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Ezrin/Radixin/Moesin Proteins in the Development of Diabetes and its Cardiovascular Complications

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Abstract

The ezrin, radixin, and moesin proteins (ERM proteins) act as linkers between membrane molecules and the F-actin cytoskeleton. The transmembrane protein-binding sites in their N-terminal (FERM) domain and F-actin-binding sites in the C-terminal region are masked by a closed conformation in the inactive state. Activation of ERM proteins depends on tyrosine phosphorylation of the N-terminal domain and threonine phosphorylation of the C-terminal. ERM proteins are expressed in various cells in a developmental and tissue-specific manner, and these proteins are involved in the regulation of diverse cellular functions that include morphogenesis, endocytosis/exocytosis, adhesion, and migration. Recent studies have demonstrated that regulation of ERM protein expression and activation plays an important role in the development of diabetes and diabetic complications. This review focuses on the role of ERM proteins in the secretion and utilization of insulin, as well as the involvement of these proteins in the pathogenesis and progression of diabetic angiopathy, nephropathy, and cardiomyopathy.

Keywords: Ezrin; Radixin; Moesin; Diabetes; Diabetic complication

Introduction

The ezrin, radixin, and moesin proteins (ERM proteins) link the cell cortex to membrane components and the actin cytoskeleton [1,2]. As members of the erythrocyte protein 4.1 superfamily, ERM proteins are characterized by a conserved NH2-terminal FERM (4.1, ezrin, radixin, moesin homology) domain, which associates with the cytoplasmic domain of various membrane proteins, such as receptors (CD43, CD44, CD95, and CD146 [3-5]) and adhesion molecules (ICAM-2, P-selectin and L-selectin [6-8]). The COOH-terminal domain forms a masking intramolecular band with the FERM domain when ERM proteins are inactive cytoplasmic molecules, while it binds to F-actin after phosphorylation of a conserved threonine residue (Thr567 in ezrin, Thr564 in radixin, and Thr558 in moesin) to activate these linking proteins [9]. ERM proteins are expressed by various cells in a developmental and tissue-specific manner [10-12], with epithelial cells predominantly expressing ezrin, endothelial cells (especially microvascular endothelial cells) predominantly expressing moesin, and hepatocytes predominantly expressing radixin [13-15].

ERM proteins participate in the regulation of diverse cellular functions, including morphogenesis, endocytosis/exocytosis, adhesion, and migration. Recent studies employing genome scan, mRNA, and proteomic analyses have demonstrated that abnormal regulation of ERM protein expression and activation plays an important role in the development of diabetes and diabetic complications [16-18]. This review focuses on the role of ERM proteins in the secretion and utilization of insulin, as well as the involvement of these proteins in the pathogenesis and progression of diabetic angiopathy, nephropathy, and cardiomyopathy.

ERM Proteins and Regulation of Insulin Secretion

There is limited evidence concerning the role of ERM proteins in the secretion of insulin. A key step in insulin secretion is the trafficking of insulin granules to the plasma membrane. ERM proteins serve as scaffolding proteins in lipid rafts and participate in granule trafficking in some secretory cells and tissues, including gastric parietal cells, bile canalicular membrane cells, and β-cells in the pancreatic islets [19-21]. Using time-lapse confocal microscopy of living cells, Lopez et al. found that ERM proteins were activated by threonine phosphorylation (Thr567, Thr564, and Thr558 for ezrin, radixin, and moesin, respectively) in a glucose- and calcium-dependent manner in β-cells, leading to translocation of these proteins to the cell periphery along with insulin granules. They also found that ERM proteins participate in insulin granule trafficking and docking to the plasma membrane, since down-regulation of ezrin activation led to impaired docking of these granules and reduced insulin secretion. More importantly, they demonstrated that the islets of diabetic mice had a low content of activated ERM proteins. Therefore, ERM proteins are involved in the regulation of insulin secretion, indicating a possible role of ERM dysfunction in the development of diabetes [21].

Role of ERM proteins in glucose uptake and disposal

In an attempt to identify potential protein targets for insulin sensitization in human adipose tissue, proteomic studies have revealed that short-term rosiglitazone treatment leads to a striking increase in the expression of proteins involved in glucose transporter-4 (GLUT4) granule transport and fusion. Moesin was one of these proteins, and its increased expression was associated with the remodeling of adipose depots and more importantly with the promotion of glucose uptake by adipocytes [22]. Therefore, ERM proteins had a role in increasing the efficiency of glucose uptake and improving insulin sensitivity during rosiglitazone treatment. Chun et al. demonstrated a decrease in the activation of Rho-associated kinase1 (ROCK1) in the skeletal muscle of patients with type 2 diabetes [23]. ROCK1 is one of the most

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important upstream molecules in the pathway leading to threonine phosphorylation of ezrin and moesin [24]. Chun et al. reported that phosphorylation of ezrin, along with other downstream targets of the ROCK1 signaling pathway, was significantly decreased in the skeletal muscle of patients with type 2 diabetes. Since ezrin is involved in the regulation of actin filaments, suppression of its phosphorylation may result in the downregulation of glucose transport and alteration of insulin signaling in skeletal muscle, leading to the development of insulin resistance. These findings imply that ERM proteins may play an important role in the pathogenesis of insulin resistance in the muscle tissue of obese patients with type 2 diabetes.

Critical role of ERM proteins in diabetic angiopathy

Diabetic vascular complications are a leading cause of acquired blindness, end-stage renal failure, diabetic neuropathy, and accelerated atherosclerosis, leading to increased disability and mortality for patients with diabetes [25]. While chronic hyperglycemia remains the primary cause of the metabolic, biochemical, and vascular abnormalities in patients with diabetes [26], advanced glycation end products (AGEs), which are increased in diabetic patients, may also be important in the pathogenesis of diabetic vascular complications. After binding with the membrane receptor for AGE (RAGE), AGEs enhance the inflammatory response of various cells [27]. Endothelial injury/dysfunction are believed to play an important role in the pathogenesis of diabetic macrovascular and microvascular complications [28-30]. Disruption of the endothelial barrier and an increase of vascular permeability are early pathological changes during the development of diabetes and its complications in both animals and humans [31]. We previously demonstrated that moesin, the ERM protein predominantly expressed in endothelial cells, is phosphorylated at Thr558 after exposure of human microvascular endothelial cells to AGEs [32]. Increased threonine phosphorylation of moesin has also been confirmed in the cerebral and retinal vascular endothelial cells of AGE-stimulated mice [33,34]. Threonine phosphorylation of moesin is accompanied by cytoskeletal rearrangement, opening inter-endothelial junctions, an increase of endothelial monolayer permeability, and disruption of the cerebral and retinal microvascular barrier. We have also shown that moesin phosphorylation in response to AGEs involves RAGE and activation of the RhoA/ROCK and p38 pathways, while blocking of AGE-RAGE binding, down-regulation of RhoA expression, and inhibition of ROCK and p38 activity significantly attenuate AGE-induced moesin phosphorylation and hyperpermeability of endothelial monolayers and microvessels. On the other hand, the endothelial barrier is protected by decreasing ERM phosphorylation through a TIMAP-mediated mechanism. TIMAP (TGF- inhibited, membrane-associated protein) is abundant in endothelial cells and has a role in regulating protein phosphatase 1 (PP1) activity. Csortos et al. found that TIMAP improved pulmonary endothelial barrier function [35]. In addition, Czikora et al. demonstrated that cAMP-dependent activation of protein kinase A (PKA) induced in endothelial cells by the adenylyl cyclase activator forskolin causes the double phosphorylation of TIMAP and consequent activation of PP1c, resulting in dephosphorylation of ERM proteins localized at the cell membrane and attenuation of thrombin-evoked barrier dysfunction [36]. These evidences confirms the involvement of ERM protein phosphorylation in endothelial barrier dysfunction. The intervention of ERM phosphorylation might be an effective approach in preventing the increase of vascular permeability in the early stage during the development of diabetic complications.

Furthermore, it has been reported that AGEs not only induce the phosphorylation of moesin via ligand-receptor signaling pathways, but also cause methylglyoxal-derived imidazole modification of moesin in human elastic arteries [37]. Considering that moesin is involved in the recruitment of leukocytes from the blood to the vessel wall by coordinating the functions of cytokine-induced adhesion molecules [7,8], we can postulate that AGE-induced modification of moesin may lead to endothelial dysfunction and development of atherosclerosis in patients with diabetes.

The extracellular matrix protein fibronectin (FN) is a ligand for integrin receptors. Secretion and assembly of FN is involved in regulating a number of cellular and tissue functions, including cell growth, differentiation, adhesion, migration, tissue remodeling, and morphogenesis [38]. Increased FN deposition is associated with various pathological conditions, including diabetic macroangiopathy, nephropathy, and retinopathy [39-41]. Barber et al. reported that direct binding of the Na^+/H^+ exchanger NHE1 to ERM proteins regulates the cortical cytoskeleton and cell shape independently of H^+ translocation [42]. A mutant form of NHE1 lacking binding sites for PI [4,5] P2 and the ERM proteins shows abnormal intracellular localization and inhibits FN production, while the assembly of FN into fibrils is blocked by inhibiting the RhoA/ROCK pathway, an up-stream signal for threonine phosphorylation of ERM protein [43]. These results suggest the participation of threonine-phosphorylated ERM proteins in promoting the expression and deposition of FN in extracellular matrix, whici probably may result in the thickening and stiffing of vascular wall and the development of diabetic angiopathy.

Taken together, the findings of the above-mentioned studies suggest that altered regulation of ERM proteins, especially moesin, could impair the barrier function of endothelial cells, recruit leukocytes to interact with the endothelium, and promote the expression and deposition of FN in the extracellular matrix. Such events are well known to contribute to the development and progression of diabetic macro-angiopathy and micro-angiopathy.

An investigation into the involvement of ezrin/radixin/moesin proteins in sphingosine 1-phosphate (S1P)-induced enhancement of the human pulmonary endothelial cell barrier was performed by Adyshev et al., who obtained evidence that radixin had a prominent and essential role in the promotion of EC barrier function by S1P, while moesin had an opposing inhibitory effect that resulted in increased permeability [44]. Such findings suggest that despite their structural similarity and reported functional redundancy, ERM proteins function differently. This seems to be especially true when we explore the influence of ERM proteins on the development of diabetic nephropathy.

Important role of ERM proteins in the progression of diabetic nephropathy

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide. It begins with microalbuminuria (excretion of a low level of albumin in the urine) and progresses to overt proteinuria. Diabetic nephropathy develops in about 40% of patients with type 1 diabetes and is not only associated with the duration of diabetes and with glycemic control, but also has a genetic predisposition. Glomerular endothelial cells are particularly vulnerable to chronic hyperglycemia because of their strategic function as a biological barrier between the blood and the mesangium. In addition, there is new evidence to suggest that glomerular podocytes have a key role in early proteinuria, and a decrease of podocytes has been reported in patients with diabetic nephropathy [45].

A genome-wide association scan study of 13 SNPs located in

four genomic loci associated with diabetic nephropathy revealed that the FRMD3 (4.1 protein ezrin, radixin, moesin [FERM] domain containing 3) locus had the strongest association [16]. Research into the podocyte mRNA profile has shown that the expression of podocalyxin and other podocyte-associated genes increases with the progression of diabetic nephropathy [17]. Wegner et al. indicated that the interaction between podocalyxin and subjacent filamentous actin (which requires ezrin) is compromised in the podocytes of CLIC5A-deficient mice, leading to dysfunction of these cells under unfavorable genetic or environmental conditions [46], implying the possible role of ezrin in maintaining proper function of podocalyxin in podocytes. It has been shown that various microRNAs are enriched in the kidneys of humans and are required for maintenance of normal renal structure and function. MicroRNA-192 has been implicated in the pathogenesis of diabetic nephropathy in mice [47]. Conditional knockout of the dicer allele to disrupt microRNA biogenesis in podocytes causes early loss of synaptopodin and altered glomerular expression of ERM proteins (ezrin and moesin), followed by cytoskeletal disorganization and dedifferentiation with progressive glomerulonephritis [48], suggesting the participation of ERM proteins in development of glomerulonephritis. A proteomic approach study has revealed the increased expression of moesin, along with other cytoskeletal proteins, in cultured skin fibroblasts from type I diabetic patients with nephropathy. The constitutive expression of cytoskeletal proteins in cultured skin fibroblasts from type I diabetics with nephropathy may have pathophysiological implications [18]. Hyperglycemia leads to an immediate transient increase in the number of "large pores" (shunt pathways) in the glomerular barrier and this change can be prevented by a Rho-kinase (ROCK) inhibitor [49], suggesting that activation of ROCK is critical to this hyperpermeability response. As mentioned above, moesin is a typical downstream target of ROCK and activation of moesin contributes to the induction of endothelial contraction and vascular barrier disruption. It would therefore be interesting to explore the possibility that moesin phosphorylation is also involved in opening of the glomerular barrier. Sustained activation of the renin-angiotensin system (RAS) has a crucial role in the pathogenesis and progression of diabetes and diabetic complications [50]. Inhibition of the RAS with angiotensin receptor blockers (ARB) and pitavastatin has a renoprotective effect against diabetic nephropathy [51,52]. RAS activation also induces podocyte injury and causes proteinuria. Hsu et al. reported that treatment of podocytes with angiotensin II led to a decrease in phosphorylation of ERM proteins and cortical F-actin ring formation, resulting in a phenotypic shift from stable to adaptively migratory, which may eventually exhaust podocytes due to high actin cytoskeletal turnover, causing their depletion and focal segmental glomerulosclerosis [53]. Thus, evidence obtained at the genetic, mRNA, microRNA and protein levels indicates the extensive involvement of ERM proteins in regulating glomerular function, with alterations of ERM protein expression and activation participating in the development and progression of diabetic renal dysfunction and diabetic nephropathy.

Tubular injury and epithelial apoptosis feature prominently in renal dysfunction associated with diabetes [54,55]. Investigation of a proximal tubule cell line (LLC-PK1) showed that tyrosine phosphorylation of ezrin increases cell survival [56]. Phosphorylation of activated ezrin at Tyr353 recruits prosurvival PI3K, which phosphorylates PI(4,5)P2 and subsequently promotes Akt-dependent activation of multiple cell survival pathways, culminating in increased viability and resistance to apoptotic stress in renal tubular epithelial cells [57,58]. It has been demonstrated that diabetes related-AGEs inhibit tyrosine phosphorylation of ezrin in LLC-PK1 cells and hence attenuate the tubulogenesis of LLC-PK1 cells [59]. In addition, Gallicchio et al. showed that this AGEs-induced inhibition of ezrin-dependent processes of tubular epithelial migration and tubulogenesis could be overcome by overexpression of ezrin [60]. Such findings suggest that Tyr353 phosphorylated ezrin plays an important role in proximal tubule cell function and tubulogenesis, and AGEs may have significant pathologic effects during the course of diabetic nethropathy by inhibiting the effects of Tyr353 phosphorylated ezrin. In a rat model of lithium-induced nephrogenic diabetes insipidus, cDNA microarray screening revealed that ezrin protein expression was upregulated in the inner medulla, where it was predominantly expressed in the apical area of cytoplasm in collecting duct cells. Increased ezrin expression was associated with remodeling of the actin cytoskeleton and/or altered regulation of transporters in inner medullary collecting duct cells [61]. In parallel, it was shown that lithium treatment induced marked proliferation of principal cells in the inner medullary collecting ducts [62], corresponding with reports that overexpression and Tyr phosphorylation of ezrin trigger the PI3K/PI(4,5)P2/Akt survival pathway and promote the proliferation of renal tubular epithelial cells [57-60]. Accordingly, it could be speculated that in the presence of hyperglycemia and accumulation of AGEs, ezrin expression and Tyr phosphorylation are inhibited, exposing renal tubular epithelial cells to apoptotic stress [57,58], resulting in tubular injury and related nethropathy. However, ezrin was found to inhibit the proliferation of bovine arterial endothelial cells and human umbilical vascular endothelial cells in response to TNF-α via transcriptional repression of the cell cycle regulatory protein cyclin A [63]. Such findings indicate that activation of ERM proteins, including ezrin, results in the induction of various signaling pathways that depend on the stimulus and cell type.

Role of ERM protein activation in diabetic cardiomyopathy

Cardiomyopathy is a common complication of both type 1 and type 2 diabetes [64,65], and there is evidence that the RhoA/ROCK pathway is activated in the hearts of diabetic rats [66]. Overactivity of the RhoA/ROCK pathway leads to myocardial contractile dysfunction in diabetic rats because of an increase in actin polymerization. Immunofluorescence microscopy has revealed that activated ERM proteins are chiefly localized at the intercalated discs in ventricular myocytes, indicating the possible role of ERM protein in myocardial contraction [67]. It has been demonstrated that, as one of the downstream targets of ROCK, ERM proteins' threonine phosphorylation are increased in the hearts of rats with chronic streptozotocin (STZ)-induced diabetes [68], showing the potential involvement of ERM protein in development of diabetic cardiomyopathy. Besides their roles as cytoskeletal cross-linkers and an important component of cell structure, ERM proteins have been found to bind directly with NHE1 in fibroblasts [42], epithelial cells [69], and cardiac myocytes. Immunofluorescence microscopy has revealed that activated ERM proteins are chiefly localized at the intercalated discs in left ventricular myocytes and may mediate the downstream effects of NHE1 activation in response to intracellular acidification. A decrease of the intracellular pH is also associated with impaired myocardial perfusion, which is likely to be frequent during the development of diabetic angiopathy. ERM-mediated activation of NHE1 might also play a role in cardiac hypertrophy, probably through the Akt and ERK pathways [67].

In summary, ERM proteins were originally identified as important structural components that link membrane molecules to the cytoskeleton. They have also been found to mediate the effects of some

specific proteins, such as activation of NHE1 in response to acidification. ERM proteins are expressed in various cells, but most attention has been paid to their role in regulating endothelial cells, epithelial cells, and podocytes since structural and functional alterations of these cells play a crucial role in the development of diabetes, especially in the pathogenesis and progression of diabetic angiopathy and nephropathy. ERM proteins also act as scaffolding proteins and have a role in regulating insulin secretion, insulin uptake, and insulin sensitivity. However, the underlying mechanisms of these multiple actions are still unclear, and we also need to identify the differential functions of ezrin, radixin, and moesin in various cells and tissues.

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References

1. Niggli V, Rossy JR (2008) Ezrin/radixin/moesin: versatile controllers of signaling molecules and of the cortical skeleton. Int J Biochem Cell Biol 40: 344-349.
2. Fehon RG, McClatchey AI, Bretscher A (2010) Organizing the Cell Cortex: The role of ERM proteins. Nat Rev Mol Cell Biol 11: 276-287.
3. Mori T, Kitano K, Terawaki S, Maesaki R, Fukami Y, et al. (2008) Structural Basis for CD44 Recognition by ERM Proteins J Biol Chem 283: 29602-29612.
4. Lozupone F, Lugini L, Matarrese P, Luciani F, Federici C, et al. (2004) Identification and relevance of the CD95-binding domain in the N-terminal region of ezrin J Biol Chem 279: 9199-9207.
5. Luo Y, Zheng C, Zhang J, Lu D, Zhuang J, et al. (2011) Recognition of CD146 as an ERM-binding protein offers novel mechanisms for melanoma cell migration. Oncogene.
6. Hamada K, Shimizu T, Yonemura S, Tsukita S, Tsukita S, et al. (2003) Structural basis of adhesion-molecule recognition by ERM proteins revealed by the crystal structure of the radixin-ICAM-2 complex. EMBO J 22: 502-514.
7. Takai Y, Kitano K, Terawaki S, Maesaki R, Hakoshima T, et al. (2007) Structural basis of PSGL-1 binding to ERM proteins. Genes Cells 12: 1329-1338.
8. Killock DJ, Parsons M, Zarrouk M, Ameer-Beg SM, Ridley AJ, et al. (2009) In Vitro and in Vivo Characterization of Molecular Interactions between Calmodulin, Ezrin/Radixin/Moesin, and L-selectin. J Biol Chem 284: 8833-8845.
9. Bretscher A, Edwards K, Fehon RG (2002) ERM proteins and merlin: integrators at the cell cortex. Nat Rev Mol Cell Biol 3: 586-599 .
10. Persson A, Lindwall C, Curtis MA, Kuhn HG (2010) Expression of ezrin radixin moesin proteins in the adult subventricular zone and the rostral migratory stream. Neuroscience 167: 312-322.
11. Wakayama T, Nakata H, Kurobo M, Sai Y, Iseki S, et al. (2009) Expression, localization, and binding activity of the ezrin/radixin/moesin proteins in the mouse testis. J Histochem Cytochem 57: 351-362.
12. Shaffer MH, Huang Y, Corbo E, Wu GF, Velez M, et al. (2010) Ezrin is highly expressed in early thymocytes, but dispensable for T cell development in mice. PLoS One 5: e12404.
13. Berryman M, Franck Z, Bretscher A (1993) Ezrin is concentrated in the apical microvilli of a wide variety of epithelial cells whereas moesin is found primarily in endothelial cells. J Cell Sci 105: 1025-1043.
14. Zhu L, Crothers J, Zhou R, Forte JG (2010) A possible mechanism for ezrin to establish epithelial cell polarity. Am J Physiol Cell Physiol 299: C431-C443.
15. Amieva MR, Wilgenbus KK, Furthmayr H (1994) Radixin is a component of hepatocyte microvilli in situ. Exp Cell Res 210: 140-144.
16. Pezzolesi MG, Poznik GD, Mychaleckyj JC, Paterson AD, Barati MT, et al. (2009) Genome-wide association scan for diabetic nephropathy susceptibility genes in type 1 diabetes. Diabetes 58(6): 1403-1410.
17. Zheng M, Lv LL, Ni J, Ni HF, Li Q, et al. (2011) Urinary podocyte-associated mRNA profile in various stages of diabetic nephropathy. PLoS One 6: e20431.
18. Millioni R, Iori E, Puricelli L, Arrigoni G, Vedovato M, et al. (2008) Abnormal cytoskeletal protein expression in cultured skin fibroblasts from type 1 diabetes mellitus patients with nephropathy: A proteomic approach. Proteomics Clin Appl 2: 492-503.
19. Cao X, Ding X, Guo Z, Zhou R, Wang F, et al. (2005) PALS1 specifies the localization of ezrin to the apical membrane of gastric parietal cells. J Biol Chem 280: 13584-13592.
20. Kikuchi S, Hata M, Fukumoto K, Yamane Y, Matsui T, et al. (2002) Radixin deficiency causes conjugated hyperbilirubinemia with loss of Mrp2 from bile canalicular membranes. Nat Genet 31: 320-325.
21. Lopez JP, Turner JR, Philipson LH (2010) Glucose-induced ERM protein activation and translocation regulates insulin secretion. Am J Physiol Endocrinol Metab 299: E772-E785.
22. Ahmed M, Neville MJ, Edelmann MJ, Kessler BM, Karpe F, et al. (2010) Proteomic analysis of human adipose tissue after rosiglitazone treatment shows coordinated changes to promote glucose uptake. Obesity (Silver Spring) 18: 27-34.
23. Chun KH, Choi KD, Lee DH, Jung Y, Henry RR, et al. (2011) In vivo activation of ROCK1 by insulin is impaired in skeletal muscle of humans with type 2 diabetes. Am J Physiol Endocrinol Metab 300: E536-E542.
24. Matsui T, Maeda M, Doi Y, Yonemura S, Amano M, et al. (1998) Rho-kinase phosphorylates COOH-terminal threonines of ezrin/radixin/moesin (ERM) proteins and regulates their head-to-tail association. J Cell Biol 140: 647-657.
25. Yamagishi S, Nakamura K, Matsui T, Noda Y, Imaizumi T, et al. (2008) Receptor for advanced glycation end products (RAGE): a novel therapeutic target for diabetic vascular complication. Curr Pharm Des 14: 487-495.
26. Geraldes P, Hiraoka-Yamamoto J, Matsumoto M, Clermont A, Leitges M, et al. (2009) Activation of PKC-delta and SHP-1 by hyperglycemia causes vascular cell apoptosis and diabetic retinopathy. Nat Med 15: 1298-1306.
27. Yamagishi S (2011) Role of advanced glycation end products (AGEs) and receptor for AGEs (RAGE) in vascular damage in diabetes. Exp Gerontol 46: 217-224.
28. Singh DK, Winocour P, Farrington K (2011) Oxidative stress in early diabetic nephropathy: fueling the fire. Nat Rev Endocrinol 7: 176-184.
29. Madonna R, De Caterina R (2011) Cellular and molecular mechanisms of vascular injury in diabetes--part II: cellular mechanisms and therapeutic targets. Vascul Pharmacol 54: 75-79.
30. Esper RJ, Vilariño JO, Machado RA, Paragano A (2008) Endothelial dysfunction in normal and abnormal glucose metabolism. Adv Cardiol 45: 17-43.
31. Swärd P, Rippe B (2011) Acute and sustained actions of hyperglycaemia on endothelial and glomerular barrier permeability. Acta Physiol (Oxf) doi: 10.1111/j.1748-1716.2011.02343.x.
32. Guo X, Wang L, Chen B, Li Q, Wang J, et al. (2009) ERM protein moesin is phosphorylated by advanced glycation end products and modulates endothelial permeability. Am J Physiol Heart Circ Physiol 297: H238-H246.
33. Li Q, Liu H, Du J, Chen B, Li Q, et al. (2011) Advanced glycation end products induce moesin phosphorylation in murine brain endothelium. Brain Res 1373: 1-10.
34. Wang L, Li Q, Du J, Chen B, Li Q, et al. (2011) Advanced glycation end products induce moesin phosphorylation in murine retinal endothelium. Acta Diabetol.
35. Csortos C, Czikora I, Bogatcheva NV, Adyshev DM, Poirier C, et al. (2008) TIMAP is a positive regulator of pulmonary endothelial barrier function. Am J Physiol Lung Cell Mol Physiol 295: L440-L450.
36. Czikora I, Kim KM, Kása A, Bécsi B, Verin AD, et al. (2011) Characterization of the effect of TIMAP phosphorylation on its interaction with protein phosphatase 1. Biochimie 93: 1139-1145.
37. Lund T, Svindland A, Pepaj M, Jensen AB, Berg JP, et al. (2011) Fibrin(ogen) may be an important target for methylglyoxal-derived AGE modification in elastic arteries of humans. Diab Vasc Dis Res 8: 284-294.
38. Larsen M, Artym VV, Green JA, Yamada KM (2006). The matrix reorganized: extracellular matrix remodeling and integrin signaling. Curr Opin Cell Biol 18: 463-471.
39. Andresen JL, Rasmussen LM, Ledet T (1996) Diabetic macroangiopathy and atherosclerosis. Diabetes 45: S91–S94.

40. Hohenadel D, van der Woude FJ (2004) Gene expression in diabetic nephropathy. Curr Diab Rep 4: 462-469.

41. George B, Chen S, Chaudhary V, Gonder J, Chakrabarti S, et al. (2009) Extracellular matrix proteins in epiretinal membranes and in diabetic retinopathy. Curr Eye Res 34: 134-144.

42. Denker SP, Huang DC, Orlowski J, Furthmayr H, Barber DL, et al. (2000) Direct binding of the Na-H exchanger NHE1 to ERM proteins regulates the cortical cytoskeleton and cell shape independently of H^+ translocation. Mol Cell 6: 1425-1436.

43. Karydis A, Jimenez-Vidal M, Denker SP, Barber DL (2009) Mislocalized scaffolding by the Na-H exchanger NHE1 dominantly inhibits fibronectin production and TGF-beta activation. Mol Biol Cell 20: 2327-2336.

44. Adyshev DM, Moldobaeva NK, Elangovan VR, Garcia JG, Dudek SM, et al. (2011) Differential involvement of ezrin/radixin/moesin proteins in sphingosine 1-phosphate-induced human pulmonary endothelial cell barrier enhancement. Cell Signal.23: 2086-2096.

45. Spurney RF, Coffman TM (2008) Stressed-out podocytes in diabetes? J. Am. Soc. Nephrol 19: 2035-2037.

46. Wegner B, Al-Momany A, Kulak SC, Kozlowski K, Obeidat M, et al. (2010) CLIC5A, a component of the ezrin-podocalyxin complex in glomeruli, is a determinant of podocyte integrity. Am J Physiol Renal Physiol 298: F1492-F1503.

47. Kato M, Zhang L, Wang M, Lanting L, Yuan H, et al. (2007) MicroRNA-192 in diabetic kidney glomeruli and its function in TGF-β-induced collagen expression via inhibition of E-box repressors. Proc Natl Acad Sci 104: 3432-3437.

48. Harvey SJ, Jarad G, Cunningham J, Goldberg S, Schermer B, et al. (2008) Podocyte-specific deletion of dicer alters cytoskeletal dynamics and causes glomerular disease. J Am Soc Nephrol 19: 2150-2158.

49. Axelsson J, Rippe A, Rippe B (2010) Acute hyperglycemia induces rapid, reversible increases in glomerular permeability in nondiabetic rats. Am J Physiol, Renal Physiol 298: F1306-F1312.

50. Hayashi T, Takai S, Yamashita C (2010) Impact of the renin-angiotensin-aldosterone-system on cardiovascular and renal complications in diabetes mellitus. Curr Vasc Pharmacol 8: 189-197.

51. Saitoh S, Takeishi Y (2011) Pleiotropic effects of ARB in diabetes mellitus. Curr Vasc Pharmacol 9: 136-144.

52. Toba H, Mitani T, Takahashi T, Imai N, Serizawa R, et al. (2010) Inhibition of the renal renin-angiotensin system and renoprotection by pitavastatin in type1 diabetes. Clin Exp Pharmacol Physiol 7: 1064-1070.

53. Hsu HH, Hoffmann S, Endlich N, Velic A, Schwab A, et al. (2008) Mechanisms of angiotensin II signaling on cytoskeleton of podocytes. J Mol Med (Berl) 86: 1379-1394.

54. Nath K (1998) The tubulointerstitium in progressive renal disease. Kidney Int 54: 992-994.

55. Gilbert R, Cooper M (1999) The tubulointerstitium in progressive diabetic kidney disease:More than an aftermath of glomerular injury? Kidney Int 56: 1627-1637.

56. Gautreau A, Poullet P, Louvard D, Arpin M (1999) Ezrin, as plasma membrane-microfilament linker, signals cell survival through the phosphatidylinositol 3-kinase/Akt pathway. Proc Natl Acad Sci 96: 7300-7305.

57. Khan S, Wu KL, Sedor JR, Abu Jawdeh BG, Schelling JR, et al. (2006) The NHE1 Na^+/H^+ exchanger regulates cell survival by activating and targeting ezrin to specific plasma membrane domains. Cell Mol Biol (Noisy-le-grand) 52: 115-121.

58. Schelling JR, Abu Jawdeh BG (2008) Regulation of cell survival by Na^+/H^+ exchanger-1. Am J Physiol Renal Physiol 295: F625-F632.

59. McRobert E, Gallicchio M, Jerums G, Cooper M, Bach L, et al. (2003) The amino-terminal domains of the ezrin, radixin and moesin (ERM) proteins bind advanced glycation end products: An interaction that may play a role in the development of diabetic complications. J Biol Chem 278: 25783-25789 .

60. Gallicchio MA, McRobert EA, Tikoo A, Cooper ME, Bach LA, et al. (2006) Advanced glycation end products inhibit tubulogenesis and migration of kidney epithelial cells in an ezrin-dependent manner. J Am Soc Nephrol 17: 414-421.

61. Rojek A, Nielsen J, Brooks HL, Gong H, Kim YH, et al. (2005) Altered expression of selected genes in kidney of rats with lithium-induced NDI. Am J Physiol Renal Physiol 288: F1276-F1289.

62. Christensen BM, Kim YH, Kwon TH, Nielsen S (2006) Lithium treatment induces a marked proliferation of primarily principal cells in rat kidney inner medullary collecting duct. Am J Physiol Renal Physiol 291: F39-F48.

63. Kishore R, Qin G, Luedemann C, Bord E, Hanley A, et al. (2005) The cytoskeletal protein ezrin regulates EC proliferation and angiogenesis via TNF-alpha-induced transcriptional repression of cyclin A. J Clin Invest 115: 1785-1796.

64. Taegtmeyer H, McNulty P, Young ME (2002) Adaptation and maladaptation of the heart in diabetes. Part I: general concepts. Circulation 105: 1727-1733.

65. Young ME, McNulty P, Taegtmeyer H (2002) Adaptation and maladaptation of the heart in diabetes. Part II: potential mechanisms. Circulation 105: 1861-1870.

66. Lin G, Craig GP, Zhang L, Yuen VG, Allard M, et al. (2007) Acute inhibition of Rho-kinase improves cardiac contractile function in streptozotocin-diabetic rats. Cardiovasc Res 75: 51-58.

67. Darmellah A, Rücker-Martin C, Feuvray D (2009) ERM proteins mediate the effects of Na^+/H^+ exchanger (NHE1) activation in cardiac myocytes. Cardiovasc Res 81: 294-300.

68. Soliman H, Craig GP, Nagareddy P, Yuen VG, Lin G, et al. (2008) Role of inducible nitric oxide synthase in induction of RhoA expression in hearts from diabetic rats. Cardiovasc Res 79: 322-330.

69. Wu KL, Khan S, Lakhe-Reddy S, Jarad G, Mukherjee A, et al. (2004) The NHE1 Na^+/Hexchanger recruits ezrin/radixin/moesin proteins to regulate Akt-dependent cell survival. J Biol Chem 279: 26280-26286.

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