

## Invited Review

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# Adipokines-AMPK Cross-Talk in Avian Species: A Translational Model for Human Obesity

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### ABSTRACT

Adipocytokines, or adipokines, are circulating hormones mainly produced by adipose tissue and are key regulators of whole body metabolism and immune homeostasis. Due to a rise in human obesity-related diseases, pathways related to metabolism are being studied using several animal models to identify key molecular signatures for development of mechanism-based therapeutic strategies. Previous work published in our laboratory has used chickens as a model for obesity because of its peculiarities that will be described in this article. In particular, recent advances in our understanding of adipokine AMP-activated protein kinase (AMPK) interactions in the regulation of energy balance will be summarized as well as facilitating the discussion by asking new questions which may open new vistas for future research.

**KEYWORDS:** Adipocytokine; AMP-activated protein kinase (AMPK); Obesity; Chicken.

**ABBREVIATIONS:** AMPK: AMP-activated protein kinase; ARC: Arcuate nucleus; PVN: Paraventricular nucleus; GLUT4: Glucose transporter type 4; SOCS3: Suppressor of cytokine signaling 3; LDL: Low-density lipoprotein.

The relationship between adipocytokines and AMP-activated protein kinase (AMPK) in the regulation of several metabolic processes has been the subject of many studies. AMPK has been shown to be activated/deactivated by several adipokine-inducing cellular energy alteration. The adipokines adiponectin, leptin, resistin and visfatin play pivotal roles in obesity, insulin resistance and related inflammatory disorders.<sup>1-6</sup> Adiponectin is involved in regulating glucose levels as well as fatty acid breakdown, with circulating levels varying in healthy adults but may be inversely correlated with body fat percentage.<sup>7</sup> Leptin regulates energy balance through its anorexigenic effects in the hypothalamus. In obesity, leptin sensitivity decreases although it has high circulating levels.<sup>8,9</sup> Resistin is also known as adipose tissue-specific secretory factor (ADSF) and is secreted by immune and epithelial cells, playing a role in high levels of low-density lipoprotein (LDL) and serves endocrine functions involved in insulin resistance.<sup>10</sup> Visfatin has been shown to activate insulin receptor and to have insulin-mimetic effects such as lowering blood glucose and improving insulin sensitivity.<sup>11</sup> This cytokine is highly expressed in visceral fat and its serum levels is high in obese subjects.<sup>11</sup>

Studies detailing the control of hepatic glucose production by activated AMPK was demonstrated in resistin knockout mice and adiponectin treated rodents, and suggested that hepatic AMPK is a specific target of both adipocytokines with resistin inhibiting AMPK and adiponectin activating AMPK.<sup>12,13</sup> AMPK is expressed in feeding-related hypothalamic nuclei such as arcuate nucleus (ARC) and paraventricular nucleus (PVN) and has been shown to mediate the (an)orexigenic effects of adipocytokine.<sup>14</sup> For instance, adiponectin increases food intake, but leptin decreases food intake through activating AMPK in the hypothalamus.<sup>15</sup> These results, along with others, show that food intake and nutrient metabolism are regulated by the AMPK pathway<sup>15</sup> as shown in a fasting study that resulted inactivation of AMPK whereas re-feeding inhibited AMPK activity in mice.<sup>16</sup> Feed efficiency in poultry, (the ability of the

animal to convert their feed into usable energy) is an important economic and agricultural trait, therefore, understanding its underlying signaling pathways is critical. For example, it has been found that, in chickens, 24 h fasting altered gene expression of AMPK subunits<sup>17</sup> and a separate study showed that Suppressor of cytokine signaling 3 (SOCS3) (define SOCS3) regulates growth and development through three adipocytokine signaling pathways: 1) SOCS3 inhibiting IRS1, this inhibits insulin signaling, affecting growth; 2) SOCS3 inhibiting LEPR, leptin has a range of biological effects, most notably in metabolic regulation which suppresses appetite, reduces energy intake, increasing energy expenditure, and inhibiting fat synthesis; 3) SOCS3 inhibits JAK, this pathway is involved in cell proliferation, differentiation, apoptosis, immune regulation, and other important biological processes.<sup>18</sup>

While most studies have been conducted in mammals (mainly murine models), few studies have been carried out in chickens as they have physiological characteristics making them useful models to study the pathophysiology of obesity.<sup>19</sup> Whereas lipogenesis occurs in both adipose tissue and liver in rodents<sup>20-22</sup> chickens are similar to humans in that lipogenesis occurs exclusively in the liver.<sup>23</sup> In addition, broiler chickens are also hyperglycemic, insulin resistant, and lack both Glucose transporter type 4 (GLUT4) (although they do have analogous GLUT8 and GLUT12) and brown adipose tissue. They are genetically selected for rapid growth rate and, consequently, are hyperphagic, heavy, and adults are prone to obesity and several metabolic disorders. These peculiarities make chicken a very useful human-relevant animal model to study this disease. A major focus in poultry research is developing mechanism-based strategies (nutrition, management, genetics) to improve feed efficiency and animal well-being and health. Adipocytokines-AMPK interaction could be one such mechanism that can aid poultry research in determining underlying causes of fat deposition and, subsequently, how to gain better muscle yield.

The past two decades have seen a surge in obesity and obesity related illness. Due to its role in cardiovascular disease, airway disorders, neurodegenerative diseases, hypertension, and fatty liver disease. Obesity is one of the most important diseases afflicting modern society today. Efforts to delineate the pathophysiological mechanisms underlying this disease have become paramount and adipocytokine therapy tops that list. Dysfunction of this pathway may be a key factor in obesity-related illness and, subsequently, its treatment. Although pathways affecting satiety and feeding upstream of AMPK are somewhat understood, there remains much to gather about the downstream effects of such pathways in both mammals and avian species. Therefore, while much is known about adipocytokines as well as their relation to obesity-linked illness, much has yet to be elucidated.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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