Exercise is one of the only non-drug-related remedies known to counteract chronic diseases by enhancing health and improving life span. Although the many benefits of regular physical activity have been recognized for some time, the complex signaling system triggered at the onset of exercise have only recently begun to be uncovered. Exercising muscles initiate a coordinated, whole-body metabolic rewiring which is communicated to distant organs by various molecular mediators. The field of exercise research has been expanding beyond the musculoskeletal system, with interest from industry to provide realistic models and exercise mimetics that evoke a whole-body rejuvenation response. The 18th International Biochemistry of Exercise conference took place in Toronto, Canada, from May 25th to May 28th, 2022, with more than 400 attendees. This review provides an overview of the most cutting-edge exercise-related research presented by 66 speakers, focusing on new developments in topics ranging from molecular and cellular mechanisms of exercise adaptations, diabetes, and aging. It also provides descriptions on how manipulation of these signaling pathways may provide therapeutic avenues for improving human health and quality of life.