

# Class IIa histone deacetylases contribute to skeletal muscle transcriptional and metabolic remodelling and oxidative stress in insulin resistance



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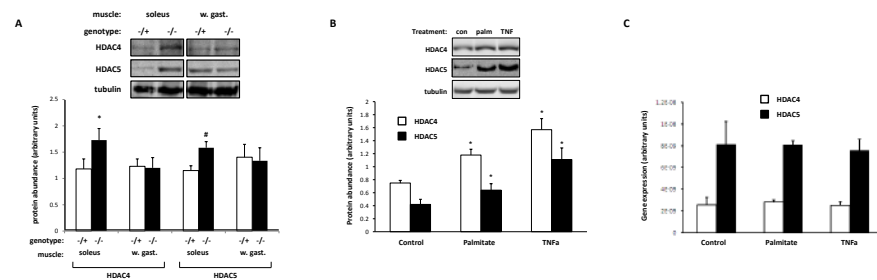
## Introduction and Aims

- Skeletal muscle metabolic dysfunction plays a role in the pathogenesis of metabolic diseases, such as obesity and type 2 diabetes
- The class IIa histone deacetylases (HDAC) are key regulators of muscle phenotype
- The aim of this study was to determine the role of the class IIa HDACs in skeletal muscle metabolism in insulin resistance

## Results

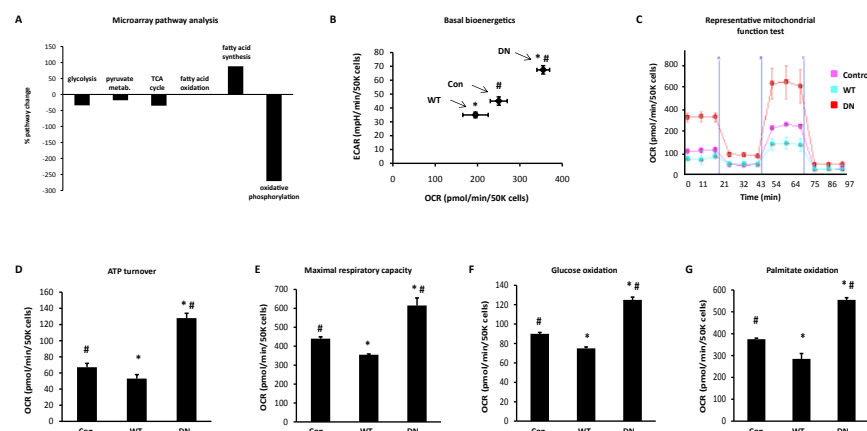
### 1. HDAC4 and 5 are increased in insulin resistance

- HDAC4 and 5 are increased in oxidative skeletal muscle of diabetic *db/db* mice (Fig. 1A).
- Insults that induce insulin resistance, such as palmitate and TNF, increased HDAC4 and 5 in C2C12 myoblasts (Fig. 1B), independently of changes in HDAC4 and 5 gene expression (Fig. 1C).



### 2. HDAC4 and 5 regulate metabolic genes and metabolism

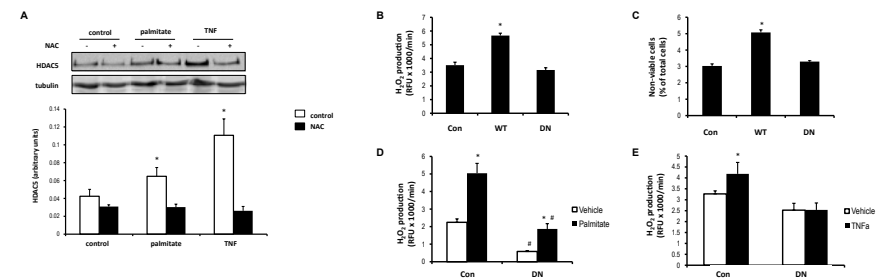
- Microarray analyses revealed down-regulation of metabolic pathways following HDAC4 and 5 over expression in C2C12 myoblasts (Fig. 2A).
- Over expression of HDAC4 and 5 also reduced basal bioenergetics (Fig. 2B), ATP turnover (Fig. 2D), maximal respiratory capacity (Fig. 2E) and glucose and fatty acid oxidation (Fig. 2F and G), as assessed using the Seahorse XF analyzer. Expression of dominant negative HDAC4 and 5 showed reciprocal increases in these parameters.



## Results

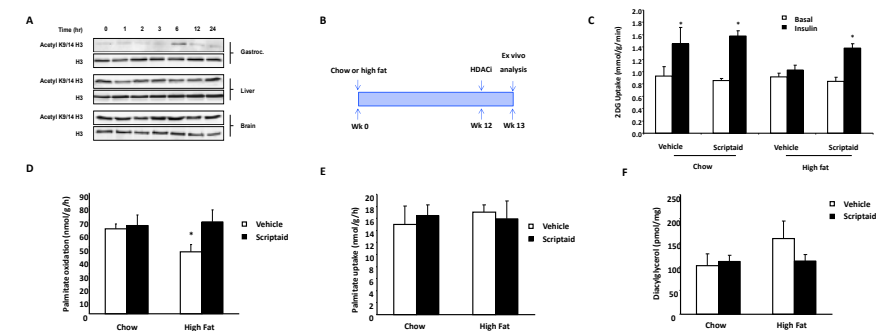
### 3. HDAC4 and 5 are sensitive to, and induce oxidative stress

- The ROS scavenger n-acetylcysteine prevented the increase in HDAC5 by palmitate and TNF (Fig. 3A), suggesting that HDACs are increased due to oxidative stress.
- Over expression of HDAC4 and 5 increased H<sub>2</sub>O<sub>2</sub> production (Fig. 3B), reduced cell viability (Fig. 3C) and expression of DN HDAC4 and 5 ameliorated the oxidative stress response of palmitate (Fig. 3D) and TNF (Fig. 3E).



### 4. HDAC inhibition normalises muscle metabolism in insulin resistance

- The HDAC inhibitor Scriptaid, increased skeletal muscle H3 acetylation (Fig. 4A).
- Mice fed a high fat diet (45%) for 13 weeks received daily Scriptaid i.p. for the final week (Fig. 4B). Scriptaid restored insulin stimulated glucose uptake (Fig. 4C) and fatty acid oxidation (Fig. 4D) in high fat fed mice. Scriptaid did not increase lipid uptake into muscle (Fig. 4E) and showed a tendency to decrease muscle DAGs (Fig. 4F).



## Conclusions

- HDAC4 and 5 are increased in insulin resistant skeletal muscle due to oxidative stress and they down regulate metabolic genes and metabolism, further increasing oxidative stress.
- Inhibition of HDACs normalised metabolism in insulin resistant muscle and could be an effective strategy to treat metabolic disease

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