EXERCISE-INDUCED EPIGENETIC CHANGES IN MUSCLE DIFFER BY HIV SEROSTATUS

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BACKGROUND

- We have previously shown that exercise is effective in improving physical function among people with HIV (PWH).
- Whether PWH experience many of the other benefits of exercise is less clear
- Furthermore, whether the mechanisms underlying the effects of exercise are unique among PWH is not well understood.

METHODS

- Sedentary PWH and controls aged 50 to 75 years of age enrolled in a supervised exercise program
- Both PWH and controls completed 24 weeks of supervised exercise, including both cardiovascular (treadmill) and resistance exercise.
- Participants underwent percutaneous skeletal muscle biopsy of the vastus lateralis at baseline and following 24 weeks of exercise.
- Skeletal muscle DNA methylation was quantified on MethylationEPIC BeadChip 850K array (Illumina). Data was normalized and adjusted for batch effects. Pathway analysis was performed using Ingenuity.
- Linear models were fit for methylation values to test for the association of HIV status or exercise, adjusted for age and race/ethnicity to generate differentially methylated positions (DMPs).
- DMPs were used to identify differentially methylated regions (DMRs) between pre- and post-exercise intervention for PWH and controls using Comb-p and adjusted for multiple comparisons.

RESULTS

- Skeletal muscle biopsy samples were available for 16 PWH and 18 controls at baseline, and 14 PWH and 15 controls at week 24.

	HIV (n=16)	Controls (n=18)
Age (years)	55 (53, 60)	55 (51, 61)
Male	16 (100)	18 (100)
Black	3 (19)	1 (6)
Hispanic	2 (13)	3 (17)
Current smoker	5 (31)	2 (11)
Cannabis	9 (56)	4 (22)
Body mass index	25.4 (2.4)	28.5 (5.1)
≥3 comorbidities	12 (75)	7 (39)

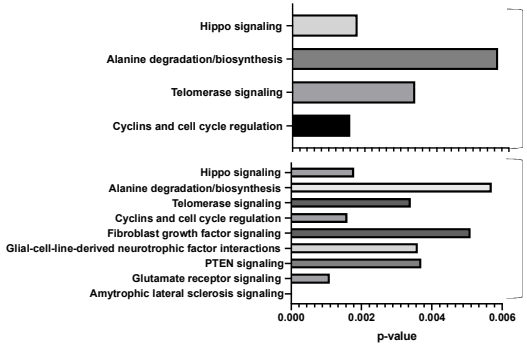
Values presented as median (IQR), mean (SD), or N (%)



Skeletal muscle epigenetic responses to exercise differed by HIV serostatus. ***Adults with HIV*** experienced changes in DNA methylation status of genes involved in oxidative damage, neurotransmission, angiogenesis, and metabolism. ***Controls*** experienced changes in cell cycle, proliferation, protein synthesis.

RESULTS

- Pre-exercise, 983 DMPs differed between PWH and controls.
  - Top canonical pathways included: gas (*γ-interferon*-activated site) signaling (p=3.5E-3), IL-1 signaling (p=6.9E-3) and androgen signaling (p=1.3E-2).
- Post-exercise, 237 DMPs differed between PWH and controls, enriching neuroinflammation signaling (p=5.0E-3) and interferon pathways (p=1.6E-2).



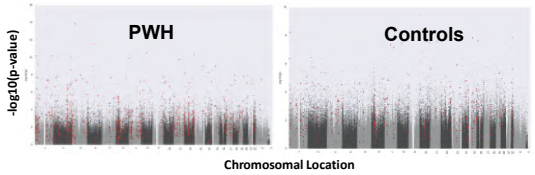
Exercise Effect in Controls: ***Among controls*****, exercise training induced 75 genome-wide significant DMRs.**

Exercise Effect in PWH: ***Among PWH*****, exercise induced 209 genome-wide significant DMRs.**

RESULTS (continued…)

Pathway	Implications	P-value
PWH		
ALS	• Relationship between retroviruses and ALS-like disease	1.3E-6
Glutamate receptor	• Glutamate is the most abundant neurotransmitter	1.3E-6
PTEN	• Regulates signaling pathways involved in cell growth, migration, and apoptosis; cellular metabolism	3.7E-3
Glial-cell-line-derived neurotrophic factor family ligand-receptor interactions	• Broad set of growth factors that tightly regulate many critical aspects of neurons	3.6E-3
Fibroblast growth factor signaling	• Signal transduction, angiogenesis, cell growth	5.1E-3
Controls		
Cyclins and cell cycle regulation	• Cell cycle controls	1.6E-3
Telomerase signaling	• DNA replication, aging	3.4E-3
Alanine degradation/biosynthesis		5.7xE-3
Hippo signaling	• Coordination cell proliferation, death, differentiation	1.8E-3

Differentially Methylated CpGs Pre vs. Post Intervention



DISCUSSION & CONCLUSIONS

- Differences in skeletal muscle by HIV serostatus were less apparent after 24 weeks of exercise.
- Epigenetic response to exercise differed by HIV serostatus, with nearly completely different DMPs among PWH vs controls.
- Future studies will investigate changes in skeletal muscle epigenetic age with exercise

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