Targeting inflammation in metabolic syndrome

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The metabolic syndrome (MetS) is comprised of a cluster of closely related risk factors, including visceral adiposity, insulin resistance, hypertension, high triglyceride, and low high-density lipoprotein cholesterol; all of which increase the risk for the development of type 2 diabetes and cardiovascular disease. A chronic state of inflammation appears to be a central mechanism underlying the pathophysiology of insulin resistance and MetS. In this review, we summarize recent research which has provided insight into the mechanisms by which inflammation underlies the pathophysiology of the individual components of MetS including visceral adiposity, hyperglycemia and insulin resistance, dyslipidemia, and hypertension. On the basis of these mechanisms, we summarize therapeutic modalities to target inflammation in the MetS and its individual components. Current therapeutic modalities can modulate the individual components of MetS and have a direct anti-inflammatory effect. Lifestyle modifications including exercise, weight loss, and diets high in fruits, vegetables, fiber, whole grains, and low-fat dairy and low in saturated fat and glucose are recommended as a first line therapy. The Mediterranean and dietary approaches to stop hypertension diets are especially beneficial and have been shown to prevent development of MetS. Moreover, the Mediterranean diet has been associated with reductions in total and cardiovascular mortality. Omega-3 fatty acids and peroxisome proliferator–activated receptor α agonists lower high levels of triglyceride; their role in targeting inflammation is reviewed. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone blockers comprise pharmacologic therapies for hypertension but also target other aspects of MetS including inflammation. Statin drugs target many of the underlying inflammatory pathways involved in MetS. (Translational Research 2016;167:257–280)

Abbreviations: AA = arachidonic acid; ABCA1 = adenosine triphosphate-binding cassette transporter A1; ACE-I = angiotensin-converting enzyme inhibitor; ACSL1 = acyl-CoA synthase 1; ADMA = asymmetric dimethylarginine; Akt = protein kinase B; Aldo = aldosterone; AMPK = adenosine monophosphate-activated protein kinase; ANGPTL = angiopoietin-like protein; Ang = angiotensin; AngII = angiotensin II; AP-1 = activator protein 1; Apo = apolipoprotein; ARB = angiotensin receptor blocker; Aspirin-COX-2 = aspirin-acetylated cyclooxygenase-2; AT-LX = aspirin-triggered lipoxins; AT-PD1 = aspirin-triggered protectins; AT-RvD = aspirin-triggered resolvins; C = cholesterol; CAD = coronary artery disease; CD = cluster of differentiation; CE = cholesterol ester; CETP = CE transfer protein; CoQ10 = coenzyme Q10; COX = cyclooxygenase; COX-2 = cyclooxygenase-2; CRP = C-reactive protein; c-Src = tyrosine-protein kinase C-Src Kinase; CVD = cardiovascular disease; DAG = diacylglycerides; DHA = docosahexaenoic acid; EF = ejection fraction; eNOS = endothelial nitric oxide synthase; EPA = eicosapentaenoic acid; ET = endothelin; FetA = Fetuin A; FFA = free fatty acids; FoxO1 = forkhead box protein O1; Glu = glucose; GLUT-4 = glucose transporter type 4; GPR = G-protein–coupled receptor; GRK2 = G-protein–coupled receptor kinase 2; HDL = high-density lipoprotein; HL = hepatic lipase; HR = hazard ratio; ICAM-1 = intercellular adhesion

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molecule-1; IDL = intermediate-density lipoprotein; IKK = inhibitor of nuclear factor kappa-B kinase; IL = interleukin; ILR = interleukin receptor; iNOS = inducible nitric oxide synthase; LT = leukotriene; IRS = insulin receptor substrate; IκB = inhibitor of nuclear factor kappa-B; JNK = c-Jun N-terminal kinase; LOX = lipoxygenase; LPL = lipoprotein lipase; LX = lipoxin; MAPK = Mitogen-activated protein kinases; MCP-1 = monocyte chemoattractant protein-1; MetS = metabolic syndrome; MI = myocardial infarction; MMP = matrix metalloproteinase; MTP = microsomal triglyceride transfer protein; NF-κB = nuclear factor kappa-B; NLR = nod-like receptor; NO = nitric oxide; Omega-3 FAs = omega-3 fatty acids; oxLDL = oxidized low-density lipoprotein; PAI-1 = plasminogen activator inhibitor-1; PD1 = protectins; PG = prostaglandins; PI3K = phosphatidylinositol 3-kinase; PKC = protein kinase C; PPAR = peroxisome proliferator–activated receptor; RAAS = renin–angiotensin–aldosterone system; RCT = reverse cholesterol transport; ROS = reactive oxygen species; RvD = DHA-derived resolvins; RvE = EPA-derived resolvins; S1P = sphingosine-1-phosphate; SAA = serum amyloid A; SFA = saturated fatty acids; SOCS-3 = suppressor of cytokine signaling 3; SPMs = specialized proresolving lipid mediators; TF = tissue factor; TG = triglycerides; Th = T-helper cells; TLR = toll-like receptor; TNF-α = tumor necrosis factor α; Treg = T-regulatory cell; TX = thromboxane; VCAM-1 = vascular cell adhesion molecule-1; VLDL = very low–density lipoprotein

INTRODUCTION

The metabolic syndrome (MetS) is comprised of a cluster of closely related risk factors, including visceral adiposity, insulin resistance, hypertension, and dyslipidemia; all of which increase cardiovascular risk.[1] MetS as defined by the adult treatment panel III includes at least 3 of the following: central obesity (waist circumference ≥ 88 cm, 35 inches, 80 cm Asian in women and ≥102 cm, 40 inches, 90 cm Asian in men), fasting blood glucose (Glu) ≥ 5.56 mmol/L (100 mg/dL), triglyceride (TG) levels ≥ 1.7 mmol/L (150 mg/dL), low levels of high-density lipoprotein-cholesterol (HDL-C) (<1.04 mmol/L [40 mg/dL] in men and <1.7 mmol/L [50 mg/dL] in women), and systolic and/or diastolic blood pressure ≥ 130/85 mm Hg.[2] The MetS has a prevalence of 24% in U.S. adults and 43% of adults older than 60 years.[3] MetS is a precursor of type 2 diabetes mellitus and increases the risk of cardiovascular disease (CVD) outcomes 2-fold and all-cause mortality, 1.5-fold.[1] Each of the individual components of MetS is a risk factor for CVD; therefore, recognizing and treating each component is important to lower risk of CVD. Inflammation appears to be a central mechanism underlying the pathophysiology of MetS. In this review, we summarize recent research which has provided insight into the mechanisms by which inflammation contributes to the development of MetS. On the basis of these mechanisms, we summarize therapeutic modalities to target inflammation in the MetS and its individual components.

ROLE OF VISCERAL ADIPOSITY IN MetS

Visceral adiposity is the major risk factor responsible for the development of insulin resistance and the common pathophysiologic link to MetS. The pathophysiology of MetS is related to a diet-containing excess calories and/or high saturated fat or Glu content and physical inactivity. Triacylglycerols provide the major source of energy which is used by skeletal muscle. They are comprised of a glycerol backbone in which each of the 3 hydroxyl groups is esterified with a fatty acid.[4] The function of white adipose tissue is to store excess energy as TGs and then lipolyze and release free fatty acids (FFAs) into the circulation for use as energy in muscle. When nutrient intake exceeds the metabolic demand for energy, the excess TG is stored in adipocytes, liver, and skeletal muscle. White adipose tissue is a highly active metabolic tissue which releases >50 different molecules known as adipocytokines, which regulate inflammation and immune function and the components of MetS including insulin sensitivity and blood pressure homeostasis as well as Glu and lipid metabolism.[5]

There are several ways in which products of adipocytes cause insulin resistance and thus MetS (illustrated in Fig 1A). First, adipocytes secrete monocyte chemoattractant protein-1 (MCP-1) and the cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6, which cause infiltration of macrophages into adipose tissue.[6] These macrophages in turn release TNF-α and IL-6. TNF-α signaling activates intracellular kinases, c-Jun N-terminal kinase (JNK) and IκB kinase (IKK), which lead to increased serine phosphorylation of insulin receptor substrate-1 (IRS-1), rather than the normal tyrosine phosphorylation (Fig 1A).[7,8] Serine phosphorylation of IRS-1 impairs insulin signaling and causes insulin resistance in muscle, liver, and other tissues by leading to decreased activation of phosphoinositide 3-kinase (PI3K) which in turn inhibits protein kinase Akt2 (protein kinase B), a protein which catalyzes the translocation of the insulin-responsive Glu transporter 4 (GLUT-4) to the plasma membrane, thus inhibiting the transport of Glu into cells (Fig 1B).[6,9] Activation of Akt inhibits Forkhead box protein O1 (FoxO1), a process which inhibits