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Review

Immunometabolism of AMPK in insulin resistance and atherosclerosis

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ABSTRACT

Obesity leads to insulin resistance and atherosclerosis, which precede Type 2 diabetes and cardiovascular disease. Immunometabolism addresses how metabolic and inflammatory pathways converge to maintain health and a contemporary problem is determining how obesity-induced inflammation precipitates chronic diseases such as insulin resistance and atherosclerosis. AMP-activated protein kinase (AMPK) is an important serine/threonine kinase well known for regulating metabolic processes and maintaining energy homeostasis. However, both metabolic and immunological AMPK-mediated effects play a role in disease. Pro-inflammatory mediators suppress AMPK activity and hinder lipid oxidation. In addition, AMPK activation curbs inflammation by directly inhibiting pro-inflammatory signaling pathways and limiting the build-up of specific lipid intermediates that elicit immune responses. In the context of obesity and chronic disease, these reciprocal responses involve both immune and metabolic cells. Therefore, the immunometabolism of AMPK-mediated processes and therapeutics should be considered in atherosclerosis and insulin resistance.

Contents

Abbreviations: AMPK, AMP-activated protein kinase; CaMKKβ, calmodulin-dependent kinase kinase β; ACC, acetyl-CoA carboxylase; HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; SREBP, sterol regulatory element binding protein; PGC1α, peroxisome proliferator-activated receptor γ co-activator 1α; NAD+, nicotinamide adenine dinucleotide; SIRT1, sirtuin 1; IL, Interleukin; NO, nitric oxide; iNOS, inducible nitric oxide synthase; TNFα, tumor necrosis factor α; TLR4, toll-like receptor 4; LPS, lipopolysaccharide; NFκB, nuclear factor κB; JNK, Jun N-terminal kinase; IKKβ, inhibitor of κB kinase β; IRS, insulin receptor substrates; BMDM, bone marrow-derived macrophages; DN, dominant negative; CA, constitutively active; AICAR, 5-Aminoimidazole-4-carboxamide 1-β-D-ribofuranoside; HFD, high fat diet; CD36, fatty acid translocase; NLRP3, nod-like receptor pyrin domain-containing 3; ROS, reactive oxygen species; PPAR, peroxisome proliferator-activated receptor; BMT, bone marrow transplant; LDL, low-density lipoprotein; ABC, ATP-binding cassette transporters; eNOS, endothelial nitric oxide synthase; VCAM-1, vascular cell adhesion molecule; MCP-1, monocyte chemotactic protein-1; HDL, high-density lipoprotein; SR-BI, scavenger receptor class B type I; PKC, protein kinase C; Ox, oxidized; FAS, fatty acid synthase.

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1. The bridge between immunology and metabolism

Metabolism fuels life by converting nutrients into useable energy allowing the synthesis of cellular constituents. The balance of cellular energy production and utilization necessary for survival is achieved by metabolic regulators of anabolic and catabolic processes. Specific metabolic pathways dictate whether environmental substances are nutritious or poisonous. This is related to one of the fundamental tasks of metabolism: to drive processes that allow for defense against pathogens. Given that metabolism and pathogen defense (i.e. immunity) are fundamental requirements for sustained life, it is not surprising that these processes are intricately linked in health and disease. Pathogen detection and removal by tissue-resident or circulating immune cells requires a very complex repertoire of sensors and chemical signals built and constantly modified using energy consuming processes (Medzhitov, 2010).

It has been long appreciated that the activation of immune responses in response to acute infection or injury prompts alterations in metabolism (Beisel, 1972, 1975). Metabolic changes can be elicited by the invading pathogen, or indirectly if the host dedicates sufficient energy intensive resources to facilitate necessary immune function and resolution. In recent years, it has become increasingly evident that in addition to the metabolic response to immune activation, there can be reciprocal perturbations in innate immune cells in response to chronic metabolic stress. Nutrient overload and consequent obesity has emerged as a factor that elicits chronic immune responses (Mathis and Shoelson, 2011).

There has been a staggering increase in the incidence of obesity over the past decades. It is widely accepted that energy imbalance and the adipose tissue expansion characteristic of obesity is due to both decreased energy expenditure (i.e. sedentary lifestyle) and increased energy intake via diets inappropriately high in calories and saturated fats. Obesity is a principle component of the metabolic syndrome, and predisposes for insulin resistance, type 2 diabetes, cardiovascular disease, as well as cancer and certain neurological diseases (Berrington de Gonzalez et al., 2010; Flegal et al., 2007). This array of obesity-driven metabolic complications presents an enormous health and financial burden on society and increasing efforts have been made to understand the molecular interactions underlying obesity-induced pathologies. Chronic low-level inflammation in key metabolic tissues, which harbor significant populations of immune cells, has emerged as an important player in the etiology of these metabolic disorders (Hotamisligil, 2006). This review highlights recent evidence linking AMPK function in immune and metabolic systems and details how this interaction plays an important role in obesity-driven chronic inflammatory diseases such as insulin resistance and atherosclerosis.

2. AMP-activated protein kinase: an energy sensor

AMP-activated protein kinase (AMPK) is an energy sensing protein kinase and a master regulator of anabolic and catabolic processes and consequently metabolic homeostasis (Steinberg and Kemp, 2009). Importantly, AMPK, in addition to activation through changes in cellular energy, can be coordinately regulated by secreted factors from both immune and metabolic tissues/cells (Hardie, 2007; Steinberg et al., 2006). This has prompted investigation into AMPK regulation of metabolic processes directly or indirectly through modulation of immune cell function. Furthermore, AMPK-mediated changes in metabolism can drive specific immune responses.

AMPK is a heterotrimeric protein containing α-catalytic and βγ-regulatory subunits, with each subunit having multiple isoforms, splice variants and tissue specific expression. Activation of AMPK in response to external stimuli relies on phosphorylation by upstream kinases. LKB1, a widely expressed tumor suppressor, was identified as a key mammalian AMPK kinase (Hawley et al., 2003; Woods et al., 2003). It was also shown that calmodulin-dependent kinase kinase β (CaMKKβ), mainly expressed in neural, endothelial and hematopoietic cells, is an upstream kinase of AMPK (Hawley et al., 2005; Hurley et al., 2005). A major regulator of lipid metabolism, AMPK inhibits malonyl-CoA production by phosphorylating acetyl-CoA carboxylase (ACC), which then allows uptake of activated fatty acids into the mitochondria for oxidation or reduces the levels of lipogenic precursors (Carlson and Kim, 1973; Saggerson, 2008). AMPK activation has also been shown to: (1) inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR), the rate-limiting enzyme in the biosynthesis of cholesterol (Beg et al., 1973), (2) decrease sterol regulatory element binding protein 1c and 2 (SREBP-1c/2) induced transcription (Kohjima et al., 2008; Li et al., 2011) and, (3) modulate fatty acid mobilization through inhibition of hormone sensitive lipase (Garton et al., 1989).

Mitochondrial homeostasis is an integral aspect of maintaining cellular energy levels and whole-body aerobic metabolism. AMPK regulates autophagy of mitochondria (mitophagy) and biogenesis of new mitochondria or mitochondrial components (Egan et al., 2011; Zong et al., 2002). Activation of AMPK causes direct phosphorylation of the transcriptional co-activator peroxisome proliferator-activated receptor γ co-activator 1α (PGC1α) (Jager et al., 2007), leading to the coordinated activation of the nuclear-encoded transcriptional program as well as increasing mitochondrial DNA transcription via mitochondrial transcription factor A (Fernandez-Marcos and Auwerx, 2011). In addition, activation of AMPK increases cellular nicotinamide adenine dinucleotide (NAD+) levels and increases sirtuin 1 (SIRT1) activity, which results in the deacetylation and increased co-activation of transcriptional activity by PGC1α (Lagouge et al., 2006). Similar to skeletal muscle, AMPK regulates mitochondrial metabolism in immune cells (Galic et al., 2011; O'Neill et al., 2011).

3. Inflammation in obesity: macrophage polarization and insulin resistance

Obesity is associated with the accumulation and expansion of triglyceride rich adipose tissue, elevated circulating lipids and increased ectopic fat deposition in the liver and muscle. Increased deposition of lipids in these key metabolic tissues coincides with (or slightly precedes) inflammation, particularly in the adipose tissue and liver (Lee et al., 2011). Obesity-induced inflammation in these metabolic tissues and increased circulating pro-inflammatory mediators are thought to originate from increased levels of pro-inflammatory-skewed tissue resident immune cells. This metabolic-immune crosstalk has been shown to contribute to obesity-induced glucose intolerance, insulin resistance and increased risk for cardiovascular disease (Hotamisligil, 2006; Olefsky and Glass, 2010).

Immune cells resident in "non-immune" tissues play a sentinel-like role by monitoring for foreign material and phagocytosing these invading components, presenting them to adaptive immune cells and in regulating tissue repair processes. Alveolar macrophages (lung), Kupffer cells (liver), osteoclasts (bone), microglia (neuronal tissue) and adipose tissue macrophages all play a vital role in maintaining tissue-specific homeostasis. Adipose tissue resident macrophages exist along an inflammatory axis ranging from pro- to anti-inflammatory (Anderson and Mosser, 2002; Umemura et al., 2008). Macrophages in adipose tissue from lean individuals exist mainly as M2, or alternatively activated, characterized by a transcriptional pattern favoring anti-inflammatory genes involved in cellular repair and resolution (Lumeng et al., 2007a,b, 2008).