

CELLULAR PERSISTENCE AFTER RESISTANCE-TRAINING WITHDRAWAL: DISTINGUISHING RETAINED MUSCLE STATES FROM ENHANCED REGROWTH

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ABSTRACT

Skeletal muscle can lose size after resistance training stops while retaining additional myonuclei or altered DNA methylation and protein abundance. The physiological question is whether these retained changes increase subsequent hypertrophy. This critical review distinguishes cellular retention from the amount and rate of muscle regrowth. In this article human training-withdrawal were examined alongside animal experiments addressing nuclear retention and growth regulation. Comparisons accounted for shared participants, assay-specific sample sizes, pre-retraining muscle size and multiple-testing thresholds. In a ten-week training, sixteen-week withdrawal and ten-week retraining sequence, type II myonuclei remained approximately 33% higher in the previously trained arm than in the control arm, without a significant between-arm difference in subsequent fibre-area change. In a seven-week training-withdrawal-retraining sequence, lower-limb lean mass increased by $6.5 \pm 1.0\%$ after initial training and $12.4 \pm 1.3\%$ after retraining relative to the initial value (mean $\pm$ standard error); the comparison of phase-specific gains favoured retraining ($P = 0.022$). A separate ten-week withdrawal investigation identified four retained proteins at a false discovery rate below 0.05 and 29 at a threshold below 0.10. These observations establish retention or altered phase responses under different measurement conditions. Nuclear, methylation and protein changes can outlast measurable muscle enlargement. Their contribution to later hypertrophy requires a growth comparison beginning at the post-withdrawal tissue state and accounting for achieved loading.

Keywords: skeletal muscle plasticity; resistance training; detraining; retraining; myonuclei; DNA methylation; proteomics

INTRODUCTION

Resistance training enlarges skeletal muscle through repeated mechanical loading. When structured training stops, muscle size and strength can decline at different rates, and cellular changes can remain after tissue enlargement has diminished. In Halonen and colleagues' randomized trial, a ten-week training interruption was followed by rapid recovery, with similar final adaptations in periodic and continuous training groups (Halonen et al., 2024). Recovery under that schedule demonstrates the response to renewed exercise; identifying its cellular cause requires measurements beyond strength and muscle size.

Three distinct observations underlie the term *muscle memory*: a training-induced cellular change survives withdrawal; a previously trained muscle grows differently during renewed loading; and the retained cellular change causes that difference. Biopsy measurements can establish retention. Comparisons with a muscle or participant lacking the same

training history can establish a difference in response. A causal explanation additionally requires the retained change to precede, and contribute specifically to, the subsequent growth advantage.

Human investigations have detected retained myonuclei in elbow flexors (Cumming et al., 2024), methylation changes in vastus lateralis (Seaborne et al., 2018), and protein-abundance differences after repeated resistance training (Hulmi et al., 2025). These measurements describe different biological quantities. Additional nuclei do not necessarily imply altered methylation at a particular CpG site, and neither quantity determines the activity of a retained protein. Reviews of animal and human muscle memory have identified nuclear retention and epigenetic regulation as candidate explanations (Snijders et al., 2020). The distinction examined here is between the persistence of each measured quantity and its physiological contribution to regrowth.

The central question is therefore anatomical and temporal: which muscle feature remains after a defined period without structured resistance exercise, and does its retention accompany greater hypertrophy from the tissue state present when exercise resumes? Strength recovery is considered separately because a one-repetition maximum also depends on motor coordination, task familiarity and neural drive.

WHAT REMAINS AFTER TRAINING WITHDRAWAL?

FIBRE SIZE AND MYONUCLEAR CONTENT

Fibre cross-sectional area measures local geometry. Myonuclear content measures nuclei assigned to the contractile fibre under a defined counting procedure. Counts per fibre section, counts per unit fibre length and nuclei per tissue area have different denominators. A decrease in fibre area can increase nuclear density without any addition of nuclei. Conversely, unchanged density can conceal a change in absolute nuclear content if fibre geometry changes concurrently.

A fibre that shrinks while retaining its nuclear complement has less cytoplasm per nucleus. This arrangement may permit greater transcriptional capacity during renewed loading, but nuclear number alone does not measure transcriptional activity or protein accretion. Histological counts at successive biopsies also do not track the survival of individually identified nuclei. Retention of a group-level count and direct demonstration of nuclear survival are distinct observations.

METHYLATION, RNA AND PROTEIN ABUNDANCE

DNA methylation quantifies modification at genomic sites within the sampled nuclear population. A bulk-muscle biopsy contains myonuclei and nuclei from other cells. A tissue-level methylation difference can therefore reflect altered regulation within a cell type, altered cellular composition, or both. Wen and colleagues separated myonuclear and interstitial nuclei in mice and found distinct methylation responses (Wen et al., 2021). Cell identity is consequently necessary when linking a retained methylation change to fibre growth.

Resting RNA abundance measures transcription under the conditions preceding biopsy. A persistent regulatory modification can remain detectable without continuously elevated resting RNA, and an acute exercise response can differ despite similar resting expression. Resting and post-exercise biopsies thus address different physiological states. Neither is a direct measurement of later hypertrophy.

TABLE 1. ANATOMICAL AND MOLECULAR MEASUREMENTS USED TO ASSESS RETENTION AFTER TRAINING WITHDRAWAL.

Observation	Retained quantity	Additional measurements needed
Fibre or whole-muscle size	Geometry remains different at a defined site after training withdrawal.	Comparable hydration, imaging or histology; separation of residual size from regrowth.
Myonuclear content	A specified fibre-associated nuclear count remains elevated.	Counting denominator, fibre type and nuclear assignment; functional use of the retained nuclei.
DNA methylation	A site-specific modification remains different in the sampled DNA.	Cellular origin, effect size, timing and relation to later gene regulation.
Resting RNA expression	Transcript abundance remains different under comparable resting conditions.	Whether a resting difference changes the response to renewed loading.
Protein abundance	Protein abundance remains above its pre-training value.	Protein activity, localization, turnover and contribution to subsequent tissue growth.

Protein abundance is determined by production, degradation and the existing protein pool. Persistence after training withdrawal establishes that abundance differs at the sampling time. It does not determine protein activity, subcellular localization or turnover. CBR1 retention, for example, identifies an abundance difference; demonstrating that CBR1 increases regrowth would require a separate test of its contribution to the response. Table 1 specifies the quantities measured at each biological level.

Retention must also be stated with its observation interval. Seven, ten or sixteen weeks without a prescribed programme establish persistence over those intervals, rather than lifetime permanence. Ordinary walking, occupational activity and

unsupervised exercise can continue during detraining. A period without structured lifting is therefore a different exposure from immobilization or complete unloading.

HUMAN INTERVENTION FINDINGS

ELBOW-FLEXOR NUCLEI AND THE RETRAINING COMPARISON

Cumming and colleagues enrolled twelve untrained adults in ten weeks of unilateral elbow-flexor training, sixteen weeks of withdrawal and ten weeks of bilateral retraining. Type II myonuclear content increased by $34 \pm 22\%$ during initial training (mean $\pm$ standard deviation). Before retraining, type II myonuclear content was approximately 33% higher in the previously trained arm than in the control arm. Final type II fibre area was larger in the previously trained arm ($P = 0.035$), but the between-arm difference in fibre-area change during retraining was not significant (Cumming et al., 2024).

The terminal area difference and the growth contrast answer different questions. Terminal area includes tissue already present when retraining began. Growth during retraining is the difference between final and pre-retraining area. Retained nuclei in this investigation were therefore demonstrable, whereas an additional hypertrophic response attributable to those nuclei was not. Nuclear analyses included eleven participants initially and nine at later assessments; fibre-area analyses included nine, and RNA analyses ten.

LEG TRAINING AND ACUTE MOLECULAR RESPONSES

Psilander and colleagues studied nineteen adults through ten weeks of unilateral leg training, twenty weeks of withdrawal and five weeks of bilateral retraining. Initial fibre area increased by approximately 17%, muscle thickness by 10% and strength by 20%, without a detectable increase in myonuclear number. Subsequent training responses were similar between legs (Psilander et al., 2019). Because initial nuclear acquisition was not demonstrable, the sequence did not test the retention or growth advantage of additional training-acquired nuclei.

Moberg and colleagues examined resting and one-hour post-exercise biopsies after a ten-week unilateral training and twenty-week withdrawal sequence in nineteen adults. The previously trained leg showed different signalling and transcriptional responses, including higher AMPK and eEF2 phosphorylation (Moberg et al., 2020). These findings identify a response to an acute challenge rather than an increase in subsequent muscle growth. The article refers to Psilander's training and testing procedures; Table ?? groups this acute-response analysis with cohort A rather than counting it as an independent longitudinal hypertrophy comparison.

OLDER MUSCLE DURING WITHDRAWAL AND FOLLOW-UP

Blocquiaux and colleagues measured cellular changes in six older men during twelve-week training, withdrawal and retraining phases. Type II fibre area decreased by 17% during withdrawal ($P = 0.087$), and myonuclear number decreased by 12% ($P = 0.084$). During retraining, type II fibre area increased by 29% ($P = 0.050$), and myonuclear number increased by 13% ($P = 0.048$) (Blocquiaux et al., 2020). The accompanying corrigendum qualifies the interpretation of human muscle memory (Blocquiaux et al., 2020). In a six-person cellular sample, a withdrawal contrast above $P = 0.05$ does not demonstrate that the measured quantity remained stable. The estimated decreases must be considered alongside their uncertainty. Recovery of one-repetition maximum within eight weeks describes task performance and does not establish nuclear-mediated hypertrophy.

Snijders and colleagues followed older adults for one year after twenty-four weeks of supervised resistance training. Of 53 initial participants, 35 returned: 16 had continued exercise and 19 had stopped regular exercise. Muscle-size gains were lost, whereas strength gains were partly preserved (Snijders et al., 2019). Follow-up participation and exercise continuation were self-selected. The observations describe durability under those activity histories, rather than a controlled exposure to complete training cessation. They also show that the persistence of strength cannot be equated with preservation of muscle enlargement.

METHYLATION AND LEAN-MASS CHANGES ACROSS REPEATED TRAINING

Seaborne and colleagues enrolled eight previously untrained men in successive seven-week training, withdrawal and retraining periods; seven completed the final assessment. Lower-limb lean mass measured by dual-energy X-ray absorptiometry increased by $6.5 \pm 1.0\%$ after initial training ($P = 0.013$). It decreased by $4.6 \pm 0.6\%$ during withdrawal relative to the post-training value ($P = 0.020$). After retraining, lean mass was $12.4 \pm 1.3\%$ above the initial pre-training value ($P = 0.001$); these dispersions are standard errors of the mean. Comparing the gains from each phase's own starting value favoured retraining ($P = 0.022$) (Seaborne et al., 2018,?).

Selected sites associated with *AXIN1*, *GRIK2*, *CAMK4* and *TRAF1* remained hypomethylated during withdrawal. Site selection used unadjusted $P < 0.05$ across the methylation array (Seaborne et al., 2018). These candidates link retained methylation with a subsequent training phase, but the absence of a parallel training-naïve group leaves phase order and changing training exposure unresolved. Regional lean mass also includes tissue components beyond the sampled fibres; its increase is not a direct measurement of contractile-protein accretion. The phase-specific comparison supports a larger lean-mass response during retraining, while the contribution of individual retained sites remains untested.

Blocquiaux and colleagues measured methylation and RNA in five younger and six older men. The younger group underwent two weeks of leg casting between training periods; the older group underwent twelve weeks without structured training. One younger participant withdrew after initial training, and one older final RNA sample was excluded as an outlier. Retained methylation changes included hypermethylation within *AMOTL1* in younger muscle and hypomethylation within *VCL* in older muscle (Blocquiaux et al., 2022). Retention therefore included modifications in both directions.

Within-group methylation comparisons required $P < 0.01$ and an M-value difference greater than 0.4; only one CpG survived false-discovery-rate correction. RNA comparisons used a false discovery rate (FDR) below 0.10 (Blocquiaux et al., 2022). The methylation candidates require confirmation under multiple-testing control. Because age differed together with interruption duration and casting exposure, the younger–older comparison cannot isolate an effect of age on methylation retention.

PROTEIN RETENTION AND RECOVERY WITHIN ONE TRAINING PROJECT

Hulmi and colleagues analysed vastus lateralis proteins in seventeen periodic-training participants and thirteen initial controls; eleven controls supplied samples after subsequent training. The periodic sequence comprised ten weeks of training, ten weeks of withdrawal and ten weeks of retraining. Of 150 proteins altered after initial training, four remained elevated after withdrawal at $FDR < 0.05$ and fold change > 1.2 . At $FDR < 0.10$ and the same fold-change requirement, 29 proteins remained elevated (Hulmi et al., 2025). *CBR1* belonged to the stricter retained set, whereas *CAPN2* belonged to the broader set. The count of four and the count of 29 refer to different statistical thresholds.

The linked Halonen trial randomized 55 adults and compared periodic with continuous training. Final strength and size adaptations were similar. Recovery during the first five weeks after the periodic group's break was compared with weeks 10–15 of continuous training (Halonen et al., 2024). That comparator had already trained for ten weeks; it was not a training-naïve group beginning its first five weeks. The proteomic and functional analyses place retained proteins and recovery within one project, but do not identify a protein that caused the recovery advantage.

NUCLEAR AND REGULATORY MECHANISMS IN ANIMAL MUSCLE

LOADING HISTORY AND MUSCLE-SPECIFIC NUCLEAR RETENTION

Egner and colleagues exposed mice briefly to testosterone and subsequently subjected muscle to overload. Excess myonuclei remained after the pharmacological exposure, and the previously exposed muscle enlarged more during later overload (Egner et al., 2013). The experiment connects nuclear retention with enhanced growth under a steroid-associated history. It does not establish the same duration or mechanism after ordinary human resistance training.

In voluntary weighted-wheel training, Dungan and colleagues found reversal of plantaris adaptations, including elevated myonuclear density, during twelve weeks of detraining (Dungan et al., 2019). Murach and colleagues found that plantaris and gastrocnemius adaptations reversed during withdrawal, whereas soleus adaptations were more resistant (Murach et al., 2020). Nuclear retention therefore depends on the muscle and exposure. Continued loading of a postural muscle differs from the mechanical history of another hindlimb muscle, even within the same animal.

Wen and colleagues identified nucleus-specific methylation differences that survived withdrawal. Previously trained mouse muscle grew more during retraining without a difference in myonuclear number (Wen et al., 2021). This result separates nuclear quantity from nuclear regulation: a growth difference can coincide with retained methylation without additional nuclei at the later assessment. It supports investigation of nuclear state, while leaving the contribution of each methylation site and its relevance to human hypertrophy unresolved.

GROWTH REGULATION AND A TRAINING-HISTORY EFFECT

Acute exercise alters promoter methylation in human skeletal muscle (Barrès et al., 2012). A change after a single bout establishes responsiveness, whereas persistence requires a later assessment after exercise withdrawal. The same temporal distinction applies to proteins involved in ordinary muscle growth.

UBR5, an E3 ubiquitin ligase, is associated with hypertrophy and recovery from atrophy (Seaborne et al., 2019). Reducing UBR5 expression in mouse muscle impaired anabolic activity and eventually reduced muscle mass (Hughes et al., 2021). These findings establish a role in muscle-size regulation. A role specifically in muscle memory would require the intervention to alter the additional response associated with prior training, beyond its effect on growth in muscle without that history. Impaired growth in both conditions would identify a general growth requirement rather than a retained-history mechanism.

EXERCISE MODE AND MOLECULAR RETENTION

Lindholm and colleagues found no consistent resting transcriptional memory after a nine-month interruption of unilateral endurance training (Lindholm et al., 2016). The result concerns resting RNA under an endurance-training history; it does not determine whether nuclear number or methylation remained altered.

Pilotto and colleagues studied twenty adults through two two-month high-intensity interval-training periods separated by three months of withdrawal. Retained methylation and expression patterns coexisted with similar gains in maximal oxygen consumption during the two training phases ($P > 0.58$ for the between-phase comparison) (Pilotto et al., 2025). Molecular retention therefore did not coincide with a statistically distinguishable increase in the measured aerobic response.

Weidenhamer and colleagues examined mice through four-week endurance-training, withdrawal and retraining phases under control and high-fat diets. Mitochondrial metabolism and muscle growth differed during retraining (Weidenhamer et al., 2025). The diet-dependent endurance exposure identifies metabolic candidates for retained exercise effects. Its species, exercise mode and dietary conditions limit direct application to human resistance-training hypertrophy.

QUANTIFYING GROWTH FROM THE POST-WITHDRAWAL STATE

RETAINED SIZE, REACQUISITION AND RESPONSE CONSISTENCY

Final muscle size combines tissue retained before retraining with tissue gained during retraining. A larger final size can therefore coexist with equal growth during the retraining phase, as in Cumming's between-arm comparison. Time to recover a former size is also affected by the deficit present when exercise resumes. A muscle starting closer to its former size can reach that target sooner without a higher absolute growth rate.

Four assessments distinguish these quantities: before initial training, after initial training, after withdrawal and during retraining. Absolute area change expresses tissue enlargement in the measurement unit; percentage change expresses enlargement relative to the starting value. A smaller starting area can produce a larger percentage gain for the same absolute increment. Both scales should consequently be interpreted with the pre-retraining size.

Räntilä and colleagues found correlations between individual responses across two resistance-training periods: $r = 0.697$ for vastus lateralis size, $r = 0.761$ for biceps size and $r = 0.671$ for leg-press strength (Räntilä et al., 2025). These associations describe consistency of individual responsiveness. They do not establish that the first exposure increased the second response. Stable participant characteristics can generate repeated-response correlations without a cellular effect of prior training.

ACHIEVED LOADING AND THE COMPARATOR

The same exercise prescription does not ensure the same mechanical exposure. A previously trained participant may use greater absolute loads, complete more repetitions or execute the movement more efficiently. Equal percentages of current strength impose different absolute loads when strength differs, whereas equal absolute loads impose different relative efforts. Attendance, repetitions, external load and progression are therefore needed to interpret a growth comparison.

For the total effect of a training history under usual progression, improved loading capacity can form part of that effect. For a claim that retained nuclei or methylation cause additional growth, differences in achieved loading provide an alternative pathway. Analyses must specify which effect is being estimated before adjusting for loading; adjustment can remove a history-mediated pathway, while omission can misattribute that pathway to a cellular measurement.

Contralateral designs hold age, diet and much of daily activity constant within the participant, but systemic exposure and movement learning can influence the opposite limb. Between-person comparisons permit separate training histories but introduce variation in initial size, responsiveness and earlier exercise. These designs therefore address different sources of confounding. Neither makes pre-retraining size and achieved exposure dispensable.

LONGITUDINAL CONTRASTS AND CAUSAL INTERPRETATION

Let B , T , D and $R(t)$ denote the same measured quantity before initial training, after training, after withdrawal and at retraining time t . For a cellular feature, acquisition is $T - B$, the retained difference is $D - B$, and the withdrawal change is $D - T$. For a size outcome, growth during retraining is $R(t) - D$. The difference in absolute growth between previously trained and training-naïve muscles is

$$\theta(t) = [R_{\text{prior}}(t) - D_{\text{prior}}] - [R_{\text{naïve}}(t) - D_{\text{naïve}}]. \quad (1)$$

For the training-naïve comparator, $D_{\text{naïve}}$ is its measurement immediately before the comparison training phase. Equation 1 defines the observed difference in growth. Interpreting that difference as an effect of training history requires a design and analysis that address assignment, starting size and achieved loading.

A non-significant $D - T$ contrast does not establish retention without loss, and a non-significant $D - B$ contrast does not establish complete reversal. Estimated differences and interval estimates determine the magnitude and precision of either contrast. Equivalence additionally requires a prespecified, biologically justified margin. This distinction is particularly consequential for six-person cellular samples and for genome-wide tests with many simultaneous comparisons.

TABLE 2. LONGITUDINAL CONTRASTS FOR ACQUISITION, RETENTION, LOSS AND REGROWTH. THE ANATOMICAL SITE AND MEASUREMENT UNIT REMAIN CONSTANT WITHIN EACH CONTRAST.

Question	Comparison	Condition for interpretation
Was a feature acquired?	$T - B$	A measurable initial difference; suitable technical precision.
What remains?	$D - B$	Retained difference relative to the initial state, with an interval estimate.
How much decayed?	$D - T$	Loss from the attained state; non-significance is not equivalence.
Is regrowth greater?	$\theta(t)$ in Eq. 1	A defined comparator and observation time; residual size and loading addressed.
Is recovery faster?	Time to a specified former target	Equal assessment schedules and explicit target; different starting deficits can change recovery time.

A cellular explanation also requires the retained feature to precede the growth response. Repeated measurements within each participant can test whether its magnitude relates to additional regrowth. Resting molecular assessments should be separated from acute exercise responses; fibre type, biopsy location and nuclear-assignment rules should remain consistent. A selective perturbation would provide stronger causal evidence if it removed the growth advantage associated with prior training while accounting for its effects on ordinary growth. Human intervention studies generally cannot manipulate myonuclear number or individual methylation sites directly, so the causal interpretation depends partly on complementary animal experiments.

IMPLICATIONS FOR MUSCLE TRANSFORMATION

Withdrawal separates the durability of tissue enlargement from the durability of its cellular changes. Sixteen-week elbow-flexor observations support retained myonuclear content; seven-week vastus lateralis observations support retention of selected methylation differences; ten-week proteomic observations support retention of a small threshold-dependent protein set. The duration, muscle and assay belong to each conclusion. They cannot be replaced by a single duration for muscle memory.

Similar final outcomes after periodic and continuous training do not establish that planned interruption maximizes hypertrophy. Nor do observations during ordinary detraining define responses to injury-related immobilization, severe illness or prolonged inactivity. The human cellular investigations have small assay-specific samples and selected muscles. Their observation periods do not determine durability in long-trained athletes or every age and sex group.

Interpretation is also limited by purposive literature selection, linked participants across articles and inconsistent assay denominators. Few investigations measured nuclear content, methylation, protein abundance, achieved loading and tissue growth in the same participants. The 2011–2025 date restriction excludes earlier investigations and research appearing after 2025. Within these limits, retained cellular states are better established than their causal contribution to additional human hypertrophy.

CONCLUSION

Human skeletal muscle can retain additional myonuclei and selected methylation or protein-abundance changes after resistance-training enlargement has diminished. The retained quantities differ in anatomical origin, measurement unit and observation duration. Cumming's arm comparison separates nuclear retention from subsequent fibre-area change, while Seaborne's phase-specific comparison identifies a larger regional lean-mass gain during retraining. Neither comparison alone determines which retained cellular feature caused the response. A physiological claim of muscle memory requires acquisition, retention and additional growth to be connected within a comparison that accounts for the post-withdrawal tissue state and achieved loading.

DECLARATIONS

AUTHOR CONTRIBUTIONS

All authors contributed equally and all authors read and approved the final version of this manuscript.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

DATA AVAILABILITY

The data supporting the findings of this study are included within this manuscript.

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