

Letter to the Editor

Move to tolerate: Exercise and environmental factors improve transplant outcomes

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Exercise is increasingly recognized as a potent modulator of immunity, with effects ranging from enhanced antitumor responses to attenuation of inflammation in autoimmune conditions.^{1–4} A prior study by Rael et al⁵ demonstrated that voluntary wheel running (WR) in mice significantly prolonged minor mismatched skin graft survival, despite mildly enhanced alloimmune responses, suggesting that enhanced graft resistance, rather than attenuation of alloimmune responses, was the primary mechanism.

Building on this, we investigated whether other exercise-related variables might influence transplant outcomes. Using the same C57BL/6J (B6) minor mismatch skin transplant model (male-to-female), we tested 2 conditions: (1) housing donors and recipients in larger cages (rat cages) with greater space for free movement (without wheels), and (2) structured pretransplant exercise training with voluntary WR in both donor and recipient mice. We also tested the generalizability in a haplotype-mismatched model (C57BL/6J × BALB/c F1 onto B6).

In the minor mismatched model, larger cage housing significantly prolonged graft survival compared with standard cages (Fig. 1A, B; median survival time [MST] = 25 vs 18 days, $P < .0001$). In rat cage-housed recipients, donor WR-training alone prolonged graft survival compared with nontrained donors (MST

= 38 vs 25 days, $P = .0008$). Adding WR to both donors and recipients conferred a further benefit over a rat cage alone (Fig. 1C, D; MST = 69.5 days vs MST = 25 days, $P < .0001$). In the haplotype-mismatched transplant model, cage size alone had no effect (Fig. 1E, F), whereas the rat cage + WR significantly prolonged survival (Fig. 1G, H; MST = 41 days vs MST = 13 days, $P = .0344$). Flow cytometry revealed a more tolerogenic milieu: splenic regulatory T cells increased with WR and differed between groups at endpoint (Fig. 1I–K); programmed death-ligand 1 expression on macrophages rose similarly (Fig. 1L, M). These immune shifts are consistent with a more regulatory environment that accompanies prolonged graft survival. Exercised animals showed progressive increases in heart mass normalized to body weight (Fig. 1N, O), with a significant endpoint difference (WR + rat cage > rat cage; Fig. 1P). Heart weight was included solely as an objective physiological marker of exercise adaptation and is not interpreted as mechanistically linked to skin graft antigenicity.⁵ A correlation matrix relating day-28 heart mass to immune endpoints showed a strong positive correlation with splenic regulatory T cells (Fig. 1Q).

These findings highlighted 2 underrecognized factors in transplantation studies: the impact of housing conditions on immune and physiological states in murine models and the

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<https://doi.org/10.1016/j.ajt.2026.01.022>

Received 23 September 2025; Received in revised form 30 December 2025; Accepted 18 January 2026

Available online 29 January 2026

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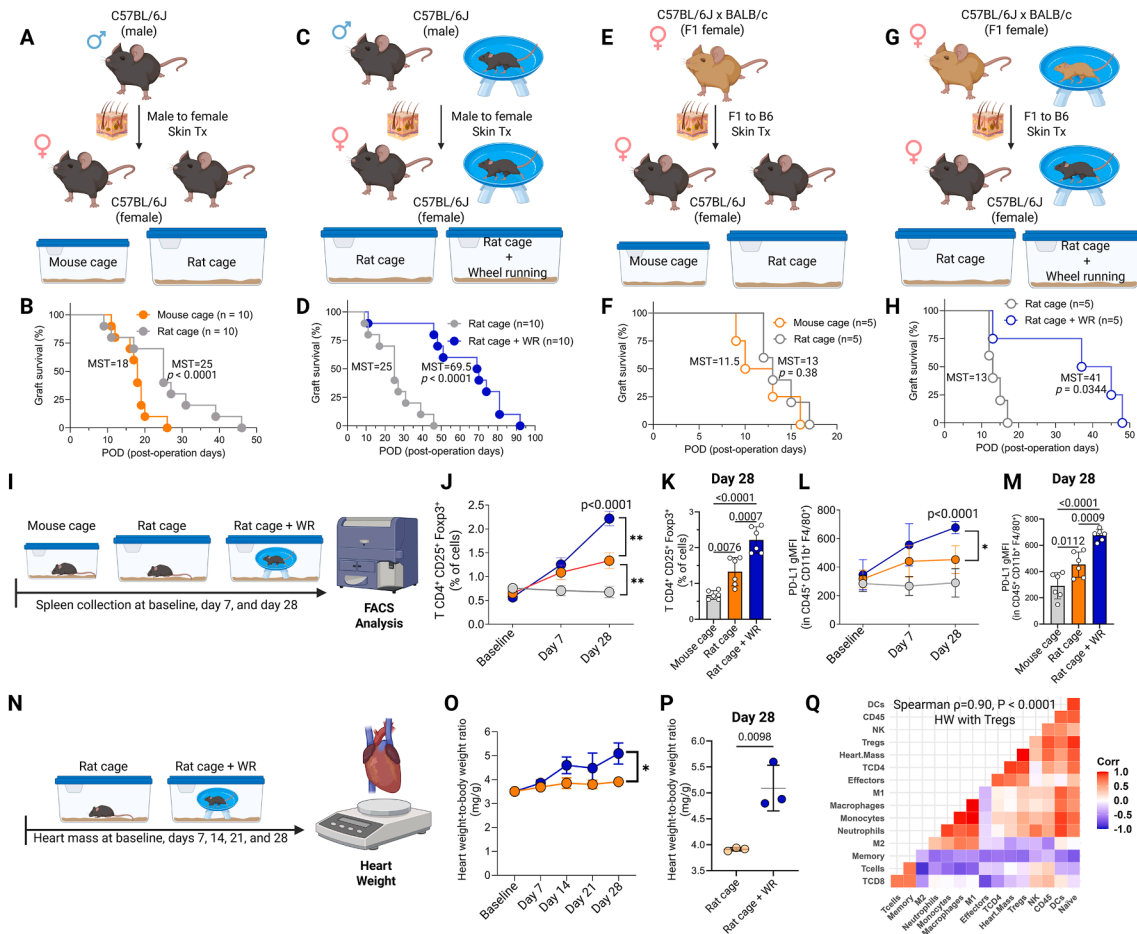


Figure 1. Housing-related mobility and voluntary exercise prolong skin allograft survival and are associated with physiological cardiac remodeling in mice. (A-H) Experimental design and survival, all with 4 weeks of housing before transplantation. (A-D) B6 minor mismatched skin transplant model, in which male skins were transplanted onto female recipients. The graph compares skin graft survival in recipients housed in mouse cages (orange), rat cages (gray), or rat cages + voluntary wheel running (WR) (blue). (E-H) A haplotype-mismatched model, in which C57BL/6J × BALB/c F1 skins were transplanted on B6 recipients under the same conditions as A-D. (B, D, F, H) Kaplan-Meier curves of graft survival (%) across postoperative days (PODs); group sizes (n) as indicated in panels; statistical analysis using two-sided log-rank test. (I-M) Flow cytometry readouts. (I) Sampling timeline (baseline, days 7 and 28). (J, K) Frequencies of CD4⁺CD25⁺Foxp3⁺ Tregs over time (J) and at endpoint (K). (L, M) Programmed death-ligand 1 (PD-L1) geometric mean fluorescence intensity (gMFI) on CD45⁺CD11b⁺F4/80⁺ macrophages over time (L) and at endpoint (M). Time-course data were analyzed using two-way ANOVA with Šidák correction; endpoint bar graphs were analyzed using one-way ANOVA with Tukey post hoc. (N-P) Exercise-related physiology. (N, O) Heart weight-to-body weight ratio (HW/BW, mg/g) over time in rat cage vs rat cage + WR; (P) endpoint comparison. Time-course using two-way ANOVA; endpoint using an independent *t*-test. (Q) Correlation analysis. Spearman rank correlations (ρ) between day-28 HW/BW and immune endpoints (per mouse); two-sided *P* from ρ with Benjamini–Hochberg FDR adjustment across all pairs. The heatmap encodes ρ (–1 to 1). Symbols denote individual mice; lines/bars show mean \pm SEM. Significance is indicated using asterisks unless otherwise noted (**** $\leq .0001$; *** $< .001$; ** $< .01$; * $< .05$). Color key: orange = mouse cage; gray = rat cage; blue = rat cage + WR. ANOVA, analysis of variance; B6, C57BL/6J; DC, Dendritic cells; FDR, false discovery rate; F1, first filial generation; FACS, Fluorescence-Activated Cell Sorter; Foxp3, forkhead box P3; HW/BW, heart weight-to-body weight; MST, median survival time; NK, Natural killer cells; SEM, standard error of the mean; ρ , Spearman’s rho; Treg, regulatory T cell; Tx, transplantation.

potential additive effects of structured exercise in both donor and recipient pairs. The observation that donor exercise training contributes to longer graft survival is particularly intriguing, as it opens a novel area of investigation into how systemic physiological states of the donor, beyond standard procurement criteria, may influence graft resilience.

As exercise gains attention as a nonpharmacologic adjunct to immunosuppression, our data support its immunologic and functional benefits in transplantation.²⁻⁴ Our results underscored

the need to control environmental variables such as cage size and mobility in preclinical models. These observations reflect targeted immune modulation rather than a global suppression of host defenses.²

The benefit was not dependent on intensity or duration but on consistent movement. Future studies should include donor and recipient exercise and consider environmental enrichment in design. Clinically, structured physical activity may complement strategies to improve graft outcomes.

Funding

H.L.C. was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Programa de Doutorado Sanduíche no Exterior (CAPES-PDSE) Process #88881.846058/2023-0. L.V.R. was partially supported by the Harold and Ellen Danser Endowed Chair in Transplantation, Harvard Medical School.

Author contributions

H.L.C. designed the experiments, performed skin transplantation, in vivo experiments, and flow cytometry, analyzed data, and wrote the original draft. D.M.M. designed the experiments, performed skin transplantation, in vivo experiments, and flow cytometry, analyzed data, and wrote the original draft. K.L. assisted with in vivo experiments. T.J.B. designed experiments, supervised all experiments, and wrote the original draft. L.V.R. designed experiments, supervised all experiments, acquired funding, and wrote the original draft.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

Ethical statement

Experiments were approved by the Massachusetts General Brigham Institutional Animal Care and Use Committee 2020N000125. All animals were housed in accordance with the

Institutional Animal Care and Use Committee and National Institutes of Health Animal Care guidelines.

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