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Cardiac Synchronous and Dys-synchronous Remodeling in Diabetes Mellitus

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ABSTRACT

Glucose-mediated impairment of homocysteine (Hcy) metabolism and decrease in renal clearance contribute to hyperhomocysteinemia (HHcy) in diabetes. The Hcy induces oxidative stress, inversely relates to the expression of peroxisome proliferators activated receptor (PPAR), and contributes to diabetic complications. Extracellular matrix (ECM) functionally links the endothelium to the myocyte and is important for cardiac synchronization. However, in diabetes and hyperhomocysteinemia, a "disconnection" is caused by activated matrix metalloproteinase with subsequent accumulation of oxidized matrix (fibrosis) between the endothelium and myocyte (E–M). This contributes to "endothelial–myocyte uncoupling," attenuation of cardiac synchrony, leading to diastolic heart failure (DHF), and cardiac dys-synchronizatrion. The decreased levels of thioredoxin and peroxiredoxin and cardiac tissue inhibitor of metalloproteinase are in response to antagonizing PPARγ. *Antioxid. Redox Signal.* 9, 971–978.

INTRODUCTION

HOMOCYSTEINE (Hcy) is accumulated in the plasma and tissues by four ways: (a) a methionine-rich protein diet; (b) a vitamin B_{12}/folate deficiency; (c) a heterozygous/homozygous trait for cystathionine β synthase (CBS) activity and vitamin B_6 deficiency in humans; and (d) renovascular stenosis and volume retention. Although Hcy plays a constitutive role in DNA/RNA gene methylation (112, 124), hyperhomocysteinemia leads to endothelial damage (64, 70), especially since mammalian endothelial cells lack the CBS enzyme (28, 29). Every 3 μ*M*/L increase in Hcy level contributes to a 10% increased risk of coronary heart diseases and a 20% increased risk of stroke (45). A common genetic polymorphism, MTHFR C677T, which determines Hcy levels, also has similar effects on heart disease and stroke (56, 58, 93, 116). The association between this polymorphism and heart disease is unlikely to be confounded by other factors, such as smoking or blood pressure, but influences Hcy levels, suggesting a causal association between Hcy and heart disease or stroke (18). A secondary prevention trial (14) of folic acid supplementation demonstrated unequivocally that folate and other B-complex vitamins protect against heart disease. Another study demonstrated a beneficial effect on the rate of revascularization (89). A trial with stroke patients did not demonstrate a robust difference in recurrent stroke associated with a reduction of Hcy levels by 2 μ*mol*/L (102). Although the overall risk of heart disease with Hcy is small, there is evidence of synergism between Hcy and other risk factors such as smoking (26, 39), hypertension (25), diabetes (4), and insulin resistance (31). Therefore, it is, in view of the associated risk factors, important to determine the role of Hcy in diabetes.

Mice homozygous for a disrupted methyltransferase (MT) allele elicited >50% reduction in circulating Hcy (72). The transgenic expression of MT in a cell line that lacked endogenous MT promoted Hcy formation (72). MT is a liver-specific enzyme that catalyzes three sequential transmethylation reactions (114). *S*-Adenosylmethionine (SAM) is the methyl donor. *S*-Adenosylhomocystene (SAH) is the demethylated

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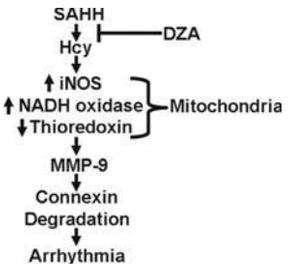

FIG. 1. Metabolomics of Hcy. During gene and protein methylation, *S*-adenosyl homocysteine (SAH) is generated by methyl transferase and methionine. SAH hydrolase generates Hcy. DZA blocks SAHH, otherwise Hcy induces NOS, NADH oxidase, and decreases thioredoxin in mitochondria. These events lead to endothelial dysfunction, vascular remodeling, and hypertension. In the heart, these events activate MMP-9 that degrades connexin and instigates tachycardia.

product that is subsequently hydrolyzed to adenosine and the Hcy (29, 114). The hydrolysis of SAH is performed by the cystolic enzyme *S*-adenosylhomocysteine hydrolase (SAHH) (15, 29). Approximately 40 different mammalian MT, including DNA/RNA/protein/lipid and small molecule MT use SAM as a methyl donor, and consequently, produce SAH during the methylation (27, 33). Because SAH from each transmethylation pathway can be used to produce Hcy, it is very interesting that genetic ablation of just one MT suffices to decrease circulating Hcy levels by 50% (72). The recent results from our laboratory demonstrated that CBS± mice treated with DZA, an SAHH blocker, ameliorates Hcy-mediated vascular complications, arrhythmias, and reduces systemic hypertension (Fig. 1) (74).

To determine insulin resistance, various methods have been used, such as euglycemic clamp (23, 37), insulin resistance syndrome phenotypes (66), minimal model analysis of the frequently sampled intravenous glucose tolerance test (31, 38), and the insulin suppression test using steady-state plasma glucose concentration (1, 83). Although these are valid measures of insulin resistance, all of these methods are incomparable. Some investigators report insulin resistance (13), while others report decreased insulin sensitivity (31) or impaired

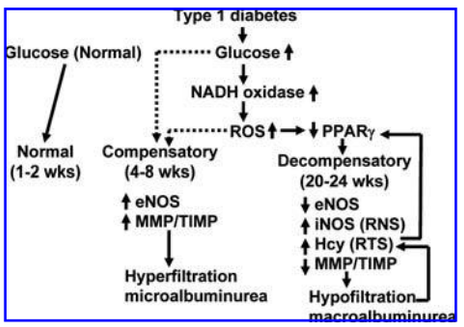

FIG. 2. In type 1 diabetes, increase in glucose causes acute compensatory renal hyperfilteration that leads to microalbuminurea. However, chronic increase in pressure leads to hypofilteration and glomerular collapse and macroalbuminurea.

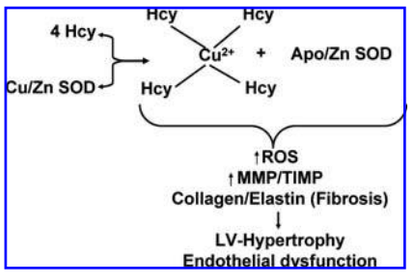

FIG. 3. During hyperhomocysteinemia, copper from SOD and cytochrome C is released, leading to decrease in antioxidants. This causes increase in ROS and fibrosis and E–M uncoupling in heart failure.

glucose utilization (37). Similarly, some studies found a negative or inverse correlation between insulin resistance and Hcy (7, 23, 31, 32, 83), others found little or no difference (1, 13, 38), and others found a positive correlation (37, 66). In an experimental study of insulin-resistant (obese) type 2 diabetes, improvement of insulin resistance with intravenous insulin over a period of 17 days did not alter Hcy levels (77). However, several lines of evidence suggested a higher risk of heart disease associated with 5 μ*mol*/L (plasma) increases in Hcy among a diabetic group compared to a nondiabetic group (4, 8, 46, 54). In a diabetic rabbit model, physiologic levels of Hcy dramatically inhibit arterial nitric oxide formation, but there is no effect in nondiabetic animals (52, 94). In diabetes, asymmetric dimethyl arginine (ADMA) is elevated (62) and there are decreased L-arginine and nitric oxide concentrations. Hcy decreases the activity of the enzyme dimethylarginine dimethylaminohydrolase (DDAH) which converts the ADMA to L-arginine (90). Although a relationship between Hcy and insulin is ambiguous, the role of Hcy in impairment of endothelial nitric oxide metabolism is unequivocal.

One study showed a decrease in MTHFR and CBS enzyme activities in response to increasing insulin and glucose concentrations, leading to increased Hcy (21). Glucose and Hcy synergistically induce ECM remodeling (97). Renal hyperfilteration in a diabetic subject without nephropathy was associated with increased Hcy catabolism and clearance (Fig. 2) (122). Insulin reduces the circulating levels of other amino acids (34) and may promote uptake of Hcy and tissues which result in lower plasma Hcy, but increased tissue Hcy (111). Plasma ceruloplasmin is associated with type 2 diabetes and is related directly to blood glucose (17). Both ceruloplasmin and copper augment the arteriopathic impact of Hcy through augmentation of superoxide formation (Fig. 3) (24, 100). Although a renal mechanism plays a significant role in Hcy clearance, the contributions of high glucose, insulin and other factors in Hcy accumulation are very important.

ENDOTHELIUM–MYOCYTE COUPLING

Sixteen percent of the myocardial mass is capillaries, including the lumen and endothelium (47). The capillary endothelium is embedded in the muscle, and plays a very important role in myocardial diastolic relaxation (41, 42, 44, 65,

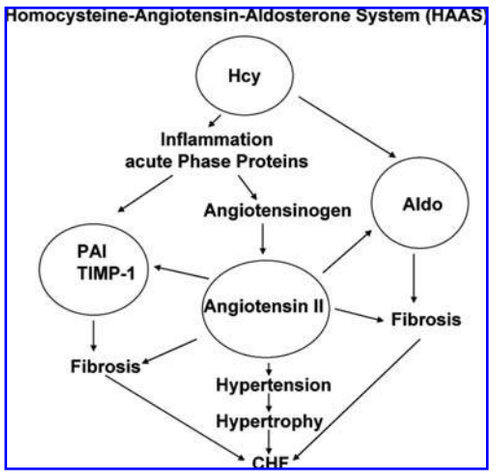

FIG. 4. Homocysteine–angiotensin–aldosterone system (HAAS). Hcy increase inflammation and acute phase proteins that lead to fibrosis, hypertension, hypertrophy, and failure.

79, 95). Nitric oxide (NO) generation from the endocardial endothelium contributes to myocyte contraction, relaxation, and heart rate (11, 76). A gradient of NO concentration (*i.e.*, high in endocardium and low in mid-myocardium) has been depicted (76) that is consistent with the notion that there is more capillary endothelium in the endocardium than in epi- or mid-myocardium (35, 87). The importance of endocardial endothelium in cardiac contraction/relaxation is illustrated by attenuation of the responses to $CaCl_2$ and acetylcholine in the endothelium-denuded myocardium (36, 117). Furthermore, the Hcy-mediated contractile dysfunction was amplified by angiotensin II and endothelin-1 (Figs. 4 and 5) (110).

We studied two forms of endothelium–myocyte (E–M) coupling. The structure coupling implies the thickness of the pericapillary matrix between the E and M. Accumulation of interstitial collagen between E and M increases distance from E to M. The functional coupling implies the efficiency of transport of endothelial-derived cardioactive agents to the cardiac muscle. The increase in distance from E to M impairs local endothelial-derived NO diffusion to the cardiac muscle and interferes with cardiac diastolic relaxation.

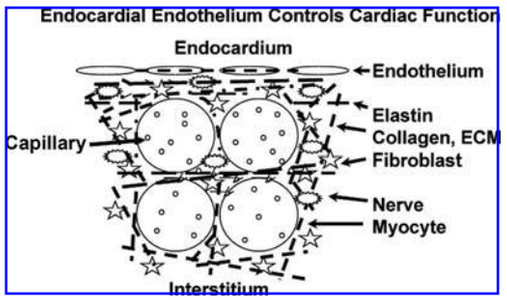

FIG. 5. Schematic of cardiac endocardium linked to myocyte endothelium, nerve, ECM–fibroblasts, and the capillary.

HCY AND ECM REMODELING IN ENDOTHELIAL–MYOCYTE UNCOUPLING

The endothelium is connected to myocytes by ECM and adhesion (junction protein connexins) in the basement membrane (BM). Remodeling implies alterations in the composition and concentration of matrix components in the BM. The overall matrix metalloproteinase (MMP) family includes gelatinases, collagenases, and membrane type (MT-MMP) (106), and also includes a disintegrin and metalloproteinase (ADAM) (106). MMPs are regulated by their interaction with tissue inhibitors of metalloproteinases (TIMPs) (113). TIMPs inactivate MMPs by binding to their catalytic site. There are four TIMPs. In general, TIMP-1 and -2 inhibit a broad range of MMPs (99, 115). TIMP-3 inhibits MMP-1, -3, -7, and -13. TIMP-4 inhibits MMP-2 and -7 and to a lesser extent, MMP-1, -3, and -9. Metalloproteinases are neutral proteases that upon activation degrade the microvascular endothelial cell BM (92), causing endothelial–myocyte disconnection (106). Studies from our laboratory demonstrated a latency of MMP activation in the normal myocardium, due to the MMP-active site bound with nitric oxide (48). However, during chronic increases in load (109), and oxidative process such as HHcy (Fig. 6) (105), latent MMPs are activated. Hcy is the only thiol that suppresses the generation of other thiols, and activates the MMPs and inactivates the TIMPs, causing a decrease in eNO bioavailability (70). Therefore, to reduce the load by dilating the heart in the absence of eNO, latent resident MMPs are activated (49). This activation increases interstitial edema, and degrades elastin and ultrastructural collagen (*i.e.*, newly synthesized collagen by proliferating cells). Interestingly, because elastin turnover is lower than collagen turnover (84), the degraded elastin is replaced with stiffer oxidized-collagen (fibrosis). Consequently, LV wall stress is increased, causing alterations in ECM that induces endothelial–myocyte uncoupling and impaired diastolic relaxation. Pretreatment of the hearts with TIMP-4/CIMP ameliorated the

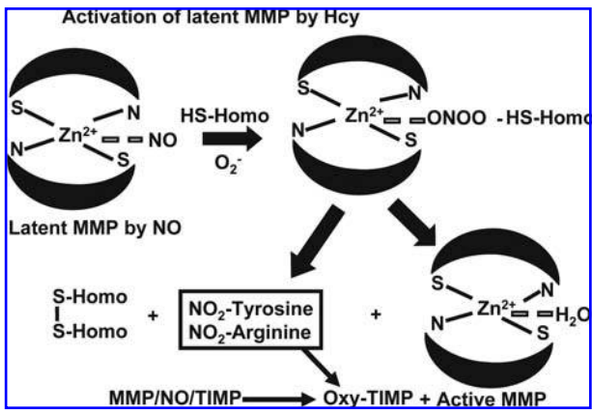

FIG. 6. Oxidative stress and increase in reactive oxygen species (ROS) and reactive thiol species (RTS) decreases constitutive NO in MMP/TIMP/NO ternary complex and generate reactive nitrogen species (RNS) and nitrotyrosine. This process oxidizes the TIMP and liberates active MMP.

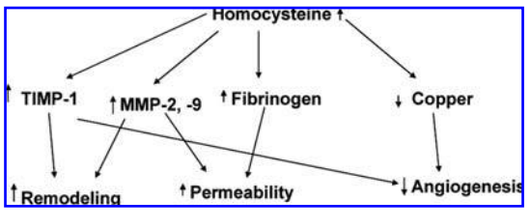

FIG. 7. Homocysteine causes remodeling, permeability, and decreased angiogenesis.

endothelial–myocyte disconnection (uncoupling) in chronic heart failure (16).

DIABETES AND ECM REMODELING

Several lines of evidence suggest that the frequency of apoptosis of capillary microvessel endothelial cells predicts the development of histologic lesions in diabetes (57). In HHcy-myocardium, the capillary endothelial cell density is reduced (67, 68). In diabetic rats, in addition to decreased endothelial cell density, the capillary surface area is reduced and tissue thickness from capillaries to myocytes is increased (Fig. 7) (120). However, the mechanism of increased tissue thickness between endothelium and muscle in DM is unclear. In DM, alteration of the ultrastructure of the myocardium has been a hallmark of cardiovascular dysfunction (2, 19, 20, 96). Structural pathological manifestations (*i.e.*, intercellular and perivascular deposition of connective tissue and thickening of the endothelium BM in diabetic cardiomyopathy) were reversed by insulin treatment in rats (101). The composition of ECM (collagen/elastin) in the basement membrane of capillary endothelium dictates the accumulation of oxidized-matrix between endothelium and myocytes. Abnormal collagen glycation, and chamber tissue stiffness, affecting diastolic function, appeared to be a major factor in impaired glucose tolerance in DM (5, 103). Alteration in LV diastolic filling is associated with reciprocal changes in the LV collagen gene (55), and accumulation of myocardial collagen is apparent in the insulin-resistant syndrome (69). ECM production in rat heart endothelial cells is enhanced (43), and the levels of MMP activity are excessive in DM (85). Furthermore, the elastinolytic proteinase is upregulated in the basement membrane of microvessels of diabetes (60). It is generally known that MMP-2 and -9 degrade elastin (91), and MMP-2 also degrades collagen ultrastructure (3). Because elastin turnover is remarkably lower than collagen (84), elastin and collagen are replaced by oxidatively modified stiffer collagen, leading to increased distance between the endothelium and myocyte, thus impairing eNO diffusion from endothelium to myocyte. This process is amplified in diabetes.

THE LINK BETWEEN HCY AND PPARγ

A correlation between increased Hcy levels and decreased PPAR expression has been shown (12). Interestingly, clinical studies have also revealed that treatment of HHcy patients with PPARγ agonists ameliorates cardiovascular dysfunction, however, the plasma levels of Hcy did not change (9, 22). Our laboratory has demonstrated convincingly the direct causal relationship between Hcy and PPARγ (48). The antibody to PPARγ induced super-shift in PPARγ–PPRE (DNA) complex in electrophoretic mobility shift assay (EMSA) (104). In addition, Murthy *et al.* (71) demonstrated that rosiglitazone (a PPARγ agonist) reduces serum Hcy levels in rats fed a high methionine diet. We have shown a novel role of tissue Hcy (*i.e.*, the increase in cardiac tissue Hcy levels contribute to cardiac complications in diabetes) and ciglitazone (a PPARγ agonist) mitigates diabetic cardiac complications (80). Glucose decreases MTHFR activity and thereby increases Hcy levels (21). Glucose and Hcy synergistically induce ECM remodeling (97). These studies support the link between Hcy and PPARγ, unequivocally.

PPAR, DIABETES, AND ECM REMODELING

PPAR mediates the metabolism of various fatty acids and induces genes related to fatty acid metabolism, and also has anti-inflammatory effects (30, 73). There are potential differences in cardiac actions of PPARγ, PPARα, and PPARδ. These include a role of PPARγ in metabolic disorders. PPARα is involved in fatty acid metabolism. PPARδ is involved in apoptosis and adiposity. There are many reports describing the role of PPARγ in the heart (6, 123). PPARγ specifically ameliorates DM complications (50, 61). DM and Hcy facilitate ROS and inflammation (86, 125), including endothelial cell desquamation (100). Hcy activates MMP (112), leading to elastinolysis/collagenolysis (59, 81). A ligand of PPARγ (PGJ_2) reduces myocardial infarct size (121). The PPARγ agonists module insulin resistance (50, 61). Activated PPARγ inhibits MMP activation (63), and therefore, ameliorates elastinolysis/collagenolysis. Although the administration of PPARγ agonists ameliorates the endothelial dysfunction, it did not decrease the high levels of Hcy (9, 10, 22). There is a negative correlation between high Hcy and PPAR expression (12). We demonstrated competition between Hcy and a PPARγ agonist (PGJ_2) for binding to PPARγ (48). ROS decreases eNO availability and generates nitrotyrosine in diabetes (53, 82). The decrease in eNO availability increases MMP activity (78). This suggests that to reduce wall stress in the absence of eNO, latent MMPs are activated to dilate the heart in DM. Unabated MMP activation, however, leads to endothelial–myocyte disconnection and diabetic cardiomyopathy (98, 107, 108). Although Hcy is elevated, endothelial cell density is decreased, oxidative-glycated matrix is increased, and PPAR is inhibited. The mechanism of Hcy-mediated endothelial–myocyte uncoupling in DM is unclear (Fig. 8). It is possible that Hcy increases oxidized-matrix accumulation between the endothelium and myocytes and impairs diastolic relaxation.

A genetic model of type 1 diabetes (Ins2–/+, Akita mice) is the unique in the sense that mutation in insulin-2 polypeptide gene causes its accumulation in the beta cell and subsequently death of the beta cell, leading to hypoinsulinemia and hyperglycemia (51, 118). These mice have normal levels of glucose at 2–4 weeks; however, they develop robust

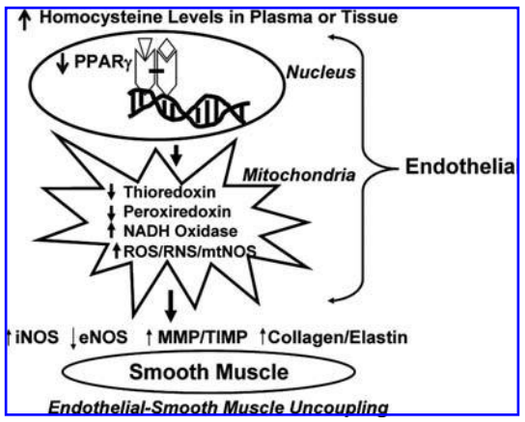

FIG. 8. In the vessel wall, Hcγ deactivates PPARγ that leads to increased mitochondrial oxidative stress, causing E–M disconnection and uncoupling.

hyperglycemia at 24 weeks and die by 40 weeks (51, 118). This model is better than other models (autoimmune-beta cell depletion (NOD), chemical (alloxan or STZ), and non-specific gene expression in the beta cell (OVE26). Although there are no studies in humans, this model may be more relevant to humans in the sense that diabetic patients may be heterozygous in insulin-2 gene expression or mutation.

SUMMARY

PPARγ agonists ameliorate diabetes mellitus (50, 61), and clinical trials demonstrated reduction in restenotic events after lowering homocysteine (40, 88). A positive correlation between Hcy and plasma creatinine is related to increased muscle mass (LVH) in DM patients (75). Hcy induces cardiac hypertrophy in rats (67, 68) and instigates bradycardia (119). Reduced expression of PPAR causes LVH in a ventricular pressure overload model in mice (6). In addition, administration of peroxisome proliferators reduces cardiac hypertrophy (123). Therefore, it is important to determine the role of Hcy and PPARγ in cardiac hypertrophy and matrix remodeling. This article has the potential to contribute to our understanding of the importance of Hcy in endocardial remodeling, structure, and function, by defining their links to NO metabolism in DM. The understanding of endothelial–myocyte uncoupling is of significant importance in determining pathophysiologic consequences of impaired diastolic relaxation in diabetes. This article proposes a novel mechanism in which Hcy antagonizes PPARγ, and increases oxidative stress, decreases eNO, and increases nitrotyrosine content and MMP activity in the diabetic hearts, causing endothelial–myocyte disconnection–uncoupling.

Peroxinitrite-thiol (ONOO-HS-R) is an intermediate of nitrotyrosine formation (Fig. 6). In HHcy, Hcy is the primary thiol. In basement membrane of endothelium and myocytes (E–M), the latent ternary MMP/TIMP/NO complex is oxidized to oxy-TIMP and active MMP (Fig. 6), causing E–M disconnection (uncoupling). Clinical studies suggest that treatment of HHcy with agonist of PPARγ ameliorate cardiovascular dysfunction. However, the plasma levels of Hcy did not change. By demonstrating direct binding of Hcy to PPARγ, without affecting total plasma Hcy levels (48), we and others have also suggested decreased MMP activity by PPARγ induction (63). The completion of the proposed studies will be able to causally link hyperhomocysteinemia with PPARγ, ROS, MMPs, and E–M coupling. More importantly, the co-treatment of diabetic patients with drugs that also ameliorate Hcy effects will be beneficial.

ACKNOWLEDGMENTS

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ABBREVIATIONS

ADAM, a disintegrin and metalloproteinase; ADMA, asymmetric dimethyl arginine; BH_4, tetrahydrobiopterin; CBS, cystathionine β synthase; CIMP, cardiac inhibitor of metalloproteinase; CZ, ciglitazone; DDAH, dimethylarginine dimethylaminohydrolase; DM, diabetes mellitus; ECM, extracellular matrix; EDHF, endothelial-derived hyperpolarizing factor; EDRF, endothelial-derived relaxing factor; EET, epoxy-eicosatrienoic acid; GFR, glomerular filtration rate; Hcy, homocysteine; HETE, 20-hydroxyeicosatetraenoic acid; L-NAME, *N*-nitro-L-arginine methyl ester; LVH, left ventricle hypertrophy; MVEC, microvascular endothelial cell; MMP, matrix metalloproteinase; MTHFR, methylene tetrahydrofolate reductase; $ONOO^-$, peroxynitrite; PGJ_2, 15-deoxy 12, 14-prostaglandin J_2; PPAR, peroxisome proliferators activated receptor; SOD, superoxide dismutase; TIMP, tissue inhibitor of metalloproteinase.

REFERENCES

1. Abbasi F, Facchini F, Humphreys MH, and Reaven GM. Plasma homocysteine concentrations in healthy volunteers are not related to differences in insulin-mediated glucose disposal. *Atherosclerosis* 146: 175–178, 1999.
2. Abe T, Ohga Y, Tabayashi N, Kobayashi S, Sakata S, Misawa H, Tsuji T, Kohzuki H, Suga H, Taniguchi S, and Takaki M. LV diastolic dysfunction in type 2 DM model rats. *Am J Physiol* 282: H138–H148, 2002.
3. Aimes RT and Quigley JP. MMP-2 is an interstitial collagenase. *J Biol Chem* 270: 5872–5876, 1995.
4. Audelin MC and Genest J, Jr. Homocysteine and cardiovascular disease in diabetes mellitus. *Atherosclerosis* 159: 497–511, 2001.
5. Avendano GF, Agarwal RK, and Bashey RI. Effects of glucose intolerance on myocardial function and collagen-linked glycation. *Diabetes* 48: 1443–1447, 1999.
6. Barger PM, Brandt JM, Leone TC, Weinheimer CJ, and Kelly DP. Deactivation of PPARá during cardiac hypertrophic growth. *J Clin Invest* 105: 1723–1730, 2000.
7. Bar–On H, Kidron M, Friedlander Y, Ben–Yehuda A, Selhub J, Rosenberg IH, and Friedman G. Plasma total homocysteine levels in subjects with hyperinsulinemia. *J Intern Med* 247: 287–294, 2000.

8. Becker A, Kostense PJ, Bos G, Heine RJ, Dekker JM, Nijpels G, Bouter LM, and Stehouwer CD. Hyperhomocysteinaemia is associated with coronary events in type 2 diabetes. *J Intern Med* 253: 293–300, 2003.
9. Bissonnette R, Treacy E, Rozen R, Boucher B, Cohn JS, and Genest J. Fenofibrate raises plasma homocysteine levels in the fasted and fed states. *Atherosclerosis* 155: 455–462, 2001.
10. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med* 83: 26–36, 1987.
11. Brady AJ, Warren JB, Poole-Wilson PA, Williams TJ, and Harding SE. Nitric oxide attenuates cardiac myocyte contraction. *Am J Physiol* 265: H176–H182, 1994.
12. Brude IR, Finstad HS, Seljeflot I, Drevon CA, Solvoll K, Sandstad B, Hjermann I, Arnesen H, and Nenseter MS. Plasma homocysteine concentration related to diet, endothelial function and mononuclear cell gene expression among male hyperlipidaemic smokers. *Euro J Clin Invest* 29: 100–108, 1999.
13. Buysschaert M, Dramais AS, Wallemacq PE, and Hermans MP. Hyperhomocysteinemia in type 2 diabetes: relationship to macroangiopathy, nephropathy, and insulin resistance. *Diabetes Care* 23: 1816–1822, 2000.
14. Clarke R and Collins R. Can dietary supplements with folic acid or vitamin B6 reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. *J Cardiovasc Risk* 5: 249–255, 1998.
15. Coulter-Karis DE and Hershfield MS. Sequence of full length cDNA for human *S*-adenysylhomocysteine hyrolase. *Ann Hum Genet* 53: 169–175, 1989.
16. Cox MJ, Hawkins UA, Hoit BD, and Tyagi SC. Attenuation of oxidative stress and remodeling by cardiac inhibitor of metalloproteinase protein transfer. *Circulation* 109: 2123–2128, 2004.
17. Daimon M, Susa S, Yamatani K, Manaka H, Hama K, Kimura M, Ohnuma H, and Kato T. Hyperglycemia is a factor for an increase in serum ceruloplasmin in type 2 diabetes. *Diabetes Care* 21: 1525–1528, 1998.
18. Davey SG and Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 32: 1–22, 2003.
19. Dhalla NS, Prierce GN, Innes IR, and Beamish RE. Pathogenesis of cardiac dysfunction in diabetes mellitus. *Canad J Cardiol* 1: 263–281, 1985.
20. Di Bello V, Giampietro O, Matteucci E, Talarico L, Giorgi D, Bertini A, Caputo MT, Piazza F, Paterni M, and Giusti C. Ultrasonic video-densitometric analysis in type I diabetic myocardium. *Coron Artey Dis* 7: 895–901, 1996.
21. Dicker–Brown A, Fonseca VA, Fink LM, and Kern PA. The effect of glucose and insulin on the activity of methylene tetrahydrofolate reductase and cystathionine-beta-synthase: studies in hepatocytes. *Atherosclerosis* 158: 297–301, 2001.
22. Dierkes J, Westphal S, and Luley S. Serum homocysteine increases after therapy with fenofibrate or bezafibrate. *LANCET* 354: 219–220, 1999.
23. Emoto M, Kanda H, Shoji T, Kawagishi T, Komatsu M, Mori K, Tahara H, Ishimura E, Inaba M, Okuno Y, and Nishizawa Y. Impact of insulin resistance and nephropathy on homocysteine in type 2 diabetes. *Diabetes Care* 24: 533–538, 2001.
24. Emsley A, Jeremy JY, Gomes G, Angelini GD, and Plane F. Copper interacts with homocysteine to inhibit nitric oxide formation in the rat isolated aorta. *Br J Pharmacol* 126: l034–1040, l999.
25. Fallon UB, Elwood P, Ben Shiomo Y, Ubbink JB, Greenwood R, and Smith GD. Homocysteine and ischaemic stroke in men: the Caerphilly study. *J Epidemiol Community Health* 55: 91–96, 2001.
26. Fallon UB, Virtamo J, Young I, McMaster D, Ben–Shlomo Y, Wood N, Whitehead AS, and Smith GD. Homocysteine and cerebral infarction in Finnish male smokers. *Stroke* 34: 1359–1363, 2003.
27. Fauman EB, Blumenthal RM, and Cheng X. Structure and evolution of SAM-dependent methyltransferase. In: *SAM-Dependent Methyltransferase: Structure and Functions*, edited by Cheng X and Blumenthal RM. Singapore: World Scientific Publishing 1999, pp. 1–32.
28. Finkelstein JD. Methionine metabolism in mammals. *J Nutr Biochem* 1: 228–237, 1990.
29. Finkelstein JD. The metabolism of homocysteine: pathways and regulation. *Eur J Pediatr* 157: S40–S44, 1998.
30. Folmes CD, Clanachan AS, and Lopaschuk GD. Fatty acid oxidation inhibitors in the management of chronic complications of atherosclerosois. *Curr Atheroscler Rep* 7: 63–70, 2005.
31. Fonseca VA, Fink UM, and Kern PA. Insulin sensitivity and plasma homocysteine concentrations in non-diabetic obese and normal weight subjects. *Atherosclerosis* 167: 105–109, 2003.
32. Fonseca VA, Mudaliar S, Schmidt B, Fink LM, Kern PA, and Henry RR. Plasma homocysteine concentrations are regulated by acute hyperinsulinemia in nondiabetic but not type 2 diabetic subjects. *Metabolism* 47: 686–689, 1998.
33. Fujioka M. Mammalian small molecule methyltransfase: their structural and functional features. *Int J Biochem* 24: 1917–1924, 1992.
34. Fukagawa NK, Minaker KU, Young VR, and Rowe JW. Insulin dose-dependent reductions in plasma amino acids in man. *Am J Physiol* 250: E13–E17, 1986.
35. Fukuchi M, Watanabe J, Kumagai K, Katori Y, Baba S, Fukuda K, Yagi T, Iguchi A, Yokoyama H, Miura M, Kagaya Y, Sato S, Tabayashi K, and Shirato K. Increased von Willebrand factor in the endocardium as a local predisposing factor for thrombogenesis in overloaded human atrial appendage. *J Am Coll Cardiol* 37: 1436–1442, 2001.
36. Gattuso A, Mazza R, Pellegrino D, and Tota B. Endocardial endothelium (EE) mediates luminal acetylcholine-nitric oxide signaling in isolated frog heart. *Am J Physiol* 276: H633–H641, 1999.
37. Giltay EJ, Hoogeveen EK, Elbers JM, Gooren U, Asscheman H, and Stehouwer CD. Insulin resistance is associated with elevated plasma total homocysteine levels in healthy, non-obese subjects. *Atherosclerosis* 139: 197–198, 1998.
38. Godsland IF, Rosankiewicz JR, Proudler AJ, and Johnston DG. Plasma total homocysteine concentrations are unrelated to insulin sensitivity and components of the metabolic syndrome in healthy men. *J Clin Endocrinol Metab* 86: 719–723, 2001.
39. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ueland PM, Palma-Reis RJ, Boers GH, Sheahan RG, Israelsson B, Uiterwaal CS, Meleady R, McMaster D, Verhoef P, Witteman J, Rubba P, Bellet H, Wautrecht JC, de Valk HW, Sales Luis AC, Parrot-Rouland FM, Tan KS, Higgins I, Garcon D, and Andria G. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project [see comments]. *JAMA* 277: 1775–178l, 1997.
40. Hackam DG, Peterson JC, and Spence JD: What level of plasma homocysteine should be treated? *Am J Hyperten* 13: 105–110, 2000.
41. Hayden MR and Tyagi SC. "A" is for amylin and Amyloid in type 2 diabetes mellitus, *J Pancreas* 2: 124–139, 2001.
42. Hayden MR and Tyagi SC. Remodeling of the endocrine pancreas: The central role of amylin and insulin resistance. *Southern Med J* 93: 24–28, 2000.
43. He Q and Spiro MJ. Isolation of rat heart endothelial cells and pericytes: evaluation of their role in the formation of ECM components. *J Mol Cell Cardiol* 27: 1173–1183, 1995.
44. Henderson AH, Lewis MJ, Shah AM, and Smith JA. Endothelium, endocardium, and cardiac contraction. *Cardiovasc Res* 26: 305–308, 1992.
45. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 288: 2015–2022, 2002.
46. Hoogeveen EK, Kostense PJ, Jakobs C, et al. Hyperhomocysteinemia increases risk of death, especially in type 2 diabetes: 5-year follow-up of the Hoorn Study. *Circulation* 101: 1506–1511, 2000.
47. Hoppeler H and Kayar SR. Capillary and oxidative capacity of muscles. *News Physiol Sci* 3: 113–116, 1988.
48. Hunt MJ and Tyagi SC. Peroxisome proliferators compete and ameliorate Hcy-mediated EE cells activation. *Am J Physiol Cell Physiol* 283: C1073–C1079, 2002.
49. Hunt MJ, Aru GM, Hayden MR, Moore CK, Hoit BD, and Tyagi SC. Induction of oxidative stress and disintegrin metalloproteinase in human heart end-stage failure. *Am J Physiol* 283: L239–L245, 2002.

50. Itoh H, Doi K, Tanaka T, Fukunaga Y, Hosoda K, Inoue G, Nishimura H, Yoshimasa Y, Yamori Y, Nakao K. Hypertension and insulin resistance: role of peroxisome proliferator-activated receptor gamma. *Clin Exp Pharmacol Physiol* 26: 558–560, 1999.
51. Izumi T, Yokota–Hashimoto H, Zhao S, Wang J, Halban PA, and Takeuchi T. Dominant negative pathogenesis by mutant proinsulin in the Akita diabetic mouse. *Diabetes* 52: 409–416, 2003.
52. Jeremy JY, Shukla N, and Angelini GD. Homocysteine and cardiovascular disease in diabetes mellitus. *Atherosclerosis* 164: 383–384, 2002.
53. Kajstura J, Fiordaliso F, Andreoli AM, Li B, Chimenti S, Medow MS, Limana F, Nadal-Ginard B, Leri A, and Anversa P. IGF-1 overexpression inhibits the development of diabetic cardiomyopathy and angII-mediated oxidative stress. *Diabetes* 50: 1414–1424, 2001.
54. Kark JD, Selhub J, Bostom A, Adler B, and Rosenberg IH. Plasma homocysteine and all-cause mortality in diabetes. *Lancet* 353: 1936–1937, 1999.
55. Katayama S, Abe M, Negishi K, Takahashi K, Ishii J, and Komeda K. Reciprocal changes in LV collagen alpha 1 chain gene expression between type I and IV in spontaneously diabetic rats. *Diabetes Res Clin Pract* 26: 163–169, 1994.
56. Kaye JM, Stanton KG, McCann VJ, Vasikaran VB, Taylors RR, and van Bockxmeer FM. Homocysteine, folate, methylenetetrahydrofolate reducatse genotype and vascular morbidity in diabetic subjects. *Clinical Science* 102: 631–637, 2002.
57. Kern TS, Tang J, Mizutani M, Kowluru RA, Nagaraj RH, Romeo G, Podesta F, and Lorenzi M. Response of capillary cell death to aminoguanidine predicts the development of retinopathy: comparison of diabetes and galactosemia. *Invest Ophthalmol* 41: 3972–3978, 2000.
58. Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ, and Schouten EG. MTHFR 677C → T polymorphism and risk of coronary heart disease: a meta-analysis. *JAMA* 288: 2023–2031, 2002.
59. Konecky N, Malinow MR, Tunick PA, Freedberg RS, Rosenzweig BP, Katz ES, Hess DL, Upson B, Leung B, Perez J, and Kronzon I. Correlation between plasma homocysteine and aortic atherosclerosis. *Am Heart J* 133: 534–540, 1997.
60. Kwan CY, Wang RR, Beazley JS, and Lee RM. Alterations of elastin and elastase-like activities in aortas of diabetic rats. *Biochim Biophys Acta* 967: 322–325, 1988.
61. Lebovitz HE and Manerji MA. Insulin resistance and its treatment by thiazolidinediones. *Recent Prog Horm Res* 56: 265–294, 2001.
62. Lin KY, Ito A, Asagami T, Tsao PS, Adimoolam S, Kimoto M, Tsuji H, Reavan GM, and Cooke JP. Impaired nitric oxide synthase pathway in diabetes mellitus: role of asymmetric dimethylarginine and dimethylarginine dimethylaminohyrolase (DDAH). *Circulation* 106: 987–992, 2002.
63. Marx N, Sukhova G, Murphy C, Libby P, and Plutzky J. Macrophages in human atheroma conain PPAR: Differential dependent peroxisomal proliferator activated receptor ã expression and reduction of MMP-9 activity through PPAR activation in mononuclear phaocytes *in vitro*. *Am J Pathol* 153: 17–23, 1998.
64. McCully KS. Homocysteine and vascular disease. *Nature Med* 2: 386–389, 1996.
65. Mebazaa A, Wetzel R, Cherian M, and Abraham M. Comparison between endothelial and great vessel endothelial cells: morphology, growth, and prostaglandin release. *Am J Physiol* 268: H250–H259, 1995.
66. Meigs JB, Jacques PF, Selhub J, Singer DE, Nathan DM, Rifai N, D'Agostino RB Sr, and Wilson PW. Fasting plasma homocysteine levels in the insulin resistance syndrome: the Framingham offspring study. *Diabetes Care* 24: 1403–1410, 2001.
67. Miller A, Mujumdar V, Palmer L, Bower JD, and Tyagi SC. Reversal of endocardial endothelial dysfunction by folic acid in homocysteinemic hypertensive rats. *Am J Hyperten* 15: 157–163, 2002.
68. Miller A, Mujumdar V, Shek E, Guillot J, Angelo M, Palmer L, and Tyagi SC. Hyperhomocysteinemia induces multiorgan damage. *Heart Vessels* 15: 135–143, 2000.
69. Mizushige K, Yao L, Noma T, Kiyomoto H, Yu Y, Hosomi N, Ohmori K, and Matsuo H. Alteration in LV diastolic filling and accumulation of myocardial collagen at insulin-resistant prediabetic stage of a type 2 diabetic rat model. *Circulation* 101: 899–907, 2000.
70. Mujumdar VS, Aru GM, and Tyagi SC. Induction of oxidative stress by homocyst(e)ine impairs endothelial function. *J Cell Biochem* 82: 491–500, 2001.
71. Murthy SN, Obregon DF, Chattergoon NN, Fonseca NA, Mondal D, Dunne JB, Diez JG, Jeter JR Jr, Kadowitz PJ, Agrawal KC, McNamara DB, and Fonseca VA. Rosiglitazone reduces serum homocysteine levels, smooth muscle proliferation, and intimal hyperplasia in Sprague–Dawley rats fed a high methionine diet. *Metabolism* 54: 645–652, 2005.
72. Noga AA, Stead LM, Zhao Y, Borsnan ME, Brosnan JT, and Vance DE. Plasma homocysteine is regulated by phospholipid methylation. *J Biol Chem* 278: 5952–5955, 2003.
73. Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK, and Milburn MV. Ligand binding and co-activator assembly of the PPARγ. *Nature* 395: 137–143, 1998.
74. Ovechkin AV, Tyagi N, Sen U, Lominadze D, Steed MM, Moshal KS, and Tyagi SC. 3-Deazaadenosine mitigates arterial remodeling and hypertension in hyperhomocysteinemic mice. *Am J Physiol Lung Cell Mol Physiol* 291: L905–L911, 2006.
75. Pavia C, Ferrer I, Valls C, Artuch R, Colome C, and Vilaseca MA. Total homocysteine in patients with type I diabetes. *Diabetes Care* 23: 84–87, 2000.
76. Pinsky DJ, Patton S, Mesaros S, Brovkovych V, Kubaszewski E, Grunfeld S, and Malinski T. Mechanical transduction of NO synthesis in the beating heart. *Circ Res* 81: 372–379, 1997.
77. Pouwels MJ, den Heijer M, Blom HJ, Tack CJ, and Hermus AR. Improved insulin sensitivity and metabolic control in type 2 diabetes does not influence plasma homocysteine. *Diabetes Care* 26*:* 1637–1639, 2003.
78. Radomski A, Sawicki G, Olson DM, and Radomski MW. The role of nitric oxide and metalloproteinases in the pathogenesis of hyperoxia-induced lung injury in newborn rats. *Brit J Pharmacol* 125: 1455–1462, 1998.
79. Roberts JT and Wearn JT. Quantitative changes in the capillary-muscle relationship in human hearts during normal growth and hypertrophy. *Am Heart J* 16: 617–633, 1941.
80. Rodriguez WE, Joshua IG, Falcone JC, and Tyagi SC. Pioglitazone prevents cardiac remodeling in high-fat high-calorie induced type 2 diabetes mellitus. *Am J Physiol Heart Circ Physiol* 291: H81–H87, 2006.
81. Rolland PH, Friggi A, Barlatier A, Piquet P, Latrille V, Faye MM, Guillou J, Charpioy P, Bodard H, Ghininghelli O, Calaf R, Luccioni R, and Garcon D. Hyperhomocysteinemia-induced vascular damage in the minipigs. *Circulation* 91: 1161–1174, 1995.
82. Rosen R, Du X, and Tschope D. Role of ROS for vascular dysfunction in the diabetic hearts. *Mol Cell Biochem* 188: 103–111, 1998.
83. Rosolova H, Simon J, Mayer 0, Jr., Racek J, Dierze T, and Jacobsen DW. Unexpected inverse relationship between insulin resistance and serum homocysteine in healthy subjects. *Physiol Res* 51: 93–98, 2002.
84. Rucklidge GJ, Milne G, McGaw BA, Milne E, and Robins SP. Turnover rates of different collagen types measured by isotope ratio mass spectrometery. *Biochim Biophys Acta* 11: 1156–1157, 1992.
85. Ryan ME, Usman A, Ramamurthy NS, Golub LM, and Greenwald RA. Excessive matrix metalloproteinase activity in diabetes: inhibition by tetracycline analogues with zinc reactivity. *Curr Med Chem* 8: 305–316, 2001.
86. Salas A, Panes J, Elizalde JI, Casadevall M, Anderson DC, Granger DN, and Pique JM. Mechanisms responsible for enhanced inflammatory response to ischemia-reperfusion in diabetes. *Am J Physiol* 275: H1773–H1781, 1998.
87. Scarabelli T, Stephanou A, Rayment N, Pasini E, Comini L, Curello S, Ferrari R, Knight R, and Latchman D. Apoptosis of endothelial cells precedes myocytes cell apoptosis in ischemia/reperfusion injury. *Circulation* 104: 353–256, 2001.

88. Schnyder G, Roffi M, Flammer Y, Pin R, and Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B(12), and vitamin B(6) on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. *JAMA* 288: 973–979, 2002.
89. Schnyder G, Roffi M, Pin R, Flammer Y, Lange H, Eberli FR, Meier B, Turi ZG, and Hess OM. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Eng J Med* 345: 1593–1600, 2001.
90. Selley ML. Homocysteine increases the production of asymmetric dimethylarginine in cultured neurons. *J Neurosci Res* 77: 90–93, 2004.
91. Senior RM, Griffin GL, Eliszar CJ, Shapiro SD, Goldberg GI, and Welgus HG. Human 92- and 72- kilodalton type IV collagenases are elastases. *J Biol Chem* 266: 7870–7875, 1991.
92. Shastry S and Tyagi SC. Homocysteine induces metalloproteinase and shedding of β-1 integrin in microvessel endothelial cells. *J Cell Biochem* 93: 207–213, 2004.
93. Shcherbak NS, Shutskaya ZV, Sheidina AM, Larionova VI, and Schwartz EI. Methylenetetrahydrofolate reductase gene polymorphism as a risk factor for diabetic nephropathy in IDDM patients. *Mol Genet Metab* 68: 375–378, 1999.
94. Shukia N, Thompson CS, Angelini GD, Mikhailidis DP, and Jeremy JY. Homocysteine enhances impairment of endothelium-dependent relaxation and guanosine cyclic monophosphate formation in aortae from diabetic rabbits. *Diabetologia* 45: 1325–1331, 2002.
95. Smith JA, Shah AM, Fort S, and Lewis MJ. The influence of endocardial endothelium on myocardial contraction. *Trends Pharmacol Sci* 13: 113–116, 1992.
96. Sokolov EI, Zaichikova OS, and Tsyplenkova VG. Ultrastructure of the myocardium in patients with cardiac pathology complicated by diabetes mellitus. *Arkh Patol* 60: 49–54, 1998.
97. Solini A, Santini E, Nannipieri M, and Ferrannini E. High glucose and homocysteine synergistically affect the metalloproteinases-tissue inhibitors of metalloproteinases pattern, but not TGFB expression, in human fibroblasts. *Diabetologia* 49: 2499–2506, 2006.
98. Sood HS, Cox MJ, and Tyagi SC. Generation of nitrotyrosine precedes the activation of matrix metalloproteinase in left ventricle of hyperhomocystenemia rats. *Antioxid Redox Signal* 4: 799–804, 2002.
99. Stamenkovic I. Extracellular matrix remodeling: the role of matrix metalloproteinases. *J Pathol* 200: 448–464, 2003.
100. Starkebaum G and Harlan JM. Endothelial cell injury due to copper-catalyzed hydrogen peroxide generation from homocysteine. *J Clin Invest* 77: 1370–1376, 1986.
101. Thompson EW. Structural manifestations of diabetic cardiomyopathy in the rat and its reversal by insulin treatment. *Am J Anat* 182: 270–282, 1988.
102. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, Sides EG, Wang CH, and Stampfer M. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 291: 565–575, 2004.
103. Turk Z, Misur I, Turk N, and Benko B. Rat tissue collagen modified by advanced glycation: co-relation with duration of diabetes and glycemic control. *Clin Chem Lab Med* 37: 813–820, 1999.
104. Tyagi N, Moshal KS, Lominadze D, Sen U, Ovechkin AV, and Tyagi SC. Ciglitazone ameliorates Hcy-mediated mitochondrial translocation and MMP-9 activation in endothelial cells by inducing PPARγ activity. *Cell Mol Biol* 52: 21–27, 2006.
105. Tyagi SC and Hayden MR. Role of nitric oxide in matrix remodeling in diabetes and heart failure. *Heart Failure Rev* 8: 23–28, 2003.
106. Tyagi SC and Hoit BD. Metalloproteinase in myocardial adaptation and maladaptation, *J Cardiovasc Pharmaol Therap* 7: 241–246, 2002.
107. Tyagi SC, Campbell SE, Reddy HK, Tjahja E, and Voelker DJ. Matrix metalloproteinase activity expression in infarcted, noninfarcted and dilated cardiomyopathic human hearts. *Mol Cell Biochem* 155: 13–21, 1996.
108. Tyagi SC, Haas SJ, Kumar SG, Reddy HK, Voelker DJ, Hayden MR, Demmy TL, Schmaltz RA, and Curtis JJ. Post-transcriptional regulation of extracellular matrix metalloproteinase in human heart end-stage failure secondary to ischemic cardiomyopathy. *J Mol Cell Cardiol* 28: 1415–1428, 1996.
109. Tyagi SC, Lewis K, Pikes D, Marcello A, Mujumdar V, Smiley L, and Moore CK. Stretch induced membrane type matrix metalloproteinases and tissue plasminogen activator in cardiac fibroblast cells. *J Cell Physiol* 176: 374–382, 1998.
110. Tyagi SC, Smiley LM, and Mujumdar VS. Homocyst(e)ine impairs endocardial endothelial function. *Canad J Physiol Pharmacol* 77: 950–957, 1999.
111. Tyagi SC, Smiley LM, Mujumdar VS, Clonts B, and Parker JL. Reduction-oxidation (redox) and vascular tissue level of homocyst(e)ine in human coronary atherosclerotic lesions and role in vascular ECM remodeling and vascular tone. *Mol Cell Biochem* 181: 107–116, 1998.
112. Tyagi SC. Homocyst(e)ine and heart disease: pathophysiology of extracellular matrix. *Clin Exper Hypertension* 21: 181–198, 1999.
113. Tyagi SC. Proteinases and myocardial extracellular matrix turnover. *Mol Cell Biochem* 168: 1–12, 1997.
114. Vance DE and Ridgway ND. The methylation of phosphatidylethanolamine. *Prog Lipid Res* 27: 61–79, 1988.
115. Visse R and Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases:structure, function, and biochemistry. *Circ Res* 92: 827–839, 2003.
116. Wald DS, Law M, and Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 325: 1202, 2002.
117. Wang J and Morgan JP. EE modulates myofilament Ca2+ responsiveness in aequorin-loaded ferret myocardium. *Cir Res* 70: 754–760, 1992.
118. Wang J, Takeuchi T, Tanaka S, Kubo SK, Kayo T, Lu D, Takata K, Koizumi A, and Izumi T. A mutation in the insulin 2 gene induces diabetes with severe pancreatic beta-cell dysfunction in the Mody mouse. *J Clin Invest* 103: 27–37, 1999.
119. Wang Y, Jones JF, Jeggo RD, de Burgh Daly M, Jordan D, and Ramage AG. Effect of pulmonary C-fibre afferent stimulation on cardiac vagal neurones in the nucleus ambiguus in anaesthetized cats. *J Physiol* 526: 157–165, 2000.
120. Warley A, Powell JM, and Skepper JN. Capillary surface area is reduced and tissue thickness from capillaries to myocytes is increased in LV of STZ-diabetic rats. *Diabetologia* 38: 413–421, 1995.
121. Wayman NS, Hattori Y, McDonald MC, Mota–Filipe H, Cuzzocrea S, Pisano B, Chatterjee PK, and Thiemermann C. Ligands of the PPAR gamma and alpha reduce myocardial infarct size. *FASEB J* 16: 1027–1040, 2002.
122. Wollesen F, Brattstrom L, Refsum H, Ueland PM, Bergiund L, and Beme C. Plasma total homocysteine and cysteine in relation to glomerular filtration rate in diabetes mellitus. *Kidney Int* 55: 1028–1035, 1999.
123. Yamamoto K, Ohki R, Lee RT. Ikeda U, and Shimada K. PPARã activators inhibit cardiac hypertrophy in cardiomyocytes. *Circulation* 104: 1670–1675, 2001.
124. Yi P, Melnyk S, Pogribna M, Pogribny IP, Hine RJ, and James SJ. Increase in plasma homocysteine associated with parallel increase in plasma *S*-adenosylhomocysteine and lymphocyte DNA hypomethylation. *J Biol Chem* 275: 29318–29323, 2000.
125. Zhang X, Li H, Jin H, Ebin Z, Brodsky S, and Goligorsky MS. Effects of homocysteine on endothelial nitric oxide production. *Am J Physiol* 279: F671–F678, 2000.

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