Topical Review

AMPK and cell proliferation – AMPK as a therapeutic target for atherosclerosis and cancer

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AMPK is a serine/threonine protein kinase, which serves as an energy sensor in all eukaryotic cell types. Published studies indicate that AMPK activation strongly suppresses cell proliferation in non-malignant cells as well as in tumour cells. These actions of AMPK appear to be mediated through multiple mechanisms including regulation of the cell cycle and inhibition of protein synthesis, *de novo* fatty acid synthesis, specifically the generation of mevalonate as well as other products downstream of mevalonate in the cholesterol synthesis pathway. Cell cycle regulation by AMPK is mediated by up-regulation of the p53–p21 axis as well as regulation of TSC2–mTOR (mammalian target of rapamycin) pathway. The AMPK signalling network contains a number of tumour suppressor genes including LKB1, p53, TSC1 and TSC2, and overcomes growth factor signalling from a variety of stimuli (via growth factors and by abnormal regulation of cellular proto-oncogenes including PI3K, Akt and ERK). These observations suggest that AMPK activation is a logical therapeutic target for diseases rooted in cellular proliferation, including atherosclerosis and cancer. In this review, we discuss about exciting recent advances indicating that AMPK functions as a suppressor of cell proliferation by controlling a variety of cellular events in normal cells as well as in tumour cells.

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AMP-activated protein kinase (AMPK) is a member of a metabolite-sensing protein kinase family that is found in all eukaryotes (Hardie *et al.* 1998). AMPK has been proposed to act as a cellular fuel sensor, and is a potent mediator of exercise-induced glucose uptake in skeletal muscles (Hardie, 2003).

AMPK consists of a heterotrimeric complexes consisting of a catalytic α subunit and regulatory β and γ subunits, and functions as a protein serine/threonine kinase (Hardie & Carling, 1997). AMPK is activated under conditions that deplete cellular ATP and elevate AMP levels such as glucose deprivation, hypoxia, ischaemia and heat shock, which are associated with an increased AMP/ATP ratio (Kemp *et al.* 2003). In addition, it is also activated by several hormones and cytokines such as adiponectin (Yamauchi *et al.* 2002) and leptin (Minokoshi *et al.* 2002), and by the anti-diabetic drug metformin (Zhou *et al.* 2001; Shaw *et al.* 2005). Once activated, AMPK phosphorylates and inactivates a number of metabolic enzymes involved in ATP-consuming cellular events including fatty acid, cholesterol and protein synthesis, involving acetyl-Co enzyme A carboxylase (ACC) and HMG-CoA reductase, and also activates ATP-generating processes, including the uptake and oxidation of glucose and fatty acids (Hardie, 2005; Luo *et al.* 2005). A number of molecules and signalling pathways have been reported to be regulated by AMPK through direct phosphorylation as an AMPK substrate and also indirectly by gene expression regulation (Hardie, 2004).

Since its discovery, investigations into the regulation and the effects of AMPK have expanded very rapidly. Among these, research on the regulation of cellular proliferation by AMPK is becoming one of the important areas. In this review, we focus on the effect of AMPK activation on cellular proliferation and discuss the possibility that AMPK might be a therapeutic target for proliferative disorders such as atherosclerosis and cancers.

Cell proliferation is regulated by the cell cycle machinery

Mammalian cell proliferation is governed by the cell cycle machinery. Cell cycle progression is a tightly controlled series of events that are positively

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regulated by cyclin-dependent kinases (CDKs) and their cyclin-regulatory subunits (Sherr, 1996), and negatively regulated by CDK inhibitors (CDKIs) and tumour suppressor genes (Grana & Reddy, 1995). Mitogenic factors bind to their receptors and initiate a series of events resulting in the activation of CDKs that in turn regulate cell cycle progression, DNA synthesis and replication and mitosis. Although a number of growth factors reportedly utilize distinct signalling pathways to promote DNA synthesis, the distinct signalling pathways activated by individual growth factors must converge upon common downstream regulators of the cell cycle such as CDKs and CDKIs (Lukas *et al.* 1996). The final common pathway leading to G0/G1/S transition is the CDK-induced hyperphosphorylation of the retinoblastoma gene product (Rb), which functions as a molecular switch that commits the cell to DNA replication. Hyperphosphorylation of Rb results in the release of the transcription factor E2F, which induces the expression of genes required for the progression through S, G2 and M phases (Weinberg, 1995). In the absence of its phosphorylation by CDKs, Rb binds and sequesters E2F, thereby preventing transcriptional activation and sequent induction of E2F-dependent genes. CDKIs, such as $p21^{CIP}$ and $p27^{KIP}$, negatively regulate this process by inhibiting cyclin/CDKs activity and phosphorylation of Rb, resulting in G1 arrest (Hunter & Pines, 1994). Progression of the cell cycle is regulated by the balance between the levels and activities of cyclin–CDK complexes, CDKIs and other growth suppressor proteins such as p53 (Grana & Reddy, 1995).

Tumor suppressor p53 expression and its function are tightly regulated by its phosphorylation state. Cellular stresses, such as γ-irradiation and glucose deprivation, induce the phosphorylation of p53 at Ser-15 (Shieh *et al.* 1997; Jones *et al.* 2005). The phosphorylated p53 induces cell-growth arrest and/or apoptosis through the transcriptional regulation of p53 response genes such as $p21^{CIP}$ and p53AIP1, which is carefully discussed in a recent review (Bode & Dong, 2004).

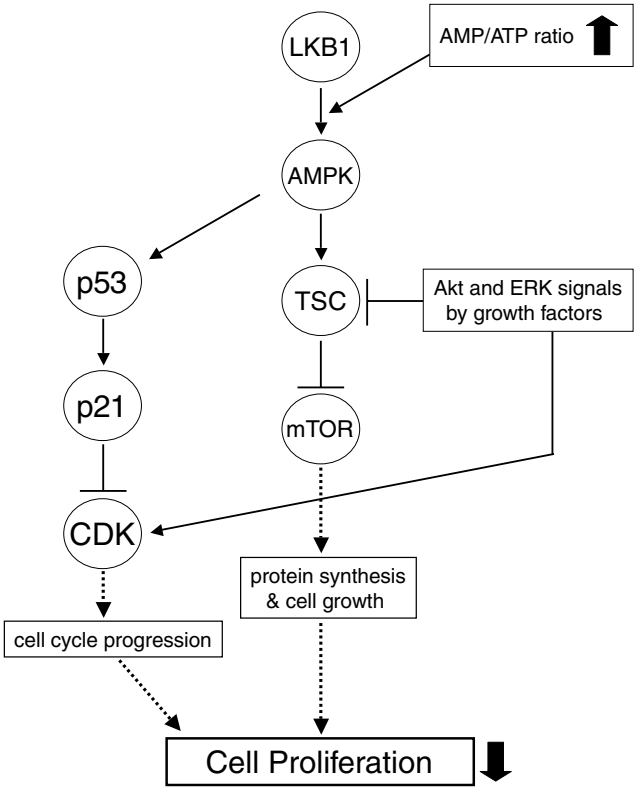

Figure 1. Mechanisms of the inhibition of cell proliferation by AMPK activation
Grow stimulation elicits activation of Akt and ERK, resulting in cell proliferation by activating both CDKs to progress cell cycle and mTOR pathway to promote protein synthesis essential for cell growth and proliferation (through pathways indicated by dashed arrows). AMPK activation overcomes the growth-stimulatory signalling via activation of p53–p21 axis as well as inhibition of mTOR signalling, resulting in suppression of cell proliferation.

AMPK causes G1 cell cycle arrest via up-regulation of the p53–p21 axis

Recently, AMPK activation by the widely used AMP-mimetic 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) has been shown to cause cell cycle arrest in hepatoma HepG2 cells (Imamura *et al.* 2001), mouse embryonic fibroblasts (Jones *et al.* 2005), human aortic smooth muscle cells (SMCs) and rabbit aortic strips (Igata *et al.* 2005). These reports also supported the hypothesis that the mechanism of cell cycle arrest by AMPK activation involves accumulation of the tumour suppressor protein p53 by phosphorylation of its Ser-15 residue (Ser-18 in mice), and the accumulated p53 protein up-regulates one of the CDKIs, $p21^{CIP}$ protein by a transcriptional mechanism (Fig. 1). Whether phosphorylation of Ser-15 on p53 is mediated by AMPK itself or by another protein kinase, which is co-immunoprecipitated with AMPK, has not been elucidated. Importantly, the amino acid sequence around Ser-15 is not a good fit to the AMPK consensus recognition motif. Future studies will provide the complete understanding for the regulation of p53 protein by AMPK activation.

The proliferative components of vascular diseases are varied and include restenosis after coronary artery intervention, a vasculopathy that accompanies cardiac transplantation and the processes in primary atherosclerosis. The entry of vascular cells, especially smooth muscle cells (SMCs), into the cell cycle plays an important role in the development and progression of these proliferative conditions. The majority of SMCs in intact blood vessels reside in the G0 phase of the cell cycle, and a growth-stimulating event(s) such as balloon injury

or platelet-derived growth factor (PDGF) stimulation, must occur in order to trigger the SMC proliferation response. Our group reported that AMPK activation in SMCs stimulated with serum or PDGF-BB resulted in cell cycle arrest at the G1 phase and inhibited cell proliferation (Igata *et al.* 2005). Consistent with our report, AICAR inhibited angiotensin II-stimulated SMC thymidine incorporation and administration of AICAR prevented neointimal formation in the rat balloon injury model (Nagata *et al.* 2004). These observations indicate that AMPK activation can overcome growth-promoting signalling from a variety of stimuli and can maintain SMCs in a quiescent state similar to G0 phase. Thus, AMPK activation in SMCs might be a therapeutic target to prevent or treat vascular proliferative diseases.

AMPK activation by AICAR has also been recently reported to inhibit proliferation of various cancer cell lines *in vitro* and *in vivo* by increasing $p21^{CIP}$, $p27^{KIP}$ and p53 (Rattan *et al.* 2005). Notably, AICAR inhibited proliferation in embryonic fibroblasts from both wild-type and LKB1 knock-out mice, suggesting that AICAR itself may also have a role in the inhibition of cancer cell growth. As discussed in the next section, AMPK is a target of the tumour suppressor gene *lkb1* that encodes the protein kinase LKB1, which is a major regulator of AMPK activity.

Tumor suppressor LKB1 is upstream of AMPK and inhibits cell proliferation

LKB1 is a serine/threonine protein kinase and is the product of the gene *lkb1*, which is mutated in cells from patients with Peutz-Jeghers syndrome (PJS) (Boudeau *et al.* 2003). PJS is characterized by mucocutaneous melanin pigmentation, gastrointestinal polyposis and markedly increased risk of cancer (Giardiello *et al.* 2000). Mutations in PJS patients were shown to be loss-of-function mutations of LKB1 (Mehenni *et al.* 1998; Ylikorkala *et al.* 1999). Overexpression of wild type LKB1 in two cancer cell lines, HeLa and G361, which do not express endogenous LKB1, suppressed the proliferation of these cells by inducing a G1 cell cycle arrest (Tiainen *et al.* 1999). Catalytically inactive LKB1 mutants including some of those isolated from PJS patients failed to suppress cell growth, indicating the proliferation-inhibitory and anti-tumour effects of LKB1. LKB1 also associates with p53 (Karuman *et al.* 2001) and induces $p21^{CIP}$ up-regulation resulting in cell cycle arrest in a p53-dependent manner in G361 melanoma cells (Tiainen *et al.* 2002), providing further evidence that LKB1 can function as a tumour suppressor.

A microarray analysis reported that overexpression of LKB1 in A549 cells induced expression of several p53 responsive genes, suggesting that LKB1 regulates the p53 pathway (Jimenez *et al.* 2003). Although numerous studies of LKB1 had shown its involvement in the cancer-prone PJS, at that time the downstream molecular system had not been identified. Recently, however, LKB1 has been convincingly shown to phosphorylate AMPK and serves as an essential component of physiological AMPK activation (Hawley *et al.* 2003; Shaw *et al.* 2004*b*) (Fig. 1). LKB1 phosphorylates AMPK at Thr-172 in the activation loop of the kinase domain in the catalytic α-subunit. The identified human mutations of LKB1 typically occur in the catalytic domain and cause a loss of its kinase activity. This failure of LKB1 phosphorylation impairs its downstream signalling of AMPK (Forcet *et al.* 2005). Today connection between LKB1- and AMPK-induced cell cycle arrest seemed to be clear (Kyriakis, 2003; Hardie, 2004) although no published work has shown the direct evidence for LKB1–AMPK association in AMPK-dependent cell cycle arrest.

Interestingly, some different effects between LKB1- and AMPK-induced cell cycle arrest seem to be present. Jimenez *et al.* (2003) reported that introduction of wild-type LKB1 in A549 cells increased the mRNA expression of PTEN (phosphatase with sequence homology to tensin) and resulted in decreased Akt signalling. PTEN functions as a lipid phosphatase metabolizing the phosphatidylinositol 3,4,5-trisphosphate (PIP_3) second messenger which stimulates proliferation and survival of cells (Cantley, 2002). On the other hand, Ouchi *et al.* (2004) reported that AMPK activation by adiponectin increased Akt signalling. We also observed that AMPK activation in both vascular endothelial cells and SMCs by AICAR treatment prolonged Akt phosphorylation compared with vehicle-treated controls (H. Motoshima *et al.* author observations). Further studies are required for the full understanding of the role of LKB1 and AMPK signalling in cell proliferation.

Regulation of the mTOR pathway and cell proliferation by AMPK

The mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase and is a key regulator of protein translation/synthesis. This kinase is centrally involved in cell growth (i.e. an increase in cell size and cell mass) (Schmelzle & Hall, 2000; Fingar *et al.* 2002). Both cellular events, cell growth and cell division (proliferation), are distinct yet tightly coupled processes (Neufeld & Edgar, 1998; Conlon & Raff, 1999). During the G1/S/G2 phases of each cell division cycle, cell mass and DNA content double, and then daughter cells with appropriate cell mass and DNA content are produced after M phase, leading to cell division (Fingar *et al.* 2004).

The mTOR pathway integrates nutrient and mitogen signals to regulate cell growth and cell division. The mTOR pathway is activated by amino acids and by growth

factors such as PDGF, epidermal growth factor (EGF) and insulin, and stimulates protein synthesis, cell growth and proliferation (Fig. 1). The growth factor-stimulated mTOR activation mediates the increased translation initiation of 5′-terminal oligopyrimidine tract-containing mRNAs, which encode components of the protein synthesis machinery. This event is one of the critical events involved in mammalian cell growth and proliferation. The most characterized downstream effectors of mTOR are the 70 kDa ribosomal protein S6 kinase 1 ($p70^{S6K1}$ or S6K1) and the eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) (Fingar & Blenis, 2004; Hardie, 2005). Through these molecules, mTOR stimulates the initiation step of translation (Carrera, 2004).

Mitogens like PDGF and EGF stimulate the mTOR pathway by activating PI3-kinase and in turn Akt and the subsequent phosphorylation of TSC2 (a precursor of mTOR) by Akt at Ser-939 and Thr-1462, leading to the inhibition of TSC2 (Inoki *et al.* 2002; Manning *et al.* 2002). In the absence of growth-promoting stimuli, TSC2 (also called tuberin) binds to TSC1 (also called hamartin) to form a tumour suppressor complex, which has growth-inhibitory activity via suppression of mTOR (van Slegtenhorst *et al.* 1998). The TSC1–TSC2 complex has GTPase activity towards Rheb, a small GTP-binding protein that is required for mTOR activation (Garami *et al.* 2003). When phosphorylated by Akt, TSC2 loses its activity to inhibit Rheb, thus switching on the mTOR pathway. Regulation of TSC2 by the ERK pathway has also recently been reported by Ma *et al.* (2005). When ERK is activated by either growth factors, PMA, or introduction of constitutive active MEK (the kinase upstream of ERK), it phosphorylates TSC2 at Ser-540 and Ser-664, causing the dissociation of the TSC1–TSC2 complex and the attenuation of TSC2 activity, resulting in mTOR-dependent S6K1 phosphorylation and increased proliferation. For further information for the regulation of mTOR pathway, see a recent review article by Fingar & Blenis (2004).

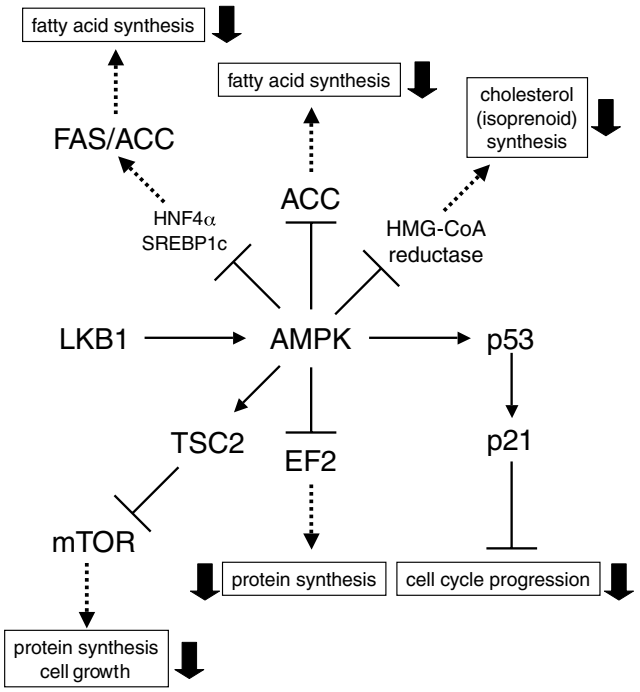

Figure 2. Various AMPK-regulated pathways which potentially modulate cell proliferation
AMPK activation may regulate cell proliferation not only by activation of p53–p21 axis and inhibition of mTOR signalling, but also by suppression of the mevalonate synthesis pathway and *de novo* fatty acid synthesis. When AMPK is activated, various pathways indicated by dashed arrows are suppressed.

Several groups have reported that activation of AMPK suppresses mTOR signalling by growth factors and amino acids (Bolster *et al.* 2002; Krause *et al.* 2002; Kimura *et al.* 2003) (Fig. 1). The molecular mechanism seems that activated AMPK by energy starvation phosphorylates TSC2 at Thr-1227 and Ser-1345, which sites are distinct from both the PKB sites and the ERK sites, and increases the activity of TSC1–TSC2 complex to inhibit mTOR (Inoki *et al.* 2003). Phosphorylation of TSC2 by AMPK is involved in the mechanism by which the TSC complex inhibits cell growth and protects cells from apoptosis induced by glucose starvation (Inoki *et al.* 2003; Shaw *et al.* 2004*a*). In addition, AMPK reportedly phosphorylates mTOR at Thr-2446 to reduce S6K1 phosphorylation by insulin, suggesting the inhibition of mTOR action (Cheng *et al.* 2004). Thus, AMPK directly and indirectly (via TSC2) suppresses mTOR activity to limit protein synthesis. Additionally, AMPK limits protein synthesis through the inhibition of translation elongation factor 2 (EF2) (Horman *et al.* 2002). Therefore, when AMPK is activated, cell growth and proliferation might be inhibited due to a limitation of protein synthesis. Thus, AMPK regulates cellular proliferation in response to energy status or nutrient availability.

Constitutive activation of PI3K-Akt signalling has been reported in many cancers including glioblastoma, melanoma, and advanced prostate cancer. AMPK activation is a feasible therapeutic strategy for these cancers since AMPK inhibits mTOR signalling downstream of Akt, and inhibition of mTOR pathway has been reported to inhibit tumour growth and metastasis in experimental animal models as well as in cultured cells.

Regulation of fatty acid synthesis and cell proliferation by AMPK

Many cancer cells exhibit a markedly increased rate of *de novo* fatty acid synthesis, which is typically quite low in non-malignant cells except for lipogenic cells such as adipocytes. Breast, prostate, colon and ovarian

cancers express high levels of fatty acid synthase (FAS), a key enzyme for the *de novo* fatty acid biosynthesis (Kuhajda *et al*. 2000; Luo *et al*. 2005). Ongoing studies have shown that human cancers and their pre-neoplastic lesions constitutively overexpress FAS, and that the expression level of FAS in breast and ovarian cancers is associated with the malignant phenotype; inhibition of FAS suppresses cancer proliferation and induces apoptotic cell death, resulting in prolonged survival in hosts with cancer (Kuhajda *et al.* 2000; Menendez & Lupu, 2004). In prostate cancer cells, up-regulation of the lipogenic pathway by androgens is mediated by activation of the sterol regulatory element-binding protein (SREBP) transcription factors, which regulate the expression of many lipogenic enzymes, including FAS and ACC (Swinnen *et al.* 2004). Therefore, the inhibition of FAS activity or suppression of FAS expression has become a clear target for the pharmacological therapy of malignant tumours (Fig. 2).

The inhibition of FAS expression by AMPK activation was previously reported in primary cultured hepatocytes (Foretz *et al.* 1998; Leclerc *et al.* 1998; Woods *et al.* 2000). Furthermore, AMPK-induced suppression of FAS gene expression either by AICAR or an anti-diabetic drug metformin in liver cells was explained by the strong suppressive effect on SREBP1c expression *in vivo* and *in vitro* (Zhou *et al.* 2001). Indeed, activation of AMPK by either AICAR or rosiglitazone, reduces expression of FAS and ACC resulting in suppression of proliferation in prostate-cancer cells (Xiang *et al.* 2004). Thus, another potential mechanism by which AMPK might function in cancer therapy is via inhibition of FAS expression (Fig. 2).

Regulation of cholesterol synthesis pathway by AMPK

Statins are the most commonly used drugs to decrease cholesterol levels acting via inhibition of 3-hydroxy-3-methylglutaryl-Co enzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. These block the conversion of HMG-CoA to mevalonate in the cholesterol synthesis pathway (Fig. 3). Recently statins have been demonstrated to reduce mortality related to cardiovascular diseases in patients with hypercholesterolaemia and their clinical use is more spreading. Furthermore, it has been reported that statins have a number of vasoprotective effects to improve endothelial function, reduce free radical formation and the risk for plaque rapture, inhibit inflammatory reaction between monocytes and vascular tissues as well as reduce cholesterol levels. For additional information of statins, see a review by Elrod & Lefer (2005). Since AMPK activation has also been reported to phosphorylate and inhibit

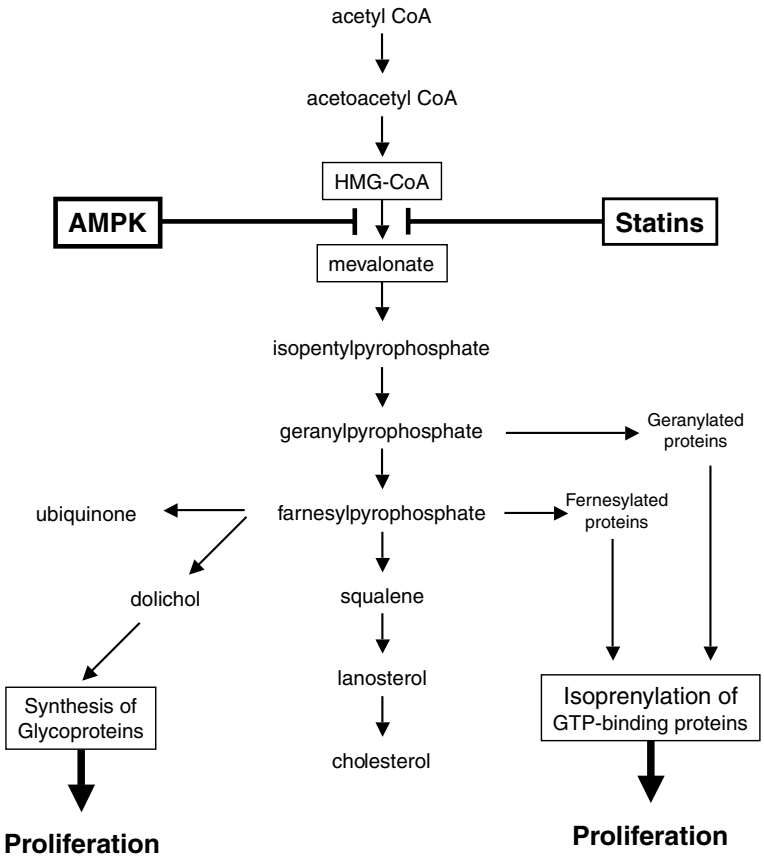

Figure 3. AMPK inhibits synthesis of mevalonate and its downstream products
AMPK activation, like statins, inhibits HMG-CoA reductase and suppresses the production of downstream metabolites including dolichol and isoprenylated GTP-binding proteins, all of which positively regulate cell proliferation.

HMG-CoA reductase activity and reduce cholesterol levels (Corton *et al.* 1994; Henin *et al.* 1995), some beneficial vaso- and cardio-protective effects, but not all, of statins described above are expected by AMPK activation in vascular tissues although investigations targeting this issue are very limited.

In recent years, statins have also been reported to exert anti-tumour and anti-proliferative activities in *in vivo* studies with experimental animals and in *in vitro* studies, and to reduce cancer incidence in patients treated with statins in several case-controlled studies. Compared with its vascular effects, available information is limited for the anti-cancer effects of statins. A putative mechanism was reported to be the decrease in mevalonate synthesis and other products (including dolichol, geranylpyrophosphate and farnesylpyrophosphate) downstream of mevalonate. Some of these are essential for cell proliferation and survival. AMPK activation is able to inhibit HMG-CoA reductase, decrease mevalonate synthesis and reduce the products downstream from mevalonate (Fig. 3). Therefore, the anti-cancer effects of AMPK activation might be mediated at least in part through the inhibition of this pathway.

Regulation of AMPK and anti-proliferative effect by adiponectin

AMPK was originally thought to be a regulator of cellular energy balance by sensing the intracellular AMP : ATP ratio. Recent studies have reported that extracellular hormonal stimulation by adiponectin and leptin, both of which are peptide hormones secreted by adipose tissue, also could activate AMPK (Yamauchi *et al.* 2002; Minokoshi *et al.* 2002). Adiponectin has a number of beneficial anti-diabetic and anti-atherosclerotic effects (Goldstein & Scalia, 2004). Adiponectin has been reported to inhibit vascular SMC proliferation (Arita *et al.* 2002) and myelomonocytic lineage cells (Yokota *et al.* 2000). We also reported that globular adiponectin activated AMPK in adipocytes (Wu *et al.* 2003) and suppressed endothelial cell proliferation induced by a low dose of oxidized low density lipoprotein (Motoshima *et al.* 2004). We revealed that an AMPK activator, AICAR, suppressed proliferation of human aortic SMCs stimulated by either 15% serum or PDGF-BB mediated through AMPK activation using a pharmacological or dominant-negative AMPK-mediated inhibition of AMPK (Igata *et al.* 2005). We also observed that another AMPK activator phenformin also inhibited the proliferation of both endothelial cells and vascular smooth muscle cells (VSMCs) (H. Motoshima *et al.* authors observations). These anti-proliferative effects on vascular cells by different reagents might be mediated through AMPK activation.

Plasma adiponectin has been shown to be decreased in patients with breast (Miyoshi *et al.* 2003; Mantzoros *et al.* 2004), endometrial (Dal Maso *et al.* 2004) and gastric cancer (Ishikawa *et al.* 2005). Interestingly, potential anti-cancer effects of adiponectin have been suggested, and it has been shown to directly inhibit the proliferation of cultured breast cancer cells (Kang *et al.* 2005). Brakenhielm *et al.* (2004) also reported that adiponectin inhibited tumour growth in a mouse model mediated by the potent inhibition of endothelial cell proliferation, consistent with our observations. Further investigations into the relation between adiponectin and cancer are appearing at a rapid pace. Future studies will provide important information as to whether the anti-tumour activity of adiponectin is mediated through activation of AMPK.

Very recently, two clinical studies showing that metformin also provides some protective effect against cancer in diabetic patients who are treated with it rather than other medications, were published (Evans *et al.* 2005; Bowker *et al.* 2006). In metformin-treated patients, several anti-proliferative and anti-tumour mechanisms via AMPK activation described here might be contributing to the reduced risk of cancer.

Conclusions

While the AMPK system is traditionally thought of as a sensor of cellular energy status and a regulator of metabolism, recent discoveries that a tumour-suppressor LKB1 is present upstream and two distinct tumour-suppressors p53 and TSC2 lie downstream, have now provided novel evidence that it may function as a suppressor of cell proliferation. AMPK promotes the maintenance of a resting cell phenotype in mature tissues which do not require proliferation to keep its function (like VSMCs in a large vessel) and also helps protect cells from transformation by oncogenic stimulation. Indeed, AMPK activation has been reported to suppress cell proliferation in a variety of cell types. These findings indicate that the AMPK system is playing a significant role in the regulation of cell proliferation.

Since AMPK can regulate a variety of signalling pathways described above, it will be interesting to determine which pathway(s) regulated by AMPK are most involved in the inhibition of cell proliferation. AMPK has pleiotropic effects that may affect cellular proliferation including: (1) inhibition of ACC resulting in suppression of fatty acid synthesis; (2) it inhibits HMG-CoA reductase resulting in suppression of synthesis of mevalonate and other products in the cholesterol synthesis pathway as well as cholesterol itself; (3) inhibition of the mTOR pathway resulting in inhibition of protein synthesis; and (4) inhibition of cell cycle progression by activating the p53–p21 axis. None of the available data has provided enough information to determine how much and how long activation of AMPK can serve to suppress protein synthesis, fatty acid synthesis as well as DNA synthesis,

respectively. Further studies are required for a full understanding of this issue. Nevertheless, activation of AMPK has emerged as an important target for the prevention and treatment of atherosclerosis as well as potentially for cancer therapy.

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