Published in final edited form as:

Endocrinol Metab Clin North Am. 2008 September ; 37(3): 603–viii. doi:10.1016/j.ecl.2008.05.001.

Insulin Resistance and Atherosclerosis

Babak Razani, MD, PhD^a, Manu V. Chakravarthy, MD, PhD^b, and Clay F. Semenkovich, MD^c

aFellow in Cardiovascular Medicine, Cardiovascular Division, Department of Medicine, Washington University School of Medicine

bInstructor in Medicine, Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, Washington University School of Medicine

cHerbert S. Gasser Professor and Chief, Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, Washington University School of Medicine

Synopsis

Insulin resistance characterizes type 2 diabetes and the metabolic syndrome, disorders associated with an increased risk of death due to macrovascular disease. In the past few decades, research from both the basic science and clinical arenas has enabled evidenced-based use of therapeutic modalities such as statins and angiotensin converting enzyme inhibitors to reduce cardiovascular (CV) mortality in insulin resistant patients. Recently, promising drugs such as the thiazolidinediones have come under scrutiny for possible deleterious CV effects. Ongoing research has broadened our understanding of the pathophysiology of atherosclerosis, implicating detrimental effects of inflammation and the cellular stress response on the vasculature. In this review, we address current thinking that is shaping our molecular understanding of insulin resistance and atherosclerosis.

Keywords

insulin resistance; metabolic syndrome; atherosclerosis; cardiovascular disease; inflammation; cellular stress

Introduction

The term “insulin resistance” has existed in the medical vernacular nearly as long as the clinical use of insulin itself. In fact, the first report of a patient resistant to the effects of insulin was published in 1924, only two years after 14-year old Leonard Thompson became the first human to be successfully treated with insulin ^{1, 2}. Although the early medical literature is replete with such examples, the etiology of this resistance was imprecise purification, varied absorption, and immune-mediated clearance of impure/canine insulin. In the modern era, insulin resistance most commonly denotes a condition in which there is an insufficient peripheral (e.g. muscle, liver, and adipose) tissue response to a given quantity of insulin. The progression of such a

cCorresponding author for proof and reprints: Clay F. Semenkovich, MD Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, Washington University School of Medicine, Campus Box 8127, 660 South Euclid Avenue, St. Louis, Missouri 63110, (314) 362-7617, (314) 362-7641 (fax), csemenko@wustl.edu.

^{a,b}Coauthor addresses and phone numbers are the same as corresponding author, Babak Razani, MD, PhD, brazani@im.wustl.edu, Manu V. Chakravarthy, MD, PhD, mchakrav@im.wustl.edu

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subnormal response is usually insidious, with affected individuals living subclinically for years with glucose levels nearly normal due to hypersecretion of insulin. In the subset of individuals with both chronic insulin resistance and pancreatic beta cell failure, glucose levels become sufficiently elevated to fulfill the diagnostic criteria for type 2 diabetes mellitus, the end-stage of the insulin resistance spectrum.

Although impaired glucose tolerance and hyperglycemia are classical manifestations of insulin resistance and type 2 diabetes, many patients present with several associated signs and laboratory abnormalities (i.e. abdominal obesity, elevated blood pressure, elevated triglycerides, and low HDL cholesterol). Insulin resistance is thought to play a role in the association of these metabolic phenotypes; indeed, such clustering of phenotypes has been termed the insulin resistance syndrome or the metabolic syndrome. The National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) and the World Health Organization (WHO) have rigorously defined the components of the metabolic syndrome in recently published/updated criteria³⁻⁵.

One of the most devastating complications of long-standing insulin resistance and its associated metabolic derangements is progressive macrovascular pathology (namely atherosclerosis). Atherosclerosis remains the major cause of morbidity and mortality among diabetic patients. Diabetics have higher rates of coronary artery disease (CAD) and myocardial infarctions (MIs) than non-diabetic patients with similar risk factor profiles⁶⁻⁸. Diabetics without a prior MI have a similar mortality risk to non-diabetics with a prior MI^{6,9}. Revealing results from such large studies prompted the most recent ATPIII guidelines to designate diabetes as a coronary disease equivalent³.

Although hyperglycemia is a hallmark of diabetes, it is not clear that elevated glucose levels alone contribute in a major way to cardiovascular disease (CVD) progression. Indeed, diabetic patients without the metabolic syndrome have less CVD than non-diabetics with the metabolic syndrome¹⁰. It is becoming increasingly clear that metabolic derangements associated with insulin resistance are important contributors to atherogenesis (Figure 1). Regardless of which criteria are used to define this syndrome, afflicted patients are at approximately 2-to-4-fold increased risk for CVD mortality¹¹. Furthermore, there is a graded risk depending on the number of risk factors present¹².

The wealth of evidence in the past few decades points to a striking relation between insulin resistance and atherosclerosis. With this background, the goal of this review is three-fold: (1) to provide an overview of the currently utilized treatment strategies to reduce CVD mortality in insulin resistant patients, (2) to establish a framework for further defining the role of insulin resistance in vascular disease, and (3) to summarize preclinical data that may lead to future therapeutics.

Prevention of CVD in Insulin Resistance (Current Approaches)

Current primary prevention treatment modalities in patients with the metabolic syndrome and/or diabetes rely on risk factor modification (i.e. reduction of hyperlipidemia, hypertension, obesity, and lifestyle changes). Although beyond the focus of this review, a few treatment options are especially worthy of mention. Beginning in the 1990s, large clinical trials demonstrated the enormous clinical utility of two classes of drugs, statins and angiotensin-converting enzyme inhibitors (ACEi) /angiotensin receptor blockers (ARB), in diminishing the cardiovascular morbidity and mortality of insulin resistant/diabetic patients.

The first large secondary prevention (i.e. patients with a prior MI) trial to demonstrate the CV benefits of statins (in this case simvastatin) was the 4S trial¹³. This was followed by WOSCOPS, the first large primary prevention trial to demonstrate statin benefits in patients

with no known CVD but including many with metabolic profiles resembling incipient insulin resistance¹⁴. These findings have been corroborated by numerous other trials showing the utility of statins as a class in different patient subgroups. One of the most surprising statin trials was the Heart Protection Study, a comparison of simvastatin versus placebo in a cohort of approximately 20,000 patients with known CVD or DM¹⁵. In addition to showing similar CV mortality benefits as prior studies, this trial also clearly demonstrated that patients with the lowest category of LDL cholesterol levels (<116 mg/dl) derived benefits from statin therapy that was comparable to benefits in statin-treated hypercholesterolemic patients. In this regard, there is accumulating evidence that statins are more than simply cholesterol-lowering agents, having beneficial effects on endothelial dysfunction, inflammation, and the coagulation cascade as well as platelet function (reviewed in¹⁶).

It has been known for some time that inhibition of the renin-angiotensin system is critical for reducing CV mortality and improving cardiac function in patients with left ventricular dysfunction/ischemic cardiomyopathy^{17, 18}. What remained unclear was whether ACEi and ARBs would be effective in patients with high risk features (including known vascular disease and diabetes) without overt heart failure. The HOPE and LIFE trials were two large randomized studies designed to address the effectiveness of the ACEi ramipril and the ARB losartan, respectively, in such patients^{19, 20}. The significant decrease in CV mortality observed with treatment in these trials has elevated this class of drugs to first-line agents in the treatment of hypertension in diabetics, even in the absence of heart failure.

Is Modulation of Insulin Resistance Beneficial for CVD Prevention?

As described above, the classical approach to the treatment of insulin resistance and diabetes is risk-factor modification (i.e. directed treatment of the most skewed parameters of the disorders). Despite clear successes with this approach, it represents a reaction to long-standing metabolic derangements rather than treatment for a potentially unifying process, such as insulin resistance. Thiazolidinediones are a class of drugs known to improve insulin resistance that were found to act by binding to Peroxisome-Proliferator-Activated Receptor gamma (PPAR γ), a discovery providing a new mechanistic approach to diabetes treatment²¹. PPARs are ligand-activated nuclear receptors of which PPAR γ is one subtype. As PPAR γ is highly expressed in adipose tissue where it is involved in lipid homeostasis (especially fatty acid uptake/storage), it stood to reason its activation might enhance insulin-sensitivity by directing toxic free fatty away from other insulin-dependent organs and into adipose tissue. This hypothesis was supported by some studies in humans focusing on glucose metabolism. Although troglitazone, the first thiazolidinedione to be approved for clinical use, was withdrawn due to hepatotoxicity, the continued success of other members of this class of drugs, rosiglitazone and pioglitazone, was heralded by some as a revolution in diabetes and insulin resistance management²².

Although not supported by disease-related outcome data, the use of thiazolidinediones in diabetic subjects was expected to not only improve surrogate end-points such as glycemic control but also end-points such as macrovascular events. The utility of these agents came under scrutiny when a meta-analysis of rosiglitazone trials showed increased CV mortality²³. Although pioglitazone fared better in the 5000+-patient PROACTIVE trial (non-significant reduction in CV events)²⁴ and a followup meta-analysis (a statistically significant decrease in death, MI, and strokes)²⁵, concerns over the lack of prospective outcomes data with thiazolidinediones and the known increased risk of volume overload/heart failure with these drugs²⁶ have raised doubts about this class of therapeutic agents.

Despite the current controversy about thiazolidinediones, an understanding of the molecular underpinnings driving insulin resistance and their relation to atherosclerosis is pivotal in the

development of rational drug design. There are several aspects of insulin resistance that are actively being pursued in hopes of better understanding atherosclerotic events.

Insulin Resistance and Proatherogenic Lipids

Despite the traditional focus on LDL and CVD risk, a portion of the connection between blunted insulin signaling, abnormal lipid metabolism, and atherosclerosis appears to be mediated by aberrations in triglyceride/VLDL and HDL levels instead of LDL²⁷. Derangements in adipocyte and hepatocyte function play a central role in these abnormalities^{28, 29}.

Insulin resistance reduces the ability of adipose tissue to clear/store circulating lipids, in part because of reduced lipoprotein lipase enzyme activity. Abnormal adipocyte insulin signaling also results in inappropriate lipolysis even during times of nutrient excess. The result is paradoxical elevations in serum triglycerides as well as circulating free fatty acids (FFA). In conjunction with elevations in apolipoprotein B (apoB) (thought to be due to posttranslational stabilization of the protein) and enhanced lipogenesis by the liver, increases in apoB-containing/ triglyceride-rich lipids (primarily present as VLDL particles) are a hallmark of patients with insulin resistance^{30, 31}.

Several trials have demonstrated the CV risks associated with the hypertriglyceridemia of insulin resistance. Hypertriglyceridemia has the strongest correlation with CVD among the five components of the metabolic syndrome³². Although the significance of fasting triglycerides (as an independent factor) with respect to CV events has been a matter of debate²⁷, elevated nonfasting triglycerides, a state classically associated with insulin resistance as described above, significantly elevates CV mortality risk^{33, 34}.

Insulin resistance can also have adverse consequences on LDL and HDL metabolism. Although elevations in LDL cholesterol levels are not a hallmark of insulin resistance/diabetes, the composition and possibly proatherogenic function of LDL is affected. The hypertriglyceridemia/VLDL excess brought on by insulin resistance expedites cholesteryl ester transfer protein (CETP)-mediated exchange of LDL cholesteryl ester for VLDL triglyceride. In turn, the newly acquired LDL triglyceride undergoes lipolysis by hepatic and lipoprotein lipase, resulting in LDL particles that are smaller in size, more dense, and depleted of their usual cholesteryl ester content^{35, 36}. A similar mechanism involving CETP-mediated exchange of lipids also occurs between VLDL and HDL; however, in addition to the eventual creation of small/dense particles, HDL clearance is also enhanced with the end result being low levels of dysfunctional HDL particles^{37, 38}.

The Role of Insulin Resistance in Inflammatory Signaling and Atherosclerosis

An obvious connection between insulin resistance and atherosclerosis is derived from observations that obesity and insulin resistance often occur in concert with significant increases in inflammatory mediators^{39, 40}. Atherosclerosis acts in many ways like an inflammatory condition with prominent cellular infiltration and robust cytokine expression⁴¹. One of the first links between obesity, insulin resistance, and inflammation was the demonstration that mouse adipose tissue can produce TNF α , its production is proportional to the degree of obesity, and neutralization of the TNF-receptor can significantly decrease obesity-induced insulin resistance⁴². Numerous subsequent studies have debunked the initial view of the adipocyte as a stagnant lipid storage entity; adipose tissue is now known to be an active secretory organ, dynamically producing a variety of pro-inflammatory mediators such as TNF α , IL-1, IL-6, MCP-1, and PAI-1, factors traditionally associated with inflammatory cells⁴³. Similar to TNF α the production of these “adipokines” is a function of the health of the tissue and under conditions of nutrient excess, obesity, and progressive insulin resistance, there is substantial proinflammatory adipokine production^{44–48}. A substantial body of work has shown that these

inflammatory mediators perpetuate the insulin resistance phenotype and result in deleterious effects on the vasculature (reviewed in ⁴³). A detailed review of the effects of proatherogenic signaling including the role of protein kinase C (PKC) has recently appeared ⁴⁹, but two of the major pathways likely to be clinically relevant to vascular disease in insulin resistance involve the Nuclear Factor kappa B (NF- κ B) and c-Jun N-terminal kinase (JNK) cascades.

NF- κ B Signaling and Atherogenesis

A central mediator of inflammatory signaling in the vasculature of an insulin resistance individual is the NF- κ B family of nuclear transcription factors (Figure 2). The classical and most prominent member of this family is a heterodimer of the p65/RelA and p50 proteins. In the cytoplasm, this dimer is bound to I κ B proteins in an inactive state ⁵⁰. The arrival of extracellular signals (including several of the cytokines described above including TNF α and IL-1), stimulates the membrane-associated I κ B kinase (IKK) to serine-phosphorylate I κ B, thus facilitating its proteasomal degradation and liberating NF- κ B to undergo nuclear translocation and set into motion a potent feed-forward production of pro-inflammatory transcripts ^{51, 52}. A global survey of such NF- κ B targets, as has been performed by both individual target gene assessment and more broad expression profiling approaches, reveals striking proatherogenic features. Broad categories include mononuclear cell chemoattractants, vascular adhesion molecules, mediators of chemotaxis, inducers of the monocyte to macrophage differentiation program, stimulators of smooth muscle cell proliferation, angiogenic factors, and amplification of proteases involved in the breakdown of the intercellular matrix, spanning the entire gamut of mediators required for plaque formation, progression, and destabilization ⁵³.

Although the potential for cytokine-mediated vascular damage is evident, attempts at studying the NF- κ B pathway with mouse models have produced contradictory results. For example, genetic targeting of p55, one of two TNF α receptors and the predominant mediator of inflammation actually protects mice against atherosclerosis ⁵⁴. Furthermore, a partial macrophage-specific deletion of IKK2 leading to ~50% reduction in NF- κ B activation increases the extent and the complexity of atherosclerotic lesions in mice ⁵⁵ while bone marrow reconstitution experiments with NF- κ B1-null macrophages in mice fed a high fat diet leads to decreased atheromatous plaque formation but an increased cellular infiltration ⁵⁶. These confounding results point to the tremendous complexity of the inflammatory response and our current inability to tease out such nuances with available technologies.

JNK signaling and Atherosclerosis

JNK is a member of the mitogen-activated protein (MAP) kinase family (which also includes extracellular signal-related kinase (ERK1/2), big MAP kinase (BMK1), and p38 MAP kinase) (reviewed in ⁵⁷). Although these serine/threonine kinases are responsive to a variety of stimuli, JNK signaling is potently activated by mediators of inflammatory and stress responses including cytokines and environmental stresses. Upon activation, JNK can phosphorylate a host of transcription factors, including the one for which it is named (c-Jun component of the AP-1 transcription factor) thereby triggering robust gene expression. Similar to NF- κ B signaling, cytokine-induced JNK signaling fuels a feed-forward cycle of proinflammatory/proatherogenic factor production including TNF α , IL-2, matrix metalloproteinases, and adhesion molecules ^{58–60}.

Initial data suggesting a role for JNK in atherosclerosis were based on observations that the macrophages and smooth muscle cells of human and animal model atheromatous plaques had prominently activated JNK signaling ^{61, 62}. Further evidence was provided by Ricci *et al.* by creating mice with macrophage-specific ablation of two of the JNK family members, JNK1 and JNK2, in an ApoE-null background ⁶³. Interestingly, only the JNK2(–/–) mice had

significantly reduced atherosclerotic burden; this was due to defective foam cell formation proposed to occur via reduced uptake of modified LDL.

Direct Effects of Insulin Resistance on the Vasculature and Atherogenesis

One of the early events in the pathophysiology of atherosclerosis appears to be endothelial dysfunction, a state of blunted vasodilatory capacity and reduced ability to protect against platelet aggregation, blood cell adhesion, and smooth muscle proliferation. A pivotal factor involved in vascular health is nitric oxide (NO), which is dynamically controlled by signaling processes^{64, 65}. As patients with either the metabolic syndrome or diabetes have impaired NO-mediated vasodilation^{66–68}, insulin resistance may have direct pathogenic effects on the vasculature. Insulin is a major stimulus for NO-mediated vasodilation⁶⁹.

In many tissues including the vasculature, insulin effects can be generally divided into two pathways, involving either PI-3-kinase/Akt or MAP kinase signaling. Upon ligand binding, the insulin receptor activates a signaling cascade involving insulin receptor substrate (IRS) adapter molecules, PI-3-kinase, and Akt, subsequently leading in the endothelium to the phosphorylation/activation of eNOS, a process independent of classical calcium-based eNOS signaling^{70, 71}. In contradistinction, the growth factor functions of insulin occur via its MAP kinase-dependent arm and are more involved with cellular migration, vascular smooth muscle cell proliferation, and prothrombotic states⁷². During insulin resistant states, there is a selective disruption of vascular PI-3-kinase/Akt-mediated signaling; interestingly, insulin-mediated MAP kinase signaling continues unabated^{73, 74} and can even further blunt PI-3-kinase signaling by serine-phosphorylation of IRS-1⁷⁵. Thus, the development of insulin resistance and compensatory hyperinsulinemia can progressively shift the balance of insulin signaling toward a mitogenic state that may contribute to atherosclerosis (Figure 2).

Are the Direct Effects of Insulin Resistance Always Pro-Atherogenic or Can Insulin Resistance Play a Paradoxical Protective Role?

As discussed above, the direct effects of insulin on the vasculature implicate insulin resistance in vascular/endothelial dysfunction. However, it should be noted that there are limited data extending this connection to atherosclerosis; regardless of the experimental system, most published studies use NO-mediated vascular reactivity/signaling as endpoints rather than more direct ones such as plaque formation/atherosclerotic burden. When one highlights studies assessing the role of insulin signaling in atherogenesis, several interesting observations arise.

ApoE-null mice with selective inactivation of the insulin receptor (IR) in the myeloid lineage have smaller atherosclerotic lesions⁷⁶. In a different approach, bone marrow transplantation of LDLR-null mice with insulin receptor-deficient cells did not affect the number of lesions but created more complex/necrotic lesions⁷⁷. Although whole-animal IRS-2 null mice on an ApoE-null background have increased plaque burden, repopulation of the hematopoietic system of lethally-irradiated ApoE-null mice with IRS-2(–/–) cells mitigates the atherosclerotic phenotype⁷⁶. Deletion of the PI-3-kinase p110 γ gene in mice, which in contrast to the PI-3-kinase p110 α and p110 β genes is predominantly expressed in hematopoietic and muscle cells, leads to diminished atherosclerosis⁷⁸. These observations highlight the complexity of insulin signaling at the level of the vasculature and demonstrate the potential disparity between systemic insulin resistance and its direct effects on the forming atherosclerotic lesion.

Emerging Themes: The Concept of “Protective Macrophages” in Insulin Resistance and Atherosclerosis

The discovery of adipose tissue as a secretory organ, capable of producing inflammatory markers especially in states of nutrient excess/obesity was an important step in understanding the initiation of insulin resistance. In the past few years, this concept has been advanced and refined by implicating specific cellular events in the obesity-insulin resistance link. Immunohistochemical analysis of obesity-induced pathological changes reveals a progressive accumulation of bone-marrow derived macrophages in the adipose tissue matrix over time^{79, 80}. These macrophages are the predominant source of adipose tissue TNF α production and a significant contributor to the production of IL-6 as well several other inflammatory markers⁸⁰. Additionally, this macrophage infiltration is observed before overt manifestations of insulin resistance as determined by compensatory increases in insulin levels⁷⁹.

It has been known for some time that macrophages are present in numerous tissues even under normal noninflammatory conditions⁸¹. These resident macrophages are phenotypically different from the more familiar “classically activated”/M1-macrophages (i.e. those elicited during acute inflammatory responses) and thus are termed “alternatively activated” or M2-macrophages. Whereas M1 macrophages are activated under inflammatory settings and express numerous proinflammatory markers, M2 macrophages are activated by different stimuli (e.g. IL-4 and IL-13) and actually produce anti-inflammatory mediators (e.g. IL-10 and IL-1 Receptor Antagonist) that are involved in tissue healing/remodeling and seem to oppose the effects of their M1 counterparts^{82, 83}. Interestingly, these observations were recently highlighted in adipose tissue. On a normal diet, the adipose tissue of lean mice is populated with “alternatively activated” macrophages, whereas diet-induced obesity produces a shift toward the M1 phenotype⁸⁴. Curiously, this shift is abrogated in obese C-C motif chemokine receptor-2 (CCR2)-null mice, suggesting that loss of this monocyte chemoattractant receptor presumably disables the robust recruitment of proinflammatory macrophages⁸⁴. This finding extends previous data showing the protective effect of MCP-1 and CCR-2 KO mice in diet-induced insulin resistance^{85, 86}.

Recently, Odegaard, *et al.* provided mechanistic insight into this phenotypic switch by demonstrating that PPAR γ is required for the presence and maturation of alternatively activated macrophages in adipose tissue⁸⁷. Furthermore, their macrophage-specific PPAR γ -KO mice were more prone to diet-induced obesity and insulin resistance⁸⁷. Using a similar gene targeting strategy, Hevener *et al.* provided a different perspective on macrophage-specific PPAR γ signaling, showing impaired hepatic and skeletal muscle insulin sensitivity, signaling, and lipid accumulation⁸⁸. Interestingly, the insulin-sensitizing effects of TZDs were only partially effective in these mice, indicating that macrophage PPAR γ signaling is at least partially required to achieve the full effects of TZDs on insulin sensitivity⁸⁸.

There is also evidence that alternatively activated macrophages may be involved in atherosclerosis⁸⁹. Both M1 and M2 markers are present in human atherosclerotic plaques and are produced by distinct pools of mononuclear cells in these plaques. Also, PPAR γ activators such as TZDs are able to drive the differentiation of monocytes into an M2 phenotype, although they are neither able to increase plaque M2 markers nor able to cause a switch of M1 cells to an M2 phenotype⁸⁹. Given the ability of macrophages to take on diametrically opposite fates, the prospect of harnessing such an ability to mitigate proatherogenic states is exciting. Another direct link between macrophages, adipocytes, and inflammation has recently emerged in the form of the adipocyte binding protein aP2 (also known as FABP4). Chemically inhibiting the function of aP2, a protein expressed in macrophages in addition to adipocytes, can suppress inflammatory pathways, decrease atherosclerosis, and treat type 2 diabetes in mice⁹⁰.

Insulin Resistance, Oxidative/Mitochondrial Stress, and Atherosclerosis

Mitochondria are the major source of ATP production by harboring both the enzymes of the tricyclic acid cycle and oxidative phosphorylation. The continuous flow of electrons from complex I through IV of the electron transport chain and pumping of protons through the inner mitochondrial membrane is contingent on steady-state nutrient delivery. In cases of nutrient excess, the surplus of effluxed protons leads to slowed electron transport chain kinetics and augmentation of alternative electron accepting mechanisms⁹¹. Enhanced production of reactive oxygen species (ROS) such as superoxide is a direct by-product of this process and a contributing factor to vascular dysfunction in insulin resistance (Figure 2)⁹².

As the predominant site of ROS production, the mitochondrion is a susceptible target for oxidative damage and several lines of evidence point to mitochondrial dysfunction in promoting atherogenesis. Studies in cell culture and rodent models show that increased free fatty acid oxidation in aortic endothelium induces enhanced mitochondrial superoxide generation and inactivation of anti-atherogenic factors (e.g. eNOS and prostacyclin synthase); direct inhibition of carnitine palmitoyl transferase I (the rate-limiting mitochondrial enzyme in fatty acid oxidation) reverses this effect⁹³. Atherosclerotic lesions from patients undergoing vascular surgery and those from ApoE-null mice show increased mitochondrial DNA damage; this process is observed even in young mice before the overt development of atherosclerotic plaques⁹⁴. Additionally, superoxide dismutase heterozygous-null mice (SOD2+/-) in the ApoE(-/-) background have accelerated atherosclerosis⁹⁴. In this regard, the fact that mitochondria lack a robust mismatch repair system might make mitochondrial DNA especially susceptible to ROS damage and mitochondrial dysfunction⁹⁵.

Another feature of mitochondrial bioenergetics relevant to atherosclerosis is the observed heterogeneity of metabolism in the vasculature (i.e. different areas of an arterial wall have varied ATP-generating efficiency probably due to variable uncoupling of respiration and oxidative phosphorylation)⁹⁶. Differences in adequate oxygen delivery to medium and large-size arteries have been proposed to underlie this heterogeneity^{96, 97}. Intriguingly, although respiratory uncoupling seems to occur in all blood vessels, it is increased in the aorta of atheroma-prone pigeons⁹⁸. Also, a dearth of essential fatty acids, a marker of atherosclerotic lesions, heightens respiratory uncoupling^{99, 100}.

The uncoupling proteins are a family of transporters found in the inner mitochondrial membrane which dissipate the mitochondrial proton-motive force by allowing protons back into the mitochondrial matrix¹⁰¹. In a direct test of the relationship between respiratory uncoupling and vascular dysfunction, Bernal-Mizrachi *et al.* created smooth-muscle transgenic mice overexpressing UCP1¹⁰²; the choice of smooth muscle cells as the site of uncoupling was based on smooth muscle being a major site for ROS production⁹¹. These “uncoupled” mice showed significant signs of vascular dysfunction with overt hypertension and when in an ApoE-null background, increased atherosclerosis¹⁰². Furthermore, superoxide production was elevated and NO availability was decreased.

Taken together, adiposity and insulin resistance create a state of nutrient excess, skewing normally functioning mitochondrial bioenergetics into excess ROS production and by respiratory uncoupling mechanisms, inefficient generation of ATP; the result is vascular dysfunction and a proatherogenic state. In this regard, it is interesting to note that caloric restriction can induce mitochondrial biogenesis, decrease ROS, and lead to more efficient ATP production^{103, 104}.

Insulin Resistance, Genomic Stress, and Atherosclerosis

Damage to mitochondrial DNA is not the only consequence of excessive production of ROS; the nuclear genome is also susceptible to damage and alterations of relevant genes involved in DNA repair and stress response contribute to insulin resistance, vascular dysfunction, and atherosclerosis (reviewed in ¹⁰⁵). Patients with established CAD and diabetes have increased markers of genomic instability and oxidative DNA damage in peripheral blood mononuclear cells ^{106, 107}. FISH analysis of human carotid endarterectomy (CEA) plaques shows chromosomal instability with polyploidy and deletions ^{108, 109}. Markers of oxidative DNA damage such as 8-oxo-deoxyguanosine (8-oxo-dG) are elevated in CEA specimens and this is accompanied by overexpression of several DNA repair proteins ¹¹⁰. Similarly, diet-induced atherosclerotic plaques in rabbits show increased 8-oxo-dG, DNA strand breaks, and DNA repair enzymes; these markers of DNA damage are significantly but not entirely reversed with normalization of the diet ¹¹¹.

These data suggesting a causal link between DNA damage and atherosclerosis are corroborated by the phenotypes of several accelerated aging and/or DNA damage disorders ¹¹². Werner syndrome occurs due to mutations in the WRN gene, encoding a DNA helicase with several functions in DNA replication and repair ¹¹³. In addition to premature aging, Werner patients develop insulin resistance, atherosclerosis, and valvular heart disease ^{112, 114}, a phenotype that is partially recapitulated in a mouse model of the disease ¹¹⁵. Patients with Hutchinson-Gilford Progeria syndrome (HGPS), the prototypical accelerated aging syndrome, also develop insulin resistance and premature atherosclerosis but at even earlier time points than Werner patients and often succumb to MI or strokes by their early teenage years ^{116, 117}. HGPS is caused by mutations in the Lamin A gene, encoding proteins essential for the integrity of the nuclear lamina/nuclear membrane ¹¹⁷. The disruption of nuclear lamina is not solely structural and is now known to affect transcriptional regulation, genomic stability, and DNA repair. Recent data show that HGPS patients accumulate a farnesylated precursor of Lamin A that likely imparts genomic instability by impairing formation of DNA repair foci ^{118, 119}. A farnesyltransferase inhibitor can reverse many of the structural and phenotypic abnormalities of a mouse model of HGPS ¹²⁰. As statins are also inhibitors of the pathway important for farnesylation, this raises the intriguing possibility that part of the non-lipid mediated effects of statins are directed at enhancing genomic stability. Another relevant human disease is Ataxia-Telangiectasia (AT), caused by mutations in ATM, a protein kinase with central roles in the response to DNA damage ¹²¹. In addition to progressive ataxia and significant predisposition to cancers, many AT patients also develop insulin resistance ^{122, 123}. Although AT patients die early from a variety of cancers (median age of death 20) ¹²⁴, carriers of ATM mutations (estimated to comprise 1.4–2% of the population) have higher CV mortality ¹²⁵. In support of a direct pathogenic role for ATM in metabolic and vascular regulation, ATM-null mice in an ApoE-null background indeed develop insulin resistance and accelerated atherosclerosis ¹²⁶. Chloroquine, used to treat malaria but also a known activator of ATM, was able to protect against atherosclerosis and many of the metabolic effects of diet-induced insulin resistance in mouse models ¹²⁶.

Summary

The metabolic syndrome and diabetes are in large part varied manifestations of an underlying process known as insulin resistance. Normally insulin sensitive metabolic organs develop a progressive inability to respond to this signal with resultant metabolic derangements. Cardiovascular disease is associated with insulin resistant states, although the presence of a myriad of insulin signaling pathways potentially affecting vascular function precludes a simple explanation for this association. Treatment of insulin resistant patients with drugs such as statins, ACEi, and ARBs can yield profound improvements in CV mortality. The development

of insulin sensitizers such as the thiazolidinediones has been conceptually exciting, but recent data showing lack of/modest benefit or possibly even an increase in CV events combined with a propensity to exacerbate heart failure have dampened enthusiasm for this class of drugs.

Insulin resistant people tend to have increased adiposity, so novel strategies that exploit the relationship between adipocytes and the inflammatory process in the vasculature to treat atherosclerosis are attractive. Interfering with cellular stress pathways, including those that involve damage to mitochondria and the nuclear genome, may also prove to be useful in the quest for developing new approaches to treat atherosclerosis in people with insulin resistance.

Acknowledgements

This work was supported by Grants HL083762 and DK076729 from the National Institutes of Health.

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Figure 1. The Central Role of Insulin Resistance in Vascular Disease

Multiple environmental and genetic factors contribute to the formation of the insulin resistance phenotype (aka the “metabolic syndrome”), marked by hypertension, dyslipidemia, obesity, and glucose intolerance. These risk factors in turn contribute to initiation and progression of type 2 diabetes and the macrovascular diseases (i.e. myocardial infarctions, strokes, and peripheral vascular disease).

Figure 2. Critical Proatherogenic Signaling Events at the Vasculature in the Setting of Insulin Resistance

The secretion of proinflammatory mediators initiated by systemic insulin resistance stimulate several intracellular signaling cascades, of which NFκB and JNK (a member of the MAP kinase family) are prominent examples; these potent inducers of proinflammatory genes create a feedforward cycle of signaling that provokes several aspects of atherogenesis. In addition, insulin resistance also selectively interferes with PI-3-kinase-mediated insulin receptor signaling, in turn suppressing eNOS activity in favor of the proliferative/proatherogenic MAP kinases. Finally, states of nutrient excess dysregulate mitochondrial energy balance thus promoting respiratory uncoupling and the generation of reactive oxygen species (ROS); this can wreak havoc on the integrity of the genome and blunt vascular defenses against atherogenesis.