

Figure S1. The main canonical pathways activated by endurance training. IPA-identified human biological processes modulated by 6 weeks of aerobic exercise training in skeletal muscle. Antigen presentation and signaling processes mediated by integrin, VEGF, IGF1, and IL-4 represented highly significant molecular signatures. Significance is denoted by the threshold line, while the enrichment ratio is denoted by the dot-to-dot orange line.

Figures S2a-c. The top three gene networks activated by endurance training. IPA-identified human biological processes modulated by 6 weeks of aerobic exercise training in skeletal muscle. The colour signifies an increase (red; >1.5 FC) or decrease (blue; >1.4 FC) of gene expression level (**Supplementary data page 1**). TGF- β regulates the response to aerobic exercise training in the highest ranked IPA network (**a**). TGF- β was up-regulated more than 3-fold by 6 weeks of aerobic exercise training in humans as analyzed by SAM, using RMA and MAS5.0 normalization and a FDR of <5%. MAPK-signaling (**b**), and calcium-dependent signaling (CaMK / calmodulin (**c**)) are key-factors in other high-ranking gene networks.

Figure S3. Of the 14 miRNAs observed to be downregulated with aerobic training, four were predicted to target the transcription factors RUNX1, PAX3, and SOX9. Relief of inhibition by these miRNAs may have increased TF activity and permitted the observed >1.5 FC upregulation of a quarter of all predicted RUNX1, PAX3, and SOX9 targets. Furthermore, reconstruction of the RUNX1/PAX3/SOX9-regulated 'interactome' through bibliometric network analysis using the Ingenuity database

generated a network of 316 interacting genes, which further explained part of the TRT.

Figure S4. TopGO (version 1.14.0) in the bioconductor suite (version 2.5) was utilized to explore the biological processes most over-represented in the high responder gene list. It was found that the genes contributed to developmental processes, including organ and muscle development. The topGO package allows genes contributing to significance at one level of the GO to be removed before testing higher levels. We used both this method and classical Fishers tests to examine functional enrichment. The data were similar. Figure S4 shows the results from the classical Fishers test. For clarity only children of the biological process GO related to development are shown. Significant ($p < 0.05$ by Classic Fishers test) GO categories are represented as grey boxes.

Figure S5. The genes identified as being able to predict which subjects will demonstrate high response to aerobic training form one robust gene network in Ingenuity IPA (58), but intriguingly the majority are not regulated by exercise themselves (>1.5 FC increase: red boxes; >1.4 FC decrease: blue boxes). However, IPA identifies ~80 established links (published articles linking two genes together) between the predictor gene network and the top two high responder gene networks (Derived from **Figures 3** and **4**)