

JAK Inhibition Induces Browning of White Adipocytes

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Abstract

The global epidemic of obesity is increasing at an alarming rate, posing a severe threat to human health. The accumulation of excess white adipose tissue in obese individuals increases their risk for type 2 diabetes, cardiovascular diseases, hypertension, stroke and even cancer. Current efforts manifest the need to identify potential anti-obesity therapeutics. One promising approach is increasing the activity of 'brown like' adipocytes in white adipose depots, which has been shown to improve the overall metabolic phenotype of the organism. This report by Moisan and coworkers demonstrates a novel and a promising approach by inhibiting JAK kinases to induce browning in white adipose tissue.

Keywords: adipose tissue, beige, browning, obesity, Hedgehog, IFN, JAK, STAT, UCP1

Introduction

Brown adipose tissue (BAT) is a unique organ in mammals. Unlike classical white adipose tissue (WAT), which is mainly involved in storage of energy in form of triglycerides, the main function of brown adipose tissue is dissipation of excess energy as heat¹⁻³. A third type of adipocyte termed 'Beige' or 'Brite' is recently gaining importance⁴⁻⁸. White adipocytes in the subcutaneous adipose depots can be 'browned' in response to a cold or β 3 adrenergic agonist stimuli⁵ to express high levels of the mitochondrial uncoupling protein UCP1. Unlike the classical brown adipocyte that is derived for the Myf5+ lineage of mesenchymal stem cells, white and beige adipocytes are derived from a Myf5 negative lineage (Figure 1). Beige adipocytes are structurally and functionally very similar to the classical brown adipocytes - multilocular lipid droplets, mitochondria rich (which gives them their 'brown' color) and thermogenesis efficient due to increased expression of the mitochondrial uncoupling protein UCP1.^{5,8-10}

Until recently, brown adipose tissue was considered to be active only in newborn babies and absent in adult humans². However, recent

reports suggest the presence of active brown fat depots in adult humans^{2,3}. Interestingly, the brown adipose depots in adult humans are more closely related to beige rather than brown adipocytes found in rodents¹¹⁻¹⁴. This makes induction of adipocyte browning in humans a very attractive target for combating obesity^{15,16}. Currently, there is lack of feasible anti-obesity therapeutic targets that induce browning.

JAKs or Janus Kinases are tyrosine kinases that are associated with the cytokine receptors and are known to activate STAT (Signal Transducers and Activators of Transcription) transcription factors¹⁷⁻²⁰. Although JAK-STAT signaling pathway has been well studied for its role in innate immunity,²¹⁻²⁵ very few studies document its role in adipogenesis²⁶⁻²⁹. One of the recent studies also implicate the role of JAK kinases in brown fat differentiation and function³⁰. The present report by Moisan and coworkers in *Nature Cell Biology*¹² shows that browning of adipose tissue can be achieved by pharmacological inhibition of JAKs.

The Study

In this study, the authors provide a novel platform of using human pluripotent stem cells (PSCs) that can be successfully differentiated into

white adipocytes for use in high throughput screening. The authors established a screening platform to identify small molecules that induce browning of human PSC derived white adipocytes, as measured by UCP1 induction. From 867 small molecules that were screened, they identified five potential candidates for changing the lipid droplet morphology and inducing UCP1 expression in adipocytes –two JAK3 kinase inhibitors and three SYK (spleen tyrosine kinase) inhibitors. The authors further validated the role of inhibition of JAK3 and SYK in induction of UCP1 expression in browning of human primary white adipocytes by using commercially available and clinically relevant inhibitors- Tofacitinib, a JAK inhibitor and R406, a SYK inhibitor. Tofacitinib is a potent inhibitor of signaling through JAK1 and JAK3, but it also inhibits JAK2 with a lower selectivity. R406 although is potent inhibitor of SYK, it also targets JAKs, c-kit, Lck and FLT3. Given the relative abundance of JAKs in PSC derived white adipocytes, the authors show that both these inhibitors act by blocking signaling downstream of the JAK-STAT pathway during the browning of adipocytes, particularly by inhibiting Stat3 phosphorylation. JAK inhibition stably induced UCP1 in mature white adipocytes by remodeling the cellular metabolism, increasing mitochondrial content and respiration. JAK inhibition also stimulated basal lipolysis in adipocytes, which is known to fuel thermogenesis. Although the cells acquire a brown like phenotype, the cells still maintain the white adipocyte lineage markers. The authors thus conclude that JAK inhibition changes the metabolic properties of the cell rather than cell fate conversion. To further decipher the molecular mechanisms underlying adipocyte browning through JAK inhibition, the authors carried out gene set analysis in Tofacitinib treated adipocytes. They identified that IFN signaling (that is primarily mediated via JAK-STAT pathway) was downregulated and the Sonic Hedgehog signaling pathway was activated upon JAK inhibition during browning. The overall conclusion of this study is that JAK inhibition downregulates IFN signaling during browning of

adipocytes. This repression of IFN pathway relieves inhibition on the Hedgehog pathway, which results in upregulation of UCP1 expression and change in metabolic parameters of white adipocytes, thus inducing browning.

Significance

This study shows a direct effect of JAK inhibition on adipocyte browning in vitro. However, the question still persists whether these studies could directly be translated in animals or even human patients. The authors could have demonstrated the role of JAK inhibitors in a rodent model to make to support the in-vivo feasibility of their study. A recent report does demonstrate the role of a kinase-inactive JAK-Tyk2, in adipocyte browning in a mouse model³³. Although inhibition of JAKs, as highlighted in these studies, looks promising, the unwanted side effects of JAK inhibition should also be taken into consideration. JAK inhibitors are currently being used in treatment of Rheumatoid Arthritis and other immune deficiencies^{31,32}. However, their role in browning has not been studied in patients that are currently undergoing treatment with these drugs. This study does highlight a yet unexplored role of JAK inhibitors in browning of adipocytes that could potentially be beneficial in treatment of obesity.

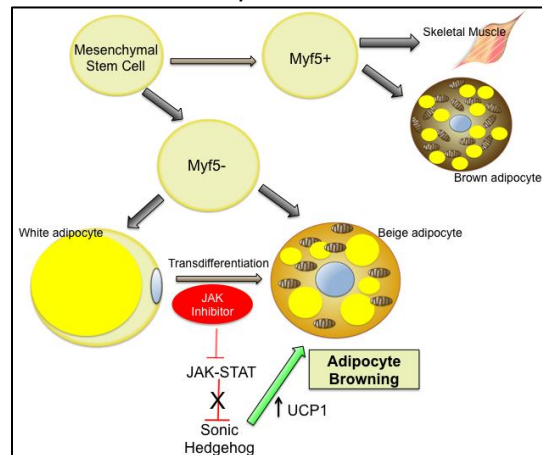


Figure 1: Proposed mechanism of JAK inhibition in adipocyte browning

Conclusion

The benefits of adipocyte browning against obesity and diabetes are gaining much attention. Obesity usually results from an imbalance between energy intake and energy expenditure. Current anti-obesity therapeutics mainly target to decrease the energy intake. Recent studies have however highlighted the importance of developing novel classes of drugs that increase energy expenditure rather than decrease energy intake by potentiating adipocyte browning. Increasing brown fat activity and browning of adipocytes in rodent models has been shown to not only have anti-obesogenic effects, but also to improve insulin sensitivity and glucose homeostasis. Browning can be effectively induced by a cold stress (hours at 4°C) which induce recruitment of beige adipocytes. However this is not really feasible to translate to the human subjects. Bone Morphogenic Proteins (BMPs), Fibroblast growth factors (FGFs) and Irisin have been used successfully in mouse models to activate the beige adipocytes. Treatment with β 3 receptor agonists also showed some promise in the rodent models, but however proved to be unsuccessful in human studies. This further raises a question - how feasible is the approach of pharmacologically targeting adipocyte browning? Additional studies are definitely needed to emphasize the clinical and translational relevance of increasing energy expenditure and translating the results from rodent models to human subjects. The current study provides a novel therapeutic approach that JAK inhibition could be effectively used to induce browning of adipocytes and potentially contributes to the development of a new class of anti-obesity drugs.

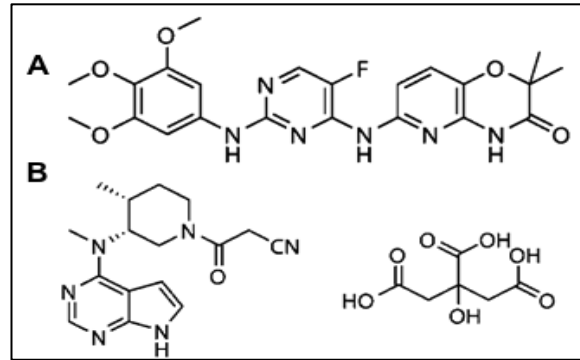


Figure 2: Chemical Structure A) SYK inhibitor R406 B) JAK inhibitor Tofacitinib.

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