, active phorbol ester, and bombesin, the last two of which are known to stimulate ERK1/2 activity in acini, have little effect on JNK activity.[47] These differences in the activation pattern support the hypothesis of a different activation mechanism, probably at the G-protein level.

It is well established that high concentrations of CCK, but not bombesin, can induce pancreatitis in rats and mice.[57] Therefore, it seems likely that the JNK activation by high concentrations of CCK may in fact be a stress response and more relevant to pathophysiological conditions. This is also underlined by the fact that JNK activation is one of the earliest observable events known to correlate with the development of pancreatitis in rats.[57] A more recently published study compared the activation of ERK1/2, JNKs, and p38 MAP kinase after cerulein hyperstimulation in rats.[58] Here, the authors report that the activation of p38 MAP kinase was followed by the activation of ERK1/2 as the earliest measurable events after cerulein-induced pancreatitis. Although CCK activates all three MAP kinases, the JNKs as stress kinases and mediators of the apoptotic pathway are most likely to be involved in the pathogenesis of cerulein-induced pancreatitis. On the other hand, whole body hyperthermia induced the expression of heat shock proteins and was shown to protect against cerulein pancreatitis when hyperstimulation was applied 24–48 h following preconditioning,[59] but the whole body hyperthermia did not induce JNKs. Unfortunately, there is presently no specific JNK inhibitor commercially available to investigate in more detail the role of JNKs in the development of experimental pancreatitis. A recent abstract reports a novel inhibitor of JNKs in pancreatic acini; however, the specificity of this compound remains to be evaluated.[60] Clearly, to dissect the individual roles of pancreatic JNKs during induction of pancreatitis more studies are needed using specific inhibitors or transgenic animals.

p38 MAP kinase pathway

The presence of the p38 MAP kinase cascade in rat pancreatic acinar cells and the tyrosyl phosphorylation of p38 MAP kinase after CCK treatment was recently demonstrated by Schäfer et al.[36] In this study it was shown that CCK, as well as carbachol, bombesin, and sorbitol-induced osmotic stress, activated p38 MAP kinase within minutes and in a dose-dependent manner with a maximal 4.4-fold activation over basal. Increased levels of intracellular Ca^{2+} with the use of cyclopiazonic acid induced only a small increase in p38 MAP kinase activity, but the combination of active phorbol ester and cyclopiazonic acid mimicked the effects of CCK on p38 MAP kinase activity. VIP, which increases intracellular cAMP levels and thereby activates protein kinase A, had no effect on p38 activity, similar to its lack of effect on ERKs and JNKs.

Using SB 203580, a specific p38 MAP kinase inhibitor, it was found that p38 MAP kinase activity was required for MAPKAP kinase-2 activation and the phosphorylation of the small heat shock protein Hsp27 in pancreatic acini.[36] In addition, it was shown by two independent methods, a rhodamine phalloidin binding assay and confocal fluorescence microscopy, that CCK-induced changes of the actin cytoskeleton were largely blocked by pretreatment with SB 203580. These data have conclusively demonstrated that this pathway is important for regulating the actin cytoskeleton in isolated pancreatic acinar cells. Furthermore, these findings elucidated a role for p38 MAP kinase not only in response to stress, but also in physiological signaling by gastrointestinal hormones such as CCK, which act via G-protein coupled receptors. P38 MAP kinase may also play an important role during induction of pancreatitis,

as its rapid, strong, and sustained activation after a single injection of a supramaximal cerulein dose was shown recently.[58] Compared with ERK1/2 and the JNKs, p38 MAP kinase was the only kinase to be activated after preconditioning through hyperthermic stress, indicating its possible role in mediating the hyperthermia-induced pancreatic expression of Hsps.[58]

Pancreatic heat shock proteins and their roles

Little is currently known about the expression or role of heat shock proteins (Hsps) in pancreas. Members of four families of the major Hsps (90, 70, 60, and 20) are either constitutively present in pancreas or can be induced. Certain stresses, including heat shock, water-immersion, hyperosmolarity or supraphysiological concentrations of CCK not only activate JNKs and p38 but also induce synthesis of heat shock proteins.[59,61–63] When the body temperature of rats was elevated to 42°C and maintained for 20 min, induction of pancreatic proteins with molecular weights of 90, 72, 59, 58, and 30 kDa was observed, with the 72-kDa protein showing the greatest response.[59] This 72-kDa protein was identified as Hsp72 and represents the inducible form of Hsp70. In addition to the inducible form of Hsp70, a constitutive form, Hsc70, was also present and it can also be induced by hyperthermia.[59] Furthermore, it was demonstrated that the induction of heat shock protein expression, most likely the expression of Hsp70, correlated well with the time course and degree of protection against cerulein-induced pancreatitis. In contrast to these data are data published by Otaka et al.,[63] who found that water immersion specifically induced Hsp60 and thereby protected against cerulein-induced pancreatitis, whereas hyperthermia-induced Hsp70 did not protect against cerulein-induced pancreatitis. The observed protective effects of Hsp60 and Hsp70 are most likely due to their chaperone function. In another study the same authors who showed previously that hyperthermia protected against cerulein-induced pancreatitis observed that cerulein without hyperthermia dose-dependently increased Hsc70 mRNA levels but led to a 50% reduction of Hsc70 protein levels.[64] For Hsp60 they found that protein levels were reduced after cerulein hyperstimulation, whereas submaximal amounts of cerulein had no effect.[64] These data are contrary to those in a previous study, which reported that cerulein-induced pancreatitis not only increased the Hsp70 mRNA expression but also increased Hsp70 protein expression.[61] One way to further investigate the role of Hsp70 in protecting the pancreas after supramaximal secretagogue stimulation will be by using transgenic animals that overexpress Hsp70.

Hsp27 in the pancreas and its phosphorylation has been the subject of several recent studies. Hsp27 was identified as a regulated phosphoprotein both by incorporation of ^{32}P into serine residues and by a shift in its isoelectric point after stimulation with CCK.[36,65] Three forms were identified as di-, mono-, and un-phosphorylated Hsp27, consistent with the fact that rat and mouse Hsp27s are phosphorylated on serines 15 and 86.[36,65] As reviewed above in the p38 MAP kinase pathway, it has been shown previously that Hsp27 affects F-actin polymerization and that CCK alters the acinar cell cytoskeleton.[36] Quantitation of the F-actin content after CCK stimulation, using a rhodamine-conjugated phalloidin binding assay, revealed a rapid decrease in total F-actin content, followed by a significant increase after 40 min. These effects were largely blocked by the p38 inhibitor SB 203580, indicating that the p38 MAP kinase/Hsp27 pathway plays a role in regulating actin dynamics after CCK treatment in isolated rat pancreatic acinar cells. Confocal fluorescence microscopy of rhodamine phalloidin-stained isolated pancreatic acinar cells supported these findings. Treatment with 1nM CCK induced a rapid loss of subapical membrane staining, followed by an increased diffuse cytoplasmic actin staining after 40 min, accompanied by disruption of the subapical actin network. These effects were also largely inhibited by pretreatment with SB 203580.[36]

A role for Hsp27 and CCK-induced phosphorylation was also investigated in CHO cells that were stably transfected with the CCK-A receptor. Similar to findings in rat pancreatic acini, CCK dose-dependently induced changes of the actin cytoskeleton, including cell-shape changes and actin fragmentation in these cells.[66] Overexpression of human wt-Hsp27, which includes three regulatory phosphorylation sites (serine[15,78,82]), and mutant 3D-Hsp27, in which the serine residues were mutated to aspartic acid, thereby mimicking the phosphorylated state, inhibited the effects on the actin cytoskeleton seen after high-dose CCK treatment. However, overexpression of non-phosphorylatable mutants in which the serine residues were mutated to alanine or glycine, 3A- and 3G-Hsp27, did not protect the actin cytoskeleton.[66]

These findings are supported by those of another study, in which arginine-induced pancreatitis increased the expression of Hsp27 and Hsp70 and also altered the actin cytoskeleton. In this study, intraperitoneal injection of 4.5 g arginine per kg bodyweight induced a form of an acute necrotizing pancreatitis with dramatic changes of the actin cytoskeleton and moderate increases of Hsp27 and Hsp70 expression. Injection of a lower dose of arginine (3.0 g/kg) induced a mild form of pancreatitis but a much bigger increase in Hsp27 expression and better preservation of the actin cytoskeleton.[67] Both studies in CHO cells and rat pancreas suggest that the p38 MAP kinase/Hsp27 pathway might play an important role in regulating the organization of

microfilaments after CCK treatment. To further investigate the role of Hsp27, the authors are currently doing studies with transgenic animals that overexpress wt-Hsp27 or mutant Hsp27 in pancreas. Other recent studies reported in abstract form showed that cerulein-induced acute pancreatitis resulted in the induction of heat shock factor-1 and the induction of Hsp70,[68] and that the induction of Hsp70 by the culturing of pancreatic fragments reduced the cerulein-induced activation of trypsinogen.[69] Another recent study examined the significance of different Hsp expression in pancreatic carcinoma. It was shown that the expression of Hsp60 was increased in pancreatic carcinoma cells compared with expression in non-neoplastic ductal cells, and that differential expression of Hsp27 and Hsp70 was found, but did not appear to affect survival.[70] Such studies may help us to further understand the pathophysiology of models of acute pancreatitis and help to identify new treatment strategies.

Conclusion

The activation and regulation of mitogen-activated protein kinases (MAPKs) in mammalian cells is a broad and rapidly growing research field. These kinase cascades play an important role in transducing environmental stimuli to the transcriptional machinery in the nucleus, thereby controlling gene expression, by phosphorylating and altering the activity of other regulatory molecules, and by affecting the microtubule and microfilament components of the cytoskeleton. Increasing knowledge of their physiological functions may help us to identify their roles in disease and thereby provide new therapeutic approaches.

We have provided an overview of the most recent studies of heat shock proteins, their expression, and their function in health and disease in the pancreas. For recent reviews on this topic in tissue other than pancreas, see references.[46,71–73]

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