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REVIEW

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Glucose transporters in diabetic nephropathy

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Abstract Changes in glucose transporter expression in glomerular cells occur early in diabetes. These changes, especially the GLUT1 increase in mesangial cells, appear to play a pathogenic role in the development of ECM expansion and perhaps other features of diabetic nephropathy. In addition, it appears that at least some diabetic patients may be predisposed to nephropathy because of polymorphisms in their GLUT1 genes. GLUT1 overexpression leads to increased glucose metabolic flux which in turn triggers the polyol pathway and activation of PKCα and B1. Activation of these PKC isoforms can lead directly to AP-1 induced increases in fibronectin expression and ECM accumulation. Other, more novel effects of GLUT1 on cellular hypertrophy and injury could also promote changes of diabetic nephropathy. Strategies to prevent GLUT1 overexpression could ameliorate or prevent the progression of diabetic nephropathy.

Keywords Podocyte · Diabetic nephropathy · Type 1 diabetes mellitus · Reactive oxygen species · Mouse · Rat

Introduction

Since the publication of the Diabetes Control and Complications Trial (DCCT) over a decade ago [1], the link between hyperglycemia and the development of microvascular diabetic complications has been incontrovertible. This landmark trial and a number of other clinical studies have strongly supported the hypothesis that enhanced cellular glucose uptake and metabolism in susceptible cells contribute to the progressive tissue damage and functional decline that characterize diabetic microvascular complications. However, the implied corollary of these studies, that glucose uptake by cells is directly proportional to extracellular glucose levels, is not true for many cells and tissues that in fact show a reduction in glucose uptake in the face of hyperglycemia [2, 3, 4]. Indeed, the failure of skeletal muscle and other insulin responsive tissues to augment glucose uptake in the face of elevated glucose levels contributes to hyperglycemia in both type1 and type 2 diabetes mellitus. It is therefore not surprising that these tissues are generally protected from diabetic microvascular complications.

Nonetheless, at least some cells in the body do show enhanced glucose uptake in diabetes and therefore are candidates for diabetic injury. It has been our fundamental hypothesis for the past decade that susceptibility of renal cells to glucose-induced injury is mediated by increased expression or activity of facilitative glucose transporters, which are integral plasma membrane proteins that conduct glucose into cells. Since the initial pathologic hallmarks of diabetic nephropathy are confined to the glomerulus and include glomerular basement thickening and mesangial expansion [5], as well as a loss of glomerular podocytes [6, 7], we and others have focused attention on glomerular glucose transporters.

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Glomerular facilitative glucose transporters in diabetes

The facilitative glucose transporters comprise a family of at least 13 members, most of which function to allow glucose to diffuse down its concentration gradient across the plasma membrane [2]. Initial studies of renal facilitative glucose transporters revealed significant expression of GLUT1 and GLUT4 in glomerular cells [8, 9], though the intensity of GLUT1 and GLUT4 immunostaining in glomeruli was much lower than in many renal tubular

segments, possibly due to the relatively low rate of metabolism compared to that of renal tubules [10]. Both GLUT1 and GLUT4 are expressed in mesangial cells and podocytes [8, 9, 11]. In cultured mesangial cells, GLUT1 appears to be the predominant transporter, but because GLUT4 is often downregulated in culture it is not absolutely certain that GLUT1 predominates in mesangial cells in vivo. GLUT3 was also detected at low levels in glomeruli [9], though the exact cellular localization has not been determined. In addition, a recent preliminary report found that GLUT8, another insulin-responsive transporter identified in the last several years, is expressed in podocytes as well as in tubular cells [12]. It is not yet known whether any of the other, more novel glucose transporters, including GLUT11, are expressed in glomerular cells. Finally, one group has identified sodium-glucose cotransporter (SGLT) activity in cultured mesangial cells [13]. However, there have been no additional studies reported to suggest that sodium-coupled glucose transport plays a major role in glucose uptake and metabolism in mesangial cells in culture or in vivo.

Hyperglycemia and diabetes mellitus often result in a reduction of glucose transporter expression in tissues, and GLUT4 expression is reduced in glomeruli from streptozotocin rats [14]. This implies that glucose uptake via GLUT4 is reduced in diabetes in both mesangial cells and podocytes [14]. However, Saleem and colleagues have shown that GLUT4 redistributes to the basal surface of podocyte foot processes during type 2 diabetes in humans [11], suggesting that functional (i.e., plasmalemmal) GLUT4 transporters may not be reduced in diabetic podocytes. More definitive studies will be required to determine the effects of GLUT4 in these cells.

In contrast to the decline in GLUT4 expression, exposure of mesangial cells to elevated extracellular glucose concentrations (an increase from 8 to 20 mM glucose) for 3 days enhances GLUT1 levels in cultured mesangial cells [15]. Similar changes occur in diabetic glomeruli. For example, diabetes induces GLUT1 in the cortex from type 1 streptozotocin diabetic rats [16] and in glomeruli from streptozotocin diabetic mice as well as in type 2 db/db diabetic mice [17]. These increases in GLUT1 occur relatively rapidly after the onset of diabetes, at least within 5–6 weeks in the db/db model and probably earlier. In addition, high glucose levels stimulate IGF-1 mediated glucose uptake in cultured mesangial cells [15], suggesting that glucose may stimulate the translocation or the activity of individual glucose transporters as well as GLUT1 gene expression in these cells. Together these data strongly suggest that mesangial cells manifest enhanced glucose uptake via GLUT1 during diabetes. As noted above, since GLUT1 appears to be the predominant glucose transporter in mesangial cells, it is likely, although not absolutely proven, that mesangial cell glucose uptake increases in diabetes despite the concomitant reduction in GLUT4 levels.

The association between GLUT1 and diabetes is less certain in podocytes. However, we have preliminary data suggesting that high glucose induces expression of GLUT1 in cultured podocytes within 4–12 h (F.C. Brosius et al., unpublished observations). Thus, it may be the case that hyperglycemia affects both mesangial cells and podocytes similarly by enhancing GLUT1 expression and glucose uptake. However, whether this occurs in podocytes remains to be demonstrated in vivo. Finally, podocyte GLUT8 levels are increased in type 2 db/db mice [12]. This could further enhance glucose metabolic flux in diabetic podocytes. On balance, it seems likely that glucose uptake and glucose metabolic flux are enhanced in diabetic glomerular podocytes.

Effects of increased GLUT1 and glucose metabolic flux on glomerular cells

Previous studies indicate that GLUT1 is rate-limiting, or nearly so, for glucose metabolism in cultured mesangial cells and that increased GLUT1 expression in glomerular cells drives many of the changes that are characteristic of diabetic nephropathy such as ECM production and accumulation [18, 19]. Overexpression of GLUT1 in cultured mesangial cells without any other changes leads to excessive ECM production and release [18], while suppression of mesangial cell GLUT1 leads to reduced ECM production [19]. Similar findings appear to take place in vivo. Preliminary data indicate that transgenic overexpression of GLU1 in db/m mice leads to enhanced glomerular ECM accumulation (Heilig et al., unpublished observations). In these transgenic mice, a modified β-actin promoter drives expression of the GLUT1 transgene. This promoter was chosen specifically to enhance GLUT1 expression in glomerular mesangial cells where it is robustly active [20, 21], although it is active in a number of other tissues as well. At 6 months of age, the nondiabetic mice that overexpress GLUT1 show normal blood sugars, but demonstrated a 67–200% increase in albuminuria by 4.5 and 6.5 months of age with substantial increases in ECM expansion when compared to nontransgenic mice [22]. At present, diabetic mice overexpressing GLUT1 in mesangial cells are being evaluated to determine whether augmented GLUT1 expression, beyond that which normally occurs in diabetes, accentuates diabetic injury. The effect of specific GLUT1 overexpression in diabetic podocytes is also being evaluated in another transgenic mouse model in a db/m background.

While the studies of glomerular GLUT1 overexpression in diabetes are still being assessed, the effects of preventing GLUT1 overexpression are clear. Transduction of cultured mesangial cells with a GLUT1 antisense construct resulted in a >50% reduction in GLUT1 expression and glucose uptake [19]. In addition, when these cells were exposed to elevated extracellular glucose concentrations, the expected increases in GLUT1 levels and glucose uptake were prevented [19]. Most importantly, GLUT1 antisense expression also prevented the increase in ECM expression, the in vitro corollary of diabetic nephropathy. Such prevention of diabetic nephropathy has recently been confirmed in an in vivo model.

Diabetic db/db mice carrying an antisense-GLUT1 transgene have been found to have GLUT1 levels and glomerular glucose uptake reduced to approximately 50% of levels in wild-type diabetic mice, levels that are not significantly different from levels in nondiabetic wild-type mice. In these GLUT1 antisense diabetic mice the mesangial cell glucose uptake rate is also reduced by 50%. Such mice with diabetes demonstrate protection against the development of glomerulosclerosis [17]. Therefore, both in cultured mesangial cells and in glomeruli in vivo, the GLUT1 transporter appears to be an important regulator of ECM production.

Possible role of GLUT1 polymorphisms in the genetic predisposition to diabetic nephropathy

Because of the likely role of enhanced glomerular GLUT1 expression in predisposing to diabetic nephropathy in animals, GLUT1 has been considered a potential disease gene in humans. Several case-control studies have implicated GLUT1 polymorphisms in the risk of developing nephropathy in different type 1 and type 2 diabetic populations. One study in British type 1 patients found that an *Xba* I (-) restriction fragment length polymorphism was associated with an increased risk for diabetic nephropathy [23]. A more recent study found that Caucasian type 1 diabetic patients who were homozygous for the A allele of a single-nucleotide polymorphism (SNP) in the enhancer-2 region in the second intron of the GLUT1 gene had a 2.4-fold increased risk for diabetic nephropathy compared to patients who did not have this genotype [24]. This SNP is very tightly linked to the *Xba* I polymorphism site identified in the previous study [23, 24]. The enhancer-2 SNP of GLUT1 is inside a predicted binding site for USF transcription factors which regulate gene expression in response to high glucose [24, 25] and therefore could be functionally significant in regulating GLUT1 expression in diabetes. In another study, recent preliminary data indicate that Caucasian type 2 diabetics and nondiabetics who were homozygous for the A allele of the GLUT1 enhancer-2 SNP were also at increased risk for renal disease manifested by albuminuria [26]. Investigations are currently underway to determine whether this SNP may affect GLUT1 expression.

Whether such an association between the GLUT1 polymorphisms and diabetic nephropathy occurs in all populations is uncertain. One study in Chinese type 2 patients has found that the *Xba* I (-) genotype is associated with a higher incidence of diabetic nephropathy [27], while another study found that the *Xba* I (+) allele was associated with increased risk in Caucasian type 2 patients in Poland [28]. Finally, another study has found no association between the GLUT1 polymorphism and diabetic nephropathy [29].

Effects of increased GLUT1 expression on signaling in glomerular mesangial cells

Since expression of the GLUT1 gene leads to morphologic features of diabetic nephropathy and since the GLUT1 gene appears to be linked to the development of diabetic nephropathy in some populations, it is important to understand the mechanisms by which GLUT1 expression can lead to such outcomes. Several studies over the past decade have helped to reveal at least some of the pathways involved, especially in cultured mesangial cells. Chronic overexpression of GLUT1 leads to activation of the polyol pathway [30], as well as PKCα and β1 activation [30, 31]. Enhanced glucose metabolism through the polyol pathway can lead to synthesis of diacylglycerol and phosphatidic acid, which may account for increased mesangial cell PKC isoform activation as well as increased PKC levels [32]. In turn, PKC α and β1 activation by GLUT1 leads to increased AP-1 levels which enhance transcription of several genes, such as those of fibronectin and other ECM proteins [31]. Thus, increased GLUT1 expression, independent of elevated extracellular glucose levels, can directly enhance ECM production through a PKC and AP-1 dependent pathway (see Fig. 1).

Interestingly, chronic GLUT1 overexpression alone does not lead to activation of MAP kinase (ERK and p38) pathways, to induction of TGF-β, or to enhanced production of reactive oxygen species (ROS) [31]. Activation of MAP kinase and TGF-β pathways and enhanced ROS

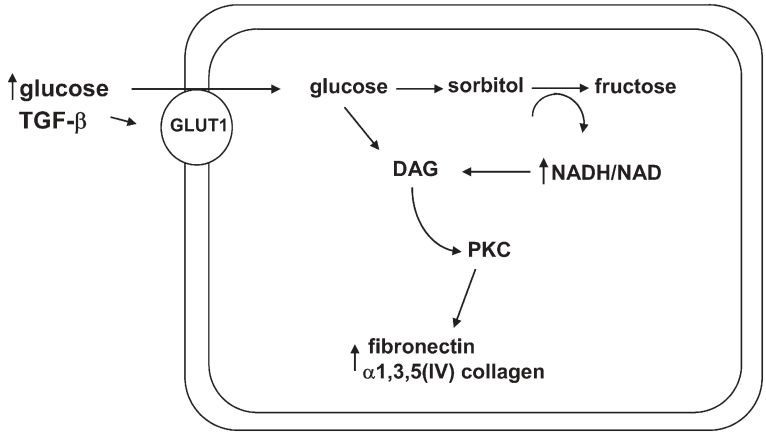

Fig. 1 GLUT1 signaling in mesangial cells. Increased GLUT1 expression leads to enhanced polyol pathway and production of PKC. In turn, this enhances the synthesis of fibronectin and other ECM proteins. Increased extracellular glucose and TGF-β augment GLUT1 expression and enhance this signaling cascade

production have all been strongly implicated in the progression of diabetic nephropathy. This curious lack of GLUT1 effect on these pathways has several implications. First, it suggests strongly that increased GLUT1 expression can lead to enhanced ECM accumulation independent of these pathways. Second, increased glucose uptake and metabolic flux alone are clearly not sufficient to trigger MAP kinase and TGF-β signaling, at least in cultured cell systems. Perhaps, as Weigert et al. speculated, stimulation of these pathways may require ROS production. Since GLUT1 is chronically overexpressed in these experimental systems, it is possible that the cells have adapted to the enhanced metabolic flux and have increased mechanisms for dealing with oxidative stress. Additionally it appears that most of the excess glucose metabolic flux is glycolytic, not oxidative, and therefore mitochondrial oxidative stress is not enhanced [31]. Whether GLUT1 overexpression in diabetic tissues in vivo fails to enhance ROS production, and signaling via MAP kinase and TGF-β pathways, is uncertain. Perhaps the oscillatory nature of hyperglycemia, and hence GLUT1 expression, in diabetic patients would stimulate a more acute response in complications-prone tissues activating mitochondrial generation of ROS as well as TGF-β and MAP kinase pathways. Although GLUT1 does not stimulate TGF-β or MAP kinase pathways in cultured mesangial cells, there is evidence that TGF-β [33] and possibly ERK [34] can stimulate mesangial cell GLUT1 expression. Thus, these important pathways in diabetic nephropathy are still ultimately linked to GLUT1.

Newer areas of investigation examining the effect of GLUT1 overexpression on cellular signaling have been performed in nonrenal tissues that have clear implications for diabetic nephropathy. One recent report confirmed that GLUT1 was necessary for cardiac myocyte hypertrophy [35], which had previously been suggested in transgenic mouse studies. This recent study found that preventing the expected increases in GLUT1 expression with an adenoviral GLUT1 antisense approach before exposure to hypertrophic stimuli blocked induction of hypertrophy in cardiac myocytes. Surprisingly, this study found that all of the effects of GLUT1 overexpression occurred equally in the absence and presence of extracellular glucose and confirmed that the effects were independent of glucose transport. One possible explanation for these findings is that GLUT1 can influence cellular adaptation and signaling via direct protein–protein interactions that may be independent of the molecule's glucose transport function. A number of investigators have already demonstrated the direct interaction of GLUT1 and other proteins [36, 37, 38, 39] and have shown that GLUT1 can thereby affect signaling [37]. Morissette et al. [35] suggest that GLUT1 may interact with signaling molecules that result in Akt phosphorylation. While this latter mechanism remains to be demonstrated, such a finding would nicely complement pathways by which glucose uptake and metabolism also enhance Akt activation [40, 41]. The observation that GLUT1 is associated with lipid rafts in several cell types [39, 42] strengthens this hypothesis since many plasma membrane signaling processes are localized adjacent to these detergent-insoluble domains in many cell types. Should similar, nonmetabolic effects of GLUT1 be demonstrated in diabetic glomerular mesangial cells and/or podocytes, novel mechanisms for diabetic cellular hypertrophy and possibly ECM expansion could be elucidated.

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References

1. The DCCT Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977–986
2. Devaskar S, Mueckler M (1992) The mammalian glucose transporters. Pediatr Res 31:1–13
3. Kahn B, Flier J (1990) Regulation of glucose transporter gene regulation in vitro and in vivo. Diabetes Care 13:548–564
4. Klip A, Tsakiridis T, Marette A, Ortiz PA (1994) Regulation of expression of glucose transporters by glucose: a review of studies in vivo and in cell cultures. FASEB J 8:43–53
5. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC (1984) Structural-functional relationships in diabetic nephropathy. J Clin Invest 74:1143–1155
6. Meyer TW, Bennett PH, Nelson RG (1999) Podocyte number predicts long-term urinary albumin excretion in Pima Indians with type II diabetes and microalbuminuria. Diabetologia 42:1341–1344
7. Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, Coplon NS, Sun L, Meyer TW (1997) Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest 99:342–348
8. Brosius FC 3rd, Briggs JP, Marcus RG, Barac-Nieto M, Charron MJ (1992) Insulin-responsive glucose transporter expression in renal microvessels and glomeruli. Kidney Int 42:1086–1092
9. Heilig C, Zaloga C, Lee M, Zhao X, Riser B, Brosius F, Cortes P (1995) Immunogold localization of high affinity GLUT isoforms in normal rat kidney. Lab Invest 73:674–684
10. Gregoire F (1975) Oxidative metabolism of the normal rat glomerulus. Kidney Int 7:86–93
11. Coward RJM, Welsh GI, Holman GD, Kerjaschki D, Tavare MJ, Mathieson PW, Saleem MA (2003) Human podocytes rapidly utilize glucose by both GLUT1 and GLUT4 in response to insulin, with significant differences in glucose transporter levels occurring in diabetic nephropathy. J Am Soc Nephrol 14:388A (abstract)
12. Schiffer M, Ranalletta M, Susztak K, Charron JM, Bottinger EP (2003) Localization of the GLUT8 glucose transporter in the kidney and regulation in vivo in non-diabetic and diabetic conditions. J Am Soc Nephrol 14:308A
13. Wakisaka M, He Q, Spiro M, Spiro R (1995) Glucose entry into mesangial cells is mediated by both Na+-coupled and facilitative glucose transporters. Diabetalogia 38:291–297
14. Marcus RG, England R, Nguyen K, Charron MJ, Briggs JP, Brosius FC 3rd (1994) Altered renal expression of the insulin-responsive glucose transporter GLUT4 in experimental diabetes mellitus. Am J Physiol 267:F816–824
15. Heilig CW, Liu Y, England RL, Freytag SO, Gilbert JD, Heilig KO, Zhu M, Concepcion LA, Brosius FC 3rd (1997) D -Glucose stimulates mesangial cell GLUT1 expression and basal and

IGF-I-sensitive glucose uptake in rat mesangial cells: implications for diabetic nephropathy. Diabetes 46:1030–1039
16. D'Agord Schaan B, Lacchini S, Bertoluci MC, Irigoyen MC, Machado UF, Schmid H (2001) Increased renal GLUT1 abundance and urinary TGF-beta 1 in streptozotocin-induced diabetic rats: implications for the development of nephropathy complicating diabetes. Horm Metab Res 33:664–669
17. Chen S, Heilig K, Brosius F III, Heilig C (2003) Diabetes increases glomerular GLUT1 and antisense-GLUT1 protects against diabetic glomerulosclerosis. J Am Soc Nephrol 14:46A
18. Heilig CW, Concepcion LA, Riser BL, Freytag SO, Zhu M, Cortes P (1995) Overexpression of glucose transporters in rat mesangial cells cultured in a normal glucose milieu mimics the diabetic phenotype. J Clin Invest 96:1802–1814
19. Heilig CW, Kreisbergh JI, Freytag S, Murakami T, Ebina Y, Guo L, Heilig K, Jin Y, Henry D, Brosius FC III (2001) Antisense-GLUT1 protects mesangial cells from D -glucose-induced transporter and fibronectin expression. Am J Physiol 280:F657–666
20. Gunning P, Leavitt J, Muscat G, Ng SY, Kedes L (1987) A human beta-actin expression vector system directs high-level accumulation of antisense transcripts. Proc Natl Acad Sci U S A 84:4831–4835
21. Oberley TD, Coursin DB, Cihla HP, Oberley LW, el-Sayyad N, Ho YS (1993) Immunolocalization of manganese superoxide dismutase in normal and transgenic mice expressing the human enzyme. Histochem J 25:267–279
22. Heilig KO, Chen S, Xiang M, Brosius FC, Heilig CW (2004) Transgenic overexpression of GLUT1 in glomeruli produces features of diabetic nephropathy in mice. J Am Soc Nephrol (abstract)
23. Hodgkinson AD, Millward BA, Demaine AG (2001) Polymorphisms of the glucose transporter (GLUT1) gene are associated with diabetic nephropathy. Kidney Int 59:985–989
24. Ng DP, Canani L, Araki S, Smiles A, Moczulski D, Warram JH, Krolewski AS (2002) Minor effect of GLUT1 polymorphisms on susceptibility to diabetic nephropathy in type 1 diabetes. Diabetes 51:2264–2269
25. Vaulont S, Kahn A (1994) Transcriptional control of metabolic regulation genes by carbohydrates. FASEB J 8:28–35
26. Hsu CC, Kao WH, Steffes M, Brancati F, Heilig C, Shuldiner A, Boerwinkle E, Coresh J (2004) Genetic variation of glucose transporter-1 (GLUT1) and albuminuria in the atherosclerosis risk in communities study. Diabetes 53:A200 (abstract)
27. Liu ZH, Guan TJ, Chen ZH, Li LS (1999) Glucose transporter (GLUT1) allele (*Xba*I-) associated with nephropathy in non-insulin-dependent diabetes mellitus. Kidney Int 55:1843–1848
28. Grzeszczak W, Moczulski DK, Zychma M, Zukowska-Szczechowska E, Trautsolt W, Szydlowska I (2001) Role of GLUT1 gene in susceptibility to diabetic nephropathy in type 2 diabetes. Kidney Int 59:631–636
29. Tarnow L, Grarup N, Hansen T, Parving HH, Pedersen O (2001) Diabetic microvascular complications are not associated with two polymorphisms in the GLUT-1 and PC-1 genes regulating glucose metabolism in Caucasian type 1 diabetic patients. Nephrol Dial Transplant 16:1653–1656
30. Henry DN, Buski JV, Concepcion LA, Brosius FC III, Heilig CW (1999) Glucose transporters control the expression of aldose reductase, PKCα, and GLUT1 genes in mesangial cells in vitro. Am J Physiol 277: F97–F104
31. Weigert C, Brodbeck K, Brosius FC III, Huber M, Lehmann R, Friess U, Aulwurm S, Häring H, Schleicher ED, Heilig CW (2003) Evidence for a novel TGF-β1-independent mechanism of fibrosis in mesangial cells overexpressing glucose transporters. Diabetes 52:527–535
32. Whiteside CI, Dlugosz JA (2002) Mesangial cell protein kinase C isozyme activation in the diabetic milieu. Am J Physiol Renal Physiol 282:F975–980
33. Inoki K, Haneda M, Maeda S, Koya D, Kikkawa R (1999) TGF-beta 1 stimulates glucose uptake by enhancing GLUT1 expression in mesangial cells. Kidney Int 55:1704–1712
34. Nose A, Mori Y, Uchiyama-Tanaka Y, Kishimoto N, Maruyama K, Matsubara H, Iwasaka T (2003) Regulation of glucose transporter (GLUT1) gene expression by angiotensin II in mesangial cells: involvement of HB-EGF and EGF receptor transactivation. Hypertens Res 26:67–73
35. Morissette MR, Howes AL, Zhang T, Brown JH (2003) Up-regulation of GLUT1 expression is necessary for hypertrophy and survival in neonatal rat cardiomyocytes. J Mol Cell Cardiol 35:1217–1227
36. Giorgino F, de Robertis O, Laviola L, Montrone C, Perrini S, McCowen KC, Smith RJ (2000) The sentrin-conjugating enzyme mUbc9 interacts with GLUT4 and GLUT1 glucose transporters and regulates transporter levels in skeletal muscle cells. Proc Natl Acad Sci U S A 97:1125–1130
37. Bandyopadhyay G, Sajan MP, Kanoh Y, Standaert ML, Burke TR Jr, Quon MJ, Reed BC, Dikic I, Noel LE, Newgard CB, Farese R (2000) Glucose activates mitogen-activated protein kinase (extracellular signal-regulated kinase) through proline-rich tyrosine kinase-2 and the Glut1 glucose transporter. J Biol Chem 275:40817–40826
38. Bunn RC, Jensen MA, Reed BC (1999) Protein interactions with the glucose transporter binding protein GLUT1CBP that provide a link between GLUT1 and the cytoskeleton. Mol Biol Cell 10:819–832
39. Zhang JZ, Hayashi H, Ebina Y, Prohaska R, Ismail-Beigi F (1999) Association of stomatin (band 7.2b) with Glut1 glucose transporter. Arch Biochem Biophys 372:173–178
40. Plas DR, Talapatra S, Edinger AL, Rathmell JC, Thompson CB (2001) Akt and Bcl-xL promote growth factor-independent survival through distinct effects on mitochondrial physiology. J Biol Chem 276:12041–12048
41. Gottlob K, Majewski N, Kennedy S, Kandel E, Robey RB, Hay N (2001) Inhibition of early apoptotic events by Akt/PKB is dependent on the first committed step of glycolysis and hexokinase. Genes Dev 15:1406–1418
42. Sakyo T, Kitagawa T (2002) Differential localization of glucose transporter isoforms in non-polarized mammalian cells: distribution of GLUT1 but not GLUT3 to detergent-resistant membrane domains. Biochim Biophys Acta 1567:165–175