LETTER TO THE EDITOR

Physical activity is associated with decreased global DNA methylation in Swedish older individuals

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Sir: Regular exercise has been associated with changes in the transcriptome, and it has been speculated that this could reflect alterations in DNA methylation status [1]. In addition, the epigenetic status of the genome changes not only with age, but also in response to environmental factors such as exercise and diet [1]. There have been a few studies looking at the effects of age and exercise in the methylation status of individual genes [2] and at the association between global methylation status and exercise in cohorts including both middle-aged and older individuals [3]. However, to the best of our knowledge, there are as yet no studies looking at the potential relationship between the amount of physical activity and the level of global methylation in older individuals. We decided to investigate if there was any association between amount of physical activity and genome-wide DNA CpG methylation in a cohort of healthy, older individuals from Uppsala, Sweden.

The analysis was performed in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort. All subjects aged 70 living in the community of Uppsala, Sweden were eligible. The subjects were chosen from the register of community living and were invited to participate in a randomized order [4]. The subjects received an invitation by letter within 2 months of their 70th birthday. Of the 2025 subjects invited, 1016 subjects participated giving a participation rate of 50.1%. The study was approved by the Ethics Committee of the University of Uppsala and the participants gave informed consent. The participants gave information regarding how many times a week they engaged in lighter and heavier (sweat-inducing) physical activity. Four self-reported exercise activity groups were defined as follows: Group 1: Light physical activity < 2 times a week and no heavy activity (n = 56). Group 2: Light physical activity > 1 time a week and no heavy activity (n = 290). Group 3: Light physical activity > 1 time a week and heavy activity once or twice a week (n = 129). Group 4: Light physical activity > 1 time a week and heavy activity > 2 times a week (n = 34).

Global methylation was measured in DNA prepared from leukocytes from a random sample of 509 of the participants using the luminometric methylation assay (LUMA), which utilizes restriction enzymes HpaII and MspI to obtain a ratio that illustrates the amount of methylation in CCGG sequences [5]. The LUMA protocol is described in detail by Karimi et al. [6]. In brief, all DNA samples (250–750 ng of each sample) were subjected to enzyme restriction by either a combination of EcoRI, MspI and Tango™ buffer (Fermentas) or EcoRI, HpaII and Tango buffer (all restriction enzymes from New England Biolabs). Each enzyme mixture was run in duplicate. Following restriction at 37°C for 4 hours, the samples were analyzed by Pyrosequencing® and the HpaII/ MspI ratio for each sample was determined.
A significant association was found between self-reported exercise activity groups and the degree of methylation (ANOVA $p$-value 0.014 following gender adjustments, Figure 1). The LUMA method yields ratios between 0 and 1, where a higher ratio indicates a lower degree of methylation. Mean and SD of the LUMA ratios were 0.24 and 0.02, respectively.

When adjusting for multiple cardiovascular risk factors (gender, systolic and diastolic blood pressure, fasting glucose, LDL and HDL-cholesterol, serum triglycerides, current smoking and BMI) the association between self-reported exercise activity groups and the degree of methylation remained significant ($p < 0.05$ in ANCOVA analysis).

The results of this study show that physical activity is correlated to the degree of global methylation in a cohort of healthy older individuals. Compared to a group with higher physical activity, decreased physical activity was associated with an increased global methylation. The association remained significant after correcting for various cardiovascular risk factors. It is possible that decreased physical activity is correlated to a worsened health status overall, and that this is reflected in the inability to engage in physical activity as well as in the epigenome. Importantly, for a healthy population, global methylation of leukocytes varies with time [7,8]. In addition, it has been found that increased inflammation increases global DNA methylation [9]. Future intervention studies are warranted to determine if increased physical activity could influence the degree of global methylation. In particular, it will be of interest to identify potential genes and gene regions that are affected by ageing and exercise.

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