MAPK signalling in cellular metabolism: stress or wellness?

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Mitogen-activated protein kinase (MAPK) signalling occurs in response to almost any change in the extracellular or intracellular milieu that affects the metabolism of the cell, organ or the entire organism. MAPK-dependent signal transduction is required for physiological metabolic adaptation, but inappropriate MAPK signalling contributes to the development of several interdependent pathological traits, collectively known as metabolic syndrome. Metabolic syndrome leads to life-threatening clinical consequences, such as type 2 diabetes. This Review provides an overview of the MAPK-signalling mechanisms that underly basic cellular metabolism, discussing their link to disease.

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See Glossary for abbreviations used in this article.

Signal transduction in response to environmental cues is a fundamental process in all cells. The mitogen-activated protein kinases (MAPKs) and their downstream targets are one of the essential signalling modules that convert environmental inputs into a plethora of cellular programmes. There are at least four subfamilies of MAPKs: the extracellular signal-regulated kinases (ERK1/2), ERK5 (also known as BMK1 or MAPK7), the Jun amino-terminal kinases (JNK1–3) and the p38 kinases (p38 α , β , γ and δ). All MAPK pathways are comprised of central, three-tiered kinase modules, distinct members and activation mechanisms, all of which have been thoroughly described elsewhere (Dhillon *et al*, 2007). We focus on the biological roles of MAPKs, drawing on a large body of evidence showing that they respond to and regulate key metabolic factors, thereby controlling basic metabolism and contributing to metabolic disorders.

MAPKs in canonical insulin signalling

Insulin has been the most studied hormone of those that are implicated in anabolic metabolism; it concurrently activates both the PI3K and MAPK pathways. Several mechanisms have been described for the activation of MAPK in response to insulin (Fig 1). Binding of the insulin receptor substrate (IRS) or SHC to the activated insulin receptor and its subsequent tyrosine phosphorylation leads to the recruitment of GRB2. GRB2 then associates with SOS to activate the Ras–ERK1/2 pathway (Pronk *et al*, 1993). Insulin has also been shown to concurrently activate p38 and JNK (Antonescu *et al*, 2005; Moxham *et al*, 1996). In the latter, this might involve the PI3K regulatory subunit p85. Interestingly, JNK activation is independent of the PI3K catalytic subunit binding to p85 but instead involves the small GTPase CDC42 (Taniguchi *et al*, 2007). The mechanisms by which p38 is activated remains unknown.

Several independent reports indicate that PI3K–PKB signalling mediates the effects of insulin on acute cellular metabolism as well as cell growth and differentiation, whereas MAPK signalling—in particular Ras–MEK–ERK1/2 signalling—predominantly controls the latter (Avruch, 1998). However, this view might be too simplistic, as accumulating evidence shows that MAPKs directly control insulin-mediated metabolism (Fig 2).

The inhibitory phosphorylation of GSK3 and activation of PP1 induced by insulin stimulation results in net dephosphorylation and the activation of glycogen synthase, leading to glycogen synthesis (Eldar-Finkelman *et al*, 1996). GSK3 was reported to be phosphorylated at its N-terminus *in vitro*—and therefore inhibited—by the cytosolic ERK1/2 substrate p90^{RSK} (Sutherland *et al*, 1993). However, it has been subsequently demonstrated that inhibitory phosphorylation at the same sites *in vivo* is exerted by PKB (Cross *et al*, 1995). It has also been suggested that the induction of JNK promotes the activation of glycogen synthase through p90^{RSK3} in skeletal muscle (Moxham *et al*, 1996). Interestingly, a recent study demonstrated that mice lacking p90^{RSK2} had increased glycogen synthase activity in skeletal muscle on insulin stimulation and increased activities of ERK1/2 and PKB (Dufresne *et al*, 2001). These results point to p90^{RSK} as a converging point in glycogen synthesis, but the downstream effects it elicits are still unclear.

Insulin-mediated activation of PKB phosphorylates the transcription factor FOXO1, leading to its nuclear exclusion. This halts the

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Glossary

BMP2/7	bone morphogenic protein 2/7
C/EBP α / β	CCAAT/enhancer binding protein β
CDC42	cell division cycle 42
CREB	cAMP response element-binding protein
ERK	extracellular-signal regulated kinase
FOXO1	forkhead box O1
GLUT4	glucose transporter type 4
GSK3	glycogen synthase kinase 3
GRB2	growth factor receptor-bound protein 2
IRS	insulin receptor substrate
JNK	Jun amino-terminal kinase
MAPK	mitogen-activated protein kinase
MEK	MAPK/ERK kinase
MKK4/7	MAPK kinase 4/7
MNK	MAPK-interacting kinase
mRNA	messenger RNA
MSK	mitogen- and stress-activated kinase
PPAR α / γ	peroxisome proliferator-activated receptor α / γ
PGC1	PPAR γ coactivator 1
PI3K	phosphatidylinositol 3-kinase
PKB/AKT	protein kinase B
PKD1	protein kinase D 1
PP1	protein phosphatase 1
p90 ^{RSK}	p90 ribosomal S6 kinase
SHC	Src homology 2 domain containing
siRNA	short interfering RNA
SOS	son of sevenless
SREBP	sterol regulatory element binding protein
TNF α	tumour necrosis factor α
UCP1	uncoupling protein 1

transcription of important enzymes of gluconeogenesis, lipid catabolism and mitochondrial function (Gross *et al.*, 2009). Interestingly, FOXO1 is phosphorylated by ERK1/2 and p38 at several sites (Asada *et al.*, 2007), but the impact of these modifications on metabolism is unknown.

Studies in different cell types using inhibitors targeting the α and β isoforms of p38 have indicated that these kinases might be required for glucose transporter type 4 (GLUT4)-mediated glucose uptake in response to insulin. As the inhibitors had no effect on insulin-mediated GLUT4 translocation, it has been suggested that p38 regulates the intrinsic activity of GLUT4. However, this idea is currently questioned as siRNAs or expression of dominant-negative p38 α and β had no effect on glucose uptake (Antonescu *et al.*, 2005). Instead, p38 inhibitors seem to interfere with GLUT4 activity through competitive inhibition, independent of p38 activity (Ribe *et al.*, 2005).

The transcription factors of the SREBP family are major regulators of insulin-mediated lipogenesis. Three SREBP isoforms have been described so far: SREBP1a, SREBP1c and SREBP2. SREBP2 is one of the main regulators of cholesterol homeostasis, whereas SREBP1c predominantly regulates *de novo* synthesis of fatty acids. By contrast, SREBP1a controls both lipogenic and cholesterogenic enzymes (Goldstein *et al.*, 2006). Insulin-activated ERK1/2 phosphorylates SREBP2 (Kotzka *et al.*, 2004) and possibly also SREBP1a (Roth *et al.*, 2000), thereby enhancing their transactivation potential and linking ERK1/2 signalling with key regulators of lipid metabolism. However, the physiological significance of these modifications *in vivo* requires further investigation.

Fig 1 | Established and potential mechanisms of MAPK activation by the insulin receptor. (1) ERK activation through GRB2/SOS-Ras-Raf: SH2-domain-containing protein GRB2 binds to tyrosine-phosphorylated IRS or SHC and recruits SOS to activate Ras and in turn Raf-MEK-ERK. (2) JNK activation through PI3K: SH2-domain-containing PI3K regulatory subunits p85 activates MKK4 through a CDC42-dependent mechanism leading to activation of JNK. The mechanisms leading to p38 activation are unknown. CDC42, cell division cycle 42; ERK, extracellular-signal regulated kinase; GRB2, growth factor receptor-bound protein 2; GTP/GDP, guanosine-tri-(di)phosphate; IRS, insulin receptor substrate; JNK, Jun N-terminal kinase; MEK, MAPK/ERK kinase; MAPK, mitogen-activated protein kinase; MKK4/7, MAPK kinase 4/7; PI3K, phosphatidylinositol 3-kinase; PIP3/PIP2, phosphatidylinositol-tri-(di)phosphate; PKB, protein kinase B; SHC, Src homology 2 domain containing; SOS, son of sevenless.

Insulin also stimulates cellular protein translation. MAPKs are important modulators of protein synthesis through the phosphorylation of various crucial factors (Fig 2; supplementary Table 1 online). This is the topic of a recent review (Anjum & Blenis, 2008) and is not discussed in detail here.

Taken together, the above results indicate that insulin stimulation elicits a complex interplay of different MAPKs. The induction of the three main MAPK modules, the existence of different isoforms in MAPK subfamilies and the complex crosstalks that occur probably underlie intricate functional redundancies in the metabolic insulin response. These have not been conclusively analyzed in recent studies that focus on single inhibitors and/or single gene knockouts/knockdowns. In fact, direct targets of PKB that mediate immediate changes in cellular metabolism in response to insulin are also phosphorylated by different MAPKs (Fig 2; supplementary Table 1 online). In several cases, however, whether MAPK-dependent post-translational modifications also occur after insulin stimulation and whether they lead to similar effects remains to be tested. More systematic gain- and loss-of-function studies *in vivo*, dissecting the individual functions of key MAPK signalling nodes in different organs after insulin stimulation, are required.

Fig 2 | Complex regulation of cellular metabolism by MAPKs. Cytokines (such as TNF α), insulin, other hormones (such as glucagon), growth factors (such as IGF1 or EGF) and environmental stress converge into MAPK signalling nodes that directly or indirectly—through MNK, MSK or p90^{RSK}—regulate numerous metabolic factors and processes. Only targets that are directly phosphorylated by the indicated kinases have been depicted. A more comprehensive list of targets and their functions, including references, can be found in supplementary Table 1 (online). ATF2, activating transcription factor 2; CREB, cAMP response element-binding protein; C/EBP α / β , CCAAT/enhancer binding protein- α / β ; EGF, epithelial growth factor; EGFR, EGF receptor; eIF4B/E, eukaryotic translation initiation factor-4B/E; FOXO1, forkhead box O1; GCGR, glucagon receptor; GR, glucocorticoid receptor; HSL, hormone sensitive lipase; IGF1, insulin growth factor 1; IGF1R, IGF1 receptor; IR, insulin receptor; MNK, MAPK-interacting kinase; mTORC1, mammalian target of rapamycin complex 1; MSK, mitogen- and stress-activated kinase; p90^{RSK}, p90 ribosomal S6 kinase; PGC1 α , PPAR γ co-activator- α ; PPAR α / γ , peroxisome proliferator-activated receptor- α / γ ; SREBP1a/2, sterol regulatory element binding protein 1a/2; TNF α , tumour necrosis factor- α ; TNFR, TNF receptor; TSC1/2, tuberous sclerosis complex 1/2.

p38 regulates hepatic-fasting-induced pathways

Insulin suppresses gluconeogenesis and lipid catabolism in the liver, whereas glucagon and glucocorticoids have the opposite effect during fasting. Glucagon enhances the expression of PPAR γ and PGC1 through stimulation of the cAMP pathway and the transcription factor CREB (Mayr & Montminy, 2001). PGC1 in turn coactivates many transcription factors, including the glucocorticoid receptor, FOXO1 and PPAR α . PGC1 α has been identified as a direct target of p38, which enhances its activity by phosphorylation (Puigserver *et al*, 2001). CREB is a direct target of MSK that is activated by ERK1/2 and p38 (Deak *et al*, 1998). A recent study demonstrated that p38 stimulates hepatic gluconeogenesis by regulating the phosphorylation of

CREB and the expression of PGC1 α (Cao *et al*, 2005). Interestingly, the glucocorticoid receptor is also a target of different MAPKs. In this context, phosphorylation by p38 seems to enhance its transcriptional activity (Miller *et al*, 2005), whereas phosphorylation by JNK and ERK1/2 inhibits its function (Itoh *et al*, 2002; Krstic *et al*, 1997). Furthermore, the transcriptional activity of PPAR α is also enhanced by phosphorylation by ERK1/2 and p38 (Juge-Aubry *et al*, 1999). Finally, p38-mediated C/EBP α phosphorylation and activation was demonstrated to regulate hepatic gluconeogenesis (Qiao *et al*, 2006). p38 was also shown to be required for glucagon- and fasting-mediated suppression of hepatic lipogenesis, possibly through the inhibition of SREBP1c transcription (Xiong *et al*, 2007).

Fig 3 | Involvement of MAPK signalling in adipogenesis. Mesenchymal stem cells give rise to white and brown pre-adipocytes. After proper stimulation, distinct transcriptional pathways are initiated that ensure terminal differentiation of these precursors into adult white and brown adipocytes. Early upregulation of C/EBP β and δ during white adipogenesis leads to activation of PPAR γ and C/EBP α , which in turn regulate the expression of most genes responsible for triglyceride uptake and storage. PPAR γ is also important for brown adipogenesis. However, the induction of additional genes such as PGC1 α , helps to establish the brown adipocyte gene expression profile. MAPK signalling can regulate crucial events during both differentiation processes at different levels. ATF2, activating transcription factor 2; BMP2/7, bone morphogenic protein 2/7; C/EBP α / β / δ , CCAAT/enhancer binding protein α / β / δ ; MAPK, mitogen-activated protein kinase; PGC1 α , PPAR γ co-activator 1 α ; PPAR γ , peroxisome proliferator-activated receptor γ ; Pref1, pre-adipocyte factor 1; RA, retinoic acid; UCP1, uncoupling protein 1.

In summary, these data show that p38 is a positive regulator of the glucagon-mediated fasting response in the liver through the phosphorylation of various key factors. As described above, p38 is also activated by insulin, but this seems to occur mainly in adipocytes and skeletal muscle (Antonescu *et al*, 2005). This indicates organ-specific functions of p38 in response to different hormones, with corresponding opposing effects in metabolism. *In vivo*, the involvement of JNK and ERK1/2 in the hepatic fasting response is unknown. There is some evidence for positive or negative regulation of fasting response factors through phosphorylation by these kinases, but the metabolic context in which these mechanisms might act remains unclear.

MAPKs in adipocyte physiology and development

Adult adipose tissue regulates an array of physiological processes and is largely involved in nutrient and energy homeostasis. When energy is demanded, triacylglycerides can be hydrolysed to release free fatty acids and glycerol in white adipose tissue through the step-wise action of three different lipases, in a process known as lipolysis. The activation of JNK and ERK1/2 by TNF α leads to increased basal lipolysis due to the downregulation of perilipin mRNA and protein

(Ryden *et al*, 2004). Perilipin is a crucial component of the lipid droplet surface and restrains the action of triacylglyceride lipases under basal conditions (Martin & Parton, 2006). Furthermore, ERK1/2 regulates lipolysis by the phosphorylation of hormone-sensitive lipase at Ser600, increasing catalytic activity and the release of free fatty acids from adipocytes (Greenberg *et al*, 2001).

Formation of adipose tissue depends on tightly controlled cellular growth, proliferation and differentiation. ERK1/2 has been shown to be required for adipocyte differentiation, as its down-regulation in 3T3-L1 pre-adipocytes results in a marked decrease in adipogenesis (Sale *et al*, 1995). In addition, mice deficient in ERK1 have fewer adipocytes and reduced adipose tissue mass (Bost *et al*, 2005). However, the phosphorylation of PPAR γ —the master regulator and main driver of adipocyte differentiation and a direct target of ERK1/2 and JNK—results in decreased transcriptional activity, thereby attenuating differentiation (Hu *et al*, 1996). Precisely timed regulation of ERK1/2 activity is therefore necessary during adipogenesis. In fact, ERK1/2 is activated early in the differentiation process—possibly in response to retinoic acid (Bost *et al*, 2002)—and would need to be subsequently deactivated to prevent inhibitory PPAR γ phosphorylation. A recent study confirmed that late inhibition

Sidebar A | In need of answers

- (i) How does the activation of mitogen-activated protein kinase (MAPK) modules in response to different extracellular inputs lead to distinct effects in cellular metabolism?
- (ii) Through which molecular mechanisms does the activation of the same MAPK module affect different factors responsible for the regulation of specific metabolic responses?
- (iii) How does the disturbance of MAPK-dependent metabolic adaptation contribute to metabolic disorders in different organs?

of ERK1/2 during adipogenesis enhances terminal differentiation, supporting this hypothesis (Kim *et al*, 2007; Fig 3).

Adipocyte differentiation is positively regulated by p38 through the phosphorylation of C/EBP β (Engelman *et al*, 1998). p38 kinase signalling also occurs during BMP2-induced adipogenic differentiation, leading to PPAR γ upregulation (Hata *et al*, 2003). It might also be involved in brown adipogenesis, enhancing UCP1 expression—probably through its action on PGC1 α —in response to BMP7 (Tseng *et al*, 2008). Another interesting study showed that ATF2—a known p38 target—is involved in adipocyte differentiation (Maekawa *et al*, 2010). Overall, most studies support the idea that p38 positively regulates adipogenesis (Fig 3). MAPKs also regulate several other metabolic factors, including other nuclear receptors (Fig 2; supplementary Table 1 online), which are not discussed here. There is an increasing amount of literature that supports a crucial role for MAPK signalling in physiological metabolic homeostasis.

MAPK in metabolic syndrome and type 2 diabetes

Excessive caloric intake leads to fat accumulation if sufficient energy is not expended. This evolutionary adaptation has become a disadvantage in today's affluent society, as it can lead to various metabolic imbalances including insulin resistance, obesity, dyslipidemia, inflammation and hypertension—which are collectively known as metabolic syndrome. Metabolic syndrome is one of the better established risk factors for type 2 diabetes mellitus and atherosclerosis (Despres & Lemieux, 2006). Obesity-related insulin resistance is an important contributor to the metabolic disturbances that define metabolic syndrome. Many studies have causally implicated MAPKs in the development of insulin resistance. Global deletion of JNK, or its specific deletion in adipose tissue, skeletal muscle and brain has been shown to attenuate diet-induced insulin resistance in mice that are fed a high-fat diet (Sabio & Davis, 2010). Experiments with global knockout mice showed that JNK1 is important for increasing adipose mass under hypercaloric conditions, suggesting that reduced obesity could improve insulin resistance (Hirosumi *et al*, 2002). However, evidence from tissue-specific knockout mice suggests alternative mechanisms for the improvement of insulin sensitivity in the absence of JNK, which have been summarized in a recent review (Sabio & Davis, 2010). A prevailing concept is that stress-induced activation of JNK—and probably also p38—inhibits insulin signalling by enhancing the phosphorylation of IRS1 at Ser307, a mechanism that positively correlates with insulin resistance (Hotamisligil, 2010). However, mice in which Ser307 was replaced by alanine actually showed reduced insulin sensitivity (Copps *et al*, 2010). Interestingly, insulin stimulation itself leads to Ser307 phosphorylation of IRS1, particularly in hepatocytes (Copps *et al*, 2010). These data suggest a physiological role for this modification in hepatic insulin action, which is supported by a recent report demonstrating that hepatocyte-

specific deletion of JNK1 enhances insulin resistance (Sabio *et al*, 2009). Thus, JNK might positively regulate hepatic insulin signalling, possibly through Ser307 phosphorylation of IRS1. However, in other insulin-sensitive organs, JNK negatively regulates insulin action, particularly under stress conditions. This is thought to occur through the phosphorylation of other IRS1 sites, or by interfering with other components of the insulin signalling cascade.

As described above, ERK1 is required in the early steps of adipogenesis. It also seems to promote adipose accretion in mice under hypercaloric conditions, as ERK1 knockout mice are protected from diet-induced obesity and insulin resistance (Bost *et al*, 2005). The signalling adaptor p62 has been shown to interact with ERK1; mice lacking p62 have reduced insulin sensitivity due to late-onset obesity that is normalized by simultaneous inactivation of ERK1 (Lee *et al*, 2010). The negative regulation of ERK1 by p62 might be important in late steps of adipogenesis, when ERK1 needs to be inactivated to allow PPAR γ activity. In contrast to JNK and ERK1, the role of p38 in insulin resistance has not yet been established *in vivo*.

Systemic insulin resistance triggers chronic hyperglycaemia, which causes pancreatic β cells to secrete more insulin. In the long term, this adaptation is associated with stress-induced β -cell death and leads to insulin deficiency and diabetes. As such, stress mechanisms that trigger insulin resistance are also known to contribute to β -cell failure. *In vitro* data indicate that JNK activation promotes β -cell failure through different mechanisms (Kaneto *et al*, 2005). Interestingly, JNK-interacting protein 1—a scaffold protein regulating JNK activity—was identified as a potential regulator of type 2 diabetes in humans (Waeber *et al*, 2000). Although it has been speculated that p38 cooperates with JNK to promote β -cell failure, little evidence—apart from *in vitro* inhibitor studies—exists to support this. However, our laboratory has recently identified a novel mechanism in β -cell function and integrity: the δ isoform of p38 (p38 δ) negatively regulates the activity of PKD1, which regulates insulin secretion and β -cell survival. Under stress, there might be an exaggerated p38 δ -dependent inhibition of PKD1 that would contribute to β -cell failure (Sumara *et al*, 2009).

The ERK1/2 signalling branch in β cells is poorly understood. Nevertheless, the existing data imply that Ras–ERK1/2 signalling is essential for β -cell growth and proliferation (Burns *et al*, 2000; Font de Mora *et al*, 2003). Interestingly, liver-specific activation of ERK1/2 has been shown to reverse insulin-deficient diabetes owing to increased β -cell mass, which suggests that complex endocrine mechanisms function in islet growth regulation (Imai *et al*, 2008).

The majority of studies indicate that enhanced MAPK signalling is detrimental to insulin sensitivity and β -cell function. However, a growing body of evidence indicates that MAPKs are involved in physiological metabolic adaptation, the disturbance of which might contribute to metabolic diseases.

Conclusions

It is well established that MAPK signalling is required for an array of metabolic events, but the excessive activation of MAPKs is associated with detrimental effects in obesity and diabetes that contribute to disease progression. Further investigation is needed to clarify in which cell types MAPKs act, which MAPK is involved and in which cellular compartments different MAPKs function (Sidebar A). Scaffold proteins that assemble a variety of MAPK signalling modules, and dual-specificity MAPK phosphatases that have a rather broad specificity for inactivation of different MAPKs, add to the

complexity of the system. It is therefore disputable whether studies that rely on the deletion of a limited number of single MAPK signalling elements or on the inhibition of closely related MAPKs by chemical compounds—mostly in combination with simple metabolic readouts *in vitro*—can elucidate their role in metabolic adaptation, as there is probably redundancy in the system. High-throughput microscopy—that also considers the spatial and temporal behaviour of single MAPK signalling elements—should be used to conclusively answer this question. Finally, computational modelling has and will continue to help in the prediction of complex networks of interacting MAPK signalling modules. These need to be comprehensively investigated in the context of their effects on cellular metabolism.

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