ENDURANCE EXERCISE TRAINING is one of the fundamental cornerstones in any lifestyle intervention aiming at reducing risk of metabolic disease and improving quality of life (2, 8). However, the molecular events that are induced by exercise have not been fully elucidated. It is for example not known which transcriptional programs are activated or repressed in response to certain types of exercise. Even less is known about the regulatory mechanisms that control these molecular pathways and whether differences in volume, duration, frequency, and intensity of exercise affect their regulation. It has also been observed in exercise intervention studies that not all participants benefit from the intervention, which has led to the conclusion that some individuals may be less prone to respond to exercise than others. It is however likely that not all of these identified “nonresponders” indeed are factual observations and that issues like study design and confounding factors like compliance to the intervention may explain some of these findings.

In a series of papers Timmons and coworkers have battled these questions and substantially increased our knowledge of these fundamental mechanisms in exercise physiology (5). They have previously reported that ~800 transcripts are differentially regulated in response to 6 wk of endurance exercise training in young sedentary males, a group of transcripts coined to “the training-responsive transcriptome” (TRT) (6). In this issue of the Journal of Applied Physiology, these previous studies have been extended with a comprehensive investigation of potential regulatory mechanisms influencing the TRT, like the identification of important transcription factors (TF), genetic variations (both in humans and a novel outbred rodent model), and microRNAs (miRNAs) (4).

The promoter sequences of genes in the TRT were compared in a search for overrepresented TF binding motifs, and three TFs were identified [Runx-related transcription factor-1 (RUNX1), Sex-determining region Y box-9 (SOX9), and Paired box gene-3 (PAX3)]. Interestingly, these TFs have previously been implicated in processes related to adaptation to exercise training, i.e., erythropoiesis (9), oxygen tension (1), and oxidative stress (3). RUNX1 has also been shown to be regulated by muscle activity (10) and influences muscle remodeling (7). Regulation of gene expression by non-coding RNAs, e.g., by miRNA, has emerged in the last years as an important controlling mechanism; however, little is known of how these molecules influence the response to exercise training. Here, Keller et al. (4) report, using a microarray screen of miRNAs, that most of the differentially regulated miRNAs in response to exercise training are downregulated. The functional categorization of targeted pathways indicates that classes of genes like regulation of transcription and metabolism are indeed under the regulation of miRNAs. Several miRNAs targeting the identified TFs—RUNX1, SOX9, and PAX3—were also found to be downregulated by endurance exercise training, thereby identifying an important regulatory system consisting of several miRNAs and the mentioned TFs.

In a complementary analysis, Keller et al. (4) compared the skeletal muscle transcriptional regulation in low vs. high responders with respect to aerobic capacity (n = 8). In this analysis they found more than 100 transcripts differentially expressed (of the ~800 in the TRT), indicating that these genes indeed are important for the adaptation to exercise training. Biological processes found to be overrepresented among these genes were developmental processes, including organ and muscle development. In this context it would be interesting to also investigate if individuals with proportionally high expression of the identified TFs (RUNX1, SOX9, and PAX3) would also be classified as high responders with respect to their ability to adapt to exercise training.

In addition, Keller et al. (4) report the transcriptional regulation of the TRT in a novel rat model selected across 10 generations for high aerobic training responsiveness. The selection did not render any differences in body mass or running capacity before the exercise period between the groups but resulted in a ~43% increase in aerobic running capacity in high responder rats vs. a ~10% reduction in low responder rats. One-hundred seventy-six genes of 457 TRT genes mapped from human to rat were found to have increased expression in high responder vs. low responder rats, supporting the authors’ conclusion that the TRT genes are important denominators for exercise training responsiveness.

In an effort to investigate the influence of genetic variation on the differentially expressed genes in high responders to exercise, Keller et al. (4) present intriguing data of genetic variation in a human population (the HERITAGE Family Study). Here, 3,400 single-nucleotide polymorphisms (SNPs) proximal to 86 genes were investigated in 473 individuals, and 24 SNPs were found to be nominally significant (P < 0.01). Although this is a relatively large exercise intervention study that has been investigated, a much larger sample set is needed to be able to dissect out the genetic contribution to variation in exercise responsiveness. A comprehensive and well-powered screen most probably would call for a collaborative effort similar to what has been conducted for several other traits, like obesity and type II diabetes.

To design and validate exercise programs aiming to reduce risk of disease in a safe and effective way for specific groups of patients, increased knowledge of the molecular response to exercise and the regulation of these processes is crucial. With respect to these needs important knowledge of the complex response to aerobic exercise training is provided by Keller et al. (4) in this issue of the Journal of Applied Physiology, thereby presenting a first step toward individualized exercise interventions to prevent and treat disease.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
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