This Review is part of a thematic series on the Atherosclerosis in Diabetes: Dyslipidemia vs Hyperglycemia, which includes the following articles:

Do Glucose and Lipids Exert Independent Effects on Atherosclerotic Lesion Initiation or Progression to Advanced Plaques?

Recipes for Creating Animal Models of Diabetic Cardiovascular Disease

The Macrophage at the Crossroads of Insulin Resistance and Atherosclerosis

Lipids, glucose, and oxidative reactions in diabetes and atherosclerosis

Karin E. Bornfeldt, Guest Editor

The Macrophage at the Crossroads of Insulin Resistance and Atherosclerosis

Chien-Ping Liang, Seongah Han, Takafumi Senokuchi, Alan R. Tall

Abstract—The macrophage has emerged as an important player in the pathogenesis of both atherosclerosis and insulin resistance. Cross-talk between inflammatory macrophages and adipocytes may be involved in insulin resistance in peripheral tissues. Defective insulin signaling in cells of the arterial wall including macrophages may promote the development of atherosclerosis. Insulin resistant macrophages are more susceptible to endoplasmic reticulum stress and apoptosis in response to various stimuli such as nutrient deprivation, free cholesterol loading, and oxidized LDL. Increased apoptosis of insulin resistant macrophages and impaired phagocytic clearance of apoptotic cells by insulin resistant macrophages in atherosclerotic lesions may lead to enhanced postapoptotic necrosis, larger lipid-rich cores, increased inflammation, and more complex vulnerable plaques. (Circ Res. 2007;100:1546-1555.)

Key Words: atherosclerosis ■ insulin resistance ■ diabetes mellitus ■ macrophages ■ apoptosis

The risk of atherosclerotic cardiovascular disease is increased 2- to 3-fold in type 2 diabetes mellitus1 and metabolic syndrome.2 In type 2 diabetes both insulin resistance and hyperglycemia may promote atherosclerosis and its complications,3-5 while insulin resistance is likely a key underlying factor driving the complications of metabolic syndrome including atherosclerosis.6 Hyperinsulinemia is an independent risk factor for atherosclerosis in some but not all epidemiological studies.7,8 Because hyperinsulinemia is often associated with other risk factors such as dyslipidemia, it may be difficult to segregate out independent effects of insulin resistance in such studies. An alternative view to the central role of insulin resistance is that in obesity and metabolic syndrome an inflammatory reaction in adipose and blood vessels drives atherosclerosis and its complications.9 These are not mutually exclusive concepts as inflammation may induce insulin resistance,10,11 and as suggested below insulin resistance could lead to cellular events that provoke inflammatory responses.

Insulin resistance likely acts via dyslipidemia (increased VLDL and reduced HDL levels), hypertension, and a hypercoagulable state to accelerate atherosclerosis and its complications.3,12 Dyslipidemia reflects both peripheral insulin resistance and increased flux of fatty acids to the liver, as well as direct effects of insulin signaling in hepatocytes, leading to increased secretion of VLDL.12 The mechanisms of reduced HDL levels in metabolic syndrome are poorly understood but may in part reflect accelerated cholesteryl ester (CE) transfer...
protein–mediated transfer of CE from HDL to VLDL and consequent hypercatabolism of HDL particles. Insulin resistance in adipose tissue leads to increased synthesis of plasminogen activator inhibitor-1, contributing to a prothrombotic state. Vascular insulin resistance causes impaired nitric oxide–mediated arterial dilation and likely smooth muscle cell proliferation. In addition, recent results suggest that insulin resistance in macrophages may worsen atherosclerosis, and this will be the major topic of this review. These findings will also be examined in the context of a larger body of work implicating macrophage inflammatory responses in the induction of insulin resistance and atherosclerosis.

Insulin resistance is characterized both by hyperinsulinemia, as well as defective insulin signaling in a variety of different tissues. On a cellular level, hyperinsulinemia leads to increased degradation and reduced levels of insulin receptors (IRs; also named as CD220), and reduced levels of insulin receptor substrate proteins (IRSs) in various target tissues, such as liver, muscle, and vascular cells. Thus, defective insulin signaling in cells is the sine qua non of insulin resistance. Many of the complications of insulin resistance reflect defective insulin signaling in cells. In addition, there may be mixed features of both insulin resistance and insulin sensitivity within the same cell or there may be varied insulin resistance and sensitivity in different organs. A prominent example of the picture of mixed insulin sensitivity and resistance is the liver in obese (ob/ob) mice, where insulin resistance leads to increased nuclear activity of the forkhead transcription factor FOXO1 and increased expression of gluconeogenic genes, whereas increased insulin signaling induces SREBP1c, enhanced expression of lipogenic genes, and increased VLDL secretion. The mixed picture could reflect divergent pathways of insulin signaling or different thresholds for activation of lipogenic and gluconeogenic genes.

The Insulin Signaling Pathway and Its Role in Monocytes and Macrophages

Monocyte-macrophages in human and experimental animal models are known for a wide spectrum of distinct phenotype, possibly reflecting their stages of differentiation and the nature of tissue microenvironments. Although different macrophage populations have been recently described to enter adipose tissue in obesity or vascular lesions in atherosclerosis, the functional significance is unknown and the relationship to studies on insulin signaling is uncertain. Thus we use the general terms monocytes or macrophages for discussion in this review.

Insulin Signaling

In insulin-responsive tissues, insulin signaling networks exert metabolic effects and also play a pivotal role in normal growth and development. As an anabolic hormone, insulin enhances the synthesis and storage of carbohydrates, lipids, and proteins, and decreases degradation and release of these molecules from the tissues. At the cellular level, circulating insulin binds to its cognate receptor (IR) at the cell surface and activates its tyrosine kinase activity. This stimulates phosphorylation of receptor substrates and adaptor proteins, including IRS1/2, Gab-1, Cbl, Shc, and APS (adapter protein with a PH domain and an SH2 domain), on selected Tyr residues, thereby forming docking sites for further downstream effectors. There are two major pathways involved in insulin-mediated metabolic and growth activities: those initiated by phosphatidylinositol 3-kinase (PI3K) and those downstream of mitogen activated protein (MAP) kinase signaling. The PI3K pathway is the main pathway mediating metabolic effects of insulin. Tyr-phosphorylated IRSs recruit and interact with the regulatory p85 subunit of PI3K, resulting in synthesis of phosphatidylinositol 3,4,5-phosphate (PIP3) by the catalytic p110 subunit. The binding of downstream kinases PDK and AKT to PIP3 causes their activation. AKT is known to mediate the responses of glucose transport, glycogen synthesis, protein synthesis, and antilipolytic effects of insulin. Some of these metabolic effects are mediated through AKT phosphorylation of FOXO transcription factors. Tyr phosphorylated IRS proteins also interact with the Grb2-mSOS complex followed by activation of Ras and signaling via the MAP kinase pathway. Plasma membrane-associated Ras binds Raf kinase, which in turn stimulates MEK activity. MEK activates ERK1/2 and is involved in the regulation of mitogenesis or differentiation, and other cellular activities.

Insulin Signaling and Action in Monocyte-Macrophages

The insulin signaling cascade and its role in cell metabolism and growth have been widely characterized in classic insulin-sensitive mammalian organs such as liver, muscle, and fat. However the literature on insulin signaling and action in macrophages is relatively sparse. Most insulin signaling molecules are expressed in macrophages. The notable exceptions are IRS1 and the glucose transporter GLUT-4. The expression of other IRS isoforms in macrophages remains to be determined. Treatment of macrophages with insulin stimulates the IR/IRS2/PI3K/AKT signaling cascade, similar to its effects in canonical insulin-responsive cells. Less clear is the responses of the MAP kinase pathway to insulin in macrophages though it is known that the Ras/Raf/MEK/ERK pathway is active in these cells.

The biological functions of insulin signaling in macrophages remain largely unknown, but could involve support of viability, protein synthesis and secretion, and phagocytosis, and thus the overall role of the macrophage innate immunity. Early studies documented several effects of insulin on macrophage metabolism. In the glycolytic pathway insulin was found to increase hexokinase and citrate synthase activities in rat macrophages, while inhibiting glucose 6-phosphate dehydrogenase in the pentose phosphate pathway. Although mouse macrophages express PI3K/AKT and Cbl/flotillin/Rho components, thought to be involved in insulin-stimulated glucose transport, insulin has no effects on 2-deoxy-D-glucose uptake by macrophages. Perhaps glucose transport in these GLUT-4–deficient cells is facilitated mainly by GLUT-1. Regarding macrophage innate immunity, hyperinsulinemia is known to increase phagocytic NADPH oxidase activity in human macrophages, possibly through protein.
kinase C, and to stimulate H$_2$O$_2$ production. In rat macrophages, insulin can increase the activities of antioxidant enzymes such as Cu/Zn superoxide dismutase. In addition, insulin has been reported to affect phagocytosis by macrophages. Thus insulin may modulate macrophage carbohydrate metabolism, redox activity, and phagocytic capacity. It remains unclear whether insulin affects antigen processing and presentation in macrophages.

**Abnormal Functions in Insulin Resistant Macrophages**

**Macrophage Abnormalities in Diabetes**

Monocyte-macrophages in type 2 diabetes and metabolic syndrome show some altered immune and inflammatory activities. For example, these macrophages have decreased phagocytosis of microbes. The expression of inflammatory mediators such as interleukin (IL)-6 is increased in adipose tissue macrophages in obesity. Macrophages of obese mice show an increase in oxidative stress. In addition, monocytes from diabetic subjects exhibit enhanced adherence to the endothelium, suggesting an increased ability of tissue infiltration under diabetic conditions. These abnormalities therefore may contribute to the development of systemic inflammation and insulin resistance associated with obesity and diabetes (see below).

Macrophages play a central role in mediating atherogenesis. In 70’s and 80’s, most studies used LDL and VLDL isolated from diabetic patients or diabetic animal models to examine lipoprotein metabolism in wild-type monocytes/macrophages. These studies showed increased association, degradation, and CE synthesis after incubation of macrophages with diabetic VLDL or LDL compared with lipoproteins from normal controls, suggesting a role of diabetic lipoproteins in the acceleration of atherosclerosis in diabetes. The enhancement of uptake is likely related to altered composition and modification of these lipoproteins.

More recent studies addressed the defects of macrophages in diabetes relevant to the pathogenesis of atherosclerosis. For instance, there is some evidence for impairment of cholesterol efflux pathways in macrophages. In macrophages isolated from type 2 diabetic db/db or KKAY mice, ABCG1 mediated cholesterol efflux to HDL (but not apo A-I) is reduced, though no significant difference in efflux was found in ob/ob LDLR$^{-/-}$ macrophages. Some of the derangements (eg, aberrant expression of ABCG1) found in diabetes are attributable to hyperglycemia, whereas others appear to be related to distinct metabolic parameters such as insulin resistance.

**Insulin Resistant Macrophages**

Previous studies suggested an intimate association of reduced monocyte IR activity with systemic insulin resistance in human. Monocyte-macrophages isolated from diabetic subjects and animal models show decreased surface expression and tyrosine kinase activity of IR and diminished insulin-stimulated signaling of IRS2, PI3K, and AKT. Thus macrophages in insulin-resistant states and diabetes are resistant to circulating insulin at the cellular level.

Recently we examined lipoprotein metabolism in insulin resistant macrophages from obese ob/ob mice and from IR knockout mice. Mice with a generalized inactivation of the IR die in the neonatal period from keto-acidosis, but viability can be rescued by expressing an IR transgene in the liver. Primary macrophages from ob/ob and transgenically rescued IR-deficient mice exhibit enhanced binding and uptake of modified LDL and elevated CE formation, suggesting that macrophage insulin resistance promotes uptake of atherogenic lipoproteins and foam cell formation. Conversely, in vivo the PPAR-γ activator rosiglitazone, a insulin sensitizing agent, reverses abnormal macrophage phenotype with improved insulin signaling and decreased modified LDL binding in macrophages from treated ob/ob LDLR$^{-/-}$ mice. These findings thus suggest macrophage insulin resistance as a key parameter potentially determining atherosclerotic responses in diabetes and metabolic syndrome.

**Mechanisms of CD36 and SR-A Induction**

Scavenger receptors CD36 and SR-A (CD204) are responsible for about 75% to 90% of the uptake of modified lipoproteins by macrophages in culture. Altered macrophage lipoprotein metabolism in insulin-resistant states and diabetes was shown to reflect increased surface expression of CD36 and/or SR-A. In insulin resistant macrophages, we found both CD36 and SR-A are posttranscriptionally upregulated (Figure 1), though distinct mechanisms may underlie the abnormalities of each receptor. Increased expression of CD36 is associated with enhanced recycling of the receptor to the cell surface, and is related to defective macrophage PI3K activity. The induction of SR-A is secondary to the unfolded protein response (UPR) which is exaggerated in insulin resistant macrophages (see below).

Elevated expression of CD36 on the surface of human monocyte-macrophages and in arterial foam cells was reported in diabetic subjects. Alternative mechanisms thought to be related to glucose-regulated CD36 protein translation and SR-A mRNA and protein expression in human cells have been proposed. Such an effect of hyperglycemia on CD36 and SR-A expression was not observed in C57BL/6J mouse macrophages. Therefore, macrophage CD36 and SR-A may be posttranslationally induced in insulin-resistant states and diabetes, potentially involving several different mechanisms.

**Macrophage Insulin Resistance, Apoptosis, and Advanced Lesion Formation**

**Insulin Resistant Macrophages and Atherosclerotic Lesion Complexity**

Our studies suggested a potential proatherogenic role of defective macrophage insulin signaling in diabetic atherosclerosis. Two animal studies with extreme cellular insulin resistance have been performed to directly test this hypothesis. In the first study, we performed bone marrow transplantation from transgenically rescued IR knockout mice into LDLR$^{-/-}$ mice fed Western diet containing 0.2% cholesterol. Plasma levels of lipoproteins, insulin or glucose were similar in animals transplanted with IR$^{+/+}$ or IR$^{-/-}$ bone. In the second study, we performed bone marrow transplantation from transgenically rescued IR knockout mice into LDLR$^{-/-}$ mice fed Western diet containing 0.2% cholesterol. Plasma levels of lipoproteins, insulin or glucose were similar in animals transplanted with IR$^{+/+}$ or IR$^{-/-}$ bone.
mice. These mice were fed a diet containing a very high cholesterol content (5%) and showed reduced areas of aortic lesions. Plaque formation in apoE−/− transplanted with fetal liver cells of IRS2−/−apoE−/− mice was also decreased. In vitro IR−/−apoE−/− macrophages when chronically challenged with lipopolysaccharide exhibited reduced secretion of proinflammatory IL-6 without significant changes in the release of TNF-α, possibly reflecting some selective defects in toll-like receptor signaling or NF-κB activity in mutant cells. This study suggests a protective role of impaired insulin signaling in myeloid lineage cells in atherosclerosis, related to a reduced inflammatory response.

The reasons for the somewhat disparate results of these two studies30,57 are not completely clear. The characterization of lesions was performed in different regions and at different stages of plaque development. Perhaps more importantly, different atherogenic diets were used in these studies, ie, the Western-type diet containing 0.2% cholesterol (0.15% added and 0.05% from fat)30 versus a diet supplemented with 5% cholesterol.57 A high dietary cholesterol content has been shown to cause a profound hepatic inflammatory response.58 Thus, it is possible that a decreased inflammatory response of insulin resistant macrophages could ameliorate the atherosclerotic response in animals fed a very high cholesterol diet, whereas enhanced apoptosis of insulin resistant macrophages may worsen advanced lesions in animals fed the Western type diet. Our results are also consistent with a recent study in apoE−/− mice transplanted with ATM (Ataxia Telangiectasia Mutated)-deficient bone marrow. ATM−/− macrophages show reduced IRS2 expression and elevated c-Jun N-terminal kinase (JNK) activity.59 When fed the Western diet, apoE−/− mice receiving ATM−/− bone marrow exhibit increased aortic lesion area.59

Diabetic patients are known to exhibit more advanced lesion development and increased acute coronary syndrome. In this context, our results30 are consistent with recent autopsy data60 from human type 2 diabetics who show increased necrotic core and enhanced macrophage apoptosis in their atherosclerotic lesions, apparently predisposing to plaque rupture, coronary thrombosis, and sudden death. Thus our work demonstrates a causal link between macrophage insulin resistance, death of macrophage foam cells, and necrotic core formation in advanced atherosclerotic plaques in diabetes and metabolic syndrome, and this may lead to increased vulnerability of the plaques in these disease states.

Potential Mechanisms: Role of Macrophage Apoptosis and Phagocytosis

The features in advanced lesions in IR−/− bone marrow recipients30 may result from adverse enhanced macrophage apoptosis and/or impaired phagocytic clearance of apoptotic macrophages (Figure 1). Insulin exerts antiapoptotic effects in macrophages, endothelial cells, and smooth muscle cells in vitro.61–63 During phagocytosis of apoptotic cells, both PI3K/AKT64,65 and MEK/ERK65–67 signaling cascades in normal phagocytic macrophages are involved. Further research is needed to determine whether engulfment of apoptotic cells by macrophages is altered in type 2 diabetes.

Insulin Resistant Macrophages and Inflammation

In a second study, J. Baumgartl et al used LysM Cre to inactivate the floxed IR gene in macrophages in apoE−/− mice. No significant difference in the area of early foam cell lesions was found in mice receiving IR-deficient bone marrow. However, IR−/− bone marrow recipients developed larger, more complex lesions at a later stage, accompanied by a pronounced increase in apoptotic cells and necrotic core formation. Examination of lesion cellularity showed that macrophages were the predominant cell type, occupying about 50% of lesion area. Lipid-rich necrotic cores in advanced atherosclerotic lesions arise from macrophages that have undergone either necrotic or apoptotic cell death.

Figure 1. A schematic representation of the mechanisms for increased formation of lipid-rich necrotic cores within atherosclerotic lesions in diabetes and metabolic syndrome. Defective macrophage insulin signaling induces expression of scavenger receptors SR-A and CD36 and promotes modified LDL uptake. Trafficking of lipoprotein free cholesterol after lysosomal hydrolysis to the ER increases ER cholesterol contents. The heightened ER stress triggered by cholesterol accumulation in turn leads to an increase in SR-A expression and a decrease in IR signaling. These amplified responses cause increased susceptibility of insulin resistant macrophages to apoptosis induced by modified lipoproteins. Enhanced macrophage apoptosis and impaired phagocytosis by insulin resistant macrophages in the plaques may augment lipid core formation and inflammatory responses as a result of increased macrophage necrosis. IR indicates insulin receptor; SR-A, scavenger receptor class A; FC, free cholesterol; ER, endoplasmic reticulum; mφ, macrophage.
Apoptosis, Phagocytosis, and Atherosclerosis In Vivo

The relationship of macrophage apoptosis to atherosclerosis is complex. Results of bone marrow transplantation from mice deficient in AIM (apoptosis inhibitor expressed by macrophages) or BAX suggest that in early fatty streak lesions there is efficient macrophage-mediated clearance of apoptotic cells. As plaques advance to the later stages of development, the responses to apoptosis seem different. This is supported by the studies with tissue inhibitor of metalloproteinase-2 gene transfer and IR-deficient transplantation.

The role of macrophage phagocytic defects in advanced plaque formation in vivo is largely unexplored. In one study, macrophage-mediated phagocytosis of apoptotic cells appears impaired in advanced human and rabbit atherosclerotic lesions. LDLR⁻/⁻ mice transplanted with transglutaminase 2-deficient bone marrows show increased aortic lesion areas along with defective phagocytosis of apoptotic cells by macrophages. In all, these data suggest that enhanced apoptosis and/or failed phagocytosis can be important contributors to the progression or complications of atherosclerotic plaques.

Insulin Resistant Macrophages and Cholesterol-Induced Apoptosis In Vitro

Two different pathways relevant to macrophage apoptosis in atherosclerosis have been described, one involving the uptake of oxidized cholesterol in LDL and another initiated by loading with lipoprotein free cholesterol (FC). Our results indicate an increase in susceptibility of IR-deficient macrophages to apoptosis triggered by oxidized LDL or FC loading in vitro. FC-induced apoptosis in macrophages requires a "multi-hit" mechanism involving both FC loading and ligation of SR-A. Thus an increase in SR-A in IR⁻/⁻ macrophages predisposes to apoptosis both by enhanced uptake of modified LDL and by providing a stronger "second hit" related to SR-A engagement (Figure 1). Apart from cholesterol accumulation, macrophage ATP depletion, a feature of advanced atherosclerotic plaques, may also contribute to apoptosis. Indeed IR-deficient macrophages are more susceptible to apoptosis induced by glucose deprivation. Overall our findings are consistent with the idea of increased susceptibility to apoptosis of IR⁻/⁻ macrophage foam cells in the lesions.

Cholesterol Accumulation, ER Stress, and Atherosclerosis In Vivo

In vitro FC loading promotes the UPR and eventually leads to apoptosis as a result of CHOP induction and SR-A engagement. The UPR is an adaptive program that assists cells to withstand endoplasmic reticulum (ER) stress such as conditions produced by protein overload and misfolding in the ER, nutrient deprivation, or pathogen infection. While this adaptive response may facilitate recovery from stress, it can also induce apoptosis if stressful stimuli continue or if there are additional insults. Persistent imbalances of ER stress and UPR in the arterial wall may be relevant to atherogenesis or lesion progression. For example, several markers of ER stress including CHOP are found in atherosclerotic plaques. Decreased NPC1-mediated cholesterol trafficking to the ER is associated with fewer apoptotic macrophages and smaller acellular lipid regions in advanced aortic lesions, as shown in NPC1⁻/⁻ apoE⁻/⁻ versus NPC1⁻/⁻ apoE⁻/⁻ mice. Therefore, sustained ER stress in vivo appears to promote macrophage death and advanced lesion formation.

Mechanisms of Macrophage Survival Following Cholesterol Overload

PI3K/AKT and MEK/ERK are both induced in response to ER stress produced by FC, thapsigargin, or tunicamycin treatments, thereby counteracting ER stress–induced apoptosis as survival mechanisms. Primary IR⁻/⁻ macrophages show modestly increased ER stress, and reduced AKT activity on serum starvation. After FC overload, the AKT response in these cells is attenuated and short-lived with more robust induction of CHOP and apoptosis.

Potential Roles of AKT, Autophagy, and SR-A Signaling in Insulin Resistant Cells

Several potential mechanisms can explain increased apoptosis of IR⁻/⁻ macrophages by FC loading (Figure 2). First, impaired induction of AKT appears to predispose IR-deficient macrophages to death. Some AKT substrates have been implicated as important in cell survival. For example, AKT directly phosphorylates and inactivates the proapoptotic protein BAD. Another target the FOXO transcription factor is known to induce apoptosis in lymphocytes and neurons. AKT may promote survival by nuclear exclusion of FOXO...
through phosphorylation. Alternatively, AKT can phosphorylate and stimulate p300/CBP acetyltransferase, which in turn may inhibit FOXO activity via acetylation. Macrophage FC loading leads to nuclear translocation of NF-κB RelA/p65. Genetic ablation of p65 increases susceptibility to ER stress–induced apoptosis. AKT reportedly activates NF-κB activity through phosphorylation or p300-mediated acetylation. Inhibition or knockdown of AKT substrate GSK3 rescues ER stress–induced apoptosis. GSK3 activity is suppressed by AKT phosphorylation. Thus abnormal activity of a variety of different AKT substrates in response to ER stress in lipid-laden IR−/− macrophages could result in enhanced apoptosis.

Second, as noted above, FC loading induces macrophage MEK/ERK signaling. Activation of MAP kinase pathways as a cellular protection against apoptosis can occur through multiple mechanisms. A potential role of this cascade in preventing FC-induced cell death and in causing the defects in IR−/− macrophage survival remains to be evaluated.

Third, ER stress induces autophagy, a regulated process of lysosome-mediated degradation of cellular proteins and organelles, promoting cell survival. IRS2 activation is indispensable for promoting death of ER-stressed macrophages. Treatment of human monocytes with interferon-γ or interleukin-6 releases from the macrophages may induce cellular insulin resistance in adipocytes or muscle cells by activating JNK signaling pathways and causing serine phosphorylation of IRS1/2. Therefore, the paracrine cross-talk between macrophages and adipocytes can promote insulin resistance in obesity and metabolic syndrome. Consistent with this model, TLR-4 is expressed in macrophages and other cell types in atherosclerotic lesions, and activation of TLR-4 signaling (eg, by fatty acids) in these cells may cause macrophage insulin resistance through direct stimulation of the macrophage TLR-4/JNK cascade or via cytokine-mediated autocrine effects on macrophage JNKs.

Fourth, SR-A engagement is required for FC-induced apoptosis in macrophages. ER stress alone cannot trigger death unless SR-A is ligated, suggesting a role of SR-A signaling events in driving stressed cells toward apoptosis. Recently, SR-A–mediated suppression of antiapoptotic TLR-4/IRF3/interferon β signaling cascade was shown to be indispensable for promoting death of ER-stressed macrophages. Treatment of human monocytes with interferon β leads to activation of PI3K/AKT. Thus the contribution of inhibitory actions on the survival branch of TLR-4 signaling by SR-A ligation to increased apoptosis of FC-engorged IR−/− macrophages needs to be further analyzed.

The Role of Macrophages and Inflammation in Insulin Resistance

Proinflammatory cytokines derived from adipose tissue have a role in the pathogenesis of insulin resistance in metabolic syndrome. Adipose tissue contains adipocytes and resident macrophages, both of which can be the sources of cytokine production. Recent studies have demonstrated increased accumulation of macrophages in adipose tissue of obese animals and humans, and have suggested they may have a direct role in the development of insulin resistance. Adipose tissue and perhaps muscle macrophages can secrete proinflammatory cytokines, thereby promoting cellular insulin resistance in fat, muscle, and liver. Fatty acids have been shown to activate TLR-4 and act via NF-κB to induce insulin resistance. The myeloid cell-specific knockout of IKKβ results in increased macrophage inflammatory responses and peripheral and hepatic insulin resistance. Thus, it is possible that fatty acids released from adipocytes act in a paracrine fashion to trigger TLR-4–mediated, NF-κB–dependent inflammatory responses in macrophages. Subsequently, cytokines such as TNF-α and IL-6 released from the macrophages may induce cellular insulin resistance in adipocytes or muscle cells by activating JNK signaling pathways and causing serine phosphorylation of IRS1/2. Therefore, the paracrine cross-talk between macrophages and adipocytes can promote insulin resistance in obesity and metabolic syndrome. Consistent with this model, TLR-4 is expressed in macrophages and other cell types in atherosclerotic lesions, and activation of TLR-4 signaling (eg, by fatty acids) in these cells may cause macrophage insulin resistance through direct stimulation of the macrophage TLR-4/JNK cascade or via cytokine-mediated autocrine effects on macrophage JNKs.

Conclusions

Individuals with diabetes and metabolic syndrome have a higher risk of developing atherosclerosis and vascular complications. Experimental evidence presented in this review suggests that the emerging interplay between cellular insulin resistance, persistent ER stress, and apoptotic death in cells of the arterial wall may be a common denominator in the development of macrovascular complications in type 2 diabetes (Figures 1 and 2). Pharmacological therapies and management directed at abnormalities associated with insulin resistance and ER stress can likely reduce the burden of excess coronary events in diabetes and metabolic syndrome. Medications currently in use that improve peripheral insulin sensitivity include thiazolidinediones (eg, pioglitazone, rosiglitazone) and biguanides (metformin). Several human studies suggested antiatherogenic benefit of thiazolidinediones in diabetes, as revealed by the changes in carotid artery intimal medial thickness or in features of carotid atherosclerotic plaques in treated versus placebo diabetic patients. However, in another study, rosiglitazone treatment may be accompanied by an increase in some adverse cardiovascular outcomes, possibly related to effects of PPAR-γ activation on the vasculature and heart independent of atherosclerosis. In mouse models of diabetes and obesity, induction of hepatic ER stress is associated with decreased insulin signaling in the liver. Oral administration to these animals of chemical chaperones, which alleviate cellular ER stress, leads to an improvement of systemic and hepatic insulin sensitivity accompanied by attenuated ER stress. Only limited information is available to date regarding direct action on macrophages of these chaperone agents. For example, trimethylamine oxide and tauroursodeoxycholic acid were shown to stimulate phagocytosis by macrophages or Kupffer cells. 4-phenylbutyrate (also a deacylase inhibitor) can rescue cells of various types from ER stress–induced apoptosis. Two chaperones (tauroursodeoxycholic acid and 4-phenylbutyrate) are used in the treatment of other disorders. Their efficacy in the treatment and prevention of atheroscle-
rosis in diabetes and metabolic syndrome remains to be assessed.

Acknowledgments

We thank Drs Ira Tabas and Domenico Accili for many helpful discussions and insights, and Dr Andreas W. Jehle and Suzhao Li for comments on the manuscript.

Sources of Funding

This work was supported by National Institutes of Health Grant HL22682.

Disclosures

None.

References


Liang et al. Insulin Resistance and Atherosclerosis


