Diabetes and obesity have emerged as global epidemics. At present more than 150 million individuals worldwide are living with diabetes and this number is expected to increase by 30% by 2015 and double to 300 million by 2025. In the US alone, there are 18.2 million diabetics (6.3% of the total population) and an estimated 1.3 million new cases are expected to be diagnosed each year. Diabetes and insulin resistance, fueled by pandemic obesity, has emerged as an explosive worldwide epidemic that encompasses all ethnicities, economic classes, and age groups. While diabetes affects several organs systems and disease processes, heart disease is the leading cause of death in diabetics. Both diabetes and cardiovascular disease share a common set of risk factors, and therefore it has been suggested that the two diseases share a similar etiology (the "common soil" hypothesis) and that diabetes and cardiovascular disease share overlapping, if not identical, molecular and cellular mechanisms. Not only does insulin resistance originate from cardiovascular dysfunction, but cardiovascular tissues are the primary targets of diabetes and obesity. Patients with both type 1 and type 2 diabetes are at high risk for developing cardiovascular disease and nearly 70% of diabetics die of heart disease. Nevertheless, diabetes and its cardiovascular complications remain poorly understood. The processes that cause insulin resistance remain unknown and the mechanisms by which diabetes accelerates cardiovascular disease are unclear.

It is currently believed that diabetes and obesity are metabolic states that lead to chronic low-grade inflammation. Although the origins of such inflammation remain unknown, it is becoming increasingly clear that metabolism is inextricably linked to immunity and that the two regulate each other. Because energy is required to fight infection, starvation suppresses immune responses. Inflammation and infection, in turn, favor catabolism and down-regulate anabolic signals such as those triggered by insulin. The emerging paradigm is that metabolic imbalance leads to immune imbalance. Obesity and other insulin-resistant states are characterized by a broad spectrum of inflammatory responses involving several cytokines, chemokines and inflammatory mediators. It has also become evident that metabolic mediators regulate immune function (leptin for instance is responsible for immunosuppression during starvation) and that lipids themselves regulate immunity. Both saturated lipids and products derived from the oxidation of unsaturated lipids have been shown to be potent regulators of immune responses. The documented ability of lipids to trigger and sustain inflammation is consistent both with a critical role of hyperlipidemia in inducing peripheral insulin resistance in obesity and diabetes and with the contribution of dyslipidemia and LDL oxidation to vascular inflammation and arterial lesion formation during atherogenesis.

Accumulating suggests that endothelial dysfunction may be another critical feature of the injury induced by nutrient excess that leads to metabolic changes resulting in an increase in adiposity and systemic insulin resistance. Endothelial dysfunction is robustly and positively linked to a decrease in nitric oxide (NO) production. When mice are fed a high fat diet, the endothelium becomes resistant to insulin before any other tissue. Similarly, studies with human diabetics demonstrate
Adipose Tissue Biology and Cardiomyopathy: Translational Implications [Review]; Turer et al

**Abstract**

It is epidemiologically established that obesity is frequently associated with the metabolic syndrome and poses an increased risk for the development of type 2 diabetes mellitus and cardiovascular disease. The molecular links that connect the phenomenon of obesity, per se, with insulin resistance and cardiovascular disease are still not fully elucidated. It is increasingly apparent that fully functional adipose tissue can be cardioprotective by reducing lipotoxic effects in peripheral tissues and by maintaining a healthy balance of critical adipokines, thereby allowing the heart to maintain its full metabolic flexibility. The present review highlights both basic and clinical findings that emphasize the complex interplay of adipose tissue physiology and adipokine-mediated effects on the heart exerted by either direct effects on cardiac myocytes or indirect actions via central mechanisms through sympathetic outflow to the heart.

**Acute Psychological Stress Accelerates Reverse Cholesterol Transport via Corticosterone-Dependent Inhibition of Intestinal Cholesterol Absorption; Silvennoinen et al**

**What Is Known?**

- Stress in humans is considered a risk factor of atherosclerosis, but its effects on experimental atherogenesis are model dependent.
- Reverse cholesterol transport (RCT) is a multistep pathway for elimination of cholesterol in feces, but only the RCT fraction that originates in macrophages (macrophage-RCT) is relevant for atherosclerosis.
- Peroxisome proliferator–activated receptors and liver X receptors regulate intestinal cholesterol homeostasis via several target genes, particularly the gene encoding Niemann-Pick C1–like 1 protein, the major transporter facilitating cholesterol influx into the enterocyte.

**What New Information Does This Article Contribute?**

- Restraint stress in mice, a model of psychological stress in humans, accelerates the rate of macrophage-RCT by suppressing cholesterol absorption in small intestine.
- Administration of corticosterone, the stress hormone in rodents, to nonstressed mice upregulates the peroxisome proliferator–activated receptors–α gene and downregulates Niemann-Pick C1–like 1 protein in the small intestine, and fully reproduced the effect of stress on macrophage-RCT.
- The mechanism of the stress-induced RCT response of the intestine appears to involve a complex cross-talk among corticosterone, peroxisome proliferator–activated receptor (PPAR)α, and liver X receptor (LXR)α.

**Conclusions**

Acute psychological stress accelerated RCT by compromising intestinal cholesterol absorption. The present results uncover a novel functional connection between the hypothalamic-pituitary-adrenal axis and RCT that can be triggered by a stress-induced increase in circulating CORT.

**Myeloid Cell–Specific ABCA1 Deletion Protects Mice From Bacterial Infection; Zhu et al**

**What Is Known?**

- ATP-binding cassette transporter A1 (ABCA1) is a plasma membrane protein that transports cellular free cholesterol and phospholipids to lipid-free apolipoprotein A1, forming nascent high-density lipoprotein particles and eliminating excess free cholesterol from tissues.
- ABCA1 attenuates macrophage inflammation by downregulating toll-like receptor signaling via reducing free cholesterol enrichment in membrane lipid rafts and the trafficking of toll-like receptors into rafts.
What New Information Does This Article Contribute?

- Myeloid cell–specific ABCA1 knockout (MSKO) mice are more resistance to acute infection with intracellular bacteria Listeria monocytogenes (Lm) compared with wild-type mice.
- MSKO mice infected with Lm have enhanced macrophage chemotaxis and increased hepatic chemokine expression, resulting in more rapid and efficient clearance and killing of Lm.
- Lm infection reduces expression of macrophage cholesterol export proteins, suggesting that diminished myeloid cholesterol efflux enhances macrophage innate immune function.

Conclusions
Myeloid-specific ABCA1 deletion favors host response to and clearance of Lm. Macrophage Lm infection reduces expression of cholesterol export proteins, suggesting that diminished cholesterol efflux enhances innate immune function of macrophages.

Restraint Stress Restrains Cholesterol in the Intestine [Editorial]; von Eckardstein

Abstract
Epidemiological studies have observed that psychosocial stress, for example, by unemployment, low socioeconomic status, or work stress, increases the risk of cardiovascular events.1 The pathophysiological basis of this association is poorly understood. Restraint stress, which is an experimental model for psychosocial stress, is characterized by the activation of the sympathetic nervous system involving the fast release of epinephrine and norepinephrine and the hypothalamic-pituitary-adrenal axis, resulting in a slow but sustained increase in circulating glucocorticoids.2 Both neuroendocrine axes elicit multiple and complex responses, aiming to protect the threatened organism. As yet, there is little and mixed epidemiological evidence about which of these pathways is relevant for the pathogenesis of cardiovascular diseases.3 to 6 Diurnal and other intraindividual variation of cortisol and catecholamine plasma concentrations make the design of meaningful observational studies difficult. More recently, measurements of cortisol in saliva or urine found positive associations between cortisol and risk of incident coronary events.5,6 Elevated cortisol levels in plasma or saliva have also been associated with increased blood pressure, diabetes mellitus, hyperglycemia, hypertriglyceridermia, and central adiposity. However, these associations have been questioned by 2 recent population studies that did not find any significant association of cortisol awakening response, evening cortisol, cortisol decline across the waking day, total cortisol output, and cortisol after dexamethasone suppression with metabolic syndrome or type 2 diabetes.

STIM1 Restores Coronary Endothelial Function in Type 1 Diabetic Mice; Estrada et al

What Is Known?
- Coronary vascular endothelial dysfunction is implicated in the development and progression of cardiac ischemia and heart failure due to a decrease in coronary blood flow.
- The Ca2+ concentration in the endoplasmic reticulum (ER) is important for generating critical Ca2+ signals to mediate endothelium-dependent vasodilation.
- Stromal interaction molecule (STIM) protein (eg, STIM1) is an important regulator that activates Ca2+-permeable channels in the plasma membrane after depletion of Ca2+ from the ER and refill Ca2+ into the ER.

Conclusions
These findings demonstrate that increased eNOS activity prevents the obesogenic effects of high-fat diet without affecting systemic insulin resistance, in part, by stimulating metabolic activity in adipose tissue.

Overexpression of Endothelial Nitric Oxide Synthase Prevents Diet-Induced Obesity and Regulates Adipocyte Phenotype; Sansbury et al

What Is Known?
- Obesity is positively and robustly associated with the risk of development of cardiovascular disease and diabetes.

Conclusions
Impaired ER Ca2+ refilling in diabetic MCECs, due to the decrease in STIM1 protein expression, attenuates endothelium-dependent relaxation in diabetic coronary arteries, while STIM1 overexpression has a beneficial and therapeutic effect on coronary endothelial dysfunction in diabetes.
HDL and Cardiovascular Risk: Time to Call the Plumber? [Commentary]; Hewing et al19

Abstract
High-density lipoprotein cholesterol (HDL-C) has been dubbed the good cholesterol because it is thought to reflect the ability of HDL particles to remove excess cholesterol molecules from peripheral cells (including those in atherosclerotic plaques) for return to the liver. Not surprisingly, then, HDL-C has frequently been assumed to be a biomarker of HDL function, consistent with the inverse relationship in observational studies between plasma levels of HDL-C and risk of coronary artery disease. Recently, Voight et al have challenged this assumption by showing that genetically elevated HDL-C did not protect against myocardial infarction. This finding has fueled a lively discussion in the lay, scientific, and medical press about the relationship between HDL-C and HDL function, and the potential effectiveness of various HDL-C raising strategies.

A New Approach to Weight Loss: Just Activate Endothelial NO Synthase! [Editorial]; Sessa20

Abstract
Sustained consumption of dietary fats induces endothelial dysfunction and insulin resistance in experimental models and humans. Endothelial dysfunction, manifested by reduced endothelium-dependent dilation, is a hallmark of several cardiovascular diseases and obesity. Indeed, exercise training and caloric restriction attenuate endothelial dysfunction and delay the onset or reduce the magnitude of vascular diseases and insulin resistance.

RTEF-1 Attenuates Blood Glucose Levels by Regulating Insulin-Like Growth Factor Binding Protein-1 in the Endothelium; Messner-Blust et al21

What Is Known?
• Related transcriptional enhancer factor-1 (RTEF-1) plays an important role in cardiac and endothelial cell function.
• Insulin-like growth factor binding proteins (IGFBPs) are key regulators of insulin-like growth factor at the cellular level.
• Low levels of IGFBP-1 are associated with metabolic syndrome and cardiovascular diseases.

What New Information Does This Article Contribute?
• RTEF-1 increases IGFBP-1 gene expression by interacting with its insulin response element.
• RTEF-1 deficiency in endothelial cells exhibited increased blood glucose and insulin sensitivity in vivo.
• The increased blood glucose and insulin sensitivity shown in RTEF-1 deficiency in vivo was exacerbated in a high-fat diet, correlating with decreasing IGFBP-1 levels.

Conclusions
To the best of our knowledge, this is the first report demonstrating that RTEF-1 stimulates promoter activity through an insulin response element and also mediates the effects of insulin on gene expression. These results show that RTEF-1-stimulated IGFBP-1 expression may be central to the mechanism by which RTEF-1 attenuates blood glucose levels. These findings provide the basis for novel insights into the transcriptional regulation of IGFBP-1 and contribute to our understanding of the role of vascular endothelial cells in metabolism.

Microvascular Management of Systemic Insulin Sensitivity [Editorial]; Rubinow & Bornfeldt22

Abstract
Microvascular disease is a well-recognized complication of long-standing diabetes mellitus and is preceded by impaired vasoreactivity, a consequence largely of decreased endothelial cell (EC) generation of NO. This loss of normal vasodilation is evident particularly in EC responses to insulin and may arise early in states of obesity and insulin resistance.1 to 3 In addition, ECs serve as purveyors of other paracrine signals, with targets beyond vascular cells. Thus, a broader scope of endothelial function is being recognized, with increased attention now focused on the dynamic interactions between the microvasculature and surrounding tissues. Indeed, recent findings suggest that ECs might be critical metabolic mediators, obscuring a clear boundary between vascular biology and metabolism. Accordingly, dysregulated EC function may prove to be not only a sequela of diabetes mellitus but also a contributing factor to the pathogenesis and progression of metabolic disease.

Novel Biological Functions of High-Density Lipoprotein Cholesterol [Review]; Mineo & Shaul23

Abstract
In addition to its role in reverse cholesterol transport, high-density lipoprotein (HDL) cholesterol has direct action on numerous cell types that influence cardiovascular and metabolic health. Cellular responses to HDL entail its capacity to invoke cholesterol efflux that causes signal initiation via scavenger receptor class B, type I, and plasma membrane receptor activation by HDL cargo molecules. In endothelial cells and their progenitors, HDL attenuates apoptosis and stimulates proliferation and migration. HDL also has diverse anti-inflammatory actions in both endothelial cells and leukocytes. In vascular smooth muscles, HDL tempers proinflammatory, promigratory, and degradative processes, and through actions on endothelium and platelets HDL is antithrombogenic. There are additional actions of HDL of potential cardiovascular consequence that are indirect, including the capacities to promote pancreatic β-cell insulin secretion, to protect pancreatic β cells from apoptosis, and to enhance glucose uptake by skeletal muscle myocytes. Furthermore, HDL decreases white adipose tissue mass, increases energy expenditure, and promotes the production of adipose-derived cytokine adiponectin that has its own vascular-protective properties. Many of these numerous actions of HDL have been observed not only in cell culture and animal models but also in human studies, and assessments of these functions are now being applied to patient
populations to better-identify which actions of HDL may contribute to its cardioprotective potential and how they can be quantified and targeted. Further work on the many mechanisms of HDL action promises to reveal new prophylactic and therapeutic strategies to optimize both cardiovascular and metabolic health.

**IRF-1 and miRNA126 Modulate VCAM-1 Expression in Response to a High-Fat Meal; Sun et al**

**What Is Known?**

- Diets high in fat are associated with hypertriglyceridemia and increased risk of cardiovascular disease.
- Cholesterol and fatty acids transported by lipoprotein particles exacerbate systemic inflammation and can initiate plaque formation in arteries.
- Genetics, diet, and lifestyle choices coalesce in determining the extent to which inflammation triggers atherosclerosis.

**What New Information Does This Article Contribute?**

- Subjects consuming an identical high-fat meal produced and circulated lipoproteins that segregated into subsets eliciting either a proinflammatory or anti-inflammatory response in arterial endothelial cells.
- A direct correlation was found between an increase in particle density of triglycerides and expression of VCAM-1 receptors that supported monocyte adhesion to endothelium, a harbinger of atherosclerosis.
- We identified a molecular mechanism by which uptake of lipoproteins bias the inflammatory response of endothelium via transcriptional and posttranscriptional editing of VCAM-1.

**Conclusions**

In response to a high-fat meal, TGRL bias the inflammatory response of endothelium via transcriptional and posttranscriptional editing of VCAM-1. Subjects with an anti-inflammatory response to a meal produced TGRL that was enriched in non-esterified fatty acids, decreased IRF-1 expression, increased miR-126 activity, and diminished monocyte arrest.

**Structural Identification and Cardiovascular Activities of Oxidized Phospholipids [Review]; Salomon**

**Abstract**

Free radical–induced oxidation of membrane phospholipids generates complex mixtures of oxidized phospholipids (oxPLs). The combinatorial operation of a few dozen reaction types on a few dozen phospholipid structures results in the production of a dauntingly vast diversity of oxPL molecular species. Structural identification of the individual oxPL in these mixtures is a redoubtable challenge that is absolutely essential to allow determination of the biological activities of individual species. With an emphasis on cardiovascular consequences, this Review focuses on biological activities of oxPLs whose molecular structures are known and highlights 2 diametrically opposite approaches that were used to determine those structures, that is, (1) the classic approach from bioactivity of a complex mixture to isolation and structural characterization of the active molecule followed by confirmation of the structure by unambiguous chemical synthesis and (2) hypothesis of products that are likely to be generated by lipid oxidation, followed by synthesis, and then detection in vivo guided by the availability of authentic standards, and last, characterization of biological activities. Especially important for the application of the second paradigm is the capability of LC-MS/MS and derivatizations to selectively detect and quantify specific oxPL in complex mixtures, without the need for their isolation or complete separation. This technology can provide strong evidence for identity by comparisons with pure, well-characterized samples available by chemical syntheses. Those pure samples are critical for determining the biological activities attributable to specific molecular species of oxPLs in complex mixtures generated in vivo as a consequence of oxidative stress.

**Leptin Signaling in Adipose Tissue: Role in Lipid Accumulation and Weight Gain; Singh et al**

**What Is Known?**

- Increased cardiovascular risk in obesity is mediated, in part, by the expansion of adipose tissue and elevated levels of adipokines, including leptin.
- Although the central role of leptin in energy homeostasis is well-known, its effects on peripheral cells such as adipocytes are unclear.
- In cultured vascular endothelial cells, high levels of leptin increase caveolin-1 expression, which in turn impairs leptin signaling.

**What New Information Does This Article Contribute?**

- Leptin decreases the accumulation of lipids in adipocytes.
- In humans, increases in leptin seen with modest weight gain could increase adipose tissue caveolin-1 expression.
- Increased caveolin-1 expression in adipose tissue could impair leptin-dependent activation of signaling pathways and allow the storage of lipids in differentiating preadipocytes.

**Conclusions**

In healthy humans, increases in leptin, as seen with modest weight gain, may increase caveolin-1 expression in adipose tissue. Increased caveolin-1 expression in turn impairs leptin signaling and attenuates leptin-dependent lowering of intracellular lipid accumulation. Our study suggests a leptin-dependent feedback mechanism that may be essential to facilitate adipocyte lipid storage during weight gain.

**More Than Just an Engine: The Heart Regulates Body Weight [Commentary]; Taegtmeyer & Rodriguez**

**Abstract**

A recent study published in Cell may represent a paradigm shift in the way we look at cardiac metabolism: The study identifies
the heart as an endocrine organ that regulates body weight. It raises two important questions: What would be the “slimming factor” released by the heart that regulates fuel homeostasis in distant organs? What are the possible mechanisms directing metabolic energy to either storage or dissipation?

**Gene Silencing of the Mitochondrial Adaptor p66Shc Suppresses Vascular Hyperglycemic Memory in Diabetes; Paneni et al**

**What Is Known?**

- Recent prospective clinical trials have failed to confirm unequivocal benefits of glycemic control on cardiovascular outcomes.
- A long-term persistence of hyperglycemic stress even after blood glucose normalization has been recently defined as “hyperglycemic memory.”
- Reactive oxygen species (ROS) are likely involved in this phenomenon but the underlying molecular mechanisms remain unknown.

**What New Information Does This Article Contribute?**

- Mitochondrial adaptor p66Shc is the key effector driving vascular hyperglycemic memory in diabetes.
- Persistent p66Shc upregulation is associated with increased ROS production, reduced nitric oxide (NO) availability, and apoptosis.
- p66Shc-derived ROS maintain protein kinase CβII (PKCβII) upregulation as well as inhibitory phosphorylation of endothelial NO synthase (eNOS) at Thr-495, leading to a detrimental vicious cycle despite restoration of normoglycemia.
- In vivo gene silencing of p66Shc, performed at the time of glucose normalization, suppresses persistent endothelial dysfunction and vascular apoptosis.

**Conclusions**

p66Shc is the key effector driving vascular hyperglycemic memory in diabetes. Our study provides molecular insights for the progression of diabetic vascular complications despite glycemic control and may help to define novel therapeutic targets.

**Antibodies to PCSK9: A Superior Way to Lower LDL Cholesterol? [Commentary]; Maxwell & Breslow**

**Abstract**

Lowering of LDL cholesterol, predominantly accomplished clinically by statins, is one of the key components of both the prevention and medical management of coronary atherosclerosis; however, additional or alternative cholesterol lowering agents are needed for patients who fail to achieve goals or have adverse effects on statins. Owing to relatively rapid translation of basic science research on a novel regulatory pathway of the LDL receptor by PCSK9, a new class of such drugs with a different mode of action, and potentially better tolerance and less off-target effects may be just over the horizon.

**Redox Mediating Epigenetic Changes Confer Metabolic Memories [Editorial]; El-Osta**

**Abstract**

It’s not always the case that it’s easy to forgive and forget, particularly when it comes to past memories. The concept of the legacy effect or hyperglycemic memory describes the deferred consequence of antecedent glycemic status on the development of diabetic complications. Anyone researching chronic hyperglycemia appreciates that glucose is still considered the major risk factor implicated in the development and progression of diabetic vascular complications. Now, the same can be concluded for transient hyperglycemia. Large clinical studies have demonstrated that prior glycemic control has a sustained benefit in reducing subsequent diabetic complications.1 to 4 The Diabetes Control and Complications Trial (DCCT) and the follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC) have determined that episodes of poor glycemic control can lead many years later to the long-term complications of diabetes.5,6 The DCCT study was designed to compare intensive versus conventional approaches to improve glycemic control and determine the effects of these regimens on the development and progression of vascular complications in patients with type-1 diabetes. Because the development of diabetic microvascular complications and cardiovascular disease takes time, the follow-up EDIC study was designed to investigate the long-lasting effects of intensive and conventional therapies. The findings of these extended studies show that early intensive intervention was more effective in slowing the development of diabetic complications and this was clearly evidenced with the benefit of 6.5 years of intensive therapy during the DCCT phase being sustained, the benefits continuing for at least 10 years after return …

**Constitutively Active TRPC Channels of Adipocytes Confer a Mechanism for Sensing Dietary Fatty Acids and Regulating Adiponectin; Sukumar et al**

**What Is Known?**

- Adiponectin secreted by adipocytes confers protection against cardiovascular disease.
- Secretion from adipocytes is calcium regulated.
- Transient receptor potential canonical (TRPC) proteins form calcium-permeable channels that promote cardiac and vascular smooth muscle cell hypertrophy, migration, and proliferation.

**What New Information Does This Article Contribute?**

- TRPC1 and TRPC5 form calcium-permeable channels in adipocytes.
- Inhibition of adipocyte TRPC channels increases the circulating concentration of adiponectin.
- ω-3 fatty acids inhibit adipocyte TRPC channels.

**Conclusions**

The data suggest that TRPC1 and TRPC5 contribute a constitutively active heteromultimeric channel of adipocytes that negatively regulates adiponectin and through which ω-3 fatty acids enhance the anti-inflammatory adipokine, adiponectin.
Glycine Normalizes Hepatic Triglyceride-Rich VLDL Secretion by Triggering the CNS in High-Fat Fed Rats; Yue et al.32

What Is Known?
• The hypothalamus senses nutrients and hormones to regulate hepatic lipid metabolism.
• Hypothalamic sensing mechanisms fail to regulate hepatic lipid metabolism in diet-induced obese rodents.

What New Information Does This Article Contribute?
• Glycine potentiates N-methyl-d-aspartate (NMDA) receptor-mediated transmission in an extrahypothalamic region termed dorsal vagal complex (DVC) to inhibit hepatic triglyceride-rich very low-density lipoproteins (VLDL-TG) via the hepatic vagus.
• Glycine normalizes high-fat diet-induced hypersecretion of VLDL-TG by triggering the NMDA receptors in the DVC.

Conclusions
Molecular and pharmacological inhibition of the NR1-containing NMDA receptors in the DVC negated the ability of glycine to inhibit hepatic secretion of VLDL-TG in vivo. Importantly, the hypersecretion of VLDL-TG from the liver induced by a model of high-fat feeding was restored by the hepatic lipid control of CNS glycine sensing. These findings collectively suggest that glycine or glycine analogues may have therapeutic benefits in lowering plasma lipid levels in diabetes and obesity by triggering the CNS.

Endothelial Cell Palmitoylproteomic Identifies Novel Lipid-Modified Targets and Potential Substrates for Protein Acyl Transferases; Marin et al.33

What Is Known?
• Palmitoylation is the reversible posttranslational modification of a protein by the attachment of a lipid to a cysteine side-chain via a thioester linkage. Palmitoylation can influence protein localization, activity, or stability.
• Palmitoylation is catalyzed by the large family of zinc finger DHHC domain–containing (ZDHHC) protein acyl transferases.
• Palmitoylation affects the function of several proteins critical to endothelial cell (EC) biology such as endothelial nitric oxide synthase (eNOS) and caveolin-1, but many palmitoylated proteins in ECs have not been identified because of technical difficulties.

What New Information Does This Article Contribute?
• Acyl-biotinyl exchange (ABE), a new method for globally isolating palmitoylated proteins, was applied to ECs and >150 palmitoyl proteins were isolated and identified by mass spectrometry.

• Superoxide dismutase-1 (SOD1), a protein important in protecting ECs from the toxicity of superoxide radical, was found to be palmitoylated.
• The protein acyl transferase ZDHHC21 was found to be associated with the palmitoylation of the cell adhesion molecule platelet endothelial cell adhesion molecule-1 (PECAM1) in ECs.

Conclusions
Our data demonstrate the utility of EC palmitoylproteomics to reveal new insights into the role of this important posttranslational lipid modification in EC biology.

Loss of Angiotensin-Converting Enzyme-2 Exacerbates Diabetic Cardiovascular Complications and Leads to Systolic and Vascular Dysfunction: A Critical Role of the Angiotensin II/AT1 Receptor Axis; Patel et al.34

What Is Known?
• Diabetes mellitus results in severe cardiovascular complications, and heart disease remains the major cause of death in patients with diabetes.
• Activation of the rennin-angiotensin system (RAS) plays a key role in the progression of diabetic complications, and AT1 receptor blockers reduce these complications.
• Angiotensin-converting enzyme 2 (ACE2; a type I transmembrane protein that converts angiotensin (Ang) II into Ang 1–7) is a negative regulator of the RAS.

What New Information Does This Article Contribute?
• Loss of ACE2 in diabetic Akita mice exhibits exacerbated diabetic cardiomyopathy, resulting in systolic dysfunction associated with increased oxidative stress and extracellular matrix (ECM) degradation.
• Loss of ACE2 increased vascular oxidative stress and dysfunction in diabetic mice.
• Treatment with AT1 receptor blocker, irbesartan, prevented the systolic and vascular dysfunction in the Akita/ACE2KO model.

Conclusions
Loss of ACE2 disrupts the balance of the renin-angiotensin system in a diabetic state and leads to an angiotensin II/AT1 receptor-dependent systolic dysfunction and impaired vascular function. Our study demonstrates that ACE2 serves as a protective mechanism against diabetes-induced cardiovascular complications.

Autophagy Mediates the Metabolic Benefits of Endurance Training [Commentary]; Galluzzi & Kroemer35

Abstract
In a recent issue of Nature, He et al demonstrate that autophagy is required for optimal physical endurance as well as for the beneficial effects of exercise on glucose and lipid metabolism.
These data not only shed new insights into the mechanisms whereby exercise is healthy, but also indirectly strengthen the notion that autophagy exerts lifespan-extending effects.

**Uncoupling Protein-2 Protects Endothelial Function in Diet-Induced Obese Mice; Tian et al**

**What Is Known?**
- Uncoupling protein-2 (UCP2) inhibits reactive oxygen species (ROS) production from the mitochondria.
- ROS play an important role in the development of endothelial cell dysfunction.
- UCP2 deficiency increases vascular dysfunction and organ damage in stroke, atherosclerosis, and hypertension.

**What New Information Does This Article Contribute?**
- UCP2 overexpression improves endothelium-dependent vasodilatation in both conduit and resistance arteries of diet-induced obese mice.
- UCP2 reduces ROS production and improves nitric oxide (NO) bioavailability in the endothelium.

**Conclusions**
UCP2 preserves endothelial function through increasing nitric oxide bioavailability secondary to the inhibition of ROS production in the endothelium of obese diabetic mice.

**Changing the Diet to Make More Mitochondria and Protect the Heart [Commentary]; Benit & Rustin**

**Abstract**
The complexity of mitochondrial diseases has made their treatment problematic. However, in a recent study from PNAS in 2011, researchers show how diet may be the key to better understanding and possibly fighting the expression of these diseases.

**Epigenetic Mechanisms of Metabolic Memory in Diabetes [Editorial]; Jayaraman**

**Abstract**
Diabetes affects 28.5 million people in the US. In addition, several million people with diabetes are estimated to be undiagnosed, thus increasing the risk for developing long-term complications, including macrovascular diseases and end-stage renal disease in a fairly significant fraction of the population. Type 1 diabetes, an autoimmune disease that mainly affects children, is characterized by the loss of insulin-producing beta cells. Until now, our understanding of this insidious disease relied on classic genetic approaches including genome-wide association studies and single nucleotide polymorphisms...

**Dietary Fat and Heart Failure: Moving From Lipotoxicity to Lipoprotection [Review]; Stanley et al**

**Abstract**
There is growing evidence suggesting that dietary fat intake affects the development and progression of heart failure. Studies in rodents show that in the absence of obesity, replacing refined carbohydrate with fat can attenuate or prevent ventricular expansion and contractile dysfunction in response to hypertension, infarction, or genetic cardiomyopathy. Relatively low intake of n-3 polyunsaturated fatty acids from marine sources alters cardiac membrane phospholipid fatty acid composition, decreases the onset of new heart failure, and slows the progression of established heart failure. This effect is associated with decreased inflammation and improved resistance to mitochondrial permeability transition. High intake of saturated, monounsaturated, or n-6 polyunsaturated fatty acids has also shown beneficial effects in rodent studies. The underlying mechanisms are complex, and a more thorough understanding is needed of the effects on cardiac phospholipids, lipid metabolites, and metabolic flux in the normal and failing heart. In summary, manipulation of dietary fat intake shows promise in the prevention and treatment of heart failure. Clinical studies generally support high intake of n-3 polyunsaturated fatty acids from marine sources to prevent and treat heart failure. Additional clinical and animals studies are needed to determine the optimal diet in terms of saturated, monounsaturated, and n-6 polyunsaturated fatty acids intake for this vulnerable patient population.

**Novel Communication Between Myocyte Lipid Storage and Fat Burning Unveiled [Commentary]; Kelly**

**Abstract**
A recent study unveils a fascinating role for an intracellular lipase in cardiac myocytes. The new results demonstrate that liberation of lipid species from myocyte neutral lipid stores results in activation of the nuclear receptor peroxisome proliferator-activated receptor α (PPARα) and the transcriptional coactivators, PPARγ coactivator 1 (PGC-1) α and β, chief regulators of cardiac mitochondrial fat burning capacity. Deficiency of this lipase in mice causes a cardiomyopathy with myocyte lipid accumulation and mitochondrial dysfunction.

**Hyperamylinemia Contributes to Cardiac Dysfunction in Obesity and Diabetes: A Study in Humans and Rats; Despa et al**

**What Is Known?**
- Patients with obesity and insulin resistance have elevated circulating levels of amylin, an amyloidogenic hormone co-expressed and cosecreted with insulin by pancreatic β-cells.
- At increased concentrations, amylin readily form amyloids, which are cytotoxic and contribute to the development of type 2 diabetes.
- The most toxic species of amylin amyloids are the soluble oligomers, which attach to cellular membranes causing Ca2+ dyshomeostasis, cell dysfunction, and apoptosis.

**What New Information Does This Article Contribute?**
- Amylin oligomers accumulate in the heart and are associated with cardiac failure in patients with obesity and type 2 diabetes.
Amylin oligomer buildup in the heart of rats transgenic for human amylin is linked to myocyte Ca2+ dysregulation, pathological cardiac hypertrophy and remodeling, and diastolic dysfunction.

Cardiac amylin accumulation accelerates the onset of diabetic cardiomyopathy.

**Conclusions**

Hyperamylinemia promotes amylin deposition in the heart, causing alterations of cardiac myocyte structure and function. We propose that detection and disruption of cardiac amylin buildup may be both a predictor of heart dysfunction and a novel therapeutic strategy in diabetic cardiomyopathy.

**What New Information Does This Article Contribute?**

We developed a contrasting animal model system through genetic selection and conducted the first set of survivorship studies and old-age comparisons to test the hypothesis that an intrinsic (inborn) capacity for aerobic metabolism sets an initial divide for longevity and a compression of age-related morbidity.

This study provides the first demonstration of the "aerobic hypothesis of longevity" and as such, is a significant step forward in the study of longevity mechanisms and aging biology, especially the role of the myocardium and the circulatory system.

**Conclusions**

These data obtained from a contrasting heterogeneous model system provide strong evidence that genetic segregation for aerobic exercise capacity can be linked with longevity and are useful for deeper mechanistic exploration of aging.

**AMP-Activated Protein Kinase Regulates E3 Ligases in Rodent Heart; Baskin & Taegtmeyer**

**What Is Known?**

- AMP-activated protein kinase (AMPK), a key regulator of metabolic homeostasis, inhibits protein synthesis and activates autophagy in the heart.
- The ubiquitin proteasome system (UPS) maintains cellular homeostasis by degrading unnecessary and/or damaged proteins through key enzymes, including ubiquitin (E3) ligases.
- Two muscle-specific E3 ligases, Atrogin-1 and MuRF1, are critical regulators of cardiac size and mass.

**What New Information Does This Article Contribute?**

- Activation of AMPK in vitro and in vivo regulates the transcription of Atrogin-1 and MuRF1 in cardiomyocytes.
- AMPK regulates MuRF1 transcription through the transcription factor MEF2.
- MuRF1 is necessary for AMPK-mediated proteolysis through the UPS in the heart.
- MuRF1-deficient mice are protected from cardiac dysfunction during the metabolic stress of fasting.

**Conclusions**

AMPK regulates the transcription of Atrogin-1 and MuRF1 and enhances UPS-mediated protein degradation in heart. Specifically, AMPK regulates MuRF1 through the
transcription factor MEF2. The absence of MuRF1 in the heart preserves cardiac function during fasting. The results strengthen the hypothesis that AMPK serves as a modulator of intracellular protein degradation in the heart.

**Repression of P66Shc Expression by SIRT1 Contributes to the Prevention of Hyperglycemia-Induced Endothelial Dysfunction; Zhou et al**

**What Is Known?**
- SIRT1 is highly expressed in the vasculature and it functions as a regulator of vascular homeostasis.
- Inactivation of the p66Shc adaptor protein protects against age-related and hyperglycemia-induced endothelial dysfunction.

**What New Information Does This Article Contribute?**
- Inhibition of Sirtuins induces p66Shc expression.
- SIRT1 decreases high-glucose-induced p66Shc expression in human umbilical vein endothelial cells (HUVECs).
- SIRT1-transgenic (Tg) diabetic mice show decreased p66Shc expression, improved endothelial function, and reduced oxidative stress.
- SIRT1 negatively regulates p66Shc expression through epigenetic chromatin modification.

**Conclusions**
Our findings indicate that repression of p66Shc expression by SIRT1 contributes to the protection of hyperglycemia-induced endothelial dysfunction.

**Lipid Metabolism by Gut Microbes and Atherosclerosis [Commentary]; Loscalzo**

**Abstract**
A recent metabolomic study provides evidence that microbial metabolism of lipids in the gut yields product(s) that promote atherosclerosis. These results add another dimension—the microbiome—to the complex determinants of atherogenesis.

**Saying Yes to Exercise and NO to Cardiac Injury [Editorial]; Bezzerides & Rosenzweig**

**Abstract**
Clinical studies demonstrate benefits of exercise in both preventing cardiovascular disease in the general population and mitigating existing disease in cardiovascular patients. Systemic effects of exercise on skeletal muscle and peripheral vessels as well as metabolism and insulin sensitivity undoubtedly contribute to these benefits. However, growing evidence from animal studies suggests that exercise also modulates intrinsic cardiac signaling mechanisms that contribute to its benefits. These benefits are probably best documented in models of ischemic injury but also appear to extend to heart failure in at least some experimental and clinical settings.

**Intravenous Gene Therapy With PIM-1 Via a Cardiotropic Viral Vector Halts the Progression of Diabetic Cardiomyopathy Through Promotion of Prosurvival Signaling; Katare et al**

**What Is Known?**
- Diabetic cardiomyopathy typically progresses from diastolic dysfunction to heart failure in the absence of coronary artery disease or hypertension.
- The proviral integration site for Moloney murine leukemia virus-1 (Pim-1) is decreased in the myocardium of diabetic mice beginning at the stage of diastolic dysfunction.
- Pim-1 plays an essential role in cardiomyocyte survival.

**What New Information Does This Article Contribute?**
- Activation of protein phosphatase-2A (PP2A) and microRNA-1 (miR-1) contributes to Pim-1 downregulation beginning at the stage of diastolic dysfunction in diabetic hearts.
- Pim-1 gene therapy with cardiotropic adeno-associated virus serotype-9 (AAV9) at the stage of diastolic dysfunction prevents heart failure in a mouse model of diabetic
cardiomyopathy by preserving cardiomyocyte and microvascular cell integrity.

- Pim-1 gene therapy counteracts the depletive effect of diabetes on c-kit+ cardiac progenitor cells.

**Conclusions**


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**The Ras Activator RasGRP3 Mediates Diabetes-Induced Embryonic Defects and Affects Endothelial Cell Migration; Randhawa et al**

**What Is Known?**

- Diabetes leads to elevation of diacylglycerol and endothelin and blood vessel dysfunction.
- Maternal diabetes leads to birth defects.
- Diacylglycerol activates RasGRP3 (Ras guanyl releasing protein 3), a mediator of cell signaling.

**What New Information Does This Article Contribute?**

- The Ras activator RasGRP3 mediates birth defects associated with diabetes.
- RasGRP3 affects the migration of endothelial cells that form blood vessels.
- RasGRP3 is required for major vessel responses to diacylglycerol and endothelin.

**Conclusions**

These findings provide the first evidence that RasGRP3 contributes to developmental defects found in embryos that develop in a diabetic environment. The results also elucidate RasGRP3-mediated signaling in endothelial cells and identify endothelin-1 as an upstream input and Ras/MEK/ERK as a downstream effector pathway. RasGRP3 may be a novel therapeutic target for the fetal complications of diabetes.

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**Widespread Increase in Myeloid Calcifying Cells Contributes to Ectopic Vascular Calcification in Type 2 Diabetes; Fadini et al**

**What Is Known?**

- Individuals with diabetes mellitus often show extensive ectopic calcifications in the vasculature, but the mechanisms are unknown.
- Several cells in the artery wall, as well as in the bloodstream, may contribute to vascular calcification.

**What New Information Does This Article Contribute?**

- We discovered a hitherto unrecognized circulating cell type capable of inducing ectopic calcification in vitro and in vivo.
- These cells are potentially involved in the excess vascular calcification seen in diabetes.

**Conclusions**

These data identify a novel type of blood-derived procalcific cells potentially involved in atherosclerotic calcification of diabetic patients.

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**Metabolic Syndrome: Is Nlrp3 Inflammasome a Trigger or a Target of Insulin Resistance? [Commentary]; Mori et al**

**Abstract**

The Nlrp3 inflammasome has recently been implicated in the development of the metabolic syndrome through the impairment of adipose tissue insulin sensitivity. Recent literature associates Nlrp3 activation with much pathology caused by prolonged insulin resistance state, therefore establishing Nlrp3 as a promising therapeutic target for type-2-diabetes treatment.

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**Human Resistin Stimulates Hepatic Overproduction of Atherogenic ApoB-Containing Lipoprotein Particles by Enhancing ApoB Stability and Impairing Intracellular Insulin Signaling; Costandi et al**

**What Is Known?**

- Serum levels of the adipose tissue secreted signaling protein resistin are elevated in obese humans compared with lean healthy individuals.
- Elevated levels of resistin in humans are highly correlated with development of cardiovascular diseases (CVD), including coronary atherosclerosis.
- Although CVD risk factors, including insulin resistance and inflammation, develop in response to elevated resistin in multiple mouse models, translation of mouse data to humans has been difficult, possibly because of the low identity between the human and mouse forms of resistin. Hence, the link between resistin and CVD in humans has remained unclear.

**What New Information Does This Article Contribute?**

- We show for the first time a direct causal role of human resistin in elevating serum apolipoprotein (apo)B-containing lipoproteins (including very-low-density lipoproteins), a major CVD risk factor.
- We identify the cellular mechanisms by which human resistin stimulates hepatic overproduction of apoB-containing lipoproteins, which include enhancing hepatocyte apoB protein stability and reducing hepatocyte insulin signal transduction.

**Conclusions**

Resistin has a direct deleterious impact on human hepatic lipid and lipoprotein regulation. Resistin greatly increased hepatocyte VLDL apoB and lipid secretion because of MTP activation and induction of hepatocyte insulin resistance. Conversely, antibody removal of serum resistin ameliorated human serum stimulation of apoB secretion. Increased hepatic
cellular lipids mediated by resistin reflects the fatty liver/steatosis observed with elevated resistin in humans. Thus, human resistin is a novel therapeutic target for mitigating common hepatic pathophysiological processes associated with human obesity, dyslipidemia and atherosclerosis.

ATP Production Rate via Creatine Kinase or ATP Synthase In Vivo: A Novel Superfast Magnetization Saturation Transfer Method; Xiong et al

**What Is Known?**
- The mechanisms and relationships between the alterations of myocardial creatine kinase (CK) and left ventricular (LV) contractile dysfunction in failing heart remain undefined.
- Although the 31P MR-based magnetization saturation transfer (MST) can measure the activity of the 2 most important energetic enzymes: CK and ATP synthase (ATPase), the conventional MST technique suffers from the lengthy acquisition time such that an in vivo transmurally differentiated enzyme activity measurement could not be obtained in the in vivo failing hearts.

**What New Information Does This Article Contribute?**
- A novel MST method was established theoretically with mathematical and numeric simulation and was verified with in vivo measurements of CK activity of swine hearts, as well as CK and ATPase activities of rat brain at 9.4 Tesla magnetic field.
- This novel MST method enables in vivo transmural differentiation studies to examine the CK activity with an unprecedented short data acquisition time.
- The in vivo swine study demonstrates that the acute inhibition of CK activity does not limit LV chamber function, suggesting that redundant multiple supporting systems of myocardial ATP production, transportation, and utilization exist in the heart.

**Conclusions**
A novel MST method for superfast examination of enzyme kinetics in vivo has been developed and verified theoretically and experimentally. In the in vivo normal heart, redundant multiple supporting systems of myocardial ATP production, transportation, and utilization exist that inhibit one mechanism does not impair the normal left ventricular contractile performance.

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**Redox Regulation of Soluble Epoxide Hydrolase by 15-Deoxy-Δ2-Prostaglandin J2 Controls Coronary Hypoxic Vasodilation; Charles et al**

**What Is Known?**
- 15-Deoxy-Δ2-prostaglandin (15d-PG)J2 is a cytoprotective lipid prostaglandin with chemical properties that allow it to couple to, and potentially regulate the function of, proteins.
- Pharmacological inhibition of soluble Epoxide Hydrolase (sEH), an enzyme that metabolizes epoxyeicosatrienoic acids, is broadly protective in models of cardiovascular disease.

**What New Information Does This Article Contribute?**
- 15d-PGJ2 covalently couples to sEH to inhibit the degradation of epoxyeicosatrienoic acids causing their accumulation.
- This inhibitory mechanism has a rational structural basis, as 15d-PGJ2 adduction occurs at a highly conserved amino acid (cysteine 521) adjacent to the known catalytic center of the hydrolase.
- This new inhibitory mechanism occurs in coronary vessels during hypoxia and contributes to the fundamental response of hypoxic vasodilation.

**Conclusions**
This represents a new paradigm for the regulation of sEH by an endogenous lipid, which is integral to the fundamental physiological response of coronary hypoxic vasodilation.

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**Tissue Kallikrein Is Essential for Invasive Capacity of Circulating Proangiogenic Cells; Spinetti et al**

**What Is Known?**
- Proangiogenic cells contribute to extracellular matrix remodeling during tissue healing. This mechanism is impaired by diabetes.
• Kinin is a potent chemoattractant for circulating leukocytes and proangiogenic cells.

What New Information Does This Article Contribute?

• Distinct subpopulations of circulating mononuclear cells, including CD34pos cells and CD16pos/CD14low monocytes, express kallikrein, a kinin-generating enzyme.
• Gene titration studies indicate that kallikrein levels are relevant for migration, invasion, and promotion of endothelial network formation activities of human proangiogenic cells.
• Enhancement of proangiogenic cell activities by kallikrein overexpression implicates a mechanism encompassing the kinin B2 receptor, phosphoinositide 3-kinase (PI3K), Akt, and inducible nitric oxide synthase (iNOS).
• Proangiogenic cells that express an enzymatically inactive polymorphic variant of the kallikrein gene or an epigenetically modified version of the wild-type gene are defective in their invasive capacity.
• Functionally defective diabetic proangiogenic cells are rescued by combined transfer of kallikrein and kinin B2 receptor genes.

Conclusions

This study reveals new interactive components of the PACs invasive machinery, acting via protease- and kinin receptor-dependent mechanisms.

Oxidation-Specific Epitopes Are Danger-Associated Molecular Patterns Recognized by Pattern Recognition Receptors of Innate Immunity [Review]; Miller et al

Abstract

Oxidation reactions are vital parts of metabolism and signal transduction. However, they also produce reactive oxygen species, which damage lipids, proteins and DNA, generating “oxidation-specific” epitopes. In this review, we discuss the hypothesis that such common oxidation-specific epitopes are a major target of innate immunity, recognized by a variety of “pattern recognition receptors” (PRRs). By analogy with microbial “pathogen-associated molecular patterns” (PAMPs), we postulate that host-derived, oxidation-specific epitopes can be considered to represent “danger (or damage)-associated molecular patterns” (DAMPs). We also argue that oxidation-specific epitopes present on apoptotic cells and their cellular debris provided the primary evolutionary pressure for the selection of such PRRs. Furthermore, because many PAMPs on microbes share molecular identity and/or mimicry with oxidation-specific epitopes, such PAMPs provide a strong secondary selecting pressure for the same set of oxidation-specific PRRs as well. Because lipid peroxidation is ubiquitous and a major component of the inflammatory state associated with atherosclerosis, the understanding that oxidation-specific epitopes are DAMPs, and thus the target of multiple arcs of innate immunity, provides novel insights into the pathogenesis of atherosclerosis. As examples, we show that both cellular and soluble PRRs, such as CD36, toll-like receptor-4, natural antibodies, and C-reactive protein recognize common oxidation-specific DAMPs, such as oxidized phospholipids and oxidized cholesterol esters, and mediate a variety of immune responses, from expression of proinflammatory genes to excessive intracellular lipoprotein accumulation to atheroprotective humoral immunity. These insights may lead to improved understanding of inflammation and atherogenesis and suggest new approaches to diagnosis and therapy.

References


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