

2023 CHS Research Symposium

Molecular Mechanisms of Muscle Atrophy in Obese and T2DM Mouse Model

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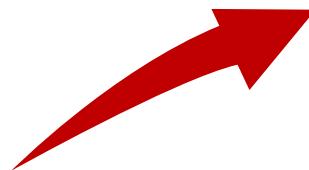
Department of Nutritional Sciences



AUBURN
UNIVERSITY

Obesity, Type 2 Diabetes Mellitus & Western-Style diet

Western-Style Diet
High-fat, high-sugar foods

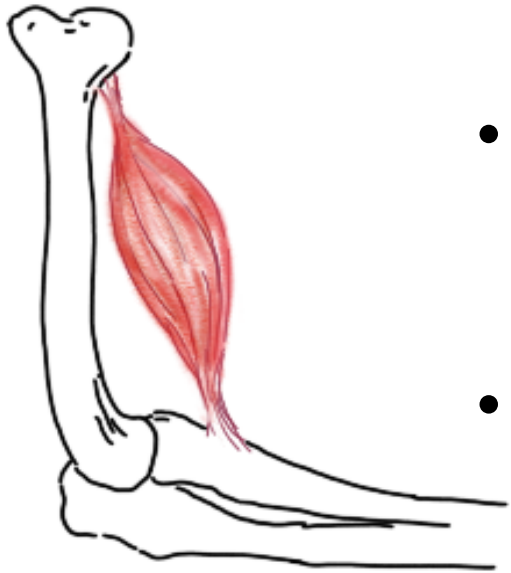


Obesity



Type 2 Diabetes Mellitus (T2DM)

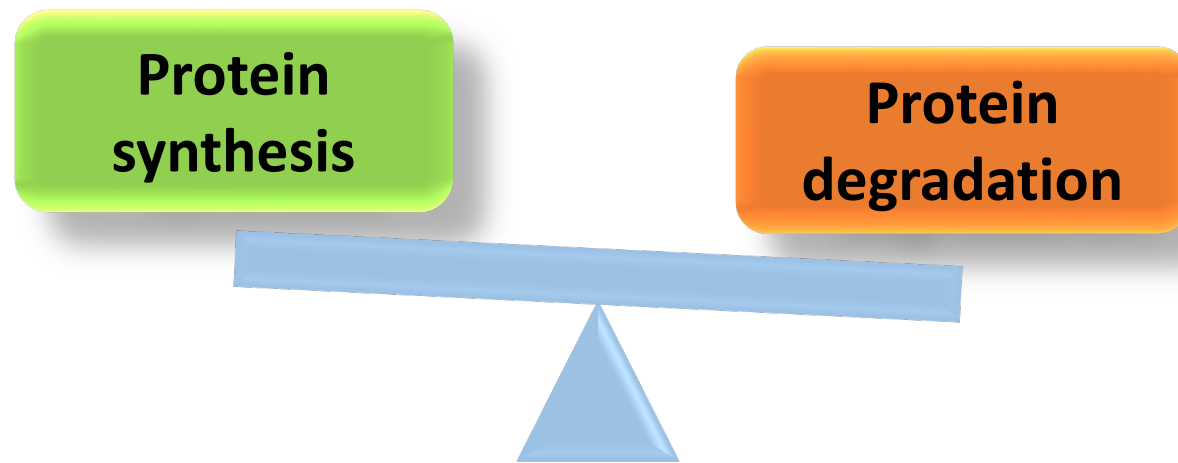
Skeletal Muscle



- Largest organ in the body
 - 30-40% the body weight
- **Functions:** posture, temperature, hormone secretion & nutrient metabolism
 - Major body tissue affected by what we eat!
- Important for prevention of obesity and T2DM

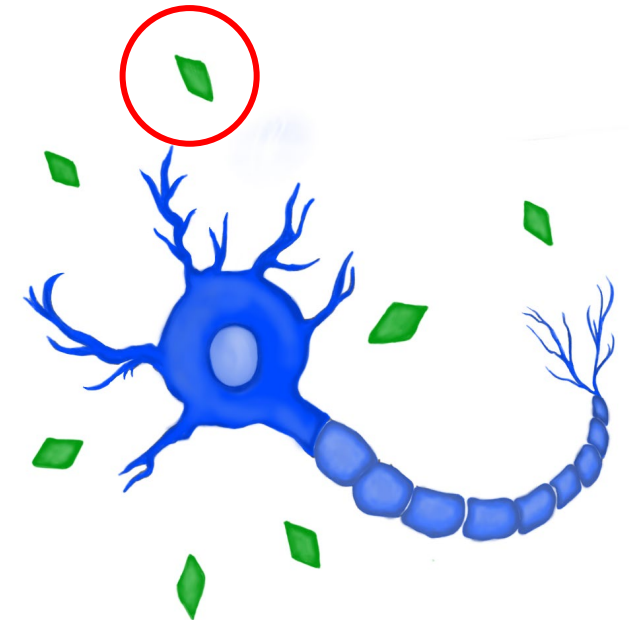
Skeletal Muscle Maintenance

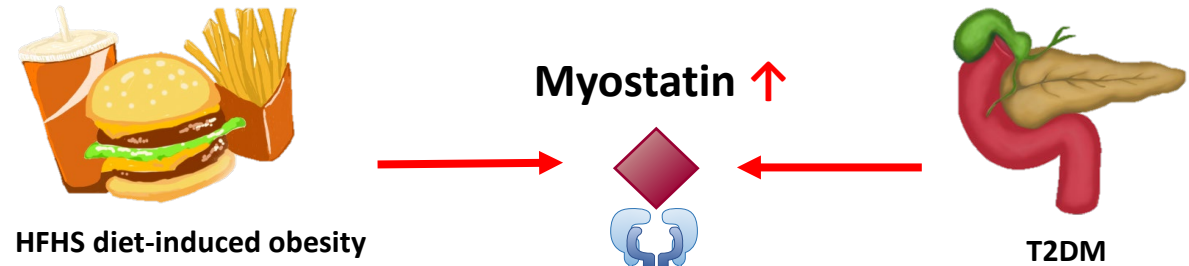
- Balance of **protein synthesis** & **degradation**
 - **Akt**: master regulator of protein synthesis
 - **Myostatin**: master regulator of muscle degeneration



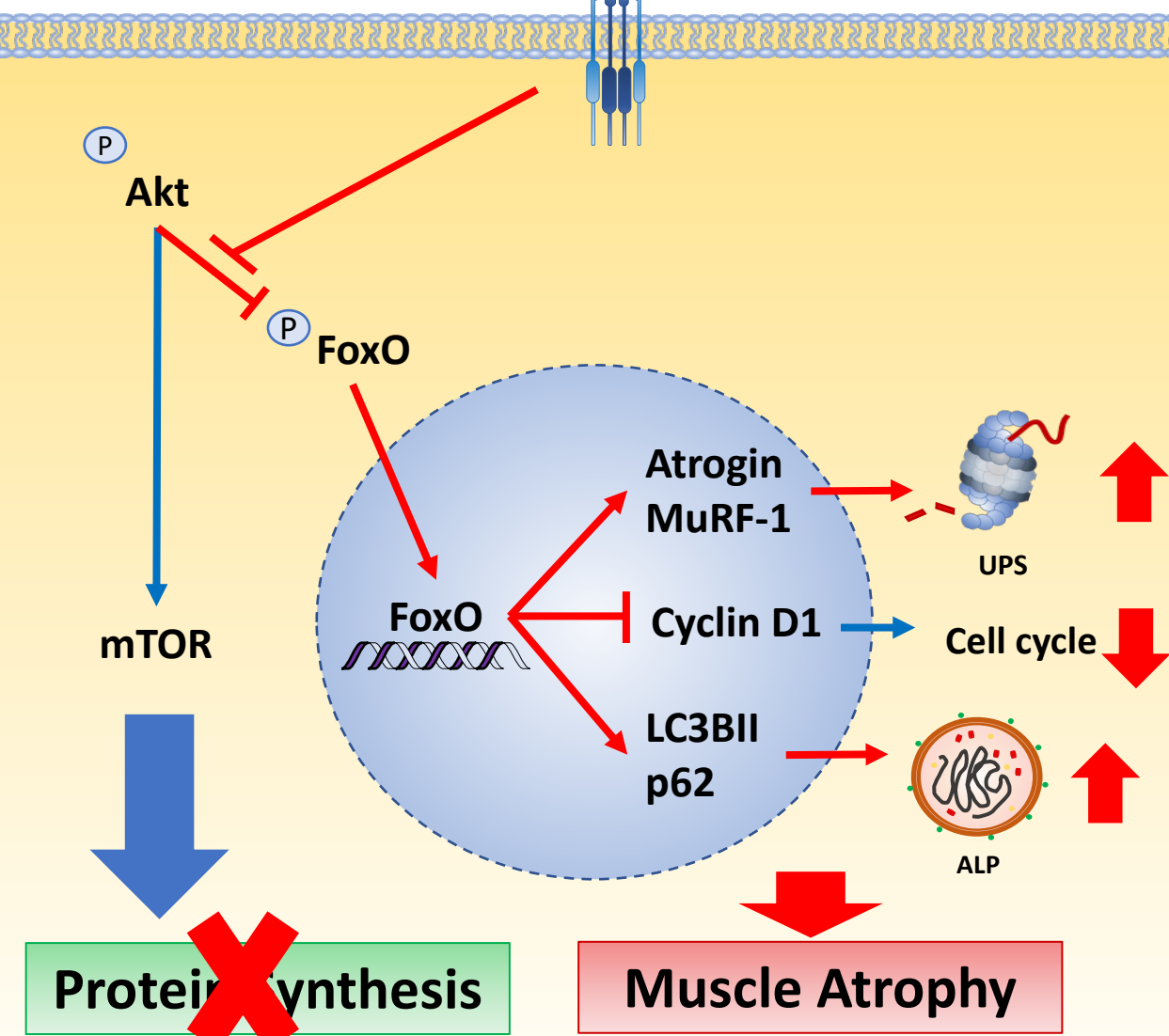
Nerve Growth Factor (NGF)

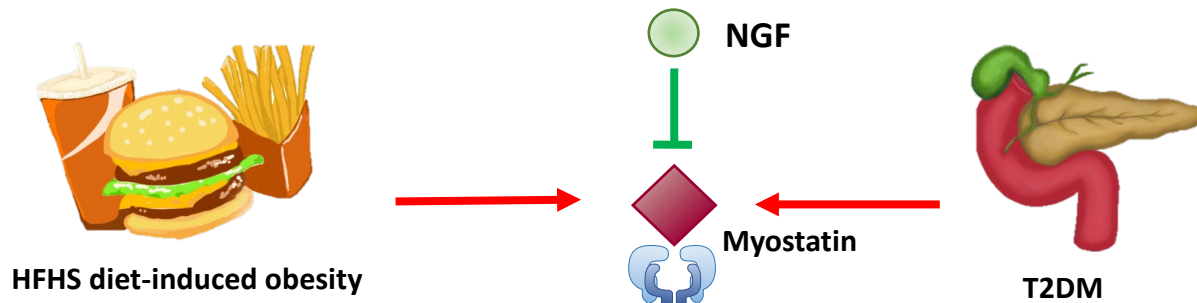
- Member of **neurotrophins**
- Important regulators of **neurons**
- Expressed in central and peripheral nervous system as well as peripheral tissues and organs
- NGF involved in muscle regeneration



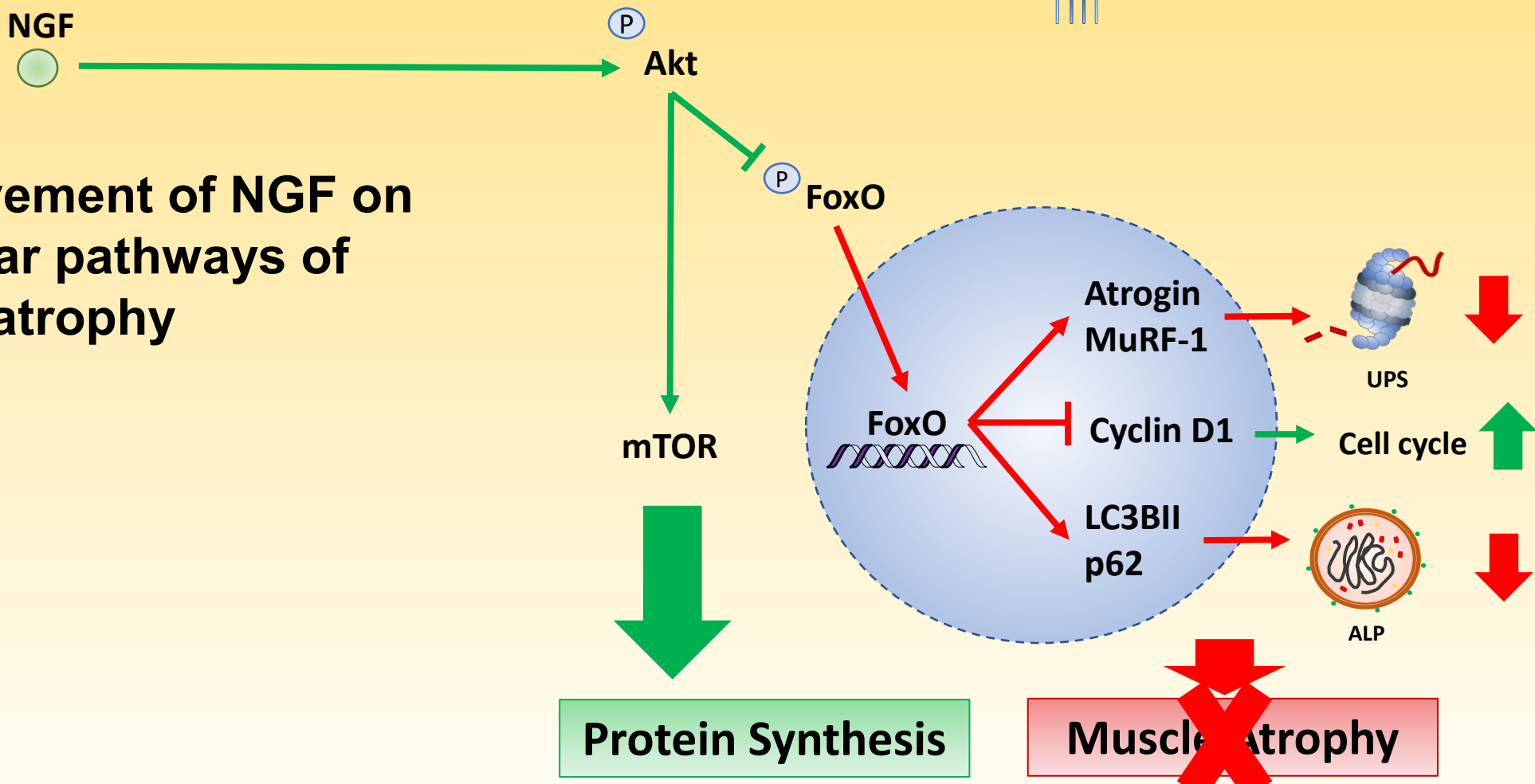


1. Effect of HFHS diet on molecular pathways of muscle atrophy





2. Involvement of NGF on molecular pathways of muscle atrophy



Mouse Model & Body Weight



Lean control

Chow diet
+PBS or +NGF



Obese

HFHS diet
+PBS or +NGF



Diabetic

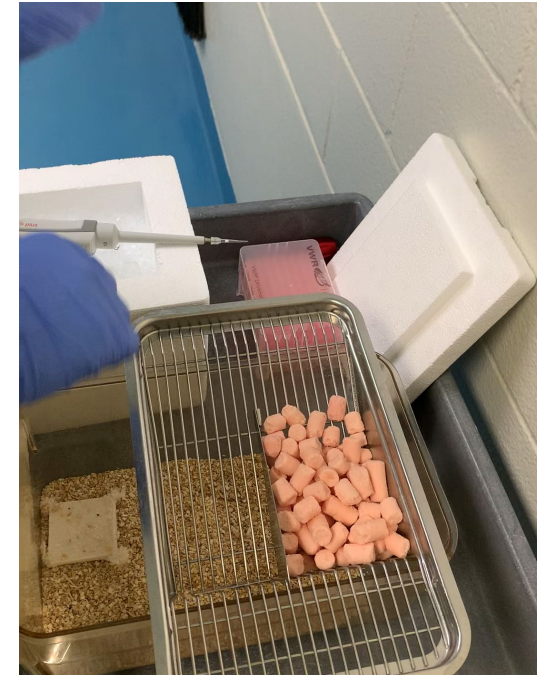
 HFHS diet
+STZ
+PBS or +NGF

*STZ: Streptozotocin

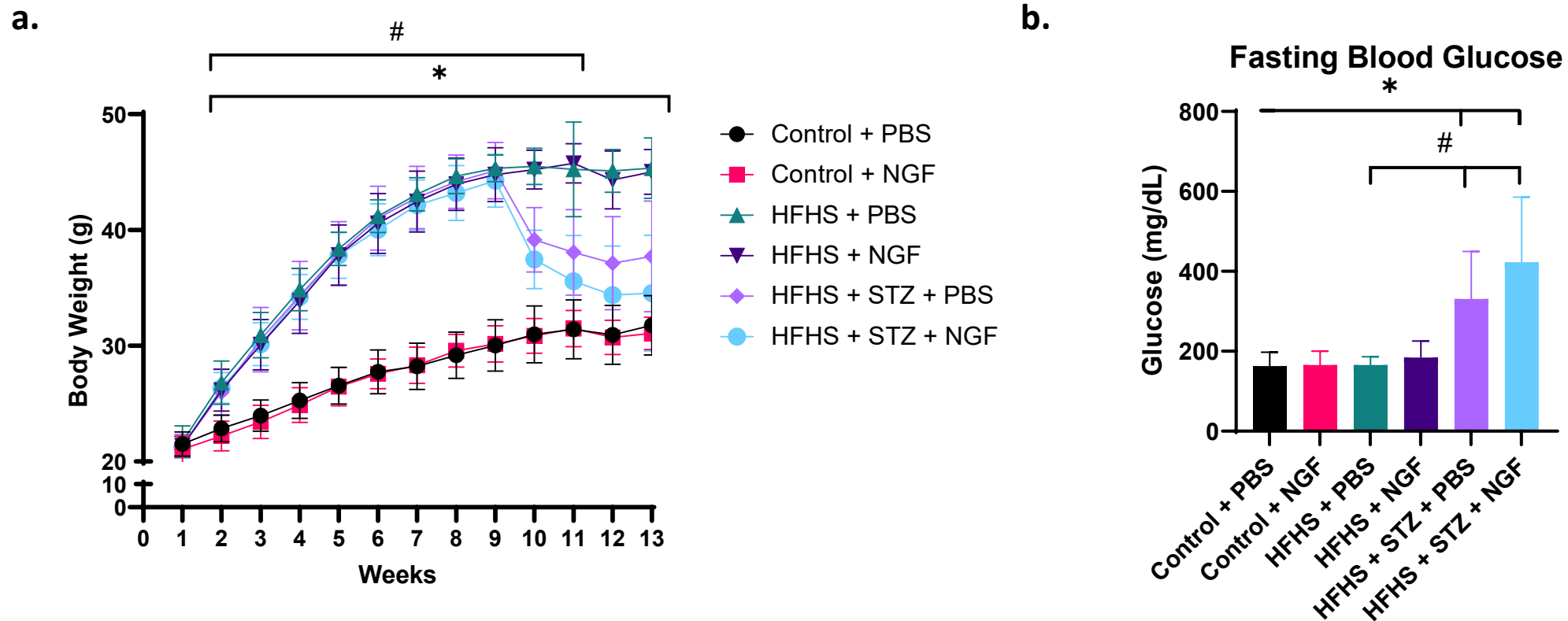
13 weeks

Mouse gastrocnemius muscles were collected and analyzed

Intranasal injection of NGF



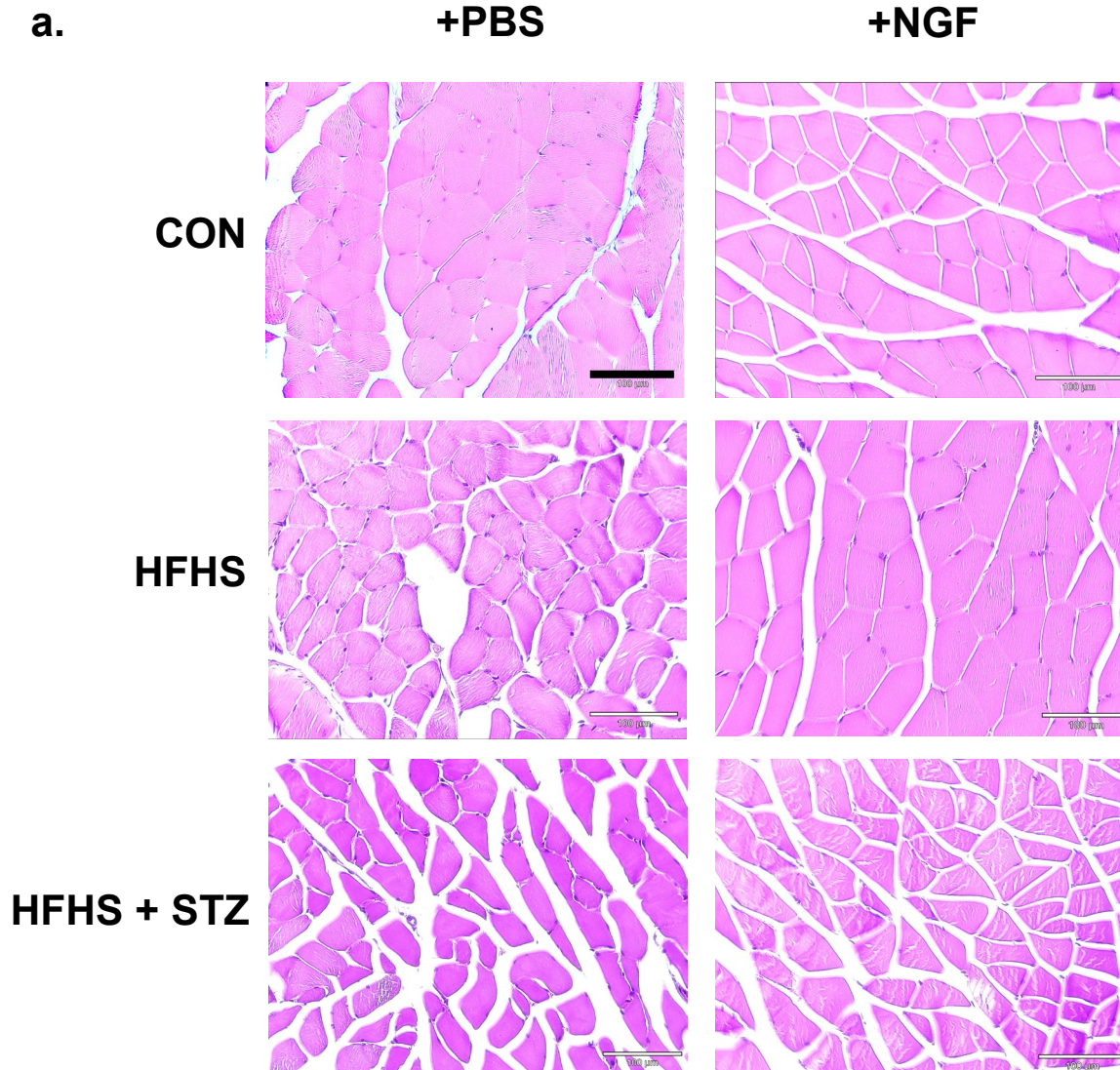
Mouse Body Weight & Fasting Blood Glucose



a. * $p < .05$, Control+PBS (group 1) vs. HFHS+STZ+PBS (group 5); Control+PBS (group 1) vs. HFHS+STZ+NGF (group 6)
 # $p < 0.05$, Control+PBS (group 1) vs. HFHS+PBS (group 3)

b. * $p < .05$, Control+PBS (group 1) vs. HFHS+STZ+PBS (group 5); Control+PBS (group 1) vs. HFHS+STZ+NGF (group 6)
 # $p < 0.05$, HFHS+PBS (group 3) vs. HFHS+STZ+PBS (group 5); HFHS+PBS (group 3) vs. HFHS+STZ+NGF (group 6)

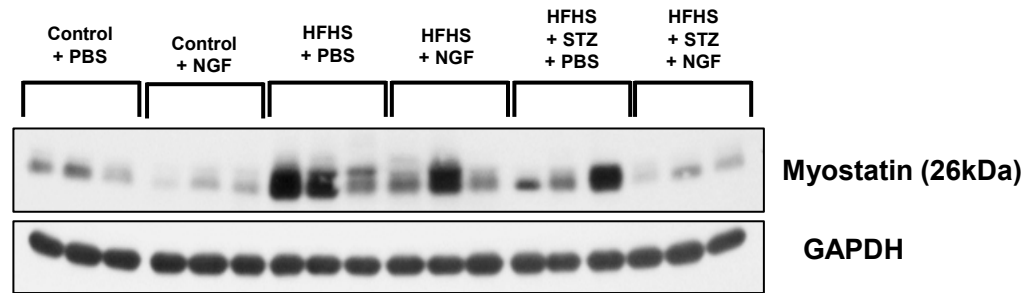
Skeletal Muscle Morphology



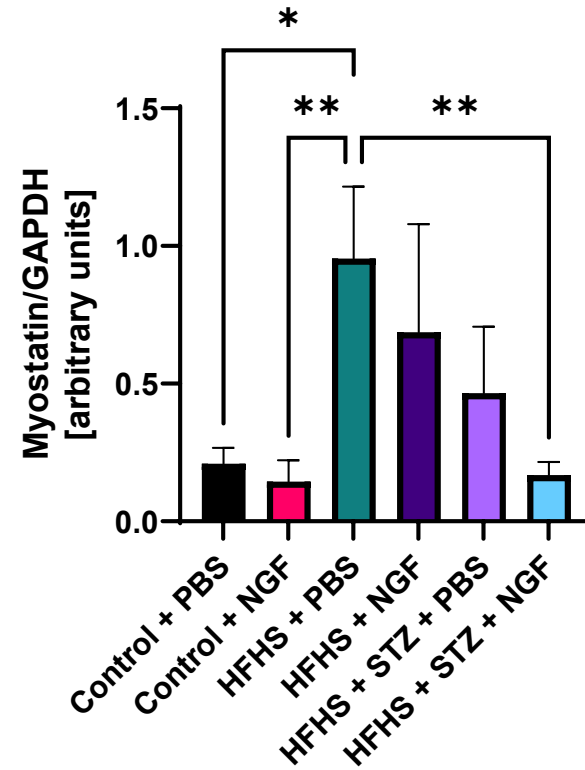
Hematoxylin and Eosin staining, 20x; scale bar 100 μ m; $n=3$

- Muscle fibers of the lean mice show no indications of atrophy
- Muscle fibers of the obese and diabetic mice show some level of muscle atrophy denoted by the separated muscle fibers and lipid droplets between muscle fibers

Myostatin: Negative Regulator of Muscle Mass



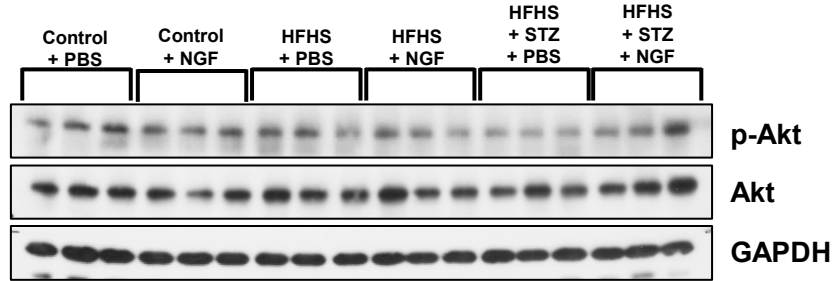
* $p < .05$, group 1 vs 3
** $p < .01$, group 2 vs 3; group 3 vs 6



- Myostatin is upregulated in the obese mice
- NGF reduced the increased myostatin level

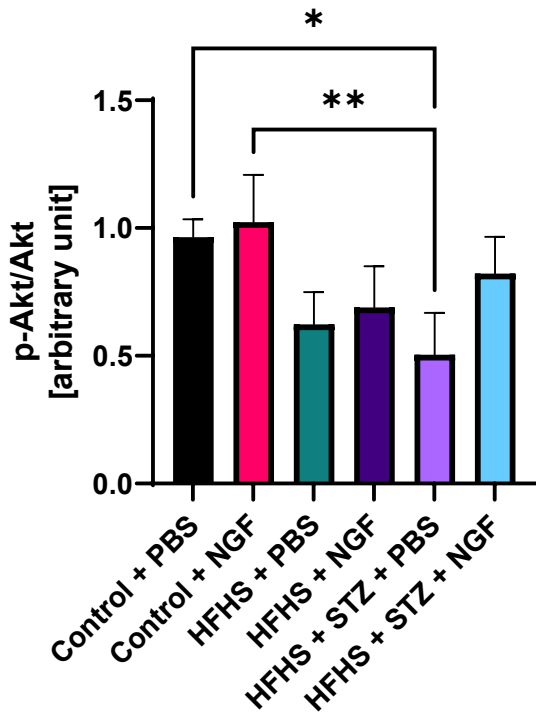
Akt-FoxO Signaling Pathway

a.

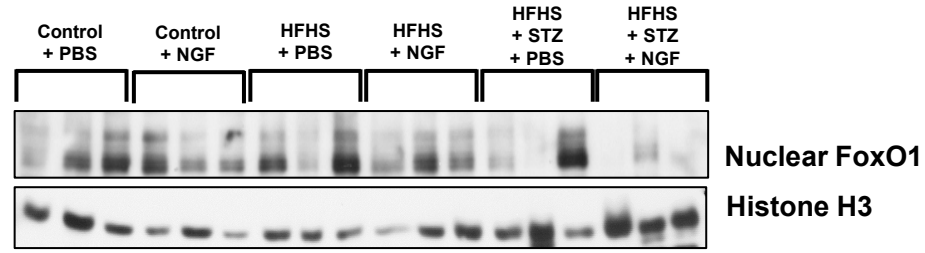


* $p < .05$, group 1 vs group 5
 ** $p < .001$, group 2 vs group 5

b.

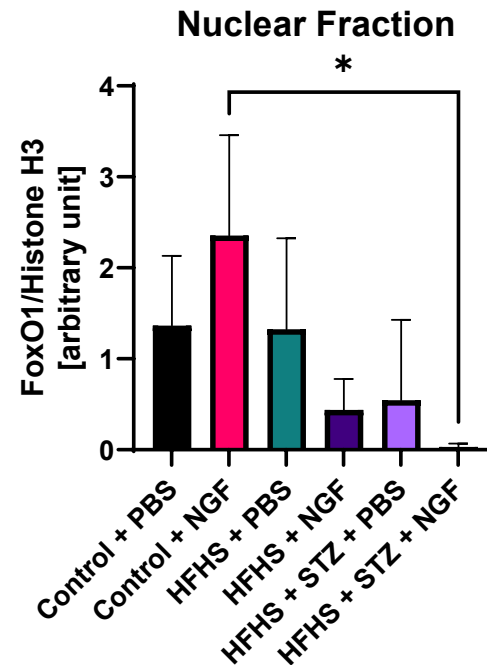


c.



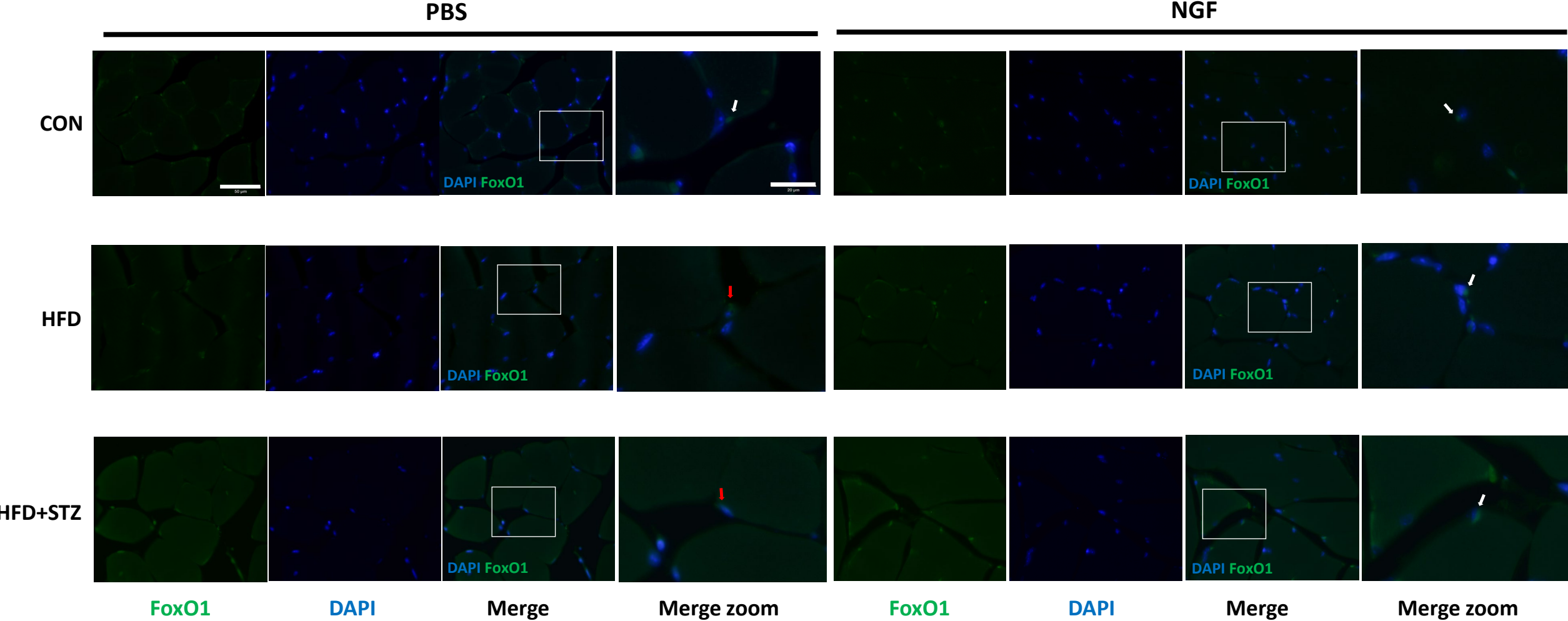
* $p < 0.05$, group 2 vs 4; group 2 vs 6

d.



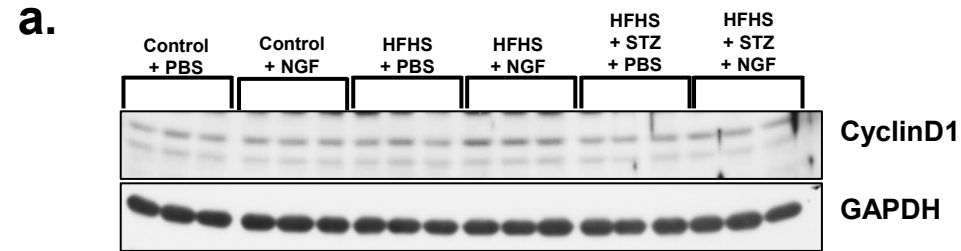
- Protein synthesis is reduced in diabetic mice but improved in NGF group
- Translocation of FoxO1 into the nucleus is reduced in NGF group

FoxO1 Translocation

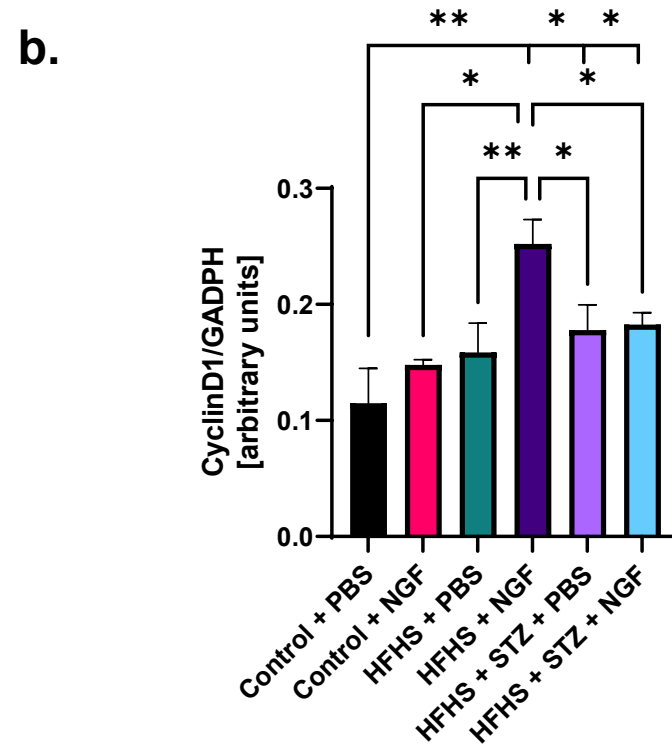


FoxO1 translocation into the nucleus (red arrow) using immunofluorescence method; scale bar 50μm & 20μm (zoom); n=3

Cell Cycling

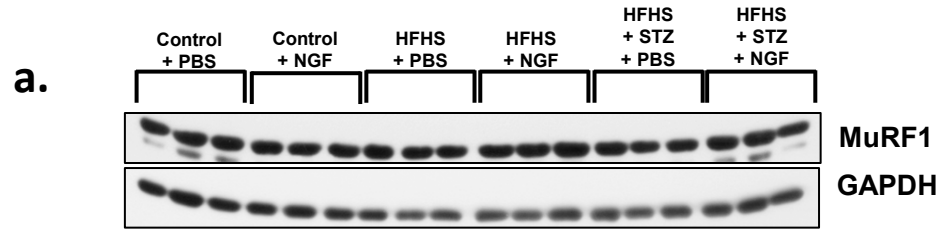


* $p < .05$, group 1 vs group 5; group 1 vs group 6; group 2 vs group 4; group 4 vs group 5; group 4 vs group 6
** $p < .01$, group 1 vs group 4; group 3 vs group 4

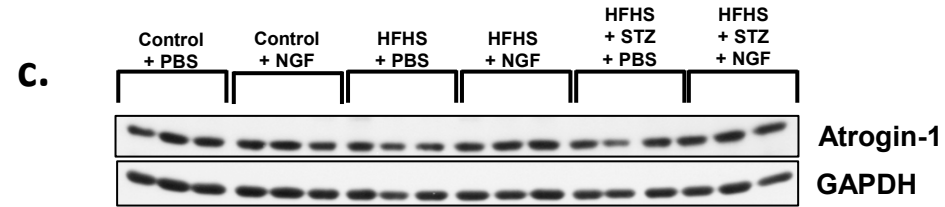


➤ NGF enhances cell cycling in obese mice

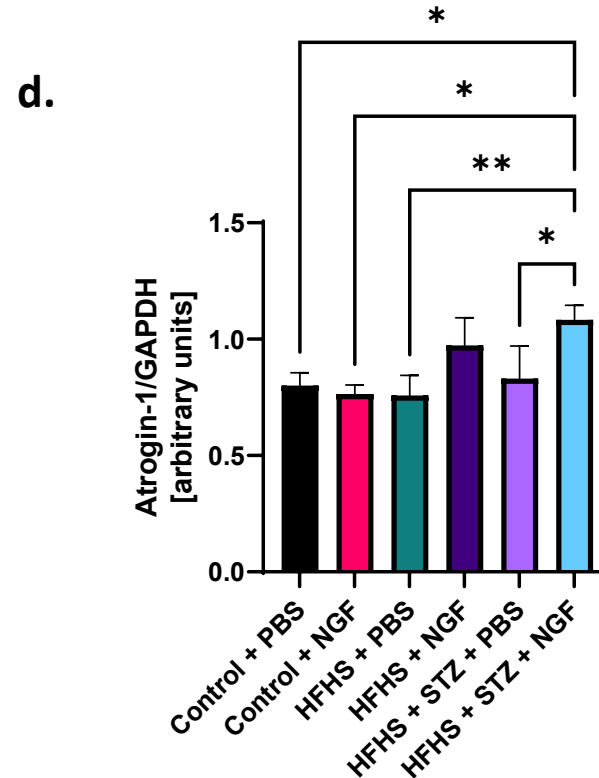
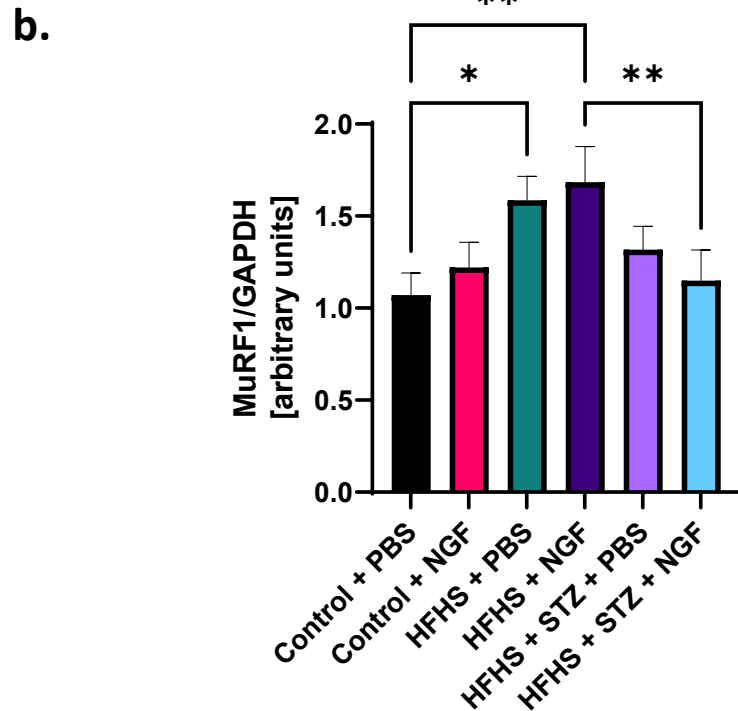
E3 Ligases of the Ubiquitin Proteasome System



* $p < .05$, group 1 vs group 3; group 2 vs group 4; group 3 vs group 6
 ** $p < .01$, group 1 vs group 4; group 3 vs group 6

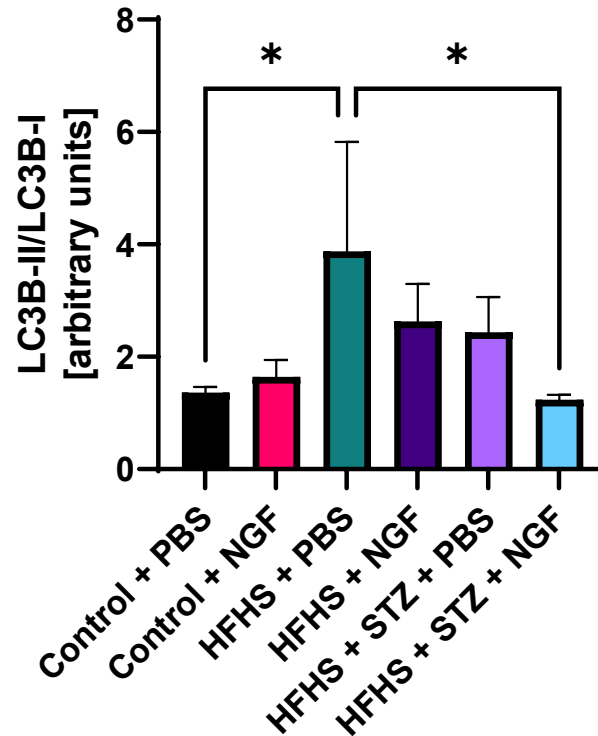
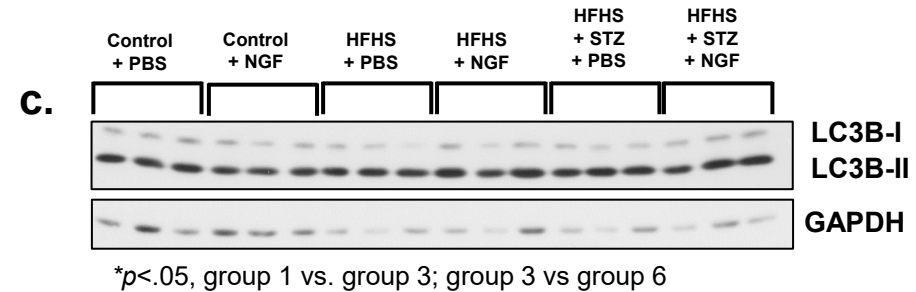
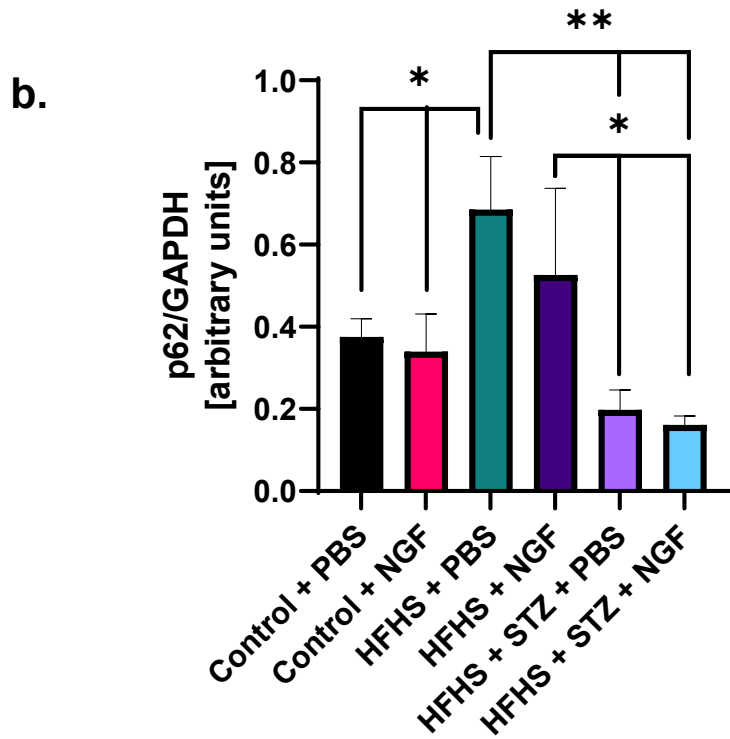
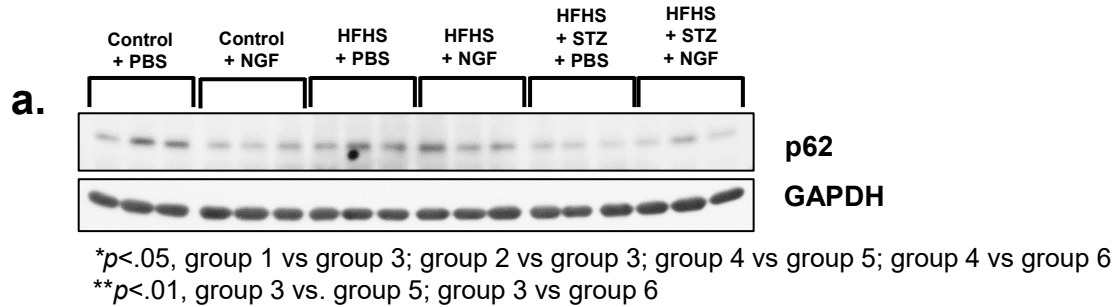


* $p < .05$, group 1 vs group 6; group 2 vs group 6; group 5 vs group 6
 ** $p < .01$, group 3 vs group 6



➤ MuRF1, but not Atrogin-1, is upregulated in obese mice
 ➤ NGF upregulates E3 ligases

Autophagy Markers



- Autophagy is increased in obese mice
- NGF reduces autophagy

Conclusion

Obesity is linked to muscle atrophy

NGF prevents muscle atrophy by inhibiting autophagy

NGF enhances muscle regeneration

- **Future works:**

- Identify the receptor binding of NGF and the subsequent signaling pathway
- Study the role of NGF on apoptosis in the skeletal muscle



**Auburn University
Presidential Graduate
Research Fellowship*

Acknowledgements

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- Hassan Jafari
- Emily Knight
- ← doobu



The image features a dense field of 3D question marks. Most are dark grey and recede into the background, creating a sense of depth. In the center, one question mark is highlighted in a bright yellow color, standing out prominently. Overlaid on this central yellow question mark is the word "Questions?" in a clean, white, sans-serif font.

Questions?