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MODULATION OF UCP2 EXPRESSION BY P38 – A LINK TO CARDIOPROTECTION

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Background: Discovery of uncoupling protein 2 (UCP2) in 1997 and demonstration of its wide tissue expression has triggered an important question about controlled oxidative phosphorylation uncoupling and the physiological function of this process. Uncoupling protein 2 (UcP2) is a mitochondrial protein that can influence the mitochondrial membrane potential and hence the production of reactive oxygen species by mitochondria. It is also thought to be involved in apoptotic signaling pathways and it has been suggested to be important in cardio- and neuroprotection.

Methods and results: We examined the recent literature (2003–2007) in the MedLine database for evidence linking p38, one of the stress-related protein kinases, with modulation of UCP2 expression in the heart. While two reports clearly demonstrate p38 as down-regulating UcP2 expression, only circumstantial evidence exists for cardiomyocytes. Conflicting results on p38-regulated cardiomyocyte survival after ischemia leave an open venue for hypotheses on the differential regulation of protein expression, including UCP2.

Conclusions: Reviewing the evidence connecting UCP2 and its cytoprotective activities, we propose a tissue specific link that may explain the variable influence of p38 via modulation of UCP2 expression.

INTRODUCTION

Mitochondria are organelles regulating various physiological functions such as calcium homeostasis and free radical generation as well as playing a key role in the signaling cascade of apoptosis[1]. They are also critical for cellular energy metabolism and storage, and for cell survival. The inner membrane potential of the mitochondrion determines ATP and free radical production, calcium transport, and the integrity and stability of various proteins including cytochrome c, adenine nucleotide translocator, voltage dependent anion channel, and Bcl-2 family members, all of which play roles in determining cellular fate[2, 3].

Uncoupling proteins

Uncoupling proteins (UCPs) are present in the inner mitochondrial membrane. They are transmembrane proteins that mediate a regulated discharge of proton gradient generated by the respiratory chain[4]. There are five UCP homologues present in various types of mammalian tissues. Of the five known, UCP1, UCP2, and UCP3 are closely related, while UCP4 and BMCP1 are more divergent[5]. The discovery of UCPs in many different eukaryotic organisms suggests that the regulation of energetic efficiency through the physiological uncoupling of oxidative phosphorylation may be a common strategy developed early in evolution[4]. The physiological role of UCPs is determined not only by the amount of protein expressed but also by the extent of their activation[6]. UCPs show high substrate specificity and low turnover numbers, general properties described for carriers[7]. UCPs are tightly regulated at two levels: transcription of the gene and protein activity in the mitochondrion. Regulation of UCP1 expression and activity is well-explained, although the exact mechanism of uncoupling is still a matter of debate[8]. The function, transport properties and regulation of other members of the UCP family are still being defined. Other UCPs may answer to nucleotides and fatty acids in a similar way to UCP1 but the physiological context is unique and thus their physiological regulation is likely to be different[9]. The importance of UCPs is clear from the list of their involvement in various processes: prevention of reactive oxygen species (ROS) formation[10], prevention of atherosclerosis[11], one of the etiologies of type-2 diabetes[12], participation in inflammation[10], body weight regulation[13], adaptive thermogenesis including fever[14, 15], and aging[16].

UCP2 and its activity

Expression of the uncoupling protein family member with the widest distribution among cell types, UCP2 is dependent on the tissue and differs among species (human, rat, mouse) and is also related to physiological state[17]. Tissues expressing UCP2 include spleen, lung, intestine, pancreatic β cells, and immune cells[5, 18, 19], where its function largely remains to be resolved. UCP2 catalyzes the translocation of protons across the mitochondrial membrane to reduce the proton-motive force, thereby hypopolarizing the mitochondrial membrane potential and reducing cellular ATP[20, 21]. UCP2 does not seem to be critical in energy balance under normal conditions. Studies carried out on UCP2 knockout (KO) mice, for example, have shown a normal thermogenic response to cold[10].

Flachs et al.[22] demonstrated for the first time expression of UCP2 in reticulocytes. The evidence shows that during the intrauterine development of mice, the UCP2 gene is first recruited in hematopoietic cells before its expression in other cell types and tissues[22, 23]. These results suggest involvement of UCP2 in erythropoiesis, beginning during the early stages of prenatal development.

UCP2 gene promoter does not contain the TATA box but is GC-rich and includes some possible binding motifs for transcription factors (Sp1, AP1, AP2, CREB). Transcription, translation, and stability are three important points in a protein life cycle. Recent evidence has demonstrated that the stability of UCP2 is much lower than UCP1. The half-life of UCP2 has been shown to be very short, approximately 30 min, compared with about 30 h for UCP1(ref.[24, 25]).

ROS formation in mitochondria and relationship with UCP2

The physiological role of UCP2 is not entirely clear[26, 27] but it appears to cover a number of processes starting from lipid metabolism[28] to calcium homeostasis regulation[29], and apoptosis regulation[30]. However, there is a general consensus linking UCP2 to ROS production in mitochondria[31, 32].

ROS are formed in the course of mitochondrial respiration[33] and mitochondrial electron transport has been demonstrated to be a key determinant for life span[34]. About 1-2 % of oxygen is converted to superoxide anion ($^{\bullet}O_2^-$) in mitochondria at Complex I sites generating semiquinones and Complex III (on the site proximal to matrix where regeneration of oxidized coenzyme Q, ubiquinone (UQ), to its reduced form UQH_2 proceeds via ubisemiquinone anion radical ($UQ^{-\bullet}$) (ref.[35-37]). Any slight increase in the H^+ backflux into the matrix, which diminishes the mitochondrial potential Δp, results in a substantial decrease in mitochondrial ROS formation. Slightly increased respiration shortens the lifetime of the ubisemiquinone anion radical ($UQ^{-\bullet}$) and leads to lowered oxygen tension in the microenvironment. Both processes cause reduced rate of $^{\bullet}O_2^-$ formation. In other words, most ROS are formed in vivo under the non-phosphorylating, "resting", state of the mitochondria. The H^+ backflow mediated by uncoupling of any type, i.e. by leak or protein-mediated uncoupling, decreases the rate of ROS formation rate accordingly[38]. Downregulation of mitochondrial ROS production seems to be the most plausible role for UCP2, the protein is expressed in a large number of mammalian tissues albeit in minute amounts[6].

Several lines of evidence indicate that UCP2 expression is elevated in oxidative stress. Under these conditions UCP2 protects different types of cells by restricting mitochondrial reactive oxygen species (ROS) production[39-41]. The role of UCP2 in the control of ROS production has been well-demonstrated using UCP2-null mice who suffer neither from obesity nor cold-sensitivity but their macrophages produce higher levels of free radicals making the animals more resistant to infection[10]. Duval et al.[42] have shown that UCP2-mediated uncoupling in endothelial cells is even able to decrease extracellular ROS in co-incubated low-density-lipoproteins (LDL). Further, mice with deleted LDL receptors exhibited extensive diet-induced atherosclerotic plaques when they received bone marrow transplanted from UCP2 (-/-) mice. These plaques were prevented by bone marrow transplants from UCP2 (+/+) mice[11].

Following infection by a pathogen, the ROS pathway plays an important role leading to activation of macrophages and other immune cells that eliminate the pathogen. Macrophages therefore react to infection by lowering UCP2 and thus magnify the production of ROS to reduce infection. This is necessary because UCP2 is activated by superoxide and in a feedback fashion this causes a reduced ROS level[43].

UCP2 in cardiomyocytes

The heart is a high-energy-demanding organ in continuous need of ATP and it has a relatively poor oxidative stress defense mechanism. Several studies have shown the presence of UCP2 protein in the rat and human heart[44-46], whereas others reported no UCP2 protein in rat or mouse heart[10, 47]. The heart has little or no regenerative capacity[48, 49] which poses a major medical problem in ischaemic heart disease. This frequently results in cardiac muscle loss and is the leading cause of morbidity and mortality in developed countries. Highly differentiated mammalian cells are thought to be incapable of proliferation and an inverse relationship exists between proliferation and differentiation[50]. In contrast to adult cardiomyocytes, mammalian cardiomyocytes do proliferate during fetal development. Adult mammalian ventricular cardiomyocytes can divide[51]. One important mechanism used by mammalian cardiomyocytes to control proliferation is p38 MAP kinase activity. It has been shown that the signaling molecule p38 mitogen-activated protein (MAP) kinase (p38) induces cell cycle exit and the differentiation of many cell types[51], including differentiation of P19 cells to cardiomyocytes[52]. Activated p38 phosphorylates downstream signaling molecules, important for cardiomyocyte differentiation and hypertrophy[53]. Bodyak et al.[54] showed that the overexpression of UCP2 in adult rat cardiomyocytes does not affect cell survival at baseline but leads to significant ATP depletion, acidosis, and accumulation of pro-death protein BNIP3 (19-kDa interacting protein 3).

Chronic β-adrenergic stimulation induces myocardial energy inefficiency via excessive oxidative stress. The antioxidant effect of edaravone has the potential of improving energy metabolism abnormalities in the case of β-adrenergic stimulation[41]. In the failing heart, increased oxidative stress produces mitochondrial damage, which leads to further self-production of reactive oxygen species (ROS) and this creates a vicious cycle of oxidative stress and energetic decline[55]. Here UCP2 may step in by breaking the ROS cycle and prevent apoptosis[30].

Mitogen-activated protein kinase p38

One important mechanism used by mammalian cardiomyocytes to control cell cycle is p38 mitogen activated protein kinase (MAPK) activity. MAPKs are a group of protein serine/threonine kinases that are activated in re-

sponse to a variety of extracelullar stimuli and mediate signal transduction in cell growth, differentiation, and apoptosis[56]. MAPK activation in mammalian systems, including p38 has been characterized in detail[56, 57]. The activation of p38 signaling pathways leads to phosphorylation of a number of targets, including transcription factors ATF-2 and c-jun, resulting in their transcriptional activity and subsequent gene expression[58, 59].

p38 MAPK phosphorylation is increased by contractile stimuli such as endothelin (ET)-1, angiotensin II, norepinephrine, and the thromboxane A2 analog U-46619 in several smooth muscle preparations[60] including canine pulmonary artery (PA)[61]. Knock et al.[62] investigated the role of p38 MAPK in PGF2-induced vasoconstriction and HPV of rat small IPA. SB-203580 and SB-202190 caused relaxation of PGF2-contracted rat IPA at low concentrations, at which they are most likely to exert a selective action on p38 MAPK, via an endothelium- and largely NO-dependent mechanism.

Role of p38 in cardioprotection

A number of studies have linked p38 activity with myocardial response to ischemia reperfusion injury and ischemic preconditioning. The results, however, remain contradictory. Early reports showed that activation of p38 is beneficial[63, 64], followed by later studies demonstrating the opposite[65, 66]. More recent data suggest alternative pathways are at work when p38 is activated, producing divergent effects[67]. This idea is discussed in a later article published by the same group. There they state that "the mode of p38 activation determines whether it has a detrimental or beneficial effect on cell survival"[68]. Indeed, pharmacological stimulation by resveratrol triggers p38, resulting in cardioprotective effect resembling that of ischemia preconditioning[69]. Selective inhibition of p38 by PD169316, shown to be cardioprotective[70], may support the divergent effects of various stimuli causing p38 activation. Pharmacological inhibitors of p38 activity may, however, display a systemic effect rather than just modulate p38 activation as p38 rescues failing myocardium after myocardial infarction[71].

Involvement of p38 in UCP2 regulation

The evidence discussed so far point to an intriguing concept of p38-regulated and CREB-mediated UCP2 expression as a factor in cardiomyocyte survival after an ischemic episode. As p38 responds to a wide range of stimuli, a more general role of UCP2 in pro/anti-apoptotic signaling is likely.

Involvement of p38 in UcP2 regulation is apparent from the stimuli causing p38 phosphorylation and consequent activation: angiotensin II and norepinephrine. Angiotensin II has been shown to protect, rather than cause apoptosis, in cardiomyocytes[72]. Norepinephrine is a known inducer of UCP2 expression[6]. Moreover, activation of p38 is decisive for cell survival in hibernating mycoradium using a swine model[73].

Two recent reports make the connection between p38, UCP2 and ROS. Selimovic et al.[74] demonstrated the involvement of mitochondria in taxol-induced ROS signaling. In melanoma cells the mitochondrial uncoupling protein 2 (UCP2) is downregulated by taxol *via* the activation of MAP kinase signaling pathways JNK and p38. To confirm the involvement of the MAP kinase signaling pathways JNK and p38, they blocked $p38^{MAPK}$ using the specific inhibitor SB-203580. SB-203580 (4-(4-fluorophenyl)-2-(4-methylsulphinylphenyl)-5-(4-pyridyl)imidazole) is a potent, selective inhibitor of p38 MAP kinase used extensively as a tool inhibitor in various pharmacological and toxicological models. The downregulation of UCP2 forms a physiological link between MAP kinase activation and ROS generation in taxol-mediated apoptosis[74].

Emre et al.[75] proposed a signal amplification loop model in which UCP2 is down-regulated in response to LPS (lipopolysaccharide) in bone marrow-derived mac-

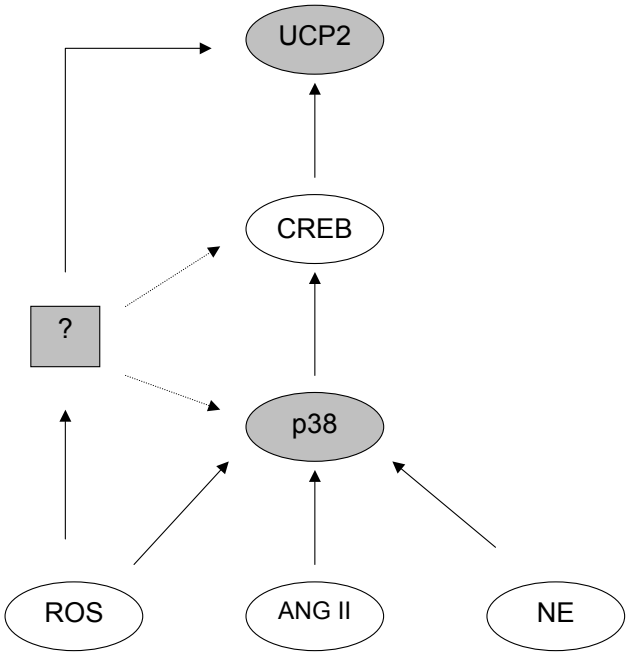

Fig. 1. A diagram illustrating the signaling pathways through which p38 influences UCP2. p38 is a member of the MAPK family that are activated by a variety of environmental stresses and inflammatory cytokines. Angiotensin II (**ANG II**) activates p38 mitogen-activated protein kinase (**p38 MAPK**) and increases reactive oxygen species (**ROS**), but the nature of the relationship in vivo is not fully understood. p38 MAPK is activated by norepinephrine (**NE**) in the vasculature and is implicated in vascular smooth muscle hypertrophy, contraction, and cell migration. The transcription factor cyclic AMP response element binding protein (**CREB**) binds DNA and activates transcription in response to a variety of extracellular signals including neurotransmitters, hormones, membrane depolarization, and growth and neurotrophic factors. Phosphorylation occurs at Ser133 via p38 MAP kinase among others. cAMP- and protein kinase A-dependent activation of p38 MAPK is an indispensable step in the transcription of the *UCP2* gene.

rophage cultures through the JNK and p38 pathways. They found evidence of a crucial role of UCP2 as regulator of mitochondrial ROS production and its signaling in early events leading to macrophage activation. Thus UcP2 down-regulation has been shown necessary in order to increase mitochondrial ROS production to potentiate MAPK activation.

CONCLUSION

There is a tentative relationship between p38 and UCP2. However, tissue specific regulation must occur to account for the divergent effects. While two reports describe down-regulation of UCP2 by p38, indirect evidence from cardiomyocyte studies suggests the opposite. A partner for p38, possibly MSK-1 (ref.[69]), which is present or absent in a particular tissue, may be the toggle switch responsible for increasing or decreasing UCP2 expression (Fig. 1). UCP2 may then serve as protective since p38 plays a role in the inflammatory response of the heart[76]. We consider the proposed p38-CREB-UCP2 pathway as an important pro-survival factor in cardiomyocytes.

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REFERENCES

1. Nübel T. respiration under Control of Uncoupling Proteins: Clinical Perspective. Hormone Research 2006; 65:300-310.
2. Kroemer G, Reed JC. Mitochondrial control of cell death. Nat Med 2000; 6:513-9.
3. Nicholls DG, Ward MW. Mitochondrial membrane potential and neuronal glutamate excitotoxicity: mortality and millivolts. Trends Neurosci 2000; 23:166-74.
4. Ledesma A GdLM, Rial E. The mitochondrial uncoupling proteins. Genome Biology 2002; 3:3015.1-3015.9.
5. Ricquier D, Bouillaud F. The uncoupling protein homologues: UCP1, UCP2, UCP3, StUCP and AtUCP. Biochem J 2000; 345 Pt 2:161-79.
6. Jezek P, Zackova M, Ruzicka M, Skobisova E, Jaburek M. Mitochondrial uncoupling proteins-facts and fantasies. Physiol Res 2004; 53 Suppl 1:S199-211.
7. Arechaga I, Ledesma A, Rial E. The mitochondrial uncoupling protein UCP1: a gated pore. IUBMB Life 2001; 52:165-73.
8. Brand MD, Esteves TC. Physiological functions of the mitochondrial uncoupling proteins UCP2 and UCP3. Cell Metab 2005; 2:85-93.
9. Jezek P. Possible physiological roles of mitochondrial uncoupling proteins–UCPn. Int J Biochem Cell Biol 2002; 34:1190-206.
10. Arsenijevic D, Onuma H, Pecqueur C, Raimbault S, Manning BS, Miroux B, et al. Disruption of the uncoupling protein-2 gene in mice reveals a role in immunity and reactive oxygen species production. Nat Genet 2000; 26:435-9.
11. Blanc J, Alves-Guerra MC, Esposito B, Rousset S, Gourdy P, Ricquier D, et al. Protective role of uncoupling protein 2 in atherosclerosis. Circulation 2003; 107:388-90.
12. Chan CB, Saleh MC, Koshkin V, Wheeler MB. Uncoupling protein 2 and islet function. Diabetes 2004; 53 Suppl 1:S136-42.
13. Son C, Hosoda K, Ishihara K, Bevilacqua L, Masuzaki H, Fushiki T, et al. Reduction of diet-induced obesity in transgenic mice over-expressing uncoupling protein 3 in skeletal muscle. Diabetologia 2004; 47:47-54.
14. Krauss S, Zhang CY, Lowell BB. The mitochondrial uncoupling-protein homologues. Nat Rev Mol Cell Biol 2005; 6:248-61.
15. Mozo J, Emre Y, Bouillaud F, Ricquier D, Criscuolo F. Thermoregulation: what role for UCPs in mammals and birds? Biosci Rep 2005; 25:227-49.
16. Brand MD, Buckingham JA, Esteves TC, Green K, Lambert AJ, Miwa S, et al. Mitochondrial superoxide and aging: uncoupling-protein activity and superoxide production. Biochem Soc Symp 2004:203-13.
17. Fleury C, Neverova M, Collins S, Raimbault S, Champigny O, Levi-Meyrueis C, et al. Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. Nat Genet 1997; 15:269-72.
18. Pecqueur C, Alves-Guerra MC, Gelly C, Levi-Meyrueis C, Couplan E, Collins S, et al. Uncoupling protein 2, in vivo distribution, induction upon oxidative stress, and evidence for translational regulation. J Biol Chem 2001; 276:8705-12.
19. Rousset S, Emre Y, Join-Lambert O, Hurtaud C, Ricquier D, Cassard-Doulcier AM. The uncoupling protein 2 modulates the cytokine balance in innate immunity. Cytokine 2006; 35:135-42.
20. Fleury C, Sanchis D. The mitochondrial uncoupling protein-2: current status. Int J Biochem Cell Biol 1999; 31:1261-78.
21. Ricquier D, Bouillaud F. Mitochondrial uncoupling proteins: from mitochondria to the regulation of energy balance. J Physiol 2000; 529 Pt 1:3-10.
22. Flachs P, Sponarova J, Kopecky P, Horvath O, Sediva A, Nibbelink M, et al. Mitochondrial uncoupling protein 2 gene transcript levels are elevated in maturating erythroid cells. FEBS Lett 2007; 581:1093-7.
23. Flachs P, Horakova O, Brauner P, Rossmeisl M, Pecina P, Franssen-van Hal N, et al. Polyunsaturated fatty acids of marine origin up-regulate mitochondrial biogenesis and induce beta-oxidation in white fat. Diabetologia 2005; 48:2365-75.
24. Rousset S, Mozo J, Dujardin G, Emre Y, Masscheleyn S, Ricquier D, et al. UCP2 is a mitochondrial transporter with an unusual very short half-life. FEBS Lett 2007; 581:479-82.
25. Puigserver P, Herron D, Gianotti M, Palou A, Cannon B, Nedergaard J. Induction and degradation of the uncoupling protein thermogenin in brown adipocytes in vitro and in vivo. Evidence for a rapidly degradable pool. Biochem J 1992; 284 (Pt 2):393-8.
26. Cannon B, Shabalina IG, Kramarova TV, Petrovic N, Nedergaard J. Uncoupling proteins: a role in protection against reactive oxygen species–or not? Biochim Biophys Acta 2006; 1757:449-58.
27. Nedergaard J, Cannon B. The 'novel' 'uncoupling' proteins UCP2 and UCP3: what do they really do? Pros and cons for suggested functions. Exp Physiol 2003; 88:65-84.
28. Arsenijevic D, Gallmann E, Moses W, Lutz T, Erlanson-Albertsson C, Langhans W. Enterostatin decreases postprandial pancreatic UCP2 mRNA levels and increases plasma insulin and amylin. Am J Physiol Endocrinol Metab 2005; 289:E40-5.
29. Trenker M, Malli R, Fertschai I, Levak-Frank S, Graier WF. Uncoupling proteins 2 and 3 are fundamental for mitochondrial Ca2+ uniport. Nat Cell Biol 2007; 9:445-52.
30. Teshima Y, Akao M, Jones SP, Marban E. Uncoupling protein-2 overexpression inhibits mitochondrial death pathway in cardiomyocytes. Circ Res 2003; 93:192-200.
31. Mattiasson G, Sullivan PG. The emerging functions of UCP2 in health, disease, and therapeutics. Antioxid Redox Signal 2006; 8:1-38.
32. Criscuolo F, Mozo J, Hurtaud C, Nubel T, Bouillaud F. UCP2, UCP3, avUCP, what do they do when proton transport is not stimulated? Possible relevance to pyruvate and glutamine metabolism. Biochim Biophys Acta 2006; 1757:1284-91.
33. Beckman KB, Ames BN. The free radical theory of aging matures. Physiol Rev 1998; 78:547-81.
34. Feng J, Bussiere F, Hekimi S. Mitochondrial electron transport is a key determinant of life span in Caenorhabditis elegans. Dev Cell 2001; 1:633-44.
35. Raha S, Robinson BH. Mitochondria, oxygen free radicals, disease and ageing. Trends Biochem Sci 2000; 25:502-8.
36. Pedersen PL. Mitochondrial events in the life and death of animal cells: a brief overview. J Bioenerg Biomembr 1999; 31:291-304.

37. Skulachev VP. Uncoupling: new approaches to an old problem of bioenergetics. Biochim Biophys Acta 1998; 1363:100-24.
38. Korshunov SS, Skulachev VP, Starkov AA. High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. FEBS Lett 1997; 416:15-8.
39. Lee KU, Lee IK, Han J, Song DK, Kim YM, Song HS, et al. Effects of recombinant adenovirus-mediated uncoupling protein 2 overexpression on endothelial function and apoptosis. Circ Res 2005; 96:1200-7.
40. Collins P, Jones C, Choudhury S, Damelin L, Hodgson H. Increased expression of uncoupling protein 2 in HepG2 cells attenuates oxidative damage and apoptosis. Liver Int 2005; 25:880-7.
41. Ishizawa M, Mizushige K, Noma T, Namba T, Guo P, Murakami K, et al. An antioxidant treatment potentially protects myocardial energy metabolism by regulating uncoupling protein 2 expression in a chronic beta-adrenergic stimulation rat model. Life Sci 2006; 78:2974-82.
42. Duval C, Negre-Salvayre A, Dogilo A, Salvayre R, Penicaud L, Casteilla L. Increased reactive oxygen species production with antisense oligonucleotides directed against uncoupling protein 2 in murine endothelial cells. Biochem Cell Biol 2002; 80:757-64.
43. Echtay KS, Roussel D, St-Pierre J, Jekabsons MB, Cadenas S, Stuart JA, et al. Superoxide activates mitochondrial uncoupling proteins. Nature 2002; 415:96-9.
44. McLeod CJ, Aziz A, Hoyt RF, Jr., McCoy JP, Jr., Sack MN. Uncoupling proteins 2 and 3 function in concert to augment tolerance to cardiac ischemia. J Biol Chem 2005; 280:33470-6.
45. Minamiyama Y, Bito Y, Takemura S, Takahashi Y, Kodai S, Mizuguchi S, et al. Calorie restriction improves cardiovascular risk factors via reduction of mitochondrial reactive oxygen species in type II diabetic rats. J Pharmacol Exp Ther 2007; 320:535-43.
46. Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. Uncoupling proteins in human heart. Lancet 2004; 364:1786-8.
47. Roshon MJ, Kline JA, Thornton LR, Watts JA. Cardiac UCP2 expression and myocardial oxidative metabolism during acute septic shock in the rat. Shock 2003; 19:570-6.
48. Rumyantsev PP. Interrelations of the proliferation and differentiation processes during cardiact myogenesis and regeneration. Int Rev Cytol 1977; 51:186-273.
49. Mummery CL. Cardiology: solace for the broken-hearted? Nature 2005; 433:585-7.
50. Studzinski GP, Harrison LE. Differentiation-related changes in the cell cycle traverse. Int Rev Cytol 1999; 189:1-58.
51. Engel FB, Schebesta M, Duong MT, Lu G, Ren S, Madwed JB, et al. p38 MAP kinase inhibition enables proliferation of adult mammalian cardiomyocytes. Genes Dev 2005; 19:1175-87.
52. Eriksson M, Leppa S. Mitogen-activated protein kinases and activator protein 1 are required for proliferation and cardiomyocyte differentiation of P19 embryonal carcinoma cells. J Biol Chem 2002; 277:15992-6001.
53. Liang Q, Molkentin JD. Redefining the roles of p38 and JNK signaling in cardiac hypertrophy: dichotomy between cultured myocytes and animal models. J Mol Cell Cardiol 2003; 35:1385-94.
54. Bodyak N, Rigor DL, Chen YS, Han Y, Bisping E, Pu WT, et al. Uncoupling protein 2 modulates cell viability in adult rat cardiomyocytes. Am J Physiol Heart Circ Physiol 2007; 293:H829-35.
55. Ide T, Tsutsui H, Kinugawa S, Utsumi H, Kang D, Hattori N, et al. Mitochondrial electron transport complex I is a potential source of oxygen free radicals in the failing myocardium. Circ Res 1999; 85:357-63.
56. Ichijo H. Differentiation of the chick retinotectal topographic map by remodeling in specificity and refinement in accuracy. Brain Res Dev Brain Res 1999; 117:199-211.
57. Minden A, Karin M. Regulation and function of the JNK subgroup of MAP kinases. Biochim Biophys Acta 1997; 1333:F85-104.
58. Zayzafoon M, Botolin S, McCabe LR. P38 and activating transcription factor-2 involvement in osteoblast osmotic response to elevated extracellular glucose. J Biol Chem 2002; 277:37212-8.
59. Zhu T, Lobie PE. Janus kinase 2-dependent activation of p38 mitogen-activated protein kinase by growth hormone. Resultant transcriptional activation of ATF-2 and CHOP, cytoskeletal re-organization and mitogenesis. J Biol Chem 2000; 275:2103-14.
60. Bolla M, Matrougui K, Loufrani L, Maclouf J, Levy B, Levy-Toledano S, et al. p38 mitogen-activated protein kinase activation is required for thromboxane- induced contraction in perfused and pressurized rat mesenteric resistance arteries. J Vasc Res 2002; 39:353-60.
61. Yamboliev IA, Hedges JC, Mutnick JL, Adam LP, Gerthoffer WT. Evidence for modulation of smooth muscle force by the p38 MAP kinase/HSP27 pathway. Am J Physiol Heart Circ Physiol 2000; 278:H1899-907.
62. Knock GA, De Silva AS, Snetkov VA, Siow R, Thomas GD, Shiraishi M, et al. Modulation of PGF2alpha- and hypoxia-induced contraction of rat intrapulmonary artery by p38 MAPK inhibition: a nitric oxide-dependent mechanism. Am J Physiol Lung Cell Mol Physiol 2005; 289:L1039-48.
63. Weinbrenner C, Liu GS, Cohen MV, Downey JM. Phosphorylation of tyrosine 182 of p38 mitogen-activated protein kinase correlates with the protection of preconditioning in the rabbit heart. J Mol Cell Cardiol 1997; 29:2383-91.
64. Maulik N, Yoshida T, Zu YL, Sato M, Banerjee A, Das DK. Ischemic preconditioning triggers tyrosine kinase signaling: a potential role for MAPKAP kinase 2. Am J Physiol 1998; 275:H1857-64.
65. Ma XL, Kumar S, Gao F, Louden CS, Lopez BL, Christopher TA, et al. Inhibition of p38 mitogen-activated protein kinase decreases cardiomyocyte apoptosis and improves cardiac function after myocardial ischemia and reperfusion. Circulation 1999; 99:1685-91.
66. Mackay K, Mochly-Rosen D. An inhibitor of p38 mitogen-activated protein kinase protects neonatal cardiac myocytes from ischemia. J Biol Chem 1999; 274:6272-9.
67. Lochner A, Genade S, Hattingh S, Marais E, Huisamen B, Moolman JA. Comparison between ischaemic and anisomycin-induced preconditioning: role of p38 MAPK. Cardiovasc Drugs Ther 2003; 17:217-30.
68. Moolman JA, Hartley S, Van Wyk J, Marais E, Lochner A. Inhibition of myocardial apoptosis by ischaemic and beta-adrenergic preconditioning is dependent on p38 MAPK. Cardiovasc Drugs Ther 2006; 20:13-25.
69. Das S, Tosaki A, Bagchi D, Maulik N, Das DK. Potentiation of a survival signal in the ischemic heart by resveratrol through p38 mitogen-activated protein kinase/mitogen- and stress-activated protein kinase 1/cAMP response element-binding protein signaling. J Pharmacol Exp Ther 2006; 317:980-8.
70. Schwertz H, Carter JM, Abdudureheman M, Russ M, Buerke U, Schlitt A, et al. Myocardial ischemia/reperfusion causes VDAC phosphorylation which is reduced by cardioprotection with a p38 MAP kinase inhibitor. Proteomics 2007; 7:4579-88.
71. Tenhunen O, Soini Y, Ilves M, Rysa J, Tuukkanen J, Serpi R, et al. p38 Kinase rescues failing myocardium after myocardial infarction: evidence for angiogenic and anti-apoptotic mechanisms. Faseb J 2006; 20:1907-9.
72. Kong JY, Rabkin SW. Angiotensin II does not induce apoptosis but rather prevents apoptosis in cardiomyocytes. Peptides 2000; 21:1237-47.
73. McFalls EO, Hou M, Bache RJ, Best A, Marx D, Sikora J, et al. Activation of p38 MAPK and increased glucose transport in chronic hibernating swine myocardium. Am J Physiol Heart Circ Physiol 2004; 287:H1328-34.
74. Selimovic D, Hassan M, Haikel Y, Hengge UR. Taxol-induced mitochondrial stress in melanoma cells is mediated by activation of c-Jun N-terminal kinase (JNK) and p38 pathways via uncoupling protein 2. Cell Signal 2008; 20:311-22.
75. Emre Y, Hurtaud C, Nubel T, Criscuolo F, Ricquier D, Cassard-Doulcier AM. Mitochondria contribute to LPS-induced MAPK activation via uncoupling protein UCP2 in macrophages. Biochem J 2007; 402:271-8.
76. Tenhunen O, Rysa J, Ilves M, Soini Y, Ruskoaho H, Leskinen H. Identification of cell cycle regulatory and inflammatory genes as predominant targets of p38 mitogen-activated protein kinase in the heart. Circ Res 2006; 99:485-93.