

## **New mechanisms of glucocorticoid-induced insulin resistance: make no bones about it**

Heather A. Ferris, C. Ronald Kahn

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### **Commentary**

Glucocorticoids are a powerful tool used to treat a range of human illnesses, including autoimmune diseases and cancer, and to prevent rejection following organ transplantation. While lifesaving for many, they come with a steep price, often leading to obesity, insulin resistance, diabetes, and osteoporosis. In this issue of the *JCI*, Brennan-Speranza and colleagues provide evidence that the osteoblast-derived peptide osteocalcin is one of the drivers of the metabolic derangements associated with glucocorticoid therapy. This novel mechanism could open up new avenues for the treatment of these disorders.

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nisms underlying their roles in kidney injury and repair are largely unknown.

Furthermore, ischemic injury, the focus of the Li et al. paper, may not have the same pathophysiologic pathways as nephrotoxic injury or sepsis. Another key step will be to understand why so many mechanistic studies in rodents have shown protection while clinical studies targeting the same pathways have failed. Does ischemic injury in native kidneys have a different pathophysiology than IRI in allografts when additional factors such as brain death, cold transport, and immunosuppressive treatment are superimposed? Finally, a recent surge of data has identified AKI as an important risk factor for CKD (21–23), and immune cells are likely important mediators between these two diseases, possibly related to autoimmunity (24). The type of immune cells involved in AKI-to-CKD transition and the details of how they function will be important to elucidate.

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Address correspondence to: Hamid Rabb, Ross 965, The Johns Hopkins Hospital, 720 Rutland Ave., Baltimore, Maryland 21205, USA. Phone: 410.502.1556; Fax: 410.614.1643; E-mail: hrabb1@jhmi.edu.

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Heather A. Ferris and C. Ronald Kahn

Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts, USA.

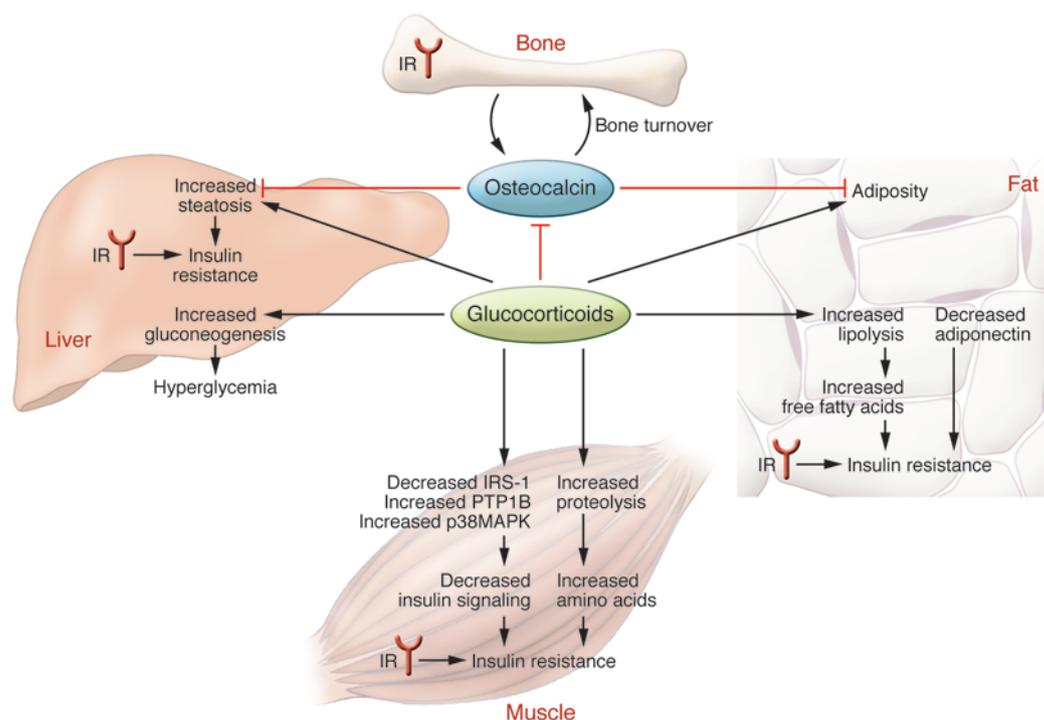
**Glucocorticoids are a powerful tool used to treat a range of human illnesses, including autoimmune diseases and cancer, and to prevent rejection following organ transplantation. While lifesaving for many, they come with a steep price, often leading to obesity, insulin resistance, diabetes, and osteoporosis. In this issue of the JCI, Brennan-Speranza and colleagues provide evidence that the osteoblast-derived peptide osteocalcin is one of the drivers of the metabolic derangements associated with glucocorticoid therapy. This novel mechanism could open up new avenues for the treatment of these disorders.**

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Glucocorticoids act by binding to the glucocorticoid receptor and promoting binding of the receptor to glucocorticoid response elements or association with

other transcription factors, such as AP1, leading to either transactivation or trans-repression of target genes. At physiological concentrations, glucocorticoids have effects on multiple metabolic, cardiovascular, and immunologic functions. Pharmacologic concentrations produce their therapeutic benefit of immune modulation by inducing antiinflammatory cytokines, inhibiting inflammatory cytokines, and inducing apoptosis of T-lymphocytes (1) but also cause many undesirable side effects, including increased susceptibility to infection, weight gain, glucose intoler-



**Figure 1**

Mechanisms leading to glucocorticoid-mediated insulin resistance. Glucocorticoids exert their impact on metabolism through several different tissues in the body. In the presence of glucocorticoids there is an increase in adiposity as well as an increase in lipolysis, leading to elevated free fatty acids in the circulation and an increase in insulin resistance. Muscle undergoes proteolysis, releasing amino acids that increase insulin resistance. Postreceptor insulin signaling defects such as a decrease in IRS-1 also contribute to insulin resistance. In the liver, there is increased steatosis, causing insulin resistance, which is compounded by increased gluconeogenesis and hyperglycemia. The bone is the site of osteocalcin production, driven by the IR. Osteocalcin normally participates in bone turnover as well as suppresses increases in adiposity and steatosis. These actions are inhibited by glucocorticoids.

ance, increased skin fragility, muscle breakdown, negative calcium balance and osteoporosis, cataracts, and CNS effects.

### Glucocorticoids and insulin resistance

One of the most distressing side effects for patients treated long term with glucocorticoids is weight gain, often with disfiguring fat deposition. In humans treated with glucocorticoids, the accumulation of adipocytes occurs primarily in the visceral fat and interscapular depots, leading to a characteristic “buffalo hump” and truncal obesity. This occurs through effects of glucocorticoids on differentiation of preadipocytes into mature adipocytes (2). Glucocorticoids also induce insulin resistance, hyperglycemia, and hyperlipidemia. While increases in visceral fat contribute to the insulin resistance that occurs with glucocorticoid therapy, direct actions of glucocorticoids on muscle, liver, and other tissues also play a role.

Glucocorticoids have been shown to inhibit a number of steps in the insulin signaling network through several differ-

ent mechanisms (Figure 1). Insulin acts by binding to its receptor (IR), leading to increased kinase activity and tyrosine phosphorylation of several downstream signaling molecules, including IRS-1 through IRS-4. These proteins then activate the PI3K and MAPK pathways, leading to a range of downstream effects (3). In skeletal muscle, glucocorticoids cause insulin resistance by decreasing transcription of IRS-1, while increasing transcription of two proteins that counter insulin action, protein tyrosine phosphatase type 1B (PTP1B) and p38MAPK (4). A similar increase in transcription of p38MAPK is observed in liver (5). Glucocorticoids also decrease IRS-1 and IRS-2 levels in fat (6, 7), while there is a decrease in IR and IRS-1 phosphorylation in response to glucocorticoids in liver (6, 8). In the 3T3-L1 mouse adipocyte cell line, there is upregulation of MAPK phosphatases, leading to downregulation of p38MAPK phosphorylation (8).

Factors secreted by adipose tissue, referred to as adipokines, also act to modify insulin sensitivity of tissues. One of

these, adiponectin, promotes insulin sensitivity in tissues and is suppressed by glucocorticoid treatment, serving as yet another component in the insulin resistance seen with glucocorticoid therapy (9). Glucocorticoids also promote proteolysis, lipolysis, free fatty acid production, and fat accumulation in the liver, which can contribute to insulin resistance (9). In addition, glucocorticoids directly promote hepatic gluconeogenesis, increasing hyperglycemia. Pancreatic  $\beta$  cell dysfunction allows further hyperglycemia to develop, likely contributing to the progression to frank diabetes sometimes seen with chronic glucocorticoid therapy (9).

In this issue of the *JCI*, Brennan-Speranza and colleagues provide evidence for a new mechanism of glucocorticoid-induced insulin resistance in which glucocorticoid action on bone decreases the levels of the osteoblast-derived peptide osteocalcin, which in turn contributes to the insulin resistance and metabolic derangements associated with glucocorticoid therapy (10).



### Bone as a modulator of glucose homeostasis and insulin resistance

Osteocalcin, or bone  $\gamma$ -carboxyglutamate (gla) protein (BGLAP), is a small, highly conserved protein made by osteoblasts that is secreted into the circulation and associates with the mineralized matrix of bone. Osteocalcin is also expressed at a low level in preadipocytes and has been shown to be secreted by human subcutaneous and omental adipose tissue in culture (11, 12). In 2007, the Karsenty laboratory reported a surprising connection between bone and glucose homeostasis when they observed that osteocalcin knockout mice are glucose intolerant and insulin resistant (13). These mice also have larger fat pads and increased triglycerides. The proposed mechanisms for these abnormalities are a decrease in pancreatic  $\beta$  cell mass, leading to hypoinsulinemia, and decreased adiponectin, causing insulin resistance. Another group demonstrated that disruption of the IR in osteoblasts was sufficient to reduce osteocalcin and produce similar metabolic changes (14). Follow-up studies have shown that osteocalcin infusion can reduce hyperphagia induced by hypothalamic toxicity and reduce high-fat diet-mediated obesity and insulin resistance, while increasing insulin secretion in response to a glucose challenge (15). Indeed, daily injections of osteocalcin in mice fed a high-fat diet result in decreased weight gain, decreased insulin resistance, reduced hepatic steatosis, and increased energy expenditure (16).

### Osteocalcin and the glucocorticoid problem

The observation that glucocorticoids inhibit the transcriptional activation of osteocalcin through transrepression made decreases in osteocalcin a possible candidate for glucocorticoid-mediated bone loss (17). However, knockout of the osteocalcin gene in mice results in increased, not decreased, bone formation (18). In an attempt to address the contribution of osteoblasts to glucocorticoid-mediated bone loss, Brennan-Speranza and colleagues used a transgenic mouse, Col2.3-11 $\beta$ HSD2, which selectively overexpresses 11 $\beta$ -hydroxysteroid dehydrogenase type 2 in osteoblasts and osteocytes (19). This results in accelerated breakdown of glucocorticoids in osteoblasts and osteocytes, without modulating glucocorticoid activity in the rest of the animal. While the bones of transgenic mice were partially protected from the adverse effects of systemic

glucocorticoids, the more surprising phenotype was protection from the obesity, hyperlipidemia, and insulin resistance produced by glucocorticoids. Indeed, these transgenic mice are protected from the weight gain, increased triglycerides, and abnormal glucose metabolism associated with 4 weeks of treatment with corticosterone. This is accompanied by a partial rescue of osteocalcin levels (10).

In order to determine whether osteocalcin is the mediator of these osteoblastic effects, as previous data would suggest, these authors expressed osteocalcin in the livers of these mice *in vivo*. This recapitulated the results of previous experiments in the transgenic Col2.3-11 $\beta$ HSD2 mice, significantly mitigating the metabolic side effects of glucocorticoid treatment. These data further strengthen the link between bone and metabolism and establish osteocalcin as a significant mediator of glucocorticoid-induced metabolic disruption.

### Strategies for preventing glucocorticoid-mediated insulin resistance

Will osteocalcin make a move into the clinical realm for the treatment of obesity, diabetes, or glucocorticoid-induced alterations in bone and metabolism? There are certainly suggestions that it has clinical promise. By acting downstream of the glucocorticoid receptor, it appears that it may reverse much of the metabolic phenotype caused by glucocorticoids without interfering with the immunosuppressive effects. Additionally, in humans, serum osteocalcin levels in obese diabetics are lower than in nondiabetics with a similar BMI (20). Likewise, the uncarboxylated form of osteocalcin decreases with increasing obesity (11). The fact that osteocalcin can be given intermittently and achieve the same results as an infusion is also of huge practical significance (16). For these reasons, there may be a place for osteocalcin "replacement" therapy in diabetes and metabolic syndrome in the future. Since osteocalcin may increase insulin secretion (15), this could add to the beneficial effect but also increase the risk of hypoglycemia. However, how systemic osteocalcin therapy will impact bone metabolism is probably the greatest area for concern in the development of osteocalcin as a drug to treat insulin resistance. When glucocorticoid-induced osteocalcin suppression is partially rescued in osteoblasts, there is preserved bone structure but no improve-

ment in bone formation rate; however, osteocalcin knockout mice have increased, not decreased, bone mass (18, 19). How osteocalcin affects bone metabolism in humans will have an enormous impact on the success of osteocalcin as a treatment for human disease.

Other strategies are already being explored to attempt to circumvent the side effects of glucocorticoids while maintaining the therapeutic benefits. One strategy for targeting endogenous glucocorticoid-mediated insulin resistance is inhibition of 11 $\beta$ -hydroxysteroid dehydrogenase-1, which is responsible for converting cortisone to the more biologically active form cortisol. Preliminary studies of one such inhibitor have demonstrated positive effects in the treatment of type 2 diabetes in humans (21), but this needs to be validated in other, larger studies. Also, such an inhibitor would not be useful to block the adverse metabolic effects of pharmacologic glucocorticoid therapy, as it would also block the immunosuppressive effects of the drugs. Another approach is to develop selective glucocorticoid receptor modulators. These take advantage of the fact that many of the genes associated with side effects (e.g., osteocalcin; ref. 17) are modulated through glucocorticoid receptor binding to glucocorticoid response elements, whereas many of the therapeutic effects occur through interactions with glucocorticoid receptor-associated transcription factors, such as AP1 (22). A number of selective glucocorticoid receptor modulators have been studied (22), and at least one is currently undergoing a phase II clinical trial for the treatment of rheumatoid arthritis (NCT01393639). The results are still a few years off, but if this compound is able to suppress the immune system while preventing some of the adverse effects of glucocorticoids, it could mark a major advance for the treatment of glucocorticoid responsive disorders.

Address correspondence to: C. Ronald Kahn, Joslin Diabetes Center, One Joslin Place, Boston, Massachusetts 02215, USA. Phone: 617.309.2635; Fax: 617.309.2593; E-mail: c.ronald.kahn@joslin.harvard.edu.

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## Amazing IL-9: revealing a new function for an “old” cytokine

Edgar Schmitt and Tobias Bopp

Institute for Immunology, University Medical Centre, Johannes Gutenberg University Mainz, Mainz, Germany.

**The incidence of melanoma — the most aggressive form of skin cancer — is dramatically increasing, while the development of innovative therapeutic strategies continues to be challenging, especially due to a lack of knowledge about the molecular mechanisms underlying melanoma progression as well as antitumor immunity. In this issue of the *JCI*, Yong Lu and colleagues report a central role for Th9 cells in antitumor immunity.**

Pro-inflammatory cytokines have long been regarded as beneficial in robust anti-tumor immunity. Specifically, cytokines of the common cytokine receptor  $\gamma$  chain family (such as IL-2, IL-15, and IL-21) have been tested for the treatment of melanoma and other tumors in humans (1). However, there is increasing evidence that depending on the individual tumor, inflammation can lead to either favorable or unfavorable clinical prognosis (2, 3). Recent clinical trials utilizing monoclonal antibodies blocking the inhibitory molecules programmed cell death 1 (PD-1) (4) or cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (5) suggest that aggravation of an adaptive immune response is a promising therapeutic strategy for the treatment of melanoma.

During the last two decades the laboratory of Qing Yi has significantly contributed to our current understanding of potential immunotherapies in human malignancies by describing the role of DCs — and particularly T cells — in multiple myeloma.

In this issue of *JCI*, Yong Lu and colleagues from the Yi laboratory elucidate the role of Th9 cells and the  $\gamma$  chain family member IL-9 in a B16 melanoma mouse model, and found that Th9-derived IL-9 inhibited tumor progression (ref. 6 and Figure 1). In addition, Th9 cells induce IL-9-dependent expression of CCL20 in lung epithelial cells, thereby promoting the recruitment of CD8 $\alpha$ <sup>+</sup>CCR6<sup>+</sup> DCs, leading to a strong activation of tumor-reactive CCR6<sup>+</sup>CD8<sup>+</sup> CTLs. Collectively, the authors demonstrate an IL-9-based antitumor potency of Th9 cells, which is in quality and quantity superior to the immune response steered by Th1 cells. Hereby, the authors corroborate similar

data quite recently published by Purwar et al., showing that IL-9-producing Th9 cells substantially inhibit melanoma growth as well as lung carcinoma growth in a murine B16F10 model (7).

### IL-9 restrains tumor progression

More than two decades ago, IL-9 was identified as p40 or TCGFIII, and it was functionally characterized as a growth factor for repetitively stimulated T cell lines, but not for naive T cells (8). In addition to its effect on T cells, a mast cell growth-enhancing activity (MEA) was demonstrated, and p40/TCGFIII/MEA was renamed IL-9 (8). Subsequent research proved an essential role for IL-9 in tolerance induction and the pathophysiology of allergic asthma, inflammatory bowel disease, microbial infections, and autoimmunity (8).

In the present study, the authors demonstrate that neutralization of IL-9 in a B16 lung metastasis model resulted in strong tumor growth associated with a significant decrease in the number of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, CD8 $\alpha$ <sup>+</sup> DCs, and CD11b<sup>+</sup> DCs in the lung. Further analyses demonstrated that Th9 cell-derived IL-9 prevented tumor progression in prophylactic and therapeutic settings. Previous findings

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