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Glucocorticoid signaling and the impact of high-fat diet on adipogenesis *in vivo*

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Abstract

Our research used glucocorticoids as a medically relevant molecular probe to identify a previously unrecognized ADAMTS1-PTN-Wnt pathway. We elucidated the role of this pathway in regulating adipose precursor cell (APC) behavior to either proliferate or differentiate in response to systemic cues, such as elevated caloric intake. Further, our studies identified the non-muscle myosin protein MYH9 as a key target of this pathway to modulate adipogenesis *in vivo*. These findings enable strategies toward developing novel therapeutics for obesity and related metabolic disorders.

1. Introduction

Adipose tissue, a critical organ with key roles in thermoregulation, metabolism, and energy homeostasis [1], is dynamic, engaging in continuous remodeling to maintain tissue health under normative conditions [1,2]. However, disturbances in this process can result in excessive adipose tissue accumulation and metabolic disease. Such disruptions are of growing concern given current global obesity trends [3], as they can contribute to a wide range of health complications [3–6].

New adipocytes are generated through adipogenesis, in which resident progenitor cells in adipose tissue depots differentiate into mature adipocytes. The mechanisms by which systemic signals converge on APCs and regulate adipogenesis are likely to provide novel insights into the foundation for tools that can be applied to the development of approaches to correct metabolic disturbances. Here, we primarily focus on reviewing our own work that was presented at the Steroid Hormones and Receptors in Health and Disease Conference. While we will also refer to some of the large body of pioneering work done by many other groups, a comprehensive review of the field in general is outside of the scope of this brief

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CRediT authorship contribution statement

Noah K. Babel: Writing – original draft, Writing – review & editing. **Brian J. Feldman:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

report and we would like to acknowledge that there are many investigators that have made seminal contributions to this area which will not be covered in this review.

Our approach was to use glucocorticoids as molecular probes to elucidate systemic signals that converge on APCs and inhibit adipogenesis. The rationale for this approach is, in part, based on the clinical presentations observed in patients with excess glucocorticoids, for example, patients with Cushing syndrome; characterized by excess cortisol levels from either endogenous or exogenous sources, Cushing syndrome shares many clinical features with metabolic syndrome in the absence of overt excess circulating levels of cortisol, including insulin resistance, diabetes, hypertension, dyslipidemia, and abdominal visceral adiposity [7]. The mechanisms behind the selective effect on the visceral adipose depot remain incompletely understood. However, this intriguing aspect of the overlapping phenotypes is consistent with broader epidemiological and biological work indicating that expansion of the visceral adipose tissue is particularly detrimental for systemic metabolism while other adipose depots, such as subcutaneous, appear to be either neutral or even potentially confer metabolic benefits [8]. The pathophysiology that develops in these patients, and the more common metabolic syndrome [7], suggests an overlap in their underlying mechanisms [9].

Our hypothesis, built upon this overlap, posits that glucocorticoids influence the fate of progenitor cells by promoting adipogenic signaling. Indeed, glucocorticoids have long been used as part of a cocktail that induces adipogenesis in cell culture, an invaluable tool that has elucidated important, often cell-autonomous, pathways involved in adipogenesis [10]. However, it has remained unclear which of these pathways are most relevant to the *in vivo* context and how these pathways might connect to systemic signals that modulate adipogenesis physiologically [11]. To broaden our understanding of *in vivo* regulation of adipogenesis, we investigated the effect of glucocorticoids and high-fat diets on the differentiation and proliferation of APCs *in vivo*.

2. Studying adipogenesis *in vivo*

Ex vivo studies of adipogenesis have yielded substantial advances in our understanding of adipocyte biology and cell-autonomous regulation of differentiation. Indeed, detailed maps have been generated, based on an extensive number of studies, that model the molecular events provoked by the induction of adipogenesis in tissue culture [12,13]. Such studies typically employ a cocktail of factors, including glucocorticoids [10]. However, it remains ambiguous as to which pathways are the most physiologically relevant and, furthermore, how systemic signals intersect with and modulate these pathways.

A significant advance in the field was the identification of a bona fide APC in adipose tissue [14,15]. These APCs not only exhibit robust differentiation capabilities but are also amenable to transplantation in animal models, where they are sufficient to reconstitute an adipose depot, thus meeting stringent definitions of progenitor cells [15]. Once defined, methodologies were developed to target APCs *in vivo* using murine models [16]. A suite of techniques, including the use of cell surface markers and genetic tools, enables lineage

tracing of these cells, revealing their activity and progression towards mature adipocytes [17].

3. Systemic glucocorticoid responses

Glucocorticoids serve as potent stimulators of adipocyte differentiation by binding to and activating the glucocorticoid receptor (GR), triggering the formation of a regulatory complex on DNA that modulates the transcription of target genes [18,19,20]. The glucocorticoid/GR regulation of transcription is a mechanism of action that is highly tractable to modern molecular biology techniques, rendering glucocorticoids a useful tool for adipogenesis research [21]. Using the potent glucocorticoid dexamethasone, injected into wild-type mice, we were able to pinpoint key genetic targets responsive to the glucocorticoid systemic signal. Here we will focus on our studies which identified *Adamts1* as a potent glucocorticoid-responsive target gene that modulates APC activity *in vivo* [22,23].

4. ADAMTS1 blocks adipogenesis and increases proliferation of adipocyte precursor cells

These *in vivo* approaches elucidated that systemic glucocorticoids down-regulate ADAMTS1 levels in adipose tissue. Located in the extracellular space, ADAMTS1 presented an intriguing potential link connecting systemic signals and APC activity [23]. Adipose tissue expansion, a process integral to metabolic homeostasis, occurs by both hypertrophy of existing adipocytes and hyperplasia from differentiation of APCs [24]. Systemic signals, including diet and hormones, along with strong depot-specific and context-dependent factors, appear to modulate which mode of expansion occurs. Interestingly, as seen in patients with Cushing syndrome, the glucocorticoid-ADAMTS1 pathway has distinct effects on visceral compared to subcutaneous adipose tissue [24]. Together, these results indicate that ADAMTS1 can function to relay these systemic signals to APCs, toggling the mode of adipose tissue expansion. The combined *in vivo* and *in vitro* investigations employing ADAMTS1 overexpressing transgenic mice (*Adam Tg*) and recombinant ADAMTS1 (rADAM) demonstrate ADAMTS1 as a regulatory switch in APC fate determination [23].

Elevated levels of ADAMTS1 within the adipose tissue *in vivo* result in decreased levels of adipogenesis without impacting adipocyte size, resulting in an overall reduction of adipose tissue mass. Remarkably, the block in adipogenesis was associated with increased APC proliferation, implying that APCs may be obligated to either proliferate or differentiate when prompted by specific systemic signals, including glucocorticoids [23]. Typically, healthy expansion of adipose tissue in response to increased caloric intake primarily involves hyperplasia, promoting metabolic health despite obesity [24]. In contrast, adipose tissue expansion by hypertrophy is associated with adipose tissue dysfunction and the development of metabolic disease [25,26]. Indeed, it is possible that differences in depot expansion defines, or at least contributes, to the discordant metabolic properties of visceral compared to subcutaneous adipose depots. Our findings propose that the ADAMTS1 pathway could direct this divergence, dictating whether adipose tissue expands through hyperplasia or hypertrophy by governing the APC's decision to proliferate or differentiate.

5. PTN is part of the downstream pathway regulated by ADAMTS1

Investigation of ADAMTS1-mediated regulation of APC activity identified pleiotrophin (PTN) as a critical effector downstream of the adipogenesis pathway [23]. Specifically, we observed that ADAMTS1 overexpression in *Adam Tg* APCs induced a dramatic upregulation of PTN, a response mirrored in mature adipocytes both *in vivo* and in response to recombinant ADAMTS1 (rADAM). Our findings resonate with studies conducted by other groups revealing PTN as an inhibitor of adipogenesis; PTN, for instance, is downregulated by miR-143 to facilitate adipogenic differentiation [27]. Conversely, we found that glucocorticoid treatment decreases PTN levels, positioning PTN and ADAMTS1 in an epistatic glucocorticoid-mediated adipogenic pathway. These results, alongside complementary studies in the field, depict a model wherein mature adipocytes act as systemic signal 'sensors,' secreting local factors that modulate APC activity in response to systemic signal shifts [23].

Through the administration of a neutralizing PTN antibody, we were able to suppress the effects of ADAMTS1 *in vivo* in murine models, leading to a reduction in APC proliferation and an increase in adipocyte numbers [23]. This compelling evidence highlights PTN's role in the adipogenic process, and when viewed alongside other studies, suggests that strategic or targeted modulation of this pathway is feasible. Furthermore, additional studies by others suggest a role for PTN may be conserved in humans [28,29].

6. ADAMTS1-PTN regulates Wnt signaling in APCs

In this model, changes in systemic signals are sensed by adipocytes, which, in turn, communicate with APCs to modulate activity. Notably, these communication steps within the 'relay' are extracellular by nature, facilitating the physiological pathway. Ultimately, however, the signal must converge on the APC and direct cell-autonomous molecular events to guide its activity. Our experiments indicate that this occurs through alterations in Wnt signaling within the cell. Wnt signaling is ideally poised to facilitate this transition given that Wnt receptors are membrane-bound cell-surface proteins. Moreover, alterations in Wnt signaling has been shown to profoundly impact the activity of stem and progenitor cells across a variety of contexts [30,31].

7. Diet regulates the ADAMTS1-PTN pathway

Changes in diet, particularly increased caloric intake, is a physiologically pertinent systemic signal that is directly related to obesity and metabolic disease. Therefore, it was of compelling interest to test if the ADAMTS1 pathway discussed above was also responsive to this signal. Accordingly, we first investigated if the ADAMTS1-PTN pathway is modulated in wild-type mice fed HFD. As expected, HFD led to an enlargement of both visceral gWAT and subcutaneous iWAT fat depots [23] Of note, changes in *Adamts1* and *Ptn* expression, as well as modulation in Wnt target gene expression levels, were influenced by diet, similar to glucocorticoids [23]. These changes were depot-specific with the same dichotomous response in visceral compared to subcutaneous adipose tissue, consistent with established depot-specific changes in adipogenesis accompanying increased caloric intake [32] as

well as the distinct metabolic effects mentioned above. Futhermore, the HFD-induced adipogenesis was blocked in Adamts1^{Tg} mice, suggesting that the ADAMTS1 pathway serves as a diet-sensitive switch for APC activity and, thus, is competent to coordinate the adipose tissue response to changes in diet [23].

Next, we extended our investigations to human adipocytes, finding that ADAMTS1 overexpression resulted in heightened expression of PTN and Wnt target genes and reduced adipogenesis—echoing observations from murine models. *In vivo* studies with human volunteers that were placed on a 4-week hypercaloric diet confirmed that the ADAMTS1-PTN pathway is conserved in humans and responds to physiological dietary changes. The pathway's role in both physiological adipose tissue homeostasis and obesity pathogenesis establishes a rationale for targeting this pathway as a strategy for managing metabolic disorders, particularly obesity.

Moreover, when assessing the translational potential of therapeutics, we suggest the consideration of adipogenesis-modulating compounds targeting the ADAMTS1-PTN signaling pathways. These compounds include Wnt activators and even epigenetic modulators, each offering distinct mechanisms of action. For instance curcumin, an established histone acetyltransferase (HAT) inhibitor, activates the Wnt signaling pathway [31]. Conversely, epigenetic modulators, like LSD1 inhibitors, can alter adipogenesis by suppressing the Wnt signaling pathway [33].

8. Extracellular signals converge on MYH9 to regulate adipogenesis *in vivo*

By continuing to follow the ADAMTS1 pathway into the APC, additional novel factors that modulate adipogenesis were identified [34]. An intriguing revelation was the elucidation of the role of the cytoskeletal protein myosin heavy chain 9 (MYH9), a protein previously recognized mainly for its pathogenic role in MYH9-Related Disease (MYH9-RD), but its impact on adipogenesis had not been appreciated [35]. Our studies revealed that the expression of *Myh9* is modulated upon exposure of primary APCs to rADAM [34]. Mechanistically, the ADAMTS1-MYH9 axis appears to act as a critical relay node for Wnt signals, driving adipocyte differentiation. This is of significant interest, as it implies that manipulating the ADAMTS1-MYH9 axis may provide means for crosstalk with other mediators of systemic signals, including those influenced by dietary changes, such as mTOR signaling and, by extension, adipogenesis [36]. Thus, these results suggest that modulation of the ADAMTS1-MYH9 axis could also represent a promising target for developing treatments for dysregulated adipogenesis [36] as the mTOR pathway has been implicated in cancer, type 2 diabetes, and cardiovascular disease [37]. *In vivo* evidence from our study further supports that MYH9 conveys a suppressive impact on adipogenesis, positioning it as a potential regulator of adipose tissue development [34], underscoring the importance of considering the interplay between the extracellular environment and cytoskeletal proteins in the context of adipogenesis [38,39].

9. A Glucocorticoid-HFD-ADAMTS1 pathway

The experimental outcomes elucidate a unifying pathway that interconnects glucocorticoid signaling, HFD, and the ADAMTS1-PTN-Wnt-MHY9 pathway. Given the responsiveness of the ADAMTS1 pathway to glucocorticoids, so too might the HFD response be mediated by endogenous physiological corticosteroids. Enzymes 11β-hydroxysteroid dehydrogenase type 1 and 2 (11βHSD1 and 11βHSD2) control endogenous local glucocorticoid signaling by regulating the bidirectional conversion of inactive and active forms of the hormone [9,22]. Therefore, we tested whether the expression of these enzymes changes in response to HFD. Indeed, we discovered depot-specific changes in enzyme expression levels in response to HFD, which paralleled the visceral versus subcutaneous depot-specific variances in adipogenesis described above, with increase in *Hsd11b1* expression in the gWAT depot and increased expression of *Hsd11b2* in the iWAT [23]. This relationship highlights the depot-specific responses in 11βHSD in the context of HFD [23], suggesting that local/depot-specific glucocorticoid signaling may have an underappreciated role in the adipose tissue response to dietary changes conditions (Fig. 1).

Together, these results elucidate molecular and physiological links between systemic changes (glucocorticoids and HFD) via extracellular messengers (ADAMTS1-PTN) that converge on Wnt-β Catenin signaling and regulate APCs. These pathways mediate important and metabolically relevant activities, including adipocyte progenitor cell proliferation and differentiation (Fig. 1).

10. Conclusion

This review aimed to highlight some insights about the intricate relationship between glucocorticoid signaling, adipogenesis, and obesity derived from employing glucocorticoids as probes for molecular, cellular, and *in vivo* experiments. This approach revealed the ADAMTS1-PTN-Wnt pathway as a key mediator of APC activity. A rationale for using this paradigm has its foundation in the intriguing clinical overlap in patients with Cushing syndrome and those with metabolic disease, suggesting some of the same pathways may be perturbed in both contexts. Indeed, excess caloric intake is a major driver of metabolic disease and, therefore, it is particularly compelling that there is evidence that excess caloric intake (through HFD) is epistatic to this same pathway, including in studies with human volunteers.

The identification of MYH9 as a site of convergence in the regulation of adipogenesis *in vivo* opens up new possibilities for intervention. Our work demonstrates that targeting MYH9 with a myosin inhibitor successfully restores adipose tissue and adipogenesis to normal levels in *Adam Tg*, highlighting the potential of this approach in treating obesity and related metabolic disorders. Of course, extensive further studies are needed to develop and test the translational potential of these findings.

We discussed the concepts of context depot-specificity (visceral versus subcutaneous adipose tissue) in clinical phenotypes and glucocorticoid regulation of APCs in white adipose tissues. However, the implications for other types of fat, including brown and beige

adipose, were not previously mentioned. While glucocorticoids are a canonical component of both brown and beige adipogenesis induction cocktails in *ex vivo* differentiation [40,41], it is largely underexplored if this is physiologically relevant *in vivo;* and the potentially contradictory metabolic effects of inducing brown/beige adipogenesis compared to classical white fat adipogenesis are unresolved. The results of future studies directed at addressing these questions, and the relevance of the above pathways for brown and beige adipogenesis, are anticipated with great interest.

In conclusion, we aimed to use glucocorticoid signaling to advance our understanding of the molecular mechanisms underlying adipogenesis and obesity while offering avenues for the potential development of novel interventions. In future research, we shall aim to further explore the intricacies of these pathways, with the goal of identifying additional molecular mechanisms as well as potential therapeutic targets for metabolic disorders, and their associated pathologies. We have no doubt that steroid hormones, such as glucocorticoids, will remain powerful and medically relevant tools in elucidating this area of biology and guiding the development of novel therapeutics.

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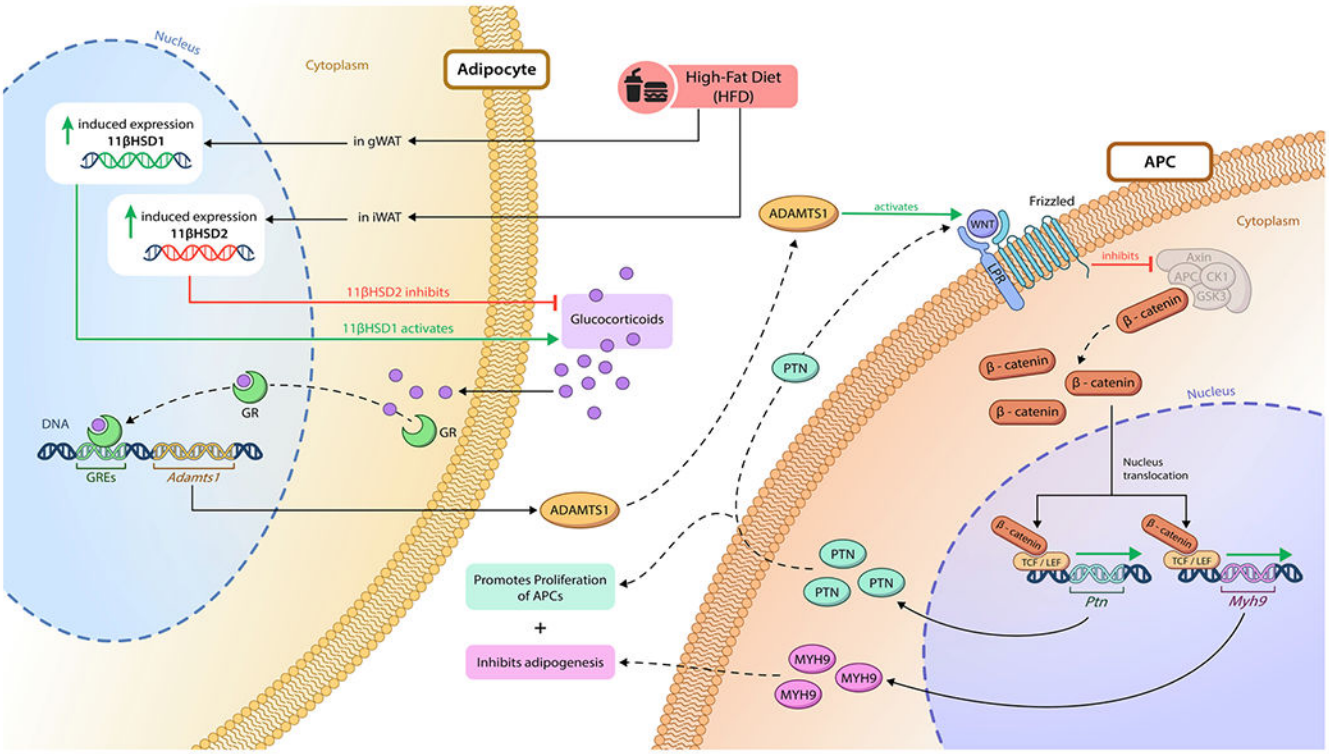

Fig. 1.

Adipocyte-APC Relay. An integrated view of hormonal and dietary influences on APC proliferation and differentiation via glucocorticoid-induced *Adamts1* Activation, PTN upregulation, and modulation of the Wnt/β-catenin-MYH9 signaling pathway.