Clinical, Medical & Diagnostic Products



How exercise changes the body: molecular atlas maps physical activity responses across 22 tissue types

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Researchers at the Salk Institute in La Jolla, California, USA, have created a detailed molecular atlas to show how sustained exercise affects organs and cells in mice. The resource reveals responses that differ by tissue, sex and biological time, and could eventually help give scientists a complete explanation of how physical activity supports health.

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Exercise can transform the body's capacity to withstand physical demands but the biological processes that underpin its benefits extend far beyond just stronger muscles. Each period of physical activity prompts molecular responses within cells, while repeated exercise can produce adaptations across multiple organs. Scientists have now mapped these responses in unprecedented detail in mice, to establish a reference for how healthy tissues adapts to sustained activity.

The Salk Institute for Biological Studies team has produced a molecular atlas that spans 22 tissues and combines several complementary methods to examine gene activity, proteins, metabolism and chemical modifications to genetic material. The work has revealed that the response to exercise depends on the tissue and cell type, as well as the sex of the animal and the phase of its daily biological cycle.

The study has provided a foundation for further research into the mechanisms through which exercise supports health. It could also help scientists identify molecular indicators of muscle adaptation and investigate approaches to improve performance, recovery and resilience. Such applications remain prospects for further investigation, rather than outcomes demonstrated by the atlas itself.



To understand disease, researchers need a reliable account of how healthy biological systems function. Exercise presents a particularly valuable opportunity to develop that account because it can influence many aspects of physiology at once. A molecular reference that captures these effects can help distinguish normal adaptation from the changes associated with inactivity, dysfunction or illness.

The health benefits of regular physical activity are well established. Research has associated exercise with greater resilience against disease, improved recovery from illness and reduced risk factors for premature death. The Salk study cited previous research that linked exercise to reductions of more than 30 per cent in mortality from all causes – including cardiovascular disease and cancers.

The harder task has been to underpin how and why exercise produces such diverse benefits. Human studies can provide important evidence, but access to tissue for experimentation is rarely possible and not feasible for a study design. Researchers can collect blood and obtain biopsies from some muscles, yet they cannot routinely examine numerous internal organs in healthy volunteers. Animal models therefore offer a means to explore responses throughout the body under controlled experimental conditions.

Here the researchers compared sedentary animals with young male and female mice that had voluntary access to an exercise wheel for a period of eight weeks. They collected samples from 22 tissues at points within both the active and rest phases of the daily cycle. This design allowed the team to examine how sustained voluntary exercise affected different tissues and whether the observed responses varied with sex or biological time.

"Exercise doesn't just change our [skeletal] muscles, it changes many of our organs and cells at different levels – some short-term, some long-term," said Dr. Geraldine Maier, a staff scientist at Salk and joint first and corresponding author of the study.

"Our experimental setup allows us to capture that detail across tissues, and sexes, and in muscle, down to the individual cell types," she said.

The atlas draws its strength from the combination of several layers of molecular evidence. No single method can describe the full response of a tissue to exercise. Gene activity indicates which biological instructions a cell uses, protein measurements reveal another aspect of its functional machinery, and metabolic analyses capture small molecules that participate in cellular processes.

The researchers first used bulk RNA sequencing across all 22 tissues. RNA molecules include the transcripts through which cells use information encoded in genes. Their abundance can therefore help researchers assess



gene activity. Bulk sequencing measures the combined signal from the cells within a sample and provides a broad picture of the response in each tissue.

The team then conducted metabolomic analyses of eight tissues and blood plasma. Metabolomics examines small molecules that cells use or produce through metabolism, the chemical reactions that sustain life. These measurements added information about biochemical activity that could not be inferred from gene expression alone.

Protein analyses provided a further layer of detail. The researchers examined protein abundance in four leg muscles: a hamstring muscle, two calf muscles and the quadriceps. Proteins perform many of the structural, regulatory and chemical functions within cells, so changes in their abundance can help explain how molecular responses relate to tissue function.

The leg muscles showed the strongest responses to exercise at the whole-tissue level. The team therefore examined three leg muscles in greater detail through single-nucleus RNA sequencing and analyses of DNA methylation at the level of individual cells or nuclei.

This finer resolution matters because muscle contains multiple cell populations. A measurement that combines their signals can obscure a strong response within a relatively small group of cells. Analyses at the level of individual cells or nuclei allow researchers to distinguish those populations and identify changes that would otherwise disappear within the tissue-wide average.

DNA methylation adds another dimension to the atlas. It involves chemical modifications to DNA that can influence gene regulation without a change to the underlying genetic sequence. Such modifications form part of the epigenetic system through which cells regulate how they use genetic information.

Some methylation changes can persist longer than fluctuations in RNA or protein abundance. They therefore offer a possible route through which repeated exercise could establish more durable patterns of gene regulation. Their presence does not, however, establish that an adaptation is permanent or reveal how long it will last after exercise ceases.

According to the institute, the study was the first to examine exercise-associated DNA methylation in muscle at single-cell resolution. The approach enabled the researchers to identify responses within particular cell types and relate them to the broader molecular changes that accompanied sustained activity.

Across the atlas, exercise produced widespread but highly tissue-specific responses. Nearly half of the genes examined showed altered activity in at least one tissue, yet no single gene changed its activity across all 22 tissues. The greatest number of transcriptional changes occurred in skeletal muscle.

This pattern illustrates why the effects of exercise cannot be reduced to one universal molecular switch. Different organs have different functions and cellular compositions, and their adaptations reflect those differences. A response that is pronounced in one tissue may be absent from another, even though both contribute to the animal's overall physiology.

Within muscle, exercise also altered DNA methylation in some cell types but not others. These findings demonstrated the value of detailed cellular analyses whereby a combined measurement from an entire tissue could conceal differences between its constituent populations.

Biological time added further complexity. Most tissues showed more changes during the animals' active phase than during their rest phase, although the hypothalamus, kidney and lung did not follow that pattern. The hypothalamus in the brain helps to coordinate physiological functions, including aspects of daily biological rhythms.

The findings suggest that the time at which researchers collect tissue can affect the molecular responses they detect. They do not – by themselves – establish an optimal time to undertake exercise for the greatest physical benefit. Mice and humans differ in their usual patterns of activity and a comparison between biological phases requires more care than a direct comparison between clock times.

Sex also influenced the response. Female mice exhibited broader transcriptional changes and patterns of gene expression that differed from those in males. The team also identified a pronounced sex-specific epigenetic response to exercise. These results reinforce the importance of both sexes within experimental designs and caution against the assumption that one molecular pattern will describe every individual.

Alongside the atlas, the researchers developed a signature of 51 genes from the gene-expression dataset. This signature distinguished exercise-trained muscle from sedentary muscle in both mice and humans. It could provide a useful research tool to identify molecular features associated with sustained exercise and to investigate muscle disuse or dysfunction.

The human result gives the signature particular interest but it does not mean that every response within the mouse atlas will apply directly in people.

"Our atlas gives the field a shared foundation to build on," she added.

In time, these investigations could support more individualised approaches to exercise. Differences associated with sex, tissue and biological phase offer possible explanations for variation in physiological responses. They also identify factors that researchers must consider before they can translate molecular observations into practical advice.

Potential applications include the identification of biomarkers, measurable biological indicators that could help assess adaptation or muscle health. The atlas could also guide research into recovery, performance and injury prevention. Each application will require dedicated studies to establish whether the relevant molecular patterns predict meaningful outcomes.

Joint first author Dr. Manoj Hariharan emphasised that exercise affects the whole body. He argued that a broad tissue atlas was essential to understand those effects and that analyses of individual cells could reveal changes obscured by bulk measurements. He also expressed the hope that the work would encourage further atlases that combine several molecular methods at cellular resolution.

A central unresolved question concerns the durability of the adaptations. Researchers still need to determine how much exercise is necessary to establish a lasting molecular change, how quickly that change fades after activity stops and whether particular cells retain a biological memory of previous exercise for months or years.

The eight-week experiment has supplied a detailed reference for the trained state under the conditions studied.



[From left] Dr. Manoj Hariharan, Dr. Geraldine Maier and Dr. Ramesh Ramasamy debuted a molecular atlas of exercise-associated changes in mice, defining the healthy, exercised-trained state, which could help improve performance and prevent injury. Credit: Salk Institute

Nor does the signature yet constitute a validated clinical test. Further work will be necessary to establish its reliability across different populations, exercise programmes and health conditions.

"Our atlas provides a comprehensive resource for understanding the systemic molecular adaptations to endurance exercise," said Dr. Ramesh Ramasamy, a former computational biologist at Salk and joint first author of the study.

"Now that we have all this data, researchers can begin developing strategies that harness exercise – either alone or in combination with other interventions – to ensure we can all live longer, healthy lives," he added.

The immediate value of the resource lies in the questions it allows other researchers to pursue. A laboratory could select a gene, protein or metabolic pathway that responded strongly in a particular tissue, then conduct experiments to establish its role. Such work would help distinguish a molecular change that contributes to adaptation from one that merely accompanies it.

"Now that we have the data, labs can identify one gene or metabolic pathway they find interesting then dissect that mechanism," Maier said.

To establish how that state develops and persists, future research will need to examine additional time points and the consequences of reduced activity. These studies could help explain why some benefits require continued exercise while other adaptations may endure.

The atlas has made the molecular complexity of exercise more accessible to scientific investigation. Its contribution is a shared reference through which researchers can examine how organs and cell populations respond to sustained activity, test explanations for those responses and assess which mechanisms may ultimately prove relevant to human health.

The research received support from federal grants and private philanthropy. It forms part of the Salk Institute's broader effort to explain the biological foundations of health. Founded in 1960 by Jonas Salk, developer of the first safe and effective polio vaccine, the independent, non-profit institute conducts research into subjects that include cancer, Alzheimer's disease and crop resilience.

For further reading please visit: 10.1016/j.cell.2026.09.044