

cell metabolism, but changes in cell metabolism can have important effects on the HIF response.

Are there therapeutic implications? For people with inherited mutations in fumarate hydratase, succinate dehydrogenase and VHL, strategies to kill cells in which HIF is fully activated might be an effective way of treating tumors and ablating any precursor lesions. From another angle, there has been considerable interest in

activating HIF in ischemic conditions such as myocardial infarction. These experiments of nature provide new clues as to how this could be achieved, but also reinforce the caution that sustained HIF activation might cause tumor development.

1. Tomlinson, I.P. *et al. Nat. Genet.* **30**, 406–410 (2002).
2. Eng, C. *et al. Nat. Rev. Cancer* **3**, 193–202 (2003).

3. Isaacs, J.S. *et al. Cancer Cell* **8**, 143–153 (2005).
4. Semenza, G.L. *Nat. Rev. Cancer* **3**, 721–732 (2003).
5. Maxwell, P.H. *et al. Nature* **399**, 271–275 (1999).
6. Garber, K. *J. Natl. Cancer Inst.* **96**, 1805–1806 (2004).
7. Harris, A.L. *Nat. Rev. Cancer* **2**, 38–47 (2002).
8. Selak, M.A. *et al. Cancer Cell* **7**, 77–85 (2005).
9. Pollard, P.J. *et al. Hum. Mol. Genet.* **14**, 2231–2239 (2005).
10. Schofield, C.J. & Ratcliffe, P.J. *Nat. Rev. Mol. Cell Biol.* **5**, 343–354 (2004).
11. Lee, S. *et al. Cancer Cell* **8**, 155–167 (2005).

Fat, keeping the heart healthy?

Koh-ichi Yuhki, Jun-ichi Kawabe & Fumitaka Ushikubi

The hormone adiponectin is secreted from fat cells and increases sensitivity to insulin in muscle and liver; adiponectin increases resistance to metabolic disorders and, it now appears, may also protect heart tissue when blood flow is restricted (pages 1096–1103).

The prevalence of obesity is increasing worldwide, caused mainly by a modern sedentary lifestyle and a high-calorie diet. In addition to being the most important energy-storing organ, adipose tissue is now recognized as an important endocrine organ. Adipose tissue secretes a number of factors central in the development of obesity-related metabolic disorders, including diabetes and dyslipidemia. Now, Shibata *et al.* report that one such factor, adiponectin, also provides protective effects in the heart¹.

Adiponectin^{2,3} is abundant in plasma, and its circulating level is decreased in obesity and diabetes. As adiponectin is an insulin-sensitizing hormone, its downregulation is a proposed mechanism whereby obesity causes insulin resistance and diabetes.

The effects of adiponectin are mediated mainly by AMP-activated protein kinase (AMPK) in responding tissues⁴. AMPK signaling facilitates fatty-acid breakdown and glucose uptake, and inhibits glucose synthesis—these changes in energy metabolism are an essential step toward insulin sensitivity. On the other hand, the AMPK pathway monitors the availability of energy stores and is activated by factors that cause energy depletion. Accordingly, adiponectin, through the AMPK system, could have a role in

protecting hearts stressed during acute myocardial infarction.

There is some precedence for this notion. Obesity-linked disorders are strongly associated with heart disease⁵, although the molecular basis of this link is poorly understood. Nonetheless, several reports suggest a relationship between adiponectin and heart diseases. For example, high blood levels of adiponectin are associated with a lower risk of heart attack, and vice versa⁶. Additionally, adiponectin levels rapidly decline after the onset of acute myocardial infarction.

More intriguingly, suppression of AMPK activity in the heart leads to increased injury when blood flow is reduced *in vitro*, suggesting that AMPK is cardioprotective⁷. Whether adiponectin acts during acute myocardial infarction, however, was unknown.

Shibata *et al.* investigated the role of adiponectin in cardiac ischemia-reperfusion injury, in which blood flow to the heart is blocked and then reestablished¹. The authors found that mice deficient in adiponectin had increased heart damage after reperfusion, whereas mice overexpressing adiponectin were protected from injury. Moreover, administration of recombinant adiponectin diminished damage in both adiponectin-deficient and normal mice. These findings clearly show that adiponectin has a cardioprotective role *in vivo* during ischemia.

To clarify the mechanism of adiponectin function in the heart, the authors focused

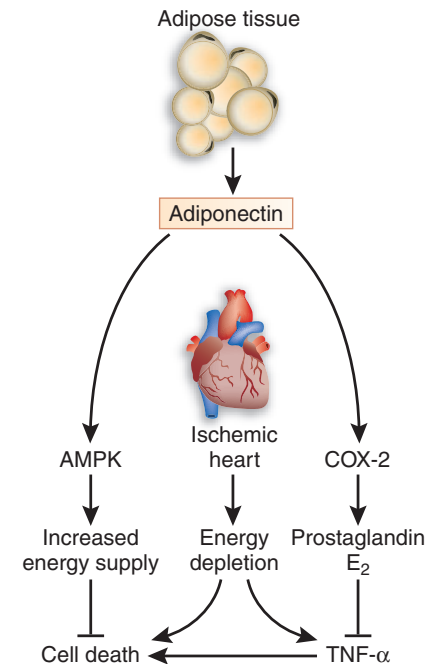


Figure 1 Adiponectin acts directly on the heart and ameliorates cardiac ischemic injury. Apart from known metabolic effects, adiponectin secreted from adipose tissue acts directly on the ischemic heart. A block in blood flow to the heart leads to depletion of energy stores, production of tumor necrosis factor (TNF)- α and cell death. Shibata *et al.* report that adiponectin protects the heart from ischemia by activating AMP-activated protein kinase (AMPK) and increasing the expression of cyclooxygenase (COX)-2, a rate-limiting enzyme for prostaglandin synthesis. Consequently, activated AMPK increases energy supply to heart cells, and COX-2 accelerates production of prostaglandin E₂, which suppresses production of TNF- α .

The authors are in the Department of Pharmacology, Asahikawa Medical College, Asahikawa 078-8510, Japan.
e-mail: ushikubi@asahikawa-med.ac.jp

on AMPK signaling and the cyclooxygenase (COX)-2-dependent pathway.

The activation of AMPK by cardiac ischemia-reperfusion injury was markedly attenuated in hearts from adiponectin-deficient mice—indicating that adiponectin is required for full activation of AMPK in the ischemic heart. In cultured heart cells, adiponectin blocked apoptosis induced by low oxygen; this effect was dependent on AMPK.

COX-2, a rate-limiting enzyme for prostanoïd synthesis, is upregulated in the ischemic heart and produces prostaglandin E₂ and other protective compounds. Shibata *et al.* found that adiponectin augmented expression of COX-2 and synthesis of prostaglandin E₂ in cultured heart cells¹. Moreover, in cardiac cells, adiponectin suppressed production of tumor necrosis factor (TNF)- α , an inflammatory cytokine that increases ischemic injury by triggering apoptosis—this suppression occurred through prostaglandin E₂ in an AMPK-independent manner. These results clearly indicate that adiponectin operates through both AMPK signaling and the COX-2–prostaglandin E₂ system to protect the heart from injury under conditions of reduced blood supply (Fig. 1).

The authors went on to show that the AMPK pathway was activated by adiponectin in the ischemic heart. A previous report noted this connection in ischemia-induced angiogenesis and hypertension—suggesting a common mechanism of adiponectin function during periods of energy depletion⁸.

Recently, the increased risk of cardiovascular events in individuals taking COX-2 inhibitors has been mainly attributed to the inhibition of the antiatherosclerotic effect of the COX-2–prostaglandin system⁹. Other studies, however, show an important cardioprotective role of endogenous prostaglandins^{10–12}. Shibata *et al.* link adiponectin with prostaglandins in the ischemic heart for the first time. Because prostaglandins protect various organs other than the heart, their findings lead to the prediction that adiponectin may exert its protective action broadly—possibly affecting other ischemic conditions, such as stroke.

Notably, when administered after an ischemic event, adiponectin retains full protective action—similar to a prostaglandin E₂–receptor activator¹⁰. Therefore, adiponectin may be a promising therapy

for acute myocardial infarction.

The adiponectin receptors, AdipoR1 and AdipoR2, seem to be abundantly expressed in the heart²; and adiponectin itself exists in multiple forms that have different affinities for these receptors. Therefore, which receptor participates in the cardioprotective action of adiponectin and which form of adiponectin most efficiently activates this receptor should be clarified. These findings would further outline the potential of adiponectin as a therapy for acute myocardial infarction.

1. Shibata, R. *et al.* *Nat. Med.* **11**, 1096–1103 (2005).
2. Kadowaki, T. & Yamauchi, T. *Endocr. Rev.* **26**, 439–451 (2005).
3. Yamauchi, T. *et al.* *Nature*, **423**, 762–769 (2003).
4. Yamauchi, T. *et al.* *Nat. Med.* **8**, 1288–1295 (2002).
5. Berg, A.H. & Scherer, P.E. *Circ. Res.* **96**, 939–949 (2005).
6. Pischon, T. *et al.* *JAMA*. **291**, 1730–1737 (2004).
7. Russell III, R.R. *et al.* *J. Clin. Invest.* **114**, 495–503 (2004).
8. Shibata, R. *et al.* *Nat. Med.* **10**, 1384–1389 (2004).
9. Couzin, J. *Science* **306**, 384–385 (2004).
10. Xiao, C.Y. *et al.* *Circulation* **109**, 2462–2468 (2004).
11. Xiao, C.Y. *et al.* *Circulation* **104**, 2210–2215 (2001).
12. Bolli, R. *et al.* *Cardiovasc. Res.* **55**, 506–519 (2002).

Fast track to the porphyrias

John D Phillips & James P Kushner

In susceptible individuals, fasting can trigger an attack of acute porphyria—a syndrome caused by the neurotoxic effects of precursors to porphyrins. The mechanistic basis for this trigger is now uncovered.

Hemoglobin and other hemoproteins mediate functions as diverse as transcription, respiration, and drug and hormone metabolism. A key component of such proteins is heme, a structure in which iron is incorporated into the porphyrin ring.

The synthesis of heme does not always go smoothly. The production of excess porphyrin precursors in the liver causes attacks of the acute porphyrias, characterized by episodic neuropathic abdominal pain, peripheral neuropathies, potentially lethal respiratory paralysis and acute psychotic

episodes¹. Susceptible individuals usually remain asymptomatic until an episode is triggered by fasting, dieting or drug exposure.

In a recent study in *Cell*, Handschin *et al.* show how calorie restriction affects the production of porphyrin precursors that can trigger an acute attack².

The heme biosynthetic pathway in mammals is regulated at the first and rate-limiting step (the formation of δ -amino levulinic acid (ALA) from glycine and succinyl-CoA). This reaction is catalyzed by ALA synthases (ALAS), which are nuclear-encoded mitochondrial matrix enzymes (Fig. 1).

Most heme is produced by developing red blood cells, but about 15% of the daily production of heme is generated in the liver. Red blood cells use a tissue-specific

ALAS (ALAS-2) that permits a constant high level of heme synthesis^{3,4}.

In contrast, heme biosynthesis in the liver must be flexible to ensure that hepatocytes can respond to changing metabolic requirements. Hepatocytes express ALAS-1, a ‘housekeeping’ form of ALAS^{3,5}. Heme downregulates transcription of ALAS-1 and inhibits its import into the mitochondrial matrix⁶, the crux of a negative feedback loop active in the liver.

Handschin *et al.* show that transcription of ALAS-1 is upregulated by the peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α ; Fig. 1)². PGC-1 α , a coactivator of nuclear receptors and transcription factors, regulates mitochondrial biogenesis and oxidative metabolism². Transcription of PGC-1 α is controlled by glucose availability. Under conditions of low glucose, PGC-1 α

The authors are in the Division of Hematology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA.
e-mail: john.phillips@hsc.utah.edu