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Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance

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ABSTRACT

Insulin resistance is a hallmark of obesity, the cardiorenal metabolic syndrome and type 2 diabetes mellitus (T2DM). The progression of insulin resistance increases the risk for cardiovascular disease (CVD). The significance of insulin resistance is underscored by the alarming rise in the prevalence of obesity and its associated comorbidities in the Unites States and worldwide over the last 40–50 years. The incidence of obesity is also on the rise in adolescents. Furthermore, premenopausal women have lower CVD risk compared to men, but this protection is lost in the setting of obesity and insulin resistance. Although systemic and cardiovascular insulin resistance is associated with impaired insulin metabolic signaling and cardiovascular dysfunction, the mechanisms underlying insulin resistance and cardiovascular dysfunction remain poorly understood. Recent studies show that insulin resistance in obesity and diabetes is linked to a metabolic inflammatory response, a state of systemic and tissue specific chronic low grade inflammation. Evidence is also emerging that there is polarization of macrophages and lymphocytes towards a pro-inflammatory phenotype that contributes to progression of insulin resistance in obesity, cardiorenal metabolic syndrome and diabetes. In this review, we provide new insights into factors, such as, the renin–angiotensin–aldosterone system, sympathetic activation and incretin modulators (e.g., DPP-4) and immune responses that mediate this inflammatory state in obesity and other conditions characterized by insulin resistance.

Abbreviations: WD, Western Diet; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease; PI3-K, phosphatidylinositol 3 kinase; Akt, protein kinase B; ERK1/2, extracellular regulated kinases ½; IRS, insulin receptor substrate; JNK, C-Jun kinase; MTOR, mammalian target of rapamycin; S6K, p70 S6 kinase; SOC3-3, cytokine signaling 3; WAT, white adipose tissue; FFAs, free fatty acids; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; PKC, protein kinase C; TLR-4, Toll-like receptor 4; LPS, lipopolysaccharide; RAAS, renin angiotensin aldosterone system; Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; ROS, reactive oxygen species; SNS, sympathetic nervous system; (SOD)3, superoxide dismutase; CVO, circumventricular organs; PET, positron emission tomography; ENOS, endothelial nitric oxide synthase; NO, nitric oxide; Tregs, regulatory T cells; IFN-γ, interferon gamma; FoxP3, forkhead/winged helix transcription factor 3; IL-10, Interleukin 10; TGF-β, transforming growth factor beta; CVB3, coxsackievirus B3; ARBs, Ang II receptor blockers; DPP-4, dipetidyl peptidase 4; GLP-1, glucagon like peptide-1; GIP, glucose-dependent insulinotrophic peptide; GLP-1R, GLP-1 receptor; HFCS, high-fructose corn syrup.

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1. Introduction

The prevalence of obesity and diabetes is increasing by alarming proportions in the United States and worldwide. Two-thirds of American adults are overweight or obese and 40% of overweight/obese individuals are diabetic. The prevalence of obesity has also increased considerably around the globe and more than 20% of the world population is overweight, while nearly 300 million are obese [1–4]. In addition, childhood–adolescent overweight and obesity, as well as obesity in premenopausal women are also emerging as major global public health concerns [5,6]. Driving forces for overweight and obesity include increasing sedentary lifestyles and consumption of a Western Diet (WD) high in fat, fructose and salt and their interaction with genetic factors and epigenetic processes [7–9]. The prevalence of hypertension in type 2 diabetes mellitus (T2DM) is increased 3-fold, and the coexistence of hypertension in diabetic patients greatly enhances the development of cardiovascular disease (CVD) and chronic kidney disease (CKD) [10]. It is estimated that 37% of the adult population has prehypertension and 40% of these people will progress to hypertension within a two year time frame [11]. Moreover, childhood obesity is associated with increased arterial stiffness as determined by pulse wave velocity [12]. Prehypertension is increasingly recognized as a risk factor for CVD. This is supported by studies demonstrating the association of increased diastolic dysfunction in a prehypertension state in genetic or diet-induced rodent models of obesity [13–15].

2. Central role of insulin resistance in the progression of cardiorenal metabolic syndrome

Overweight and obesity are associated with development of the cardiorenal metabolic syndrome which is a constellation of risk factors, such as insulin resistance, dyslipidemia, and high blood pressure that predispose affected individuals to well-characterized medical conditions such as diabetes, CVD and CKD [4,5,7]. Insulin resistance is one common underlying mechanism that contributes to the progression of CVD and renal injury in obesity and diabetes. Insulin resistance is also associated with vascular stiffness, which is an independent risk factor for CVD [12,16,17]. Although aging is associated with increased vascular stiffness, obesity and diabetes are associated with accelerated vascular stiffness [16,17]. Insulin resistance is also associated with a metabolic (obesity) cardiomyopathy characterized by diastolic dysfunction independent of hypertension and hyperglycemia [18,19]. The association of insulin resistance with cardiac dysfunction may also occur in diabetes independent of coronary heart disease or hypertension (diabetic or metabolic cardiomyopathy) [19,20]. Insulin resistance is also the underlying pathophysiologic factor contributing to the development of hypertension [10]. Moreover, parental hypertension and insulin resistance may also contribute to elevations in blood pressure and insulin resistance in both male and female offspring [21,22]. These findings suggest that progression of insulin resistance has profound effects on cardiovascular dysfunction in obesity and diabetes.

3. Impairment of insulin signaling and CVD

3.1. *Serine phosphorylation of insulin receptor substrate*

Insulin signaling occurs through activation of the phosphatidylinositol 3 kinase (PI3-K)/protein kinase B (Akt) signaling pathway linked to metabolic insulin signaling and extracellular regulated kinases ½ (ERK1/2) signaling with growth factor-like responses [4]. The major converging point contributing to insulin resistance is the docking protein insulin receptor substrate (IRS). The phosphorylation of serine residues of IRS by several kinases including protein Kinase C, C-Jun kinase (JNK), mammalian target of rapamycin (mTOR) and ribosomal p70 S6 kinase (S6K) is the major mechanism for regulation of IRS function [4,18–20]. Phosphorylation of serine residues on IRS-1 attenuates IRS-1 tyrosine phosphorylation, association with p85 subunit of PI3-K, and triggers proteasome-dependent degradation. Proteasome degradation of IRS-1 can also occur by suppression of a cytokine signaling 3 (SOC3-3) mediated mechanism that is independent of phosphorylation of IRS-1 [4].

Impaired insulin metabolic signaling results in impaired glucose uptake, endothelial dysfunction, reduced coronary flow, impaired angiogenesis, cardiac lipotoxicity, and metabolic inflexibility, all of which contribute to cardiac diastolic function. Progression of insulin resistance and endothelial dysfunction also contribute to enhanced vascular stiffness, development of hypertension and atherosclerosis [4,10,16,18].

4. Cardiovascular insulin resistance at the cross roads of metabolism, immune and inflammatory response

4.1. *Adipose tissue dysfunction, systemic immune and inflammatory responses and insulin resistance (Fig. 1)*

Although mechanisms and mediators of systemic insulin resistance are not clearly understood, recent studies link over-nutrition to a low grade systemic inflammatory response and this inflammatory response is distinct from an acute inflammatory response [23,24]. Chronic over-nutrition results in white adipose tissue (WAT) immune and inflammatory responses that contribute significantly to low grade inflammation and this condition has been often referred to as metabolic inflammation or metaflammation [23,24]. Although mechanisms underlying this inflammatory response are not well understood, endoplasmic reticular stress is one of the cellular stress events that activate inflammatory signaling pathways including activation of JNK, mTOR and S6K [23,24]. These serine kinases not only mediate adipose tissue dysfunction but also phosphorylate serine residues of IRS-1, thereby mediating insulin resistance in adipose tissue. In addition to increased release of free fatty acids (FFAs), dysregulated adipocyte function results in increased secretion of cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and resistin and decreased secretion of adiponectin [4,25].