Summary of NKFIH-KKP 126823 grant

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With the help of the present grant (NKFIH-KKP-126823), we were able to conduct widespread research that allowed us to study VO2max and exercise-associated molecular systemic adaptive response in humans and animals. On elite master athletes, we examined how microRNA levels is associated with the level of physical fitness. Adaptation has many levels from acute adaptation to genotype of adaptation, and epigenetic adaptation is a very important part of adaptive response, changes in microRNA levels are believed to be part of epigenetic changes. Epigenetic responses do not change the sequence of genes but directly regulate gene expression. Importantly, epigenetic adaptation is lifestyle-dependent and it even could be inherited. Besides measuring microRNA levels, we also measured DNA methylation levels of master rowers and sedentary subjects. There are many DNA methylation-based aging clocks to estimate the lifestyle-related progress of aging and predict mortality. It is very well known that aging is associated with decreased physiological function, therefore we measured gripping force, which is a marker of whole body strength, vertical jump, which represents anaerobic power, VO2max, which is a marker of cardiovascular fitness, and assessed memory as well. When we measured the methylation of DNA, isolated from whole blood, it turned out that we could not detect significant differences between trained and untrained individuals. This could mean that the level of physical fitness is not associated with aging, or that the currently available aging clocks are not sensitive enough. With the help of researchers from UCLA, we have created a new DNA methylation-based aging clock, called DNAmFitAge and this clock includes the methylation of physiological function-associated genes. Our paper was published in 2023 and already has 15 citations and our following paper also cited well. We also examined the relationship between DNA methylation clocks and telomere

length and klotho levels, which is considered to be an age-sensitive protein. We further extended our investigation to study the effects of physical fitness and aging on the microbiome. After placing our paper top reprint folder medRxiv, I was called by New Scientist and Euronews for a report. The paper is under revision now. We found that some pro-inflammatory bacteria strain is associated with accelerated aging and anti-inflammatory bacterial species are decelerating DNA methylation-based aging clocks.

We have conducted a six-month exercise intervention study on sedentary subjects aged between 55-70 years old. Because of the pandemic, we had to stop the intervention and restart it after vaccination. This delay was more than a year. We have assessed heart function by echocardiograph, bone and muscle mass by Dexa, gripping force, vertical jump, VO2max, and memory. We also collected stool samples for microbiome analysis. From blood samples, we measured DNA total methylation, and mtDNA methylation is also assessed. One year after the end of the intervention, we remeasured our subjects to see whether the alteration of exercise-related DNA methylations was present one year after the intervention.

In animal studies we have shown the probiotic treatment decreased the accumulation of beta-amyloid in transgenic mice and exercise with the combination of probiotics normalized the brain function of these APP/PS1 mice. We used an electromyograph to measure gut motility, we could not detect significant differences between trained and untrained rats, however training beneficially affected brain function. We further investigated the biochemistry of the intestine and found that exercise has molecular adaptive effects in the intestine. This is one of the first investigations on the effect of the microbiome on the molecular adaptation of the intestine. Our investigation in PGC-1 alpha overexpressed mice was designed to study the possible interactions between mitochondria and microbiome. Our data revealed that PGC-1 alpha overexpressed mice have different gut microbiome than wild mice and exercise training has similar effects in transgenic and wild mice. In addition, the greater endurance capacity of transgenic mice is not associated with better results in tests assessing brain function. Moreover, the difference in microbiome content was not associated with differences in cell signaling and mitochondrial biogenesis-associated proteins in the intestine.

The paper which describes the above mention results is under preparation. On the other hand, we just published our paper, which studies the differences in lipid metabolism between PGC-1 alpha overexpressed and wild mice. We have found that PGC-1 alpha overexpression and exercise training differently modulate lipid metabolism.

We made some new observations on cytosine methylation and guanine oxidation. Guanine has a low redox potential which attracts free radicals and is very prone to oxidation. The promoter regions of genes are rich in guanine, and we pointed out earlier this could influence the gene expression. However, the possible cross talk between guanine oxidation and cytosine methylation is very important and can directly modify epigenetic-related adaptation.

This grant provided a very meaningful, huge help to increase the quality of work in our laboratory. We increased the number of publications, the quality of publications (last year more than 100 impact factors), and more papers are coming. The citations of our papers also increased in the last few years. We are very thankful for the support of this KKP grant.