

DOI: <https://doi.org/10.17816/morph.642493>

EDN: IYGTDR



Characteristics of Epimorphic Regeneration of the Distal Phalanx in Spiny Mice (*Acomys cahirinus*)

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ABSTRACT

BACKGROUND: Regeneration of the distal phalanx in adult mammals is a rare example of complete tissue restoration without fibrosis. Spiny mice of the genus *Acomys* are capable of regenerating multiple tissues, including epidermis and muscle, without scar formation. However, the ability of *Acomys cahirinus* to fully regenerate the distal phalanx remains unknown.

AIM: The work aimed to assess distal phalanx regeneration after amputation in spiny mice.

METHODS: Distal phalanx regeneration in *Mus musculus* and *A. cahirinus* was evaluated over 28 days after amputation. The distal phalanx was amputated distal to the nail bed to model epimorphic regeneration via blastema formation. Amputation proximal to the nail bed was performed to model injury leading to fibrotic scar formation. Recovery was assessed visually, by micro-computed tomography, and histologically.

RESULTS: Unlike *M. musculus*, which showed complete restoration of all tissue components after distal phalanx amputation, *A. cahirinus* failed to achieve full regeneration. Following amputations distal to the nail bed, *A. cahirinus* exhibited digital shortening and clubbing. Histological analysis demonstrated an increase in bone tissue volume within the damaged phalanx in spiny mice. Micro-computed tomography revealed that the bone damaged by amputation underwent lysis up to complete degradation, with bone hypertrophy in the next phalanx of the injured digit, located proximal to the amputation plane.

CONCLUSION: *A. cahirinus* does not exhibit complete digit regeneration after distal phalanx amputation. This outcome could be attributed to excessive lysis of the damaged bone and insufficient blastema formation at the site of injury.

Keywords: regeneration; fibrosis; osteogenesis.

To cite this article:

Antropova YuG, Shilova AA, Eremichev RYu, Skribitsky VA, Shpakova KE, Finogenova YuA, Kasyanov AA, Lipengolts AA, Popov VS, Makarevich PI, Kalinina NI. Characteristics of Epimorphic Regeneration of the Distal Phalanx in Spiny Mice (*Acomys cahirinus*). *Morphology*. 2025;163(4):316–326. DOI: 10.17816/morph.642493 EDN: IYGTDR

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Особенности эпиморфной регенерации дистальной фаланги пальца у иглистых мышей (*Acomys cahirinus*)

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АННОТАЦИЯ

Обоснование. Восстановление концевой фаланги пальца у взрослых млекопитающих представляет собой редкий пример полноценной регенерации без развития фиброза. Иглистые мыши рода *Acomys* способны к восстановлению многих тканей, включая эпидермис и мышцы, без формирования рубца. Однако способность *Acomys cahirinus* к полноценному восстановлению концевой фаланги пальца не известна.

Цель — оценить динамику восстановления концевой фаланги пальца после ампутации у иглистых мышей.

Методы. Динамику регенерации концевых фаланг пальцев у мышей *Mus musculus* и *A. cahirinus* оценивали в течение 28 дней после ампутации. Для моделирования эпиморфной регенерации посредством формирования бластемы ампутацию концевой фаланги проводили дистальнее ногтевого ложа. Для моделирования повреждения, завершающегося формированием фиброзного рубца, ампутацию проводили проксимальнее ногтевого ложа. Восстановление оценивали визуально, с использованием микрокомпьютерной томографии, а также на основании результатов гистологического исследования.

Результаты. В отличие от *M. musculus*, демонстрирующих полноценное восстановление всего тканевого состава после ампутации дистальной фаланги пальца, у *A. cahirinus* этого не происходит. У *A. cahirinus* после ампутации дистальнее ногтевого ложа наблюдается укорочение пальцев и их деформация по типу «барабанных палочек». Гистологический анализ показал, что у иглистых мышей увеличивается объём костной ткани в повреждённой фаланге. С помощью микрокомпьютерной томографии установлено, что повреждённая при ампутации кость подвергается лизису вплоть до полной деградации, а гипертрофия происходит в кости следующей фаланги повреждённого пальца, расположенной проксимальнее плоскости ампутации.

Заключение. У *A. cahirinus* не происходит полноценного восстановления пальца после ампутации дистальной фаланги. Возможно, это обусловлено чрезмерным лизисом повреждённой кости, а также недостаточным формированием бластемы в участке повреждения.

Ключевые слова: регенерация; фиброз; остеогенез.

Как цитировать:

Антропова Ю.Г., Шилова А.А., Еремичев Р.Ю., Скрибицкий В.А., Шпакова К.Е., Финогенова Ю.А., Касьянов А.А., Липенгольц А.А., Попов В.С., Макаревич П.И., Калинина Н.И. Особенности эпиморфной регенерации дистальной фаланги пальца у иглистых мышей (*Acomys cahirinus*) // Морфология. 2025. Т. 163, № 4. С. 316–326. DOI: 10.17816/morph.642493 EDN: IYGTDR

DOI: <https://doi.org/10.17816/morph.642493>

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刺鼠(*Acomys cahirinus*)远端指骨的芽基样再生特征

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摘要

论证。在成年哺乳动物中，远端指骨的再生是罕见的无纤维化的完整再生实例。刺鼠属 *Acomys* 能够在无瘢痕的情况下修复包括表皮和肌肉在内的多种组织。然而，*Acomys cahirinus* 是否具备完全恢复远端指骨的能力尚不清楚。

目的。本研究旨在评估刺鼠属在远端指骨截除后的再生动态。

方法。对 *Mus musculus* 和 *A. cahirinus* 的指末节再生动态在截肢后28天内进行了评估。为模拟通过芽基形成的表型样再生，将截肢平面设在甲床远端。为模拟最终以纤维性瘢痕形成结束的损伤，将截肢平面设在甲床近端。通过肉眼观察、微型计算机断层扫描及组织学分析评估再生情况。

结果。与 *M. musculus* 在远端截肢后能够实现所有组织成分的完整再生不同，*A. cahirinus* 并未表现出完全恢复。在 *A. cahirinus* 中，甲床远端截肢导致手指缩短并出现类似“杵状指”的畸形。组织学显示损伤指骨内骨组织体积增加。微型计算机断层扫描结果显示：截肢损伤的骨骼发生溶解，直至完全降解，而肥大出现在位于截肢平面近端的下一节指骨。

结论。*A. cahirinus* 在远端指骨截肢后未能实现完整再生。这可能与损伤骨的过度溶解及损伤部位芽基形成不足有关。

关键词：再生；纤维化；成骨。

To cite this article:

Antropova YuG, Shilova AA, Eremichev RYu, Skribitsky VA, Shpakova KE, Finogenova YuA, Kasyanov AA, Lipengolts AA, Popov VS, Makarevich PI, Kalinina NI. 刺鼠(*Acomys cahirinus*)远端指骨的芽基样再生特征. *Morphology*. 2025;163(4):316–326. DOI: 10.17816/morph.642493 EDN: IYGTDR

收到: 03.12.2024

接受: 03.05.2025

发布日期: 28.07.2025

BACKGROUND

In most mammals, including humans, regeneration of the distal segment of the terminal phalanx represents a rare example of complete tissue regeneration without fibrosis. Amputation of the fingertip distal to the nail bed induces a specialized wound-healing response that culminates in the formation of a mass of undifferentiated proliferating cells known as the blastema [1]. During such healing, the damaged area is covered by a wound epidermis, immune cells partially degrade the stump tissues, and molecular signals from nail-bed cells cause a loss of cellular specialization in the regenerating tissues [2, 3]. The formation of the blastema ends with the differentiation of its cells and the development of regenerating tissues, resulting in the complete restoration of the entire tissue complex of the terminal phalanx, including bone, muscle, adipose tissue, and epidermis [4]. When amputation is performed proximal to the nail bed, blastema formation does not occur, resulting in reparative regeneration with deposition of dense lamellar fibrous tissue [5].

Spiny mice (genus *Acomys*) are a promising model for studying the mechanisms of fibrosis prevention, as they are capable of complete regeneration of tissues and organs—including the skin, myocardium, and kidneys—without scar formation. In most regenerative contexts in *Acomys*, tissue restoration is preceded by blastema formation [6, 7].

We hypothesized that in *Acomys cahirinus*, regeneration of the distal phalanx after amputation distal to the nail bed would proceed more rapidly than in *Mus musculus*. Furthermore, when amputation is performed proximal to the nail bed—a level that in *M. musculus* normally results in fibrotic repair—*A. cahirinus* might still exhibit complete regeneration.

The work aimed to perform a comparative assessment of terminal phalanx regeneration after amputation in spiny mice (*A. cahirinus*) and house mice (*M. musculus*).

METHODS

Study Design

An experimental, single-center, prospective, randomized, controlled, non-blind study was conducted.

Eligibility Criteria

The study used female mice aged 8–16 weeks: *M. musculus*, C57BL/6 line, $n = 21$, body weight 20–25 g; and *A. cahirinus*, $n = 21$, body weight 25–30 g. All animals were bred in-house at the Laboratory of Translational Medicine, Faculty of Fundamental Medicine, Lomonosov Moscow State University.

Study Setting

The experiments were carried out at the Faculty of Fundamental Medicine, Lomonosov Moscow State University. The animals were housed under standard vivarium conditions.

Study Duration

The study was conducted on days 3, 7, 10, 14, 21, 28, and 56 after amputation to compare distal phalanx regeneration in spiny mice (*A. cahirinus*) and house mice (*M. musculus*). Intervention

In this study, we used a model of phalangeal regeneration following amputation. The mice were anesthetized with a mixture of isoflurane (2%) (Laboratories Karizoo, S.A., Spain) and oxygen (93%), delivered through a face mask using a setup that included a V3000 Parkland Scientific vaporizer (Parkland Scientific Inc., USA) and an Oxygen Concentrator Nuvo Lite 525 (Nidek Medical Products Inc., USA). Amputation of the terminal phalanges of the second, third, and fourth digits on both hind limbs was performed distal or proximal to the nail bed according to a previously described protocol [5]. Analgesia was provided by subcutaneous administration of Movalis (Boehringer Ingelheim España, S.A.) at a dose of 1 mg/kg before surgery and daily for three days postoperatively.

On days 3, 7, 10, 14, 21, 28, and 56 after amputation, the animals were euthanized in a CO₂ chamber. The amputated digits were examined using a stereomicroscope (Leica MZ95, Germany), microcomputed tomography, and histological staining. Animals of the same age and body weight with intact limbs were used as the control (intact control group).

Microcomputed tomography

Three-dimensional images of digit bones 3, 7, 10, 14, 21, and 28 days after injury were obtained using a MiLabs VECTOR 6 micro-CT scanner (MiLabs B.V., Netherlands). Scanning was performed in the Ultra Focus mode designed for visualization of small objects. The following parameters were used: tube voltage 55 kV; current 0.21 mA; exposure time per projection 75 ms; and rotation step 0.2°. Image reconstruction was performed using MiLabs Rec 12.00 (MiLabs B.V., Netherlands) with a voxel size of 20 µm. RadiAnt DICOM Viewer 2024.1 (Medixant, Poland) was used for image processing and analysis.

Histological analysis

For histological analysis, digits were fixed in 10% neutral buffered formalin for 48 hours at room temperature. Decalcification was performed in 0.5 M EDTA (pH 7) for 14 days under constant agitation, with daily replacement of the decalcifying solution. Following decalcification, samples were rinsed in phosphate-buffered saline, embedded in polyalcohol-based Tissue-Tek O.C.T. Compound (Sakura Inc., Japan), and snap-frozen in liquid nitrogen vapor. Cryosections of the digits were prepared using a KD-3000 cryostat microtome (Kedee, China). Sections were stained with Mayer's hematoxylin (Arbis+, Russia) for 5 minutes at room temperature according to a standard protocol. Stained sections were dehydrated, cleared, and mounted in Leica CV Ultramount (Leica, Germany). Histological evaluation was

performed using an Axioscop 40 microscope (Zeiss, Germany) with an AxioCam MRc5 digital camera (Zeiss, Germany).

RESULTS

Study Objects

The study used female mice aged 8–16 weeks. Group 1: *M. musculus*, C57BL/6 line; $n = 21$; body weight 20–25 g. Group 2: *A. cahirinus*; $n = 21$; body weight 25–30 g.

Primary Results

Amputation of the distal segment of the terminal phalanx in spiny mice did not result in complete restoration of the nail bed or nail.

After amputation of the distal fragment of the terminal phalanx distal to the nail bed, *M. musculus* demonstrated a healing response consistent with the classical regenerative stages previously described: wound closure, blastema formation, and subsequent full or partial restoration of all fingertip structures, including nail regrowth by day 28 post-amputation (see Fig. 1). In contrast, in *A. cahirinus*, healing followed a different pattern after amputation: wound closure was delayed, and a non-healed wound persisted even at day 14 post-amputation (Fig. 1). At later time points, shortened digits with a drumstick-like deformity were observed in spiny mice. Complete structural restoration of the fingertip did not occur—no nail regrowth was observed by day 28 post-amputation; restoration of finger length also did not occur at later time points, up to 42 and 56 days post-amputation (data not shown).

Histological evaluation of sagittal sections demonstrated that at day 28 post-amputation, the architecture of the terminal phalanx in *A. cahirinus* remained disrupted due to replacement of most of its volume by hypertrophied bone tissue (see Fig. 2). In *M. musculus*, by day 28 post-amputation, the tissue composition of the terminal

phalanx was nearly identical to that of the intact phalanx. Notably, at this time point, *A. cahirinus* showed mature secondary lamellar bone with ordered lamellae typical of adult animals, whereas newly regenerated bone in *M. musculus* exhibited a primary reticulofibrous architecture. On histological sections, *M. musculus* demonstrated clear nail regrowth with structural and morphological features comparable to uninjured nails, which was consistent with visual inspection. In most *A. cahirinus*, no nail regrowth occurred by day 28 post-amputation (Fig. 2). However, in some animals, the regenerated phalanx surface was covered by a loosely adherent extracellular matrix layer resembling a nail plate in refractive properties and thickness.

Bone stump destruction following amputation is extensive in spiny mice

To assess bone changes in the digits following amputation of distal phalanx fragments, we performed microcomputed tomography of the limbs. In *M. musculus*, partial lysis of the bone stump was observed by day 14 post-amputation, often accompanied by sequestrum formation (see Fig. 3). However, by day 28 post-amputation, restoration of the third phalanx was evident. The regenerated bone resembled an intact phalanx morphologically and contained a bone marrow cavity. These findings fully reproduce previously published results [1].

In spiny mice, bone stump degradation was more pronounced and progressed to complete loss of the third phalanx (see Figs. 3 and 4). By day 28 post-amputation, the third phalanx was absent on microcomputed tomography scans in most cases (Fig. 4). Furthermore, marked hypertrophy of the epiphysis of the second phalanx was observed (Fig. 4). This finding is consistent with histological data demonstrating new bone formation in *M. musculus* and expansion of the existing bone volume in *A. cahirinus*. Moreover, assessment of distal phalanx length up to 42 and

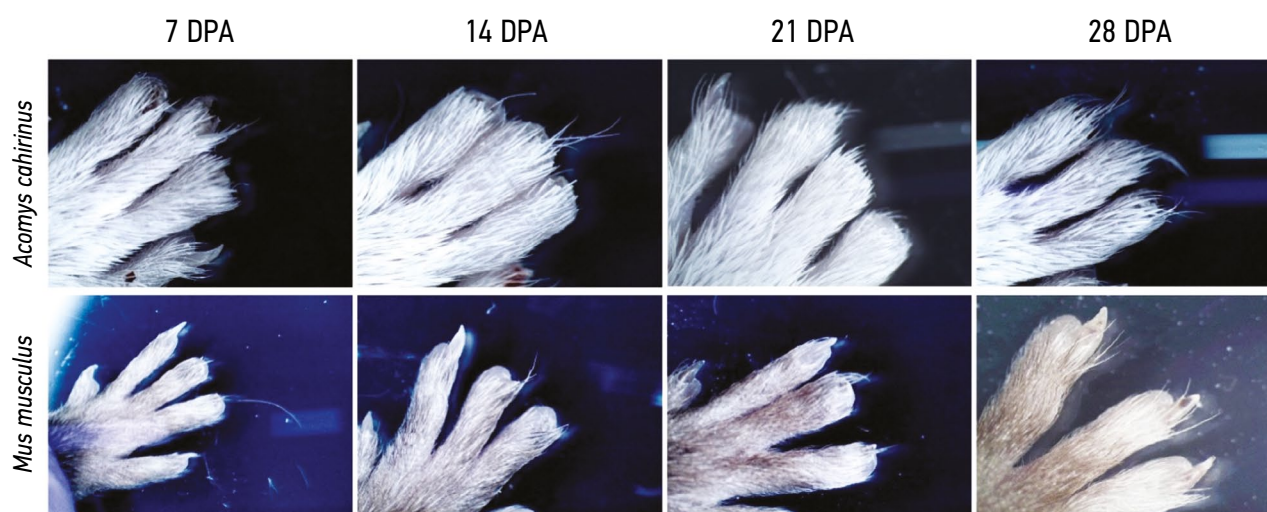


Fig. 1. Distal hind limbs of *Acomys cahirinus* (upper row) and *Mus musculus* (lower row) at 7, 14, 21, and 28 days post-amputation (DPA) of digits 2, 3, and 4.

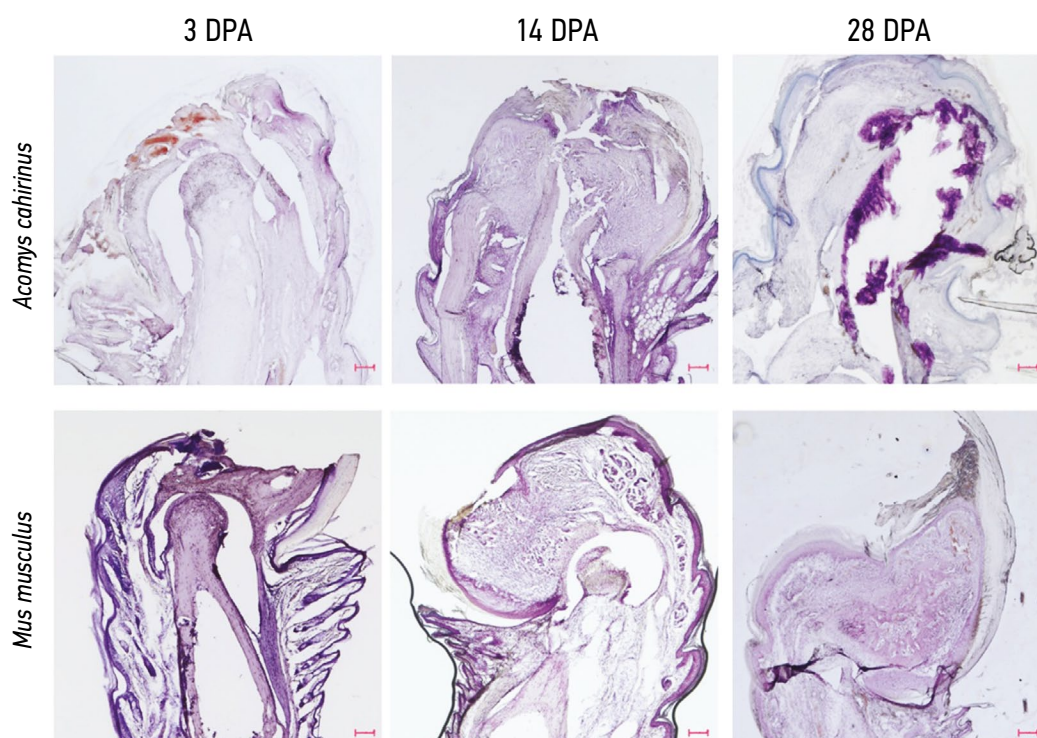


Fig. 2. Histological analysis of sagittal sections of digit tips in *Mus musculus* (lower row) and *Acomys cahirinus* (upper row) at 3, 14, and 28 days post-amputation (DPA). Upper row: at 3 DPA, the residual fragment of the third phalanx and the epiphysis of the second phalanx are visible; at 14 DPA, a blastema with early signs of differentiation is observed; by 28 DPA, mature bone tissue, a growing nail, and other restored structures of the digit pad are evident. Lower row: at 3 DPA, the wound has not fully closed, whereas the remaining third phalanx is already undergoing histolysis, which peaks by 14 DPA, when the third phalanx of *Acomys cahirinus* is completely lysed and replaced by fibrotic tissue; the epiphysis of the second phalanx also shows partial histolysis. By 28 DPA, bone hypertrophy is observed in the second phalanx, without signs of decalcification. Mayer's hematoxylin staining, light microscopy; scale bar: 100 μ m.

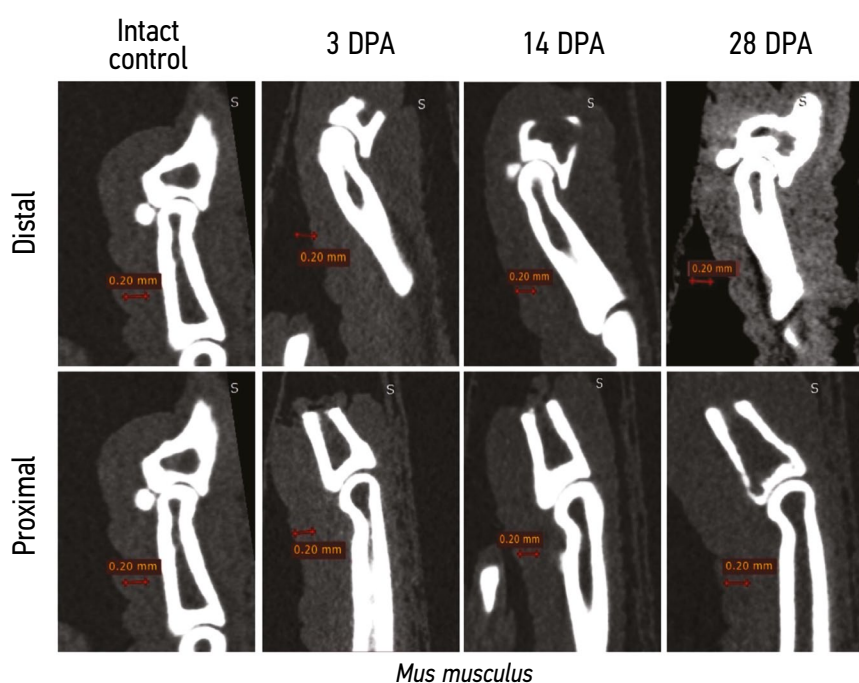


Fig. 3. Tomographic imaging of phalangeal bones in *Mus musculus*, intact animals and at 3, 14, and 28 days post-amputation (DPA). Upper row: amputation of the distal phalanx fragment distal to the nail bed; reduction in the stump of the damaged third phalanx is observed at 14 DPA, with restoration of its shape and structure by 28 DPA. Lower row: amputation of the distal phalanx fragment proximal to the nail bed.

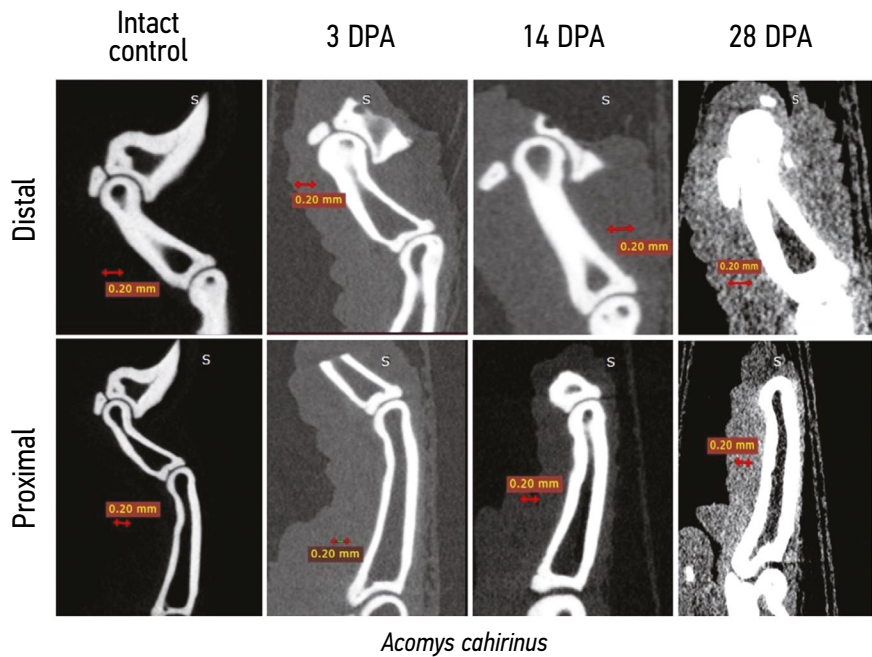


Fig. 4. Tomographic imaging of phalangeal bones in *Acomys cahirinus*, intact animals and at 3, 14, and 28 days post-amputation (DPA). Upper row: amputation of the distal phalanx fragment distal to the nail bed; reduction in the stump of the damaged third phalanx is seen at 14 DPA, progressing to complete degradation by 28 DPA. Lower row: amputation of the distal phalanx fragment proximal to the nail bed; reduction in the stump of the damaged second phalanx is evident at 14 DPA, progressing to complete degradation by 28 DPA.

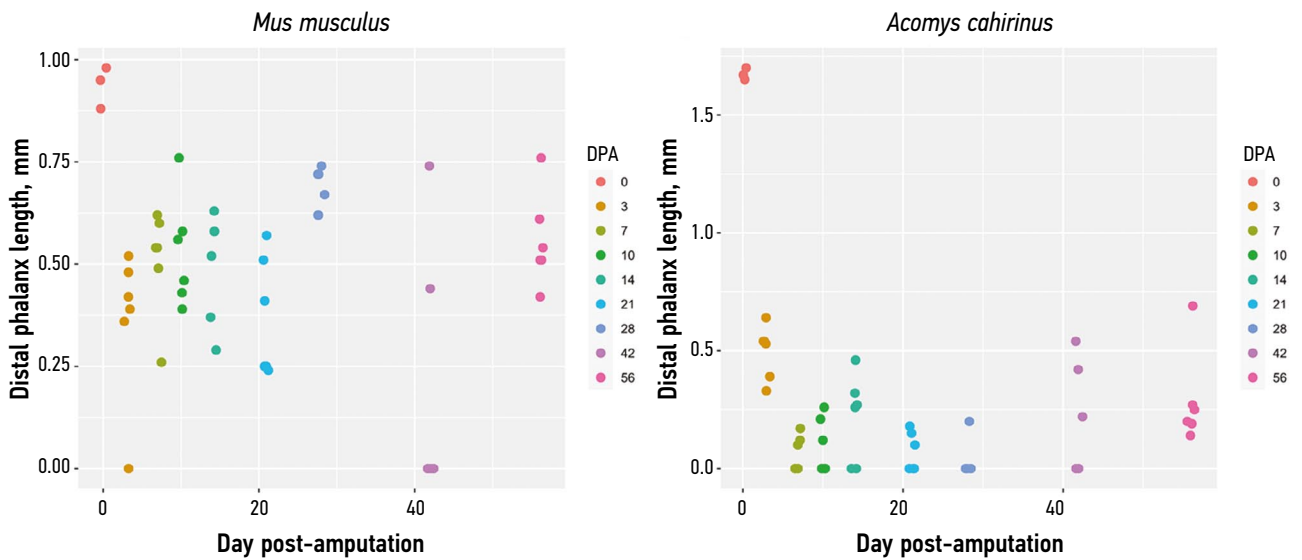


Fig. 5. Comparative analysis of distal phalanx length in *Mus musculus* and *Acomys cahirinus* at different time points after amputation.

56 days post-amputation (Fig. 5) showed no increase in digit length in *A. cahirinus*, whereas digit length increased in *M. musculus*.

Following amputation at the level of the second phalanx in *M. musculus*, no significant change in bone stump volume was detected—neither pronounced degradation nor regeneration (Fig. 3). In contrast, in spiny mice, similar to amputation of the distal portion of the third phalanx, amputation at the level of the second phalanx leads to extensive destruction of the bone stump, up to its complete degradation (Fig. 4).

DISCUSSION

Summary of Primary Results

This study is the first to characterize the trends of distal phalanx regeneration in spiny mice. Contrary to the expected accelerated regenerative response compared with *M. musculus*, we found that *A. cahirinus* fails to fully restore the tissue complex of the terminal phalanx following amputation. Instead, complete degradation of the damaged bone occurs, whereas the phalanx located

proximal to the amputation plane undergoes hypertrophic enlargement.

Discussion of Primary Results

Insufficient blastema formation following amputation of the distal fingertip phalanx in *A. cahirinus* was an unexpected finding, given prior reports demonstrating blastema formation during regeneration of the ear pinna, myocardium, and kidney in this species [6]. Three principal mechanisms are considered as potential causes of so-called limb regeneration incompetence: epithelial incompetence, mesenchymal incompetence, and impaired immune cell function [8]. Epithelial incompetence refers to inadequate or delayed formation of the wound epidermis. Even in amphibians—which display complete limb regeneration—removal of the wound epidermis or inhibition of its formation completely abrogates the regenerative process [9]. The wound epidermis serves as a source of signals that promote cell migration into the forming blastema. Moreover, the wound epidermis contributes to a locally hypoxic environment that maintains blastema cells in an undifferentiated state [10]. We found that the wound surface in *A. cahirinus* remains open for a prolonged time, which may hinder blastema formation.

Mesenchymal incompetence in adult mammalian tissues is associated with the inability of fibroblast-derived cells to undergo partial loss of specialization (dedifferentiation). However, previous studies have shown that in *A. cahirinus*, during ear pinna regeneration and epidermal repair, fibroblast-lineage cells are capable of phenotypic switching, and this process occurs more rapidly than in *M. musculus*. Therefore, this mechanism is unlikely to be the primary factor limiting regeneration of the distal fingertip phalanges in spiny mice.

For final blastema formation, the involvement of immune cells—primarily macrophages—is required [11]. Macrophages are responsible for partial degradation of stump tissues, including bone. It is believed that proteolytic breakdown of the extracellular matrix by macrophages facilitates the release of progenitor cells involved in blastema formation and promotes their migration into the regenerating area. Macrophages and their precursors (monocytes) serve as the source of osteoclasts, the specialized bone-resorbing cells. The pronounced bone stump destruction observed in *A. cahirinus* is most likely due to rapid accumulation of osteoclasts. However, it remains unknown how such macrophage activity affects other stump tissues: does their degradation proceed to complete depletion of the cellular pool that participates in finger tissue restoration in *M. musculus*?

Our findings also suggest that preservation of at least a fragment of bone is a necessary prerequisite for bone regeneration, whereas complete degradation of the bone prevents new bone formation.

The hypertrophic enlargement of the mature bone in the phalanx proximal to the injury site is presumably driven by

the activity of osteoblasts and their precursors present within this bone. However, additional studies are required to clarify the mechanisms underlying this phenomenon in *A. cahirinus*.

Study Limitations

A major limitation of this study is the lack of an assessment of cellular changes in the regenerating phalanx of *A. cahirinus*, which prevents characterization of the cellular responses responsible for both bone destruction and blastema formation.

CONCLUSION

In *A. cahirinus*, complete restoration of distal phalanx tissues, including bone, does not occur after amputation. Instead, the wound healing terminates in fibrosis, preceded by pronounced histolysis. These features are most likely the result of insufficient blastema formation at the injury site and excessive degradation of the amputated bone stump.

ADDITIONAL INFORMATION

Author contributions: Yu.G. Antropova: conceptualization, investigation, writing—original draft, writing—review & editing; A.A. Shilova: investigation, writing—original draft, writing—review & editing; R.Yu. Eremichev: conceptualization, data curation, writing—original draft, writing—review & editing; V.A. Skribitsky: investigation, writing—original draft, writing—review & editing; K.E.—Shpakova: investigation, writing—original draft, writing—review & editing; Yu.A. Finogenova: investigation, writing—original draft, writing—review & editing; A.A. Kasyanov: investigation, writing—original draft, writing—review & editing; A.A. Lipengolts: investigation, data curation, writing—original draft, writing—review & editing; V.S. Popov: conceptualization, writing—original draft, writing—review & editing; P.I. Makarevich: conceptualization, data curation, writing—original draft, writing—review & editing; N.I. Kalinina: conceptualization, data curation, writing—original draft, writing—review & editing. All the authors approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval: All animal procedures were approved by the Bioethics Committee of Lomonosov Moscow State University (application No. 3.5-sod, approved at meeting No. 141-d-z of March 17, 2022).

Funding sources: The study was supported by grants from the Russian Science Foundation No. 19-75-30007P (“*Acomys cahirinus* housing and related manipulations”) (<https://rscf.ru/project/23-75-33001/>) and No. 24-15-00165 (“*Mus musculus* housing, related manipulations, and micro-computed tomography”) (<https://rscf.ru/project/24-15-00165/>).

Disclosure of interests: The authors have no relationships, activities, or interests for the last three years related to for-profit or not-for-profit third parties whose interests may be affected by the content of the article.

Statement of originality: No previously obtained or published material (text, images, or data) was used in this study or article.

Data availability statement: All data obtained in this study are available in this article.

Generative AI: No generative artificial intelligence technologies were used to prepare this article.

Provenance and peer review: This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved two external reviewers, a member of the Editorial Board, and the in-house scientific editor.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Ю.Г. Антропова — определение концепции, проведение исследования, написание черновика рукописи, пересмотр и редактирование рукописи; А.А. Шилова — проведение исследования, написание черновика рукописи, пересмотр и редактирование рукописи; Р.Ю. Еремичев — определение концепции, работа с данными, написание черновика рукописи, пересмотр и редактирование рукописи; В.А. Скрибицкий — проведение исследования, написание черновика рукописи, пересмотр и редактирование рукописи; К.Е. Шпакова — проведение исследования, написание черновика рукописи, пересмотр и редактирование рукописи; Ю.А. Финогенова — проведение исследования, написание черновика рукописи, пересмотр и редактирование рукописи; А.А. Касьянов — проведение исследования, написание черновика рукописи, пересмотр и редактирование рукописи; А.А. Липенгольц — проведение исследования, работа с данными, написание черновика рукописи, пересмотр и редактирование рукописи; В.С. Попов — определение концепции; написание черновика рукописи, пересмотр и редактирование рукописи; П.И. Макаревич — определение концепции, работа с данными, написание черновика рукописи, пересмотр и редактирование рукописи; Н.И. Калинина — определение концепции, работа с данными, написание черновика рукописи, пересмотр и редактирование рукописи. Все авторы одобрили

рукопись (версию для публикации), а также согласились нести ответственность за все аспекты настоящей работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и достоверностью любой её части.

Этическая экспертиза. Все процедуры с животными были одобрены комиссией по биоэтике МГУ (заявка № 3.5-сод, одобрена на заседании № 141-д-з от 17.03.2022).

Источники финансирования. Исследование проведено при поддержке грантов Российского научного фонда № 19-75-30007П — содержание *Acomys cahirinus* и манипуляции с ними; (<https://rscf.ru/project/23-75-33001/>) и № 24-15-00165 — содержание *Mus musculus*, манипуляции с ними и проведение микрокомпьютерной томографии (<https://rscf.ru/project/24-15-00165/>).

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими организациями), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При проведении исследования и создании настоящей статьи авторы не использовали ранее полученные и опубликованные сведения (данные, текст, иллюстрации).

Доступ к данным. Все данные, полученные в настоящем исследовании, представлены в статье.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовались.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания.

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