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Commentary

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Epigenetic Changes Induced by Exercise

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Physical exercise offers an epigenetic propensity that holds benefits with several health domains, particularly for children and adolescents. Yet, it is only recently that that regular exercise has begun to be construed as a positive epigenetic mechanism to modify the genome-wide DNA methylation pattern in humans [1]. Epigenetics is emerging a science that examines processes-beyond DNA sequence alteration-producing heritable characteristics [2] with exercise regimes, with or without dietary restrictions, as essential epigenetic interventions [3, 4]. Nevertheless, Exercise and nutrition are synergistic in mitigating disorder states with exercise releasing exosomes that contain miRNAs. Nutrition/vitamins B6 and B12 regulate the metabolism of homocysteine, an epigenetic byproduct of DNA/RNA/protein methylation [5]. This type of development ushers in, amongst other aspects, the fact that DNA methylation induces modification of gene expression without causing any the nucleotide sequence. In the context of health problems associated with obesity, Ursu et al. [6] performed FTO rs9939609 genotyping on a Romanian sample of 53 subjects (30 obese, 23 normal).They observed that FTO rs9939609 polymorphism has been identified as a common gene variant in the Romanian Caucasian cohort, suggesting a high association with all the parameters of obesity and obesity comorbidities. It was found that an adherence to a Mediterranean diet was beneficial for participants with genetic predisposition for obesity if maintained over a long interval and combined with sustained physical exercise. Further, hyperhomocysteinemia (HHcy), implicated in elderly frailty and linked to vitamin deficiency, is a risk factor for cardiovascular and neurodegenerative diseases, as well as osteoporotic fractures and complications during pregnancy. Veeranki et al. [7] applied an exercise schedule to reverse HHcy-induced changes in CBS+/- mice showing greater fatigability, due to reduced ATP levels, with a lesser generation of contractile force. Molecular changes, elevated during HHcy were reversed after exercise: amount of NRF-1, a transcriptional regulator of mtTFA, was decreased together with mtTFA protein quantity in homocysteine treated cells, concomitant with an increase in DNMT3a and DNMT3b proteins and global DNA methylation levels.

Despite issues linked to population selection and quantification of exercise, the overall pattern emerging appears to be a product of the utilization of global methylation as an outcome measure, not depicting changes in DNA methylation at the gene-specific level. Thus, particular genes may be methylated differentially in response to exercise-activity; nevertheless, certain genes may be hypomethylated, and others hypermethylated, thereby causing little to no global alteration [8]. Brown [9] has attempted to analyse (i) the effect of exercise on DNA methylation and (ii) the role of imprinted genes in skeletal muscle gene networks. Thus, six imprinted loci (RB1, MEG3, UBE3A, PLAGL1, SGCE, INS) were important for muscle gene networks, while meta-analysis uncovered five exercise-associated imprinted loci (KCNQ1, MEG3, GRB10, L3MBTL1, PLAGL1). DNA methylation decreased with exercise (60% of loci). Exercise-associated DNA methylation change was stronger among older people (i.e. age accounted for 30% of the variation). In a critical review of physical activity and its influence on

DNA methylation from 25 selected articles, Voisin et al. [10] concluded that both acute and long-term exercise schedules impacted upon it in a highly tissues and gene-specific fashion. Among the genes whose methylation levels were changed significantly by exercise were those involved in metabolism, muscle growth, haematopoeisis and inflammation, with intensity, duration and frequency of exercise important factors.

In order to study genomic mechanisms involved in exercise-induced behavioral changes, Kim et al. [11] examined whether or not the effects of restrain stress treatment upon depression-induction and amygdaloid biomarkers together with exercise-induced reversal. Chronic restrain stress induced depressive behaviors, immobility and time spent in target zone that were ameliorated by the scheduled forceful exercise intervention. These behaviors were accompanied by a global reduction of G9a histone methyltransferase and H3K9me2 at the oxytocin and argenine vasopressin promoters; exercise intervention increased the levels of G9a histone methyltransferase and H3K9me2 at the oxytocin and arginine vasopressin promoters in the basolateral amygdala which was linked to suppression of oxytocin and arginine vasopressin expression. In a social defeat-stress (resident intruder) model of anxiety and depression in rats, Patki et al. [12] studied the influence of moderate treadmill exercise (over 2 weeks) upon anxiety-like behaviors and cognitive performance. Both social defeat induced anxiety-like behavior, e.g. time in light region, ambulation, distance travelled and fecal boli counts, and memory impairments (errors in the radial arm maze), and corticosterone levels were alleviated by the exercise regime which normalized social defeat induced elevations of oxidative stress markers (prate in carbonylation, and protein levels of GLO-1/β-actin, GSR-1/β-actin, Mn-SOD/ β-actin, and Cu-Zn SOD/ β-actin). The presence of epigenetic mechanism was implicated histone acetylation of H3 and methyl-CpG-binding modulation in the hippocampus; specifically exercise reversed the stress-induced reduction of BDNF/ β-actin, p-CREB/t-CREB, CAMKIV/ β-actin and elevations of p-ERK [1/2)/t-ERK(1/2)] and IL-6/ β-actin. Finally, Lindholm et al. [13] observed the contribution of DNA methylation and associated transcriptomic changes emerging from exercise-training regimes. These authors obtained consistent and associated modifications, DNA methylation in enhancers, gene bodies and intergenic regions and to a lesser extent in CpG islands or promoters, in methylation and expression, concordant with observed health-enhancing phenotypic adaptations.

Although conclusions concerning exercise effects upon epigenetic modifications are still relatively premature, physical activity-dietary manipulations are being selected may quantify those changes occurring among individuals particularly with immune system inflammaging. Physical exercise offers an epigenetic propensity that holds benefits with several health domains [14, 15, 16]. By applying the rat model of acute restraint stress, using Wistar rats, to examine the influence of stress on the global DNA methylation and on the expression of the DNMT1 and BDNF genes of hippocampus, cortex, hypothalamus and periaqueductal gray, Rodrigues et al. [17] found that the stress treatment induced a decrease in global DNA methylation in hippocampus, cortex and periaqueductal grey matter of sedentary animals and an increased expression of Bdnf in the periaqueductal grey matter whereas in the exercised rats no changes in DNA methylation were associated with stress, although it was linked with abnormal expression of DNMT1 and BDNF in cortex, hypothalamus and periaqueductal grey matter. They concluded that physical exercise had the potential to modulate changes in DNA methylation and gene expression consequent to stress treatment; a case of a positive epigenetic counteracting a negative one. Utilizing the circumstance of intense endurance running exercise (half-marathon) to detect global epigenetic modifications in natural killer cells in 14 cancer patients compared to 14 healthy controls, Zimmer et al. [18] observed that histone acetylation and NKG2D expression, a functional NK cell marker, were elevated for at least 24 h after the running performance. Denham et al. [19] assessed the epigenetic benefits of exercise following sprint interval training by applying a genome-wide leukocyte DNA methylation of twelve healthy young (18-24 years) men before and after four weeks (thrice weekly) of sprint interval training using the 450K BeadChip (Illumina) and validated gene expression changes in an extra seven subjects. They found that exercise increased subjects' cardiorespiratory fitness and maximal running performance, and decreased low-density lipoprotein cholesterol concentration in conjunction with the genome-wide DNA methylation changes thereby altering DNA methylation in circulating blood cells in microRNA and protein-coding genes associated with cardiovascular physiology.

Exercise intensity benefits for positive epigenetic changes in terms of mitochondrial biogenesis were shown by Edgett et al. [20]. Here, healthy human male subjects performed interval cycling at 73, 100 or 133% of peak power output (PPO) and post-exercise changes in gene expression of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1 alpha, a protein encoded by the PPARGC1A gene) and its regulators were estimated in skeletal muscle biopsies. Cycling at 100% of PPO was observed to increase PGC-1α mRNA more than cycling at 73% PPO, although supramaximal exercise seemed to blunt this response, so that a lower increase in levels of PGC- 1α mRNA was seen when compared to both 100% and 73% PPO. Notably, increases in the mRNA levels of the regulators Sirt-1, PDK4 and RIP140 occurred in a manner independent of exercise intensity and muscle activation. Brown [9] identified imprinted genes in skeletal muscle gene networks and observed exercise-associated DNA methylation alterations. These exercise-associated DNA methylation modifications make possible the propensity to rewind the 'epigenetic clock' over the course of the aging process. Denham et al. [21], using an exercise regime consisting of sprint interval training, have shown that the cardiorespiratory fitness of individual participants, 12 healthy young men (18 to 24 years) and their maximal running performance, and decreased low-density lipoprotein cholesterol concentration in conjunction with genome-wide DNA methylation changes. Several CpG island and gene promoter regions were demethylated after exercise, indicating increased genome-wide transcriptional changes, including epidermal growth factor (EGF; involved in cardiovascular disease) which was demethylated and displayed reduced mRNA expression. They observed also that in microRNAs miR-21 and miR-210 (microRNA encoded

by the MIR21 gene), gene DNA methylation was altered by exercise causing a cascade effect on the expression of the mature microRNA involved in cardiovascular function. The viability of health-promoting epigenetic changes arising from exercise must endower attainable advantages for an aging brain and body. Physical exercise and activity, as epigentic interventions, provide essential contributions to respiratory and cardiovascular health and regeneration [22]. Exercise, as a potent epigenetic regulator, implies the potential to counteract pathophysiological processes and alterations in most cardiovascular/respiratory cells and tissues not withstanding a paucity of understanding the underlying molecular mechanisms and dose-response relationships.

Physical exercise has proven cardiovascular benefits but as yet the molecular mechanisms, epigenetics and mortality rates remain largely undifferentiated. There is a plethora of studies involving links between physical exercise/activity and cardiovascular/non-cardiovascular mortality [23-25]. Not least in aging populations afflicted with cardiovascular and other high-risk conditions exercise emerges as a non-invasive 'poly'pill' [26]. Even with relatively light schedules of activity the benefits compared with a sedentary life-style were impressive [27]. Regular physical exercise reduces coronary artery disease morbidity and mortality through systemic and cardiac-specific adaptations: elevation myocardial oxygen demand, a stimulus to increase coronary blood flow and thereby myocardial oxygen supply reducing myocardial infarction and angina and augmenting coronary blood flow through direct actions on the vasculature that improve endothelial and coronary smooth muscle function, enhancing coronary vasodilation [28]. In a group of elderly hospitalized cardiac in-patients, it was observed that gait speed correlated positively with in-hospital physical activity measured by average daily step count and average daily physical activity energy expenditure in all the patients [29]. It has been observed that among clinical and exercise-activity test variables, physical fitness presented the highest C-index for predicting mortality (a measure of discrimination or generalization of survival data utilizing the sensitivity and specificity of test variables). The introduction of a physical activity classification to the model that included the traditional risk factors resulted in a net reclassification significant improvement of 22.8%; adding fitness to the traditional risk factor model resulted in a further net reclassification improvement [30]. In determining the relationships between physical activity, smoking habit and twelve year cardiovascular, non-cardiovascular and all-cause mortality, Holme and Anderssen [31] examined elderly Oslo male participants who were screened for cardiovascular diseases in the years 1972-1973 and 2000. They obtained a strong and negative dose–response relationships between all physical activity exposure variables and cardiovascular, non-cardiovascular and all-cause mortality. Thus, a mortality reduction of forty percent was associated with a moderate use of time (30 min 6 days a week), independent of whether or not the activity/exercise was light or vigorous. Factor modelling by competing risk of non-CV death on CV death and vice versa weakened associations to exposure variables to a certain extent, nevertheless the associations were still significant. Increments in physical activity were as beneficial to patients as smoking cessation in reducing all-cause mortality. They advise that public health strategies to reduce risk in elderly male patients ought to concentrate to a much greater extent on promoting increased physical activity.

Conclusion

The manifest health-beneficial expressions of physical exercise over individuals' life-cycles, whether normal or in ill-health, may be encapsulated within several domains of welfare: (i) exercise and academic performance, (ii) exercise and the developmental trajectory, (iii) exercise for the alleviation of affective disorders, and (iv) the epigenetic manifestations of physical exercise. Not least of importance are the notions of "trainability" and "epigenetic silencing" that modulate the therapeutic value of exercise. Both survival and the delay of mortality are the benefits of physical activity programs with advantages to match smoking cessation in cardiovascular conditions. Surprisingly, the effects of exercise may be determined relatively quickly: just eight weeks of pre-season training on body composition, physical fitness, anaerobic capacity, and isokinetic strength in collegiate taekwondo athletes in endurance gave improvements on all these parameters, as assessed by relative peak power and anaerobic capacity and angular velocity [32].

References

1. Ling C, Rönn T. 2014. Epigenetic adaptation to regular exercise in humans. *Drug Discov Today* 19(7): 1015-1018. doi: 10.1016/j.drudis.2014.03.006
2. Jirtle RL. 2014. The Agouti mouse: a biosensor for environmental epigenomics studies investigating the developmental origins of health and disease. *Epigenomics* 6(5): 447-450. doi: 10.2217/epi.14.58
3. Chalk TE, Brown WM. 2014. Exercise epigenetics and the fetal origins of disease. *Epigenomics* 6(5): 469-472. doi: 10.2217/epi.14.38
4. Whayne TF. 2015. Epigenetics in the development, modification, and prevention of cardiovascular disease. *Mol Biol Rep* 42(4): 765-776. doi: 10.1007/s11033-014-3727-z
5. Tyagi SC, Joshua IG. 2014. Exercise and nutrition in myocardial matrix metabolism, remodeling, regeneration, epigenetics, microcirculation, and muscle. *Can J Physiol Pharmacol* 92(7): 521-523. doi: 10.1139/cjpp-2014-0197
6. Ursu RI, Badiu C, Cucu N, Ursu GF, Craciunescu I, et al. 2015. The study of the rs9939609 FTO gene polymorphism in association with obesity and the management of obesity in a Romanian cohort. *J Med Life* 8(2): 232-238.
7. Veeranki S, Winchester LJ, Tyagi SC. 2015. Hyperhomocysteinemia associated skeletal muscle weakness involves mitochondrial dysfunction and epigenetic modifications. *Biochim Biophys Acta* 1852(5): 732-741. doi: 10.1016/j.bbadis.2015.01.008
8. Horsburgh S, Robson-Ansley P, Adams R, Smith C. 2015. Exercise and inflammation-related epigenetic modifications: focus on DNA methylation. *Exerc Immunol Rev* 21: 26-41.
9. Brown WM. 2015. Exercise-associated DNA methylation change in skeletal muscle and the importance of imprinted genes: a bioinformatics meta-analysis. *Br J Sports Med*. doi: 10.1136/bjsports-2014-094073
10. Voisin S, Eynon N, Yan X, Bishop DJ. 2015. Exercise training and DNA methylation in humans. *Acta Physiol* (Oxf) 213(1): 39-59. doi: 10.1111/apha.12414
11. Kim TK, Lee JE, Kim JE, Park JY, Choi J, et al. 2015. G9a-mediated regulation of OXT and AVP expression in the basolateral amygdala mediates stress-induced lasting behavioral depression and its reversal by exercise. *Mol Neurobiol* (In Press). doi: 10.1007/s12035-015-9160-z

12. Patki G, Solanki N, Atrooz F, Ansari A, Allam F, et al. 2014. Novel mechanistic insights into treadmill exercise based rescue of social defeat-induced anxiety-like behavior and memory impairment in rats. *Physiol Behav* 130: 135-144. doi: 10.1016/j.physbeh.2014.04.011

13. Lindholm ME, Marabita F, Gomez-Cabrero D, Rundqvist H, Ekström TJ, et al. 2015. An integrative analysis reveals coordinated reprogramming of the epigenome and the transcriptome in human skeletal muscle after training. *Epigenetics* 9(12): 1557-1569. doi: 10.4161/15592294.2014.982445

14. Archer 2014. Health benefits of physical exercise for children and adolescents. *J Novel Physiother* 4(2): 203. doi:10.4172/2165-7025.1000203

15. Archer T, Garcia D. 2014. Physical exercise improves cognition and health in ADHD. *J Novel Physiother* 4(3): 208. doi: 10.4172/2165-7025.1000208

16. Archer T, Kostrzewa RM. 2012. Physical exercise alleviates ADHD symptoms: regional deficits and development trajectory. *Neurotox Res* 21(2): 195–209. doi: 10.1007/s12640-011-9260-0

17. Rodrigues GM Jr, Toffoli LV, Manfredo MH, Francis-Oliveira J, Silva AS, et al. 2015. Acute stress affects the global DNA methylation profile in rat brain: modulation by physical exercise. *Behav Brain Res* 279: 123-128. doi: 10.1016/j.bbr.2014.11.023

18. Zimmer P, Bloch W, Schenk A, Zopf EM, Hildebrandt U, et al. 2015. Exercise-induced Natural Killer Cell Activation is Driven by Epigenetic Modifications. *Int J Sports Med* 36(6): 510-515. doi: 10.1055/s-0034-1398531

19. Denham J, O'Brien BJ, Marques FZ, Charchar FJ. 2015. Changes in the leukocyte methylome and its effect on cardiovascular-related genes after exercise. *J Appl Physiol* (1985) 118(4): 475-488. doi: 10.1152/japplphysiol.00878.2014

20. Edgett BA, Foster WS, Hankinson PB, Simpson CA, Little JP, et al. 2013. Dissociation of increases in PGC- 1alpha and its regulators from exercise intensity and muscle activation following acute exercise. *PLoS One* 8: e71623. doi: 10.1371/journal.pone.0071623

21. Denham J, O'Brien BJ, Harvey JT, Charchar FJ. 2015. Genome-wide sperm DNA methylation changes after 3 months of exercise training in humans. *Epigenomics* 13: 1-15 (In Press). doi:10.2217/epi.15.29

22. Zimmer P, Bloch W. 2015. Physical exercise and epigenetic adaptations of the cardiovascular system. *Herz* 40(3): 353-360. doi: 10.1007/s00059-015-4213-7

23. Lollgen H, Bockenhoff A, Kapp G. 2009. Physical activity and all-cause mortality; anupdated meta analysis with different intensity categories. *Int J Sports Med* 30: 213–224. doi: 10.1055/s-0028-1128150

24. Willey JZ, Moon YP, Sherzai A, Cheung YK, Sacco RL, et al. 2015. Leisure-time physical activity and mortality in a multiethnic prospective cohort study: the Northern Manhattan Study. *Ann Epidemiol* 25(7): 475-479. doi: 10.1016/j.annepidem.2015.04.001

25. Wilson MG, Ellison GM, Cable NT. 2015. Basic science behind the cardiovascular benefits of exercise. *Heart* 101(10): 758-765. doi: 10.1136/heartjnl-2014-306596

26. Sanchis-Gomar F, Fiuza-Luces C, Lucia A. 2015. Exercise as the master polypill of the 21st century for the prevention of cardiovascular disease. *Int J Cardiol* 181: 360-361. doi: 10.1016/j.ijcard.2014.12.048

27. Wen CP, Wai JP, Tsai MK, et al. 2011. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 378:1244–1253. doi: 10.1016/S0140-6736(11)60749-6

28. Bruning RS, Sturek M. 2015. Benefits of exercise training on coronary blood flow in coronary artery disease patients. *Prog Cardiovasc Dis* 57(5): 443-453. doi: 10.1016/j.pcad.2014.10.006

29. Izawa KP, Watanabe S, Hirano Y, Matsushima S, Suzuki T, et al. 2015. Gender-related differences in maximum gait speed and daily physical activity in elderly hospitalized cardiac inpatients: a preliminary study. *Medicine (Baltimore)* 94(11): e623. doi: 10.1097/MD.0000000000000623

30. Myers J, Nead KT, Chang P, Abella J, Kokkinos P, et al. 2015. Improved reclassification of mortality risk by assessment of physical activity in patients referred for exercise testing. *Am J Med* 128(4): 396-402. doi: 10.1016/j.amjmed.2014.10.061

31. Holme I, Anderssen SA. 2015. Increases in physical activity is as important as smoking cessation for reduction in total mortality in elderly men: 12 years of follow-up of the Oslo II study. *Br J Sports Med* 49(11): 743-748. doi: 10.1136/bjsports-2014-094522

32. Seo MW, Jung HC, Song JK, Kim HB. 2015. Effect of 8 weeks of pre-season training on body composition, physical fitness, anaerobic capacity, and isokinetic muscle strength in male and female collegiate taekwondo athletes. *J Exerc Rehabil* 11(2): 101-107. doi: 10.12965/jer.150196