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Abstract

Regeneration is the capacity that some organisms present to regrow tissues, appendages or even organs without scar and with full functionality. This capacity is present mostly in invertebrates and lower vertebrates such as some fish and lizards, but not in mammals.

Spiny mice (*Acomys spp*.) are a non-traditional rodent model that possess a number of interesting characteristics. This rodent is currently gaining attention as a tissue regeneration model. While most mammals repair wounds by fibrotic scarring, *Acomys* can mount a regenerative response to wounding of several organs and tissues, including skin, ear and musculoskeletal tissue.

In this manuscript, it was done a compilation and an extensive review of the *Acomys* regeneration literature published in the last decade. It is described all the information available about the characteristics and mechanisms that lead to regeneration in this animal model.

In conclusion, until now was described that *Acomys* is able to regenerate several organs and tissues such as ear, skin, skeletal muscle and spinal cord. The regeneration of these several tissues has some common features and other that are specific for each tissue. It is described that a mild immune system present in *Acomys* allows the regeneration of all this tissues. Moreover, it is also thought that this ability is due to macrophage response, lack of fibrosis and myofibroblasts production and Hippo-Yap signalling regulation. Regarding the heart and kidney, the regeneration of this tissues was never showed, however these organs are more resistant to injury and are able to regain function after injury.

With this animal model, the scientific community will try to unveil the mechanisms behind regeneration and, in the future, following the hypothesis that regenerative mechanisms are conserved throughout the vertebrates, they could then extrapolate these finding to develop therapies for humans.

Keywords: Mammalian regeneration, Spiny mice, *Acomys spp*., immune system

Resumo

A regeneração é a capacidade que alguns seres vivos têm de voltar a crescer tecidos, apêndices ou mesmo órgãos após uma lesão, recuperando a sua funcionalidade original. Esta capacidade está maioritariamente presente em invertebrados ou alguns vertebrados como os peixes e lagartos, mas não nos mamíferos.

No século XIII forma feitos os primeiros estudos sobre a regeneração, os modelos animais usados nessa altura foram Hidra, crustáceos e salamandras. Estes estudos estabeleceram o padrão para a investigação experimental. Atualmente, além destes modelos, existem também estudos feitos com peixe-zebra, lagartos, anfíbios e alguns mamíferos.

Os *Acomys spp.* são modelos roedores que têm características interessantes. Recentemente têm ganhado atenção como modelos de estudo da regeneração. Enquanto a maioria dos mamíferos repara feridas por cicatrizes fibróticas, os *Acomys* podem regenerar vários órgãos e tecidos, incluindo a pele (onde a pele é danificada por feridas ou arranhões, no entanto existem alguns estudos onde a pele é queimada, ou a radiação ultravioleta é usada), orelha (onde é feito um furo na orelha) e tecido músculo-esquelético (onde é injetado miotoxinas no músculo). Para alem disso, conseguem regenerar a coluna vertebral depois de esta ser transectada, criando uma cicatriz glial permeável à regeneração dos axónios. Estes animais pertencem à família *Muridae*, e a sua subfamília é *Deomyinae*. O seu habitat natural encontra-se em África, Médio Oriente e Ásia.

Neste manuscrito foi feita uma compilação e uma extensa revisão da literatura sobre a regeneração nos *Acomys* publicada na última década. Descreve-se toda a informação disponível sobre as características e mecanismos que conduzem à regeneração neste modelo animal.

Em conclusão, até agora foi descrito que o *Acomys* é capaz de regenerar vários órgãos e tecidos tais como orelha, pele, músculo esquelético e medula espinhal. A regeneração destes vários tecidos tem algumas características comuns e outras que são específicas para cada tecido. Descreve-se que um sistema imunológico leve presente em *Acomys* permite a regeneração de todos estes tecidos. Além disso, pensa-se também que esta capacidade se deve também à resposta dos macrófagos, à falta de produção de fibrose e de miofibroblastos, e à regulação da via de sinalização de Hippo-Yap. No que diz respeito ao coração e ao rim, a regeneração destes tecidos nunca foi mostrada, no entanto estes órgãos são mais resistentes à lesão e são capazes de recuperar a função após a lesão.

Com este Animal, a comunidade científica tentará desvendar os mecanismos por detrás da regeneração e, no futuro, seguindo a hipótese de que os mecanismos regenerativos são conservados ao longo dos vertebrados, poderiam então extrapolar estas descobertas para desenvolver terapias para os seres humanos.

Palavras-chave: Regeneração nos mamíferos, *Acomys spp.*, sistema imune, ratinho espinhoso.

Authorship Statement

I hereby declare to be the author of this work, which is original and unpublished. Authors and papers consulted are duly cited in the text and are listed in the included references.

Table of content

List of Figures

List of Tables

Abbreviations

5-HT	Serotonin
Acta2	Actin alpha 2
Aqp3	Aquaporin 3
b3galnt1	b-1,3-N-acetylgalactosaminyltransferase 1
b3gnt7	b-1,3-N-acetylglucosaminyltransferase 7
BMS	Basso mouse scale
BrdU	5-bromo-2′-deoxyuridine
BUN	Blood Urea Nitrogen
CC3	Cleaved Caspase-3
Cdh1	E-cadherin
Cdh6	Cadherin 6
Cenpa	Centromere Protein A
Clo-Lipo	Clodronate liposomes
CM	Cardiomyocytes
Col6a1	Collagen 6 alpha 1
CSPGs	Chondroitin Sulfate Proteoglycans
Ctgf	Connective tissue growth factor
Cthrc1	Collagen Triple Helix Repeat Containing 1
Cxcl1	C-X-C Motif Chemokine Ligand 1
Cxcl12	C-X-C Motif Chemokine Ligand 12
DCX	Doublecortin
DF	Dermal fibroblasts
DG	Dentate gyrus
Dnmt1	DNA Methyltransferase 1
ECM	Extracellular Matrix
eMHC	Embryonic Myosin Heavy Chain
FAP	Fibro-adipogenic progenitors
Foxm1	Forkhead Box M1
Fn1	Fibronectin 1

H19	*H19* Imprinted Maternally Expressed Transcript
HSPG	Heparan
IFTA	Interstitial Fibrosis, Inflammation, and Tubular Atrophy
Igf2	*Insulin Like Growth Factor 2*
IGFBP-2	*Insulin Like Growth Factor Binding Protein 2*
Il1b	Interleukin 1 beta
Il10	Interleukin 10
K10	Keratin 10
K14	Keratin 14
kPa	Quilopascal
KSPG	Keratan
Lor	Loricrin
Ly6G	Lymphocyte antigen 6 complex locus G6D
Ly6E	Lymphocyte Antigen 6 Family Member E
MBP	Myelin Basic Protein
MF	Myofibroblasts
mm	Millimeter
Mmp9	Matrix Metalloproteinase 9
MPO	Myeloperoxidase
Mm13	Matrix Metalloproteinase 13
MRF4	Myogenic Regulatory Factor 4
Mybl2	MYB Proto-Oncogene Like 2
Myf5	Myogenic Factor 5
Myh3	Myosin Heavy Chain 3
Myh11	Myosin Heavy Chain 11
MyoD	Myogenic Differentiation 1
Ndst3	N-deacetylase-N-sulfotransferase 3
Ndst4	N-deacetylase-N-sulfotransferase 4
Nf-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSCs	Neural Stem Cells
PAI-1	*Plasminogen Activator Inhibitor-1*

PCNA	Proliferating cell nuclear antigen
PDGFRα	Platelet-derived growth factor receptor alpha
PDGFRβ	Platelet-derived growth factor receptor beta
PHH3	Phosphorylated histone H3
pSTAT3Y705	Signal Transducers and Activators of Transcription Phosphorylation Tyrosine 705
ROS	Reactive oxygen species
Serpine1	Serine Proteinase Inhibitor
SCG10	Superior Cervical Ganglion 10
Shh	Sonic Hedgehog
Slc4a1	Solute Carrier Family 4 Member 1
Slc26a7	Solute Carrier Family 26 Member 7
SMCs	Smooth muscle cells
Sox2	SRY (sex determining region Y)-Box Transcription Factor 2
Sox9	SRY (sex determining region Y)-Box Transcription Factor 9
SVZ	Subventricular Zone
Timp1	Tissue Inhibitor of Metalloproteinases 1
TGFβ	Transforming Growth Factor Beta
Tgfβ1	Transforming Growth Factor Beta 1
Tnc	Tenascin C
UV	Ultraviolet
Vcam1	Vascular Cell Adhesion Molecule 1
VEGF-A	*Vascular Endothelial Growth Factor-A*
vGlut1	Vesicular Glutamate Transporter 1
VP	Verteporfin
Wnt	Wingless-type Mouse Mammary Tumour Virus
Wnt1	Wingless-type Mouse Mammary Tumour Virus 1
Wnt2	Wingless-type Mouse Mammary Tumour Virus 2
Wnt3	Wingless-type Mouse Mammary Tumour Virus 3
Wnt5	Wingless-type Mouse Mammary Tumour Virus 5
Wnt6	Wingless-type Mouse Mammary Tumour Virus 6

Wnt7	Wingless-type Mouse Mammary Tumour Virus 7
Wnt10	Wingless-type Mouse Mammary Tumour Virus 10
Wnt11	Wingless-type Mouse Mammary Tumour Virus 11
Znf367	Zinc Finger Protein 367

1 Introduction

Regeneration is the capacity of some living beings to regrow tissues, appendages or even organs. There are two known mechanisms of regeneration: epimorphosis and morphallaxis. While in epimorphosis there is the formation of a blastema and the tissue structure/pattern is kept the same, in morphallaxis there is a repatterning of the tissue. Morphallaxis is usually seen in *Hydra* and epimorphosis in amphibians and mammals (Agata, Saito, and Nakajima 2007).

The first studies about regeneration were performed in the XIII century and the animal models used were *Hydra*, crustaceans and salamanders. These studies set the standard for the experimental research (Gilbert SF 2000). Nowadays, aside from these models, there are also studies done with zebrafish, lizards, amphibians and some mammals (Gupta 2016; Gawronska-Kozak et al. 2014).

Most mammalian adults cannot regenerate tissues fully and heal by scar. However, this does not happen in foetal stages, so the majority of studies about mammalian regeneration are comparisons between fetal and adult regeneration (Maden and Brant 2019). Unlike adult regeneration, there is little immune response in fetal regeneration. There are very few immune cells activated and the few cells activated are only for a short period of time (Cowin et al. 1998).

Acomys is a model recently described that can regenerate skin, ear, skeletal muscle, scarlessly. Moreover, while there is no evidence of *Acomys* cardiac tissue and kidney being fully regenerated, they regain its functions after injury, preventing cells from dying, unlike *Mus*, which is usually used in studies, as a non-regenerative species for comparison (Sandoval and Maden 2020). *Acomys* is also able to regenerate spinal cord injury creating a glial scar permeable to axon regeneration (Figure1) (Nogueira-Rodrigues et al. 2022).

Acomys belongs to the *Muridae* family, and their subfamily is *Deomyinae*. These animals are found in semidry and arid regions from Africa, the Middle East, and Asia (Steppan, Adkins, and Anderson 2004). *Acomys* gestate for 38 to 45 days, and organogenesis is almost complete by then. The majority of the brain development, lungs, kidney and liver occurs while *Acomys* are still in the uterus, and due to this characteristic, *Acomys* have been used as models for pregnancy, late-gestational development, near-term birth asphyxia and neural origins of behaviour (Haughton CL, Gawriluk TR 2016). This animals are precocial, since when they are born, they already have grey hairs in contrast to the golden hairs of adults, their eyes are open and their ears are unfolded (Steppan, Adkins, and Anderson 2004).

They are also used as diet-induced type-2 diabetes models since *Acomys* spontaneously get diabetes with age and in laboratory conditions (Shafrir, Ziv, and Kalman 2006), physiologic adaptations to life in the desert, examine temporal partitioning among sympatric rodent species in the wild, diel rhythmicity, female aggression, and parental behaviour (Haughton CL, Gawriluk TR 2016).

The objective of this work is to extensively review the bibliography about *Acomys* ability to regenerate.

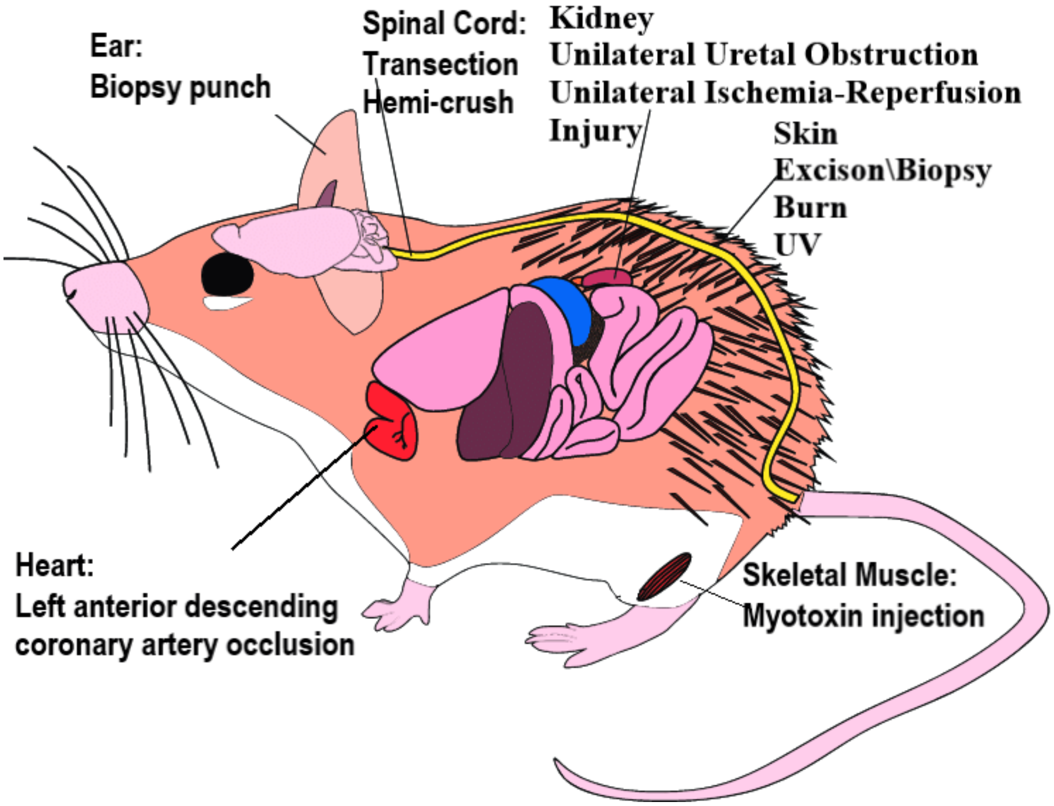

Figure 1- Study models of regeneraton in *Acomys*. Adapted from (Maden and Varholick 2020)

2 Methodology

The search was carried out on Pubmed https://pubmed.ncbi.nlm.nih.gov/ and on Google scholar https://scholar.google.lu/ between December 19, 2021 and September 29, 2022, with the keywords: *Acomys*, *Spiny Mouse*, *Regeneration*, *Ear regeneration*, *Skin regeneration*, *Cardiac tissue regeneration*, *Skeletal muscle regeneration*, *Kidney regeneration*, *Neural tissue regeneration* and *Spinal cord regeneration*. The results were filtered for studies under ten years old and in English. All the papers obtain with these criteria were used in this document. Occasionally, other older references were used at the suggestion of the consulted bibliography and supervisors.

3 Results

3.1 Skin and Hair Follicle Regeneration

Acomys is one of the animal models for skin regeneration. In most of the studies, the skin is damaged by wounding or scratching, however there are some studies where the skin is burnt, or Ultra-violet (UV) radiation is used.

3.1.1 Damage by wounds

Acomys skin is very fragile and can easily break, being 20 times weaker than *Mus*. Moreover, it is required 77 times more energy to break *Mus* skin compared to *Acomys* skin (Seifert et al. 2012).
After injury, the skin is softer than normal and its stiffness gradually increases from day 14 to day 21 (Harn et al. 2021). While this happens, keratinocytes in the wound margins start to proliferate, making the epithelium thicker. There is also a big epithelial migration of keratinocytes to the wound, but initially these cells do not show any proliferative response. Their proliferative rate increase as the wound heals (Maden and Brant 2019). Keratinocytes are important to give structure to the skin as they are made of keratins, which when arranged into tonofilaments, provide internal cellular structure. They also take part in immune response as they secrete cytokines (Barbieri, Wanat, and Seykora 2014).
Mus's keratinocytes proliferate at a slower rate. While *Acomys* keratinocytes can close scratches in 30 hours, *Mus* needs more than 48 hours (Table 1) (Stewart et al. 2018).
Like in other animals, in *Acomys* there is also the formation of granulation tissue during healing. Granulation tissue is composed by a matrix of immature collagen fibers and fibronectin that helps revascularize the wound bed and supports proliferative fibroblasts when migrating (Clark 1998). In *Acomys*, this tissue gradually loses density and their cells' axes are parallel to the wound's surface. In CD-1, a mice strain that resembles wild-type *Mus*, the granulation tissue is denser, and the cells are orientated randomly. Moreover, after injury, there is an upregulation of collagens IV, VII, VIII, XI, XIV, XXIV expression in CD-1 and the number of fibroblasts present in the wound bed is two times bigger (Maden and Brant 2019). As the *Acomys* wound heals, there is an upregulation of collagen XXIV and of the *Collagen Triple Helix Repeat Containing 1* (*Cthrc1*) gene (Maden and Brant 2019). Collagen XXIV is involved in the formation of bone during embrionic development and post-natal and is expressed at lower levels in the brain and in the cornea

(Matsuo et al. 2008, 2006; Koch et al. 2003). It also can be found in tissues undergoing collagen I fibrillogenesis (Koch et al. 2003) which is present in the wound (Maden and Brant 2019). *Cthrc1* gene reduces collagen deposition, promotes proliferation and inhibits *Transforming Growth Factor β* (*TGFβ*) (Maden and Brant 2019).

In *Acomys*, around two weeks after the injury, the hairs start to regrow (Figure 2, yellow arrows), which does not happen in *Mus*, since the wound leaves a hairless scar. Hair placodes that undergo Wnt signalling appear in the center of the wound and are induced to the wound margins centrifugally (Maden and Brant 2019). These hair placodes only form if the stiffness of the wound is higher than 5kPa and lower than 15kPa (Harn et al. 2021). As the new hairs mature, new sebaceous glands and erector pili are also formed and adipocytes at the base start to differentiate (Maden and Brant 2019). *Acomys* have three different hair types: dorsal, ventral, and lateral. The hair cycle starts before birth, unlike *Mus*, and all types of hair are regenerated after around 35 days if they are plucked. Although the newly formed hairs are thinner than the original ones, the percentage of hair remains the same (Figure 2, red arrows) (Jiang et al. 2020).

In conclusion, while *Acomys* start the regeneration process like the other mammals, they can heal without scars and can regrow their hairs.

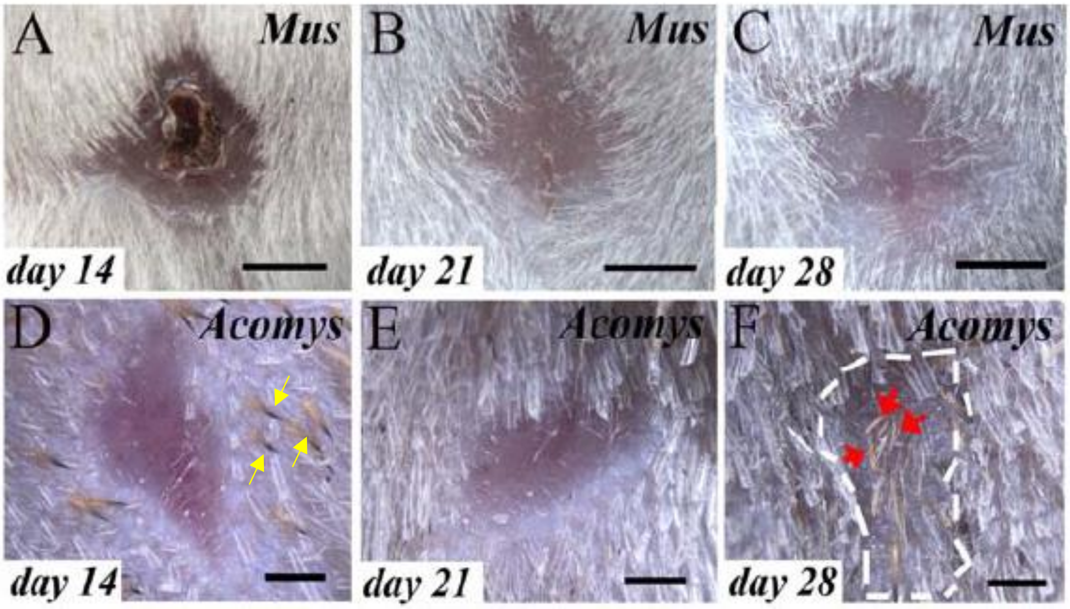

Figure 2- Comparison of wound healing in *Mus* (up) and in *Acomys* (down) at days 14, 21 and 28. Adapted from (Brant et al. 2016). Yellow arrows, hair growing in *Acomys* two weeks after injury; Red arrows, Tens que dizer o que são as setas vermelhas aqui na legenda.

Table 1- Comparison of skin wounds healing in *Acomys* and in *Mus*.

Acomys	***Mus***
Epithelial migration of keratinocytes	Epithelial migration of keratinocytes
Keratinocytes proliferate at a fast rate	Keratinocytes proliferate at a slow rate
Scratches close in 30 hours	Scratches close in 48 hours
Granulation tissue is formed	Granulation tissue is formed
Granulation tissue gradually loses density	Granulation tissue is dense
Granulation tissue cells' axes are parallel to the wound's surface	Granulation tissue cells are orientated randomly
Upregulation of collagen XXIV and of *Cthrc1*	Upregulation of collagens IV, VII, VIII, XI, XIV, XXIV
Hairs regrow	Hairs do not regrow

3.1.2 Damage by burning

When the *Acomys*' skin is burnt the area turns white and scabs. As re-epithelization occurs, the scab peels off piece by piece. After three weeks only the centre is not healed and on the fifth week hairs start to grow in the wound's surface. Even though, hairs are only observed growing on the fifth week, hair placodes appear in the wound epithelium on the second week. On the other hand, in *Mus* the re-epithelization starts three weeks after insult, only then does the scab fall off (Figure 3) (Maden 2018).

In response to the death of the burnt epithelium, the adjacent epidermis, zone of hyperaemia, starts to proliferate making this area thicker than the normal epithelium. The zone of hyperaemia did not suffer any damage by the burn and have more proliferating cells than the wounded epithelium (Maden 2018). Next to the hyperaemia zone is an area with high inflammatory response and vascular leakage. The proliferative cells in this area are in the panniculus carnosus and in the adipose tissue which can be due to initiation of skeletal muscle regeneration (Maden 2018).

On day 5 and 7 there is an increase in proliferation seen by the increase of Proliferating Cell Nuclear Antigen (PCNA) positive cells in the zone of the panniculus carnosus that is regenerating, in the dermis, in the connective tissue that surrounds the adipocytes and in the fibroblasts in their strands and in the adipocytes of the hypodermis. This happens in both *Acomys* and *Mus*, although the proliferation in *Mus* is slower. (Maden 2018). PCNA is a protein that can be found in proliferating cells in the S phase before DNA replication and is essential for this process (Takasaki, Y., Deng, J. S., & Tan 1981).

The proliferation in the dermal Layer starts to decline in the second week, while the proliferation in the wound epithelium only decreases in the fourth week, when the wound is completely healed. By this time, the skeletal muscle and the panniculus carnosus have also completely regenerated, however in *Mus* neither is fully regenerated (Maden 2018).

In summary, *Acomys* can regenerate burned skin, the skeletal muscle below and the panniculus carnosus while *Mus* cannot (Table 2).

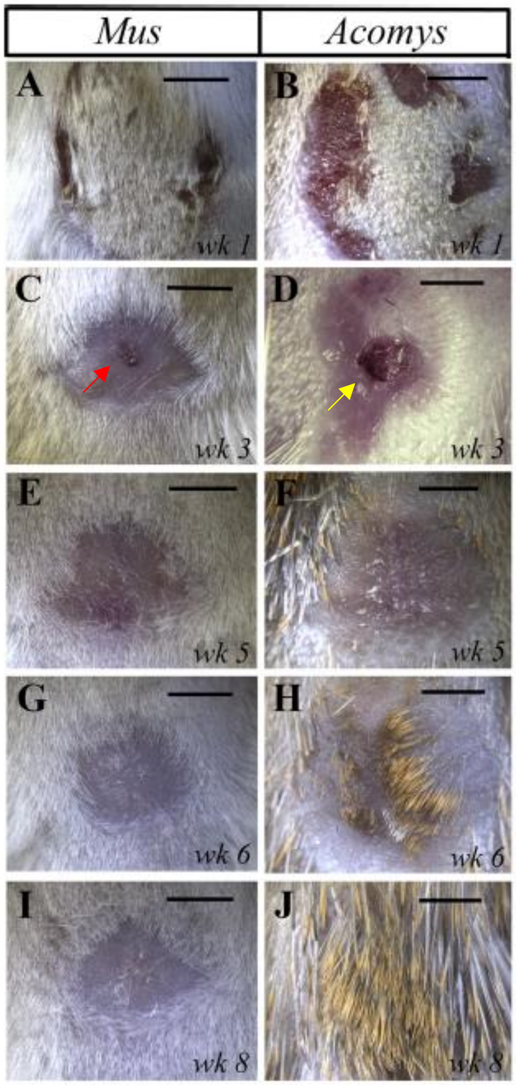

Figure 3- Comparison of burn healing in *Mus* (left) and *Acomys* (right) at weeks 1, 3, 5, 6 and 8. Adapted from (Maden 2018). At three weeks after injury, *Acomys* wound is re-epithelized and healed with the exception of the center of the

wound (yellow arrow). On the other hand, in *Mus*, re-epithelization only start at three weeks and the scab is still present (red arrow).

Table 2- Comparison of skin burns healing in *Acomys* and in *Mus*.

Acomys	***Mus***
Scab peels off piece by piece	Scab comes off whole
Only the center is not healed three weeks after insult	Re-epithelization starts three weeks after insult
Zone of hyperaemia proliferates	Zone of hyperaemia proliferates
Increase in proliferation in the zone of the panniculus carnosus	Increase in proliferation in the zone of the panniculus carnosus
Proliferation in the zone of the panniculus carnosus is fast	Proliferation in the zone of the panniculus carnosus is slow
Hair placodes appear in the wound epithelium on the second week	Hair placodes do not appear in the wound epithelium
Re-epithelization occurs at a fast rate	Re-epithelization occurs at a slow rate
Proliferation in the dermal layer declines in the second week	Proliferation in the dermal layer declines in the second week
Proliferation in the wound epithelium only declines in the fourth week	Proliferation in the wound epithelium only declines in the fourth week
Wound is fully healed in the fourth week	Wound does not fully heal

3.1.3 Damage by UV exposure

One way to damage skin is by exposure of this tissue to UV radiation. 24 hours after the UV exposure, the *Acomys* epidermis continues with the same thickness, since there is not proliferating cells, which can be seen by the lack of changes in the 5-bromo-2'-deoxyuridine (BrdU) incorporation. The cells in the basal epidermis and suprabasal epidermis start to proliferate 48 hours after the exposure, increasing the BrdU (analogue of thymine, incorporated into DNA during its replication making possible to identify cells that are proliferating) positive cells, although they are still reduced. On the contrary, *Mus* epidermis is thicker and the proliferation is higher although 24 hours after UV exposure proliferation is lower than normal (Wong et al. 2020).

In *Acomys* and in *Mus*, there is also an increase in apoptosis in the first 24 hours, as the cells have more CC3, but returns to normal levels after 48 hours (Wong et al. 2020). CC3 takes part in the induction of apoptosis (Jelínek et al. 2015).

The UV exposure of the *Acomys* skin induced a distinctive pattern of epidermal stratification. Aside from the basal layer, marked with Keratin 14 (K14), the spinous layer, marked with Keratin 10 (K10), and the cornified envelope, marked with Loricrin (Lor), there was also a new double-positive K14+/K10+ layer that has both spinous and basal characteristics, which did not occur in *Mus* (Wong et al. 2020). K14 is important for the structural support of keratinocytes in the basal epidermis and their mechanical resilience (Coulombe et al. 1991). Lor is a protein that is part of the cornified envelope (Steinert and Marekov 1995) and K10, like K14, is important for keratinocytes' structural support (Chamcheu et al. 2011).

In contrast to *Mus*, *Acomys* do not show UV-induced inflammatory response as expression levels of *C-X-C Motif Chemokine Ligand 1* (*Cxcl1*), *Interleukin 1 beta* (*Il1b*), *Tgf1b* and *Matrix metallopeptidase 9* (*Mmp9*), which are genes associated with inflammation, remain unchanged. In *Acomys*, UV also did not change keratinocyte differentiation as nuclear phosphor-Signal transducer and activator of transcription 3 Y705 (*pSTAT3Y705*) expression does not change and *Notch1* and *Notch2* expression are reduced. However, in *Mus*, keratinocyte differentiation increases (Table 3) (Wong et al. 2020).

Table 3- Comparison of skin healing after UV exposure in *Acomys* and in *Mus*.

Acomys	***Mus***
Epidermis keeps its thickness 24 hours after the UV exposure	Epidermis is thicker 24 hours after the UV exposure
Proliferation is normal 24 hours after the UV exposure	Proliferation is lower than normal 24 hours after the UV exposure
Proliferation is higher than normal 48 hours after the UV exposure	Proliferation is higher than normal 48 hours after the UV exposure
Increase in apoptosis in the first 24 hours	Increase in apoptosis in the first 24 hours
Apoptosis returns to normal 48 hours after exposure	Apoptosis returns to normal 48 hours after exposure

Formed a new layer marked with K14+/K10+ that has both spinous and basal characteristics	Only has the basal layer and the spinous layer
No UV-induced inflammatory response	UV-induced inflammatory response
Cxcl1, *Il1b*, *Tgf1b* and *Mmp9* expression remains the same	*Cxcl1*, *Il1b*, *Tgf1b* and *Mmp9* are upregulated
Keratinocyte differentiation does not change	Keratinocyte differentiation increases

3.2 Ear Regeneration

One model to study regeneration in *Acomys* is the hear punch (Figure 4). Studies using this model are largely used by the scientific community. After making a hole in the ear of *Acomys*, there is some local inflammation, shown by an increase of integrin alpha M (CD11b) expression which isolates neutrophils and macrophages (Matias Santos et al. 2016; Simkin et al. 2017). *Mus* has a greater increase of CD11b expression than *Acomys* especially on day three. To differentiate neutrophils from macrophages Lymphocyte antigen 6 complex locus G6D (Ly6G) was used, since Ly6G marks neutrophils. From day one to seven, Ly6G+ (neutrophils) cells is elevated in *Mus*, its peak being on day three; after day seven the majority of cells are Ly6G- (macrophages) (Simkin et al. 2017). *Acomys* does not have Ly6G+ cells, which might mean that *Acomys* neutrophils are like rats' and humans' neutrophils, which do not express Ly6G but Lymphocyte Antigen 6 Family Member E (Ly6E). *Acomys* neutrophils, which have multi-lobed nuclei, were identified by myeloperoxidase (MPO) reactivity and were less than *Mus* after 24 hours after injury. After day 10, neutrophils levels return to baseline in both species. *Acomys'* and *Mus'* neutrophils are mainly accumulated distally to the injury and in the scab (Simkin et al. 2017).

In the first day after wounding *Acomys* ear, there is already evidence that re-epithelization is happening, as necrotized tissue starts to peel off from the wound and is completely off the next day. Although this also happens in *Mus*, the necrosis here is more noticeable than in the *Acomys* (Matias Santos et al. 2016). As re-epithelialization starts, the local tissue undergoes histolysis, the collagen-rich ECM is fragmented and the epidermis migrates over the edge of the cartilage plate (Gawriluk et al. 2016). The re-epithelization is complete by day 7 after wounding in both species, even though re-epithelization is slower in *Acomys* (Matias Santos et al. 2016; Gawriluk et al. 2016). As regeneration occurs, genes that control neuronal growth and activity and axon guidance are upregulated, which is more pronounced in *Acomys* than in *Mus*. In day 10, there are nerve endings distally to the wound, but the re-innervation can only be seen clearly after day 20. In day 91, there are axonal extensions in the proximal side of the regrown tissue, but not in the distal side. There are also mylenated axons spread through the uninjured tissue (Gawriluk et al. 2020).

In *Acomys*, by day 21, in the wound's margins there is a layer of tissue that is starting to grow to the center of the wound and new hair follicles appear in it as it grows. Even though this tissue grows symmetrically in the right-left axis, in the proximal-distal it grows more towards the proximal side than the distal side (Matias Santos et al. 2016). The cells' organization in the new tissue is the same as the tissue in uninjured mice and the cells are round like fibroblasts. There is an elastic cartilage dividing the ear pinna dorso-ventrally. This elastic cartilage is thicker than the ear pinna and its chondrocytes are smaller than the ones in the uninjured tissue (Gawriluk et al. 2016). There is also melanocytes migrating under the dermis (Brewer et al. 2021) and a layer of adipose tissue and muscle tissue dorsally. On the contrary, in *Mus* the cells form thick nodules that may branch or develop unorganized masses (Gawriluk et al. 2016).

After 7 weeks, there is a capillary network in ventral side of the regenerated area that is well-developed and is more abundant in the posterior side than the anterior. If the hole's diametre is 4mm, it is usually completely closed by day 56. On the other hand, *Mus* heal the wound borders in two weeks, but cannot fully close the wound, even after two months (Matias Santos et al. 2016). If the diametre is 8mm, it takes *Acomys* around 150 days, but it is very usual for the holes to rip. Both females and males need the same time to fully close the holes, however if the female is lactating or if they lose blood it regenerates faster (Gawriluk et al. 2016). Three year-old *Acomys* are still able to close 2mm holes, although slower than younger mice, multiple times (Brewer et al. 2021).

Acomys and *Mus* capacity to heal the ear punch is not affected previous injuries or abdominal/flank skin injuries/fight wounds that may occur. The fight wounds are healed at the same time as the ear punch without changing the regeneration trajectory (Brewer et al. 2021).

The extra cellular matrix (ECM) organization helps in the injury response, as genes that influence it are upregulated. *Mus'* EMC is rich in collagen and the wound leaves a scar whereas *Acomys'* EMC is rich in *Mmp9, Matrix metalloproteinase 13* (*Mmp13*), *Fibronectin 1* (*Fn1*) and *Tenascin* (*Tnc*) and the wound is completely healed without a scar (Gawriluk et al. 2016).

In early stages after injury, there is an accumulation of Actin alpha 2 positive (*Acta2*+)/ Myosin Heavy Chain 11 negative (*Myh11*-) myofibroblasts (MF). While *Mus* MF numbers in the fibrotic tissue did not change, *Acomys* MFs disappeared on week three. After this loss, the wound closed and *Acta 2* was only expressed in smooth muscle cells (SMCs) in the blood vessels walls as *Acta2*+/*Myh11*+ (Brewer et al. 2021).

The *Acta2+* MFs also express Yap protein in both *Acomys* and *Mus*, however, in *Acomys*, the Yap protein is present in the nucleus and in *Mus* there is no Yap protein in the nucleus. In *Acomys* the *Acta2*- cells are also expressing Yap. *Mus'* Yap levels decrease through week two, while *Acomys'* levels remain the same. When *Acta2+* MFs disappear in *Acomys*, Yap is present in the perinuclear cytoplasm of most mesenchymal cells, but moves to the nucleus one week after and is present mainly in the ventral region of the wound (Brewer et al. 2021).

Yap signalling is inhibited by verteporfin (VP) wound closure and the rate of re-pigmentation is slower and Acta2+/Myh11- MFs numbers increase in *Acomys*, mainly around wound closure points and in the dorsal region of the wound. Moreover, *Acta2*+ MFs do not disappear leading to an increase of MFs content and a decrease of angiogenesis (Acta2+/Myh11+ SMCs) (Brewer et al. 2021)

Mature cross-linked collagen (Masson’s Trichrome) is present in *Acomys* wound at all stages meaning that collagen I is present in the *Acomys* wound, which does not happen in *Mus* (Brewer et al. 2021).

In *Acomys*, the cells in the healing tissue are constantly synthetising proteins in the ribossomes and re-entering the cell cycle since cells are Ki67+. Ki67 is a marker for proliferation as it stains cells in G1, S and G2/M phases but it does not stain cells in G0 phase. The cells also finish the cell cycle and enter mitosis since there are cells with Phosphohistone 3 (PHH3), which is used to stain mitotic cells. While this also happens in *Mus*, most of the cells do not finish the cell cycle since there is very few cells with PHH3 (Table 4) (Gawriluk et al. 2016).

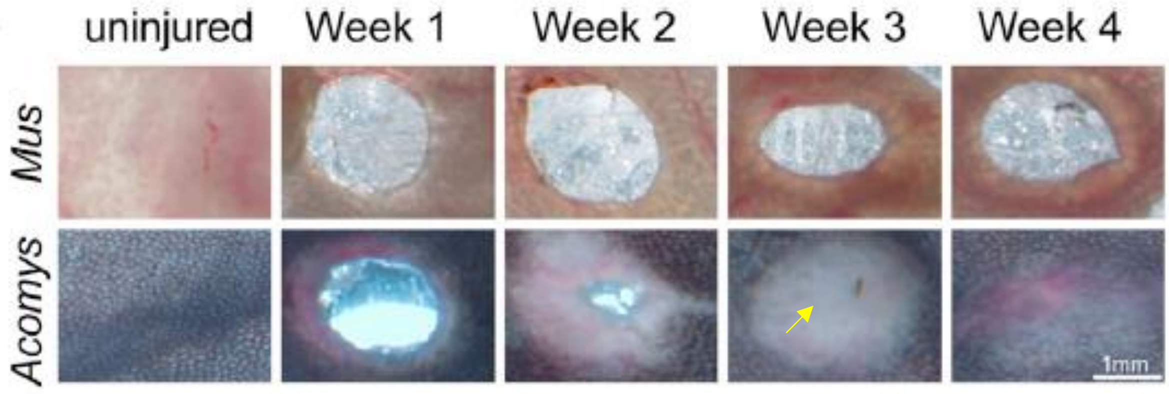

Figure 4- Comparison of 2 mm ear punch closure in *Mus* (up) and *Acomys* (down) at weeks 1, 2, 3 and 4. Contrary to *Mus*, after 3 weeks, *Acomys* presents the ear punch completely closed (yellow arrow). Adapted from (Brewer et al. 2021)

Table 4- Comparison of ear punch closure in *Acomys* and in *Mus*.

Acomys	***Mus***
Local inflammation	Local inflammation
Smaller increase of CD11b expression	Greater increase of CD11b expression
Ly6G does not marks neutrophils	Ly6G marks neutrophils
Less neutrophils	More neutrophils
Neutrophils are accumulated distally to the injury and in the scab	Neutrophils are accumulated distally to the injury and in the scab
Re-epithelization starts on day one	Re-epithelization starts on day one
Necrotized tissue starts to peel off on day one	Necrotized tissue starts to peel off on day one
Necrotized tissue is off on day two	Necrotized tissue is off on day two
Necrosis is less noticeable	Necrosis is more noticeable
Local tissue undergoes histolysis	Local tissue undergoes histolysis
Collagen-rich ECM is fragmented	Collagen-rich ECM is fragmented
Epidermis migrates over the edge of the cartilage plate	Epidermis migrates over the edge of the cartilage plate
Re-epithelization is complete by day 7	Re-epithelization is complete by day 7
Re-epithelization is slower	Re-epithelization is faster
Genes that control neuronal growth and activity and axon guidance are upregulated (more pronounced)	Genes that control neuronal growth and activity and axon guidance are upregulated (less pronounced)
In day 10, nerve endings are distally to the wound	
Re-innervation is seen clearly after day 20	
In day 91, there are axonal extensions in the proximal side of the regrown tissue and mylenated axons spread through the uninjured tissue	

A layer of tissue grows to the center of the wound from the wound's margins, by day 21	
Tissue grows symmetrically in the right-left axis, but grows more towards the proximal side than the distal side	
Cells' organization in the new is the same as the tissue in uninjured tissue and the cells are round like fibroblasts	Cells form thick nodules that may branch or develop unorganized masses
There is an elastic cartilage dividing the ear pinna dorso-ventrally which is thicker than the ear pinna and its chondrocytes are smaller than the ones in the uninjured tissue	
Melanocytes migrating under the dermis	
Layer of adipose tissue and muscle tissue dorsally	
Capillary network in ventral side of the regenerated area is well-developed and more abundant in the posterior side	
If the hole's diameter is 4mm, it is usually completely closed by day 56	Wound borders are healed in two weeks, but cannot fully close the wound
Females and males need the same time to fully close the holes	Females and males need the same time to fully close the holes
Lactating female or if they lose blood, it regenerates faster	Lactating female or if they lose blood, it regenerates faster
Three-year-old are still able to close 2mm holes, although slower	
Capacity to heal the ear punch is not affected previous injuries or	Capacity to heal the ear punch is not affected previous injuries or

abdominal/flank skin injuries/fight wounds	abdominal/flank skin injuries/fight wounds
Genes that influence ECM organization are upregulated	Genes that influence ECM organization are upregulated
EMC is rich in *Mmp9*, *Mmp13*, *Fn1* and *Tnc*	EMC is rich in collagen
Accumulation of *Acta2+*/*Myh11-* MF	Accumulation of *Acta2+*/*Myh11-* MF
MFs disappeared on week three	MF numbers in the fibrotic tissue did not change
After MFs loss, the wound closes and *Acta 2* is only expressed in SMCs in the blood vessels walls as *Acta2+*/*Myh11+*	*Acta2+* expression does not change
Acta2+ MFs and *Acta2-* cells express Yap protein	*Acta2+* MFs express Yap protein
Yap protein is present in the nucleus	There is no Yap protein in the nucleus
Yap levels remain the same	Yap levels decrease through week two
When *Acta2+* MFs disappear, Yap is present in the perinuclear cytoplasm of most mesenchymal cells	
Yap moves to the mesenchymal cells' nucleus after one week and is present mainly in the ventral region of the wound	
Mature cross-linked collagen is present in the wound at all stages	Mature cross-linked collagen is not present in the wound at all stages
Healing tissue constantly synthetases proteins in the ribossomes	
Healing tissue constantly re-enters the cell cycle	Healing tissue constantly re-enters the cell cycle
The cells also finish the cell cycle and enter mitosis	The cells do not finish the cell cycle

3.3 Cardiac Tissue Regeneration

Cardiac diseases are the number one cause of dead worldwide, mainly the myocardial infarction (H. Wang et al. 2016). Most people that suffer from myocardial infarction die immediately, however the surviving people suffer from cardiac problems due to ischemic cardiac tissue throughout the rest of their lives. Because of that, the scientific community develop efforts to find a model of cardiac regeneration and apply the knowledge obtained to humans. In the last years, *Acomys cahirinus* has being used as a model of heart disease/regeneration. Like in *Mus, in Acomys*, cardiac function starts to deplete after an infarct and there is also a decrease in the number of cardiomyocytes (CM) (Peng et al. 2021; Qi et al. 2021). CM are cells responsible for the contraction of the cardiac muscle and they also have an important role in the regeneration of the heart. *Acomys* showed a preservation of cardiac function more or less 50 days after the injury compared with *Mus* (Table 5) (Peng et al. 2021).

CMs that start to appear as the tissue heals tend to be tri- or tetra-nucleated. *Mus* CMs have bigger nuclei, while *Acomys* CMs are more immature .These cells are entering the cell cycle and the majority is shifting from G1 phase into S phase, in *Acomys*, and in *Mus* they occupy G2/M phase (Koopmans et al. 2021).

As healing occurs the tissue forms a scar. In *Acomys*, this scar is thicker compared with other mice species and it also has a higher density of cells, less compression and more pores (Peng et al. 2021; Koopmans et al. 2021). This scar starts to get smaller as days go by until it plateaus around day 42 in *Acomys*, but remains the same in *Mus*. ECM fibers in the *Acomys* scar are organized in a basket-weave pattern and in early stages they are wavy and have a high amount of collagen up until day 100, while in the *Mus* scar, the fibers are thin, straight and are aligned with each other (Koopmans et al. 2021).

In *Acomys*, whithin the scar there are *Platelet-Derived Growth Factor Receptor Beta* positive (*PDGFRβ+*) fibroblast and high levels of hydroxyproline (Koopmans et al. 2021). *PDGFRβ+* regulates angiogenesis, proliferation and without it, the body cannot form the granulation tissue after injury (Z. Gao et al. 2005; Hewitt et al. 2012). Moreover, hydroxyproline is also present in collagen.

Acomys also showed an increased vascular density extending to the center of the scar, which is correlated to the number of endothelial cells proliferating in the scar's center. This area also has a high number of mature vessels connected to each other, forming a well-branched network. On the other hand, *Mus* did not have any blood vessel in the scar. There are also 53 proteins that induce angiogenesis being expressed in the *Acomys* scar (Peng et al. 2021; Koopmans et al. 2021). Angiogenesis and vascular maturation are said to hinder the infarct expansion (Zhang et al. 2012). Two of the proteins present in *Acomys* scar are: Insulin Like Growth Factor Binding Protein 2 (IGFBP-2), that can increase Vascular Endothelial Growth Factor-A (VEGF-A), therefore inducing angiogenesis (Yau et al. 2015); and Platelet factor 4, which actually inhibits angiogenesis by binding to *VGEF-A* (Bikfalvi 2004; Lakka Klement, Shai, and Varon 2013). On the other hand, the *Mus* scar had an upregulation of Osteopontin and Serpin E1 also known as Plasminogen Activator Inhibitor-1 (PAI-1) (Koopmans et al. 2021). Osteopontin is responsible for cell migration and its accumulation attracts macrophages and inflammatory cells (O'Regan and Berman 2000). PAI-1 is involved in the coagulation system (R. Mehta and Shapiro 2008).

After injury the epicardial layer is disrupted and it shows the basement membrane or the ECM below and 100 days after, the layer is restored in *Acomys*, but not in *Mus* (Koopmans et al. 2021).

Table 5- Comparison of cardiac tissue regeneration in *Acomys* and in *Mus*.

Acomys	***Mus***
Cardiac function depletes after infarct	Cardiac function depletes after infarct
Decrease in the number of CM	Decrease in the number of CM
Preservation of cardiac function 50 days after the injury	No preservation of cardiac function after the injury
CMs in healing tissue tend to be tri- or tetra-nucleated	CMs in healing tissue tend to be tri- or tetra-nucleated
CMs have small nuclei	CMs have big nuclei
CMs tend to be immature	CMs tend to be mature
CMs are entering the cell cycle	CMs are entering the cell cycle
The majority of CMs is shifting from G1 phase into S phase	The majority of CMs is in G2/M phase
Healing tissue forms a scar	Healing tissue forms a scar
The scar is thick, has high density of cells, little compression and a lot of pores	The scar is not thick, has low density of cells, a lot of compression and a few pores

The scar gets smaller as days go by until around day 42 when it plateaus	The scar remains the same
ECM fibers in the scar are organized in a basket-weave pattern, are wavy and have a high amount of collagen up until day 100	ECM fibers in the scar are thin, straight and aligned with each other
PDGFRβ+ fibroblast and high levels of hydroxyproline are present in the scar	
Increased vascular density extending to the center of the scar and high number of mature vessels connected to each other, forming a well-branched network	No vascular density in the scar
53 proteins that induce angiogenesis being expressed in the scar like IGFBP-2 and Platelet factor 4	Upregulation of Osteopontin and Serpin E1
Epicardial layer is disrupted, and it shows the basement membrane or the ECM below and 100 days after injury the layer is restored	Epicardial layer is disrupted, and it shows the basement membrane or the ECM below the layer does not restore

3.4 Skeletal Muscle Regeneration

Skeletal muscle is one of the tissues that mammals can regenerate during their lives. After an injury and before the muscle starts to regenerate, mammals have a degeneration phase. In this phase, macrophages and neutrophils are recruited to the injury site in response to the necrotic cell death and remove the dead cells. While this happens, the macrophages present are mainly M1, while when the regeneration starts the present macrophages are mainly M2 thanks to an increase in *Il10* (Brant et al. 2019; Teixeira et al. 2003; Musarò 2014; Sulahian et al. 2000).

Muscle stem cells, or satellite cells, start to produce proliferating myoblasts and these fuse with themselves or with the damaged fibers present in the injury. The muscle stem cells also express myogenic regulatory factors as they become active. The first factors expressed are *Myf5* and *MyoD*, these factors are responsible for the cells fate. Without them, the cells do not commit to the myogenic fate. After this, *MRF4* and myogenin which are important for the fusion of the myocites to myotubes and perhaps myofibers. Myogenin also activates the expression of Myosin Heavy Chain 3 (*Myh3)* which regulates the development and the regeneration of the myofibers. These fibers undergo remodeling and become mature muscle (Maden et al. 2018; Musarò 2014; Brant et al. 2019).

In *Acomys* and in *Mus*, there is a big number of cells migrating to the injured muscle two days after the injury. While the overall structure of the tissue remains the same, the muscle fibers start to become less defined and are completely degenerated two days after in *Acomys*, however, in *Mus*, do not degenerate completely. By day six the *Acomys'* muscle fibers start to regenerate and they express embryonic myosin heavy chain (eMHC) and dystrophin while *Mus'* muscle fibers remain degenerated (Maden et al. 2018). eMHC is responsible for the regulation of the differentiation and if it is not expressed, there is an increase of the muscle stem cells differentiation, which leads to a decrease of the number of progenitors present (Agarwal et al. 2020). Dystrophin is important for the stabilization of the plasma membrane of striated muscle cells (Q. Q. Gao and McNally 2015).

The inflammatory response in *Acomys* is small as there are few cells expressing Nuclear Factor Kappa beta (*Nf-kB*), which is responsible for the cellular response for infections, and the levels of acid phosphatase activity, which indicates muscle fiber necrosis, are reduced. On the other hand, *Mus* has a higher amount of *Nf-kB*+ cells and acid phosphatase activity. Moreover, the levels of C-X-C Motif Chemokine Ligand 12 (*Cxcl12*) in *Acomys* are upregulated, while in *Mus Cxcl12* levels are downregulated (Maden et al. 2018). *Cxcl12* is a chemokine that helps regulating muscle regeneration (Brzoska et al. 2012) and it has an anti-inflammatory role (McCandless et al. 2006). There is also little fibrosis in *Acomys* since there is small levels of collagen expression compared to *Mus*, *Col3* being the highest. (Maden et al. 2018).

Unlike other mammals, *Acomys* show little M1 activity during regeneration but there is a lot of M2 macrophages present in the damaged tissue (Maden et al. 2018). The number of M2 macrophages is low until day 18 which is when they reach their peak and are throughout the dermis (Brant et al. 2019).

In both species, *Il10* expression reachs its peak on day seven, although *Mus'* levels are not as upregulated as in *Acomys* and starts to decrease on day ten. In *Acomys Il10* is still upregulated from day 18 to day 28, in *Mus* the levels are low. *Il10* is a cytokine that helps in anti-inflammatory response and is responsible for the transition from M1 to M2 (Brant et al. 2019; Sulahian et al. 2000).

The muscle stem cells start to express Myogenic Factor 5 (*Myf5)*, Myogenic Differentiation 1 (*MyoD)* and myogenin on day four. While in *Acomys*, the levels remain low until day 14 and the levels are upregulated between day 14 and day 18, in *Mus* this upregulation is higher on day four and on day six the levels decrease. In *Acomys* levels of *Myh3* are still upregulated from day 18 to day 28. There is also an increase of FAP cells in the endomysials spaces between myofibers, which is more noticeable in *Acomys*. These cells are important for the muscle regeneration and they express *PDGFRα* (Brant et al. 2019; Maden et al. 2018). *PDGFRα* induces angiogenesis which speeds up the rate of healing (Horikawa et al. 2015).

Wnt6 levels do not change in *Acomys* from days seven to 14 it is upregulated on days 18 to 28, which induces the expression of *Myf5*, *MyoD* and *col6a1*. While this upregulation also happens in *Mus* from day seven to 10, *Wnt6* levels are downregulated. (Brant et al. 2019; Tajbakhsh et al. 1998). *Col6a1* is important for the muscle regeneration as its loss induces changes in organelles such as the mitochondrias and sarcoplasmic reticulum which cause loss of contractile strength (Irwin et al. 2003). *Wnt7a* which induces *MyoD* expression, is also upregulated in *Acomys*, but it does not change in *Mus* or it is downregulated (Brant et al. 2019; Tajbakhsh et al. 1998). *Wnt2* expression regulates fibrosis, and it increases between day seven and day 10, which happens to a bigger extent in *Mus*. In *Acomys Wnt2* levels stabilize until day 28, while in *Mus* the levels are upregulated until day 18 and start to decrease on day 21 (Brant et al. 2019; Bayle et al. 2008).

Acomys are able to regenerate the muscle multiple times sequentially while *Mus* loses its ability with successive regenerations and the muscle tissue is filled with adipose tissue (Table 6) (Maden et al. 2018).

Table 6- Comparison of skeletal muscle regeneration in *Acomys* and in *Mus*.

Acomys	***Mus***
M1 macrophages and neutrophils are recruited to the injury site in response to the necrotic cell death to remove them	M1 macrophages and neutrophils are recruited to the injury site in response to the necrotic cell death to remove them
There is an increase in *Il10* that induces M1s change to M2	There is an increase in *Il10* that induces M1s change to M2
Satellite cells produce proliferating myoblasts that fuse with themselves or with the damaged fibers	Satellite cells produce proliferating myoblasts that fuse with themselves or with the damaged fibers
Satellite cells express *Myf5*, *MyoD*, *MRF4* and myogenin	Satellite cells express *Myf5*, *MyoD*, *MRF4* and myogenin
Big number of cells migrating to the injured muscle two days after injury	Big number of cells migrating to the injured muscle two days after injury
Muscle fibers become less defined and are completely degenerated on day four	Muscle fibers become less defined and degenerate
Muscle fibers degeneration is fast	Muscle fibers degeneration is slow
Muscle fibers start to regenerate, and they express eMHC and dystrophin by day six	Muscle fibers remain the same
Few *Nf-kB*+ cells	A lot of *Nf-kB*+ cells
Low acid phosphatase activity	High acid phosphatase activity
Cxcl12 is upregulated	*Cxcl12* is downregulated
Small levels of collagen expression	High levels of collagen expression
Little M1 activity during regeneration	M1 activity during regeneration
A lot of M2 macrophages present in the damaged tissue	Few M2 macrophages present in the damaged tissue

Il10 expression peaks on day seven	*Il10* expression peaks on day seven
Il10 expression decreases on day 10	*Il10* expression decreases on day 10
Il10 expression is still upregulated on days 18-28	*Il10* expression is still low on days 18-28
The muscle stem cells start to express *Myf5*, *MyoD* and myogenin on day four	The muscle stem cells start to express *Myf5*, *MyoD* and myogenin on day four
Myf5, *MyoD* and myogenin levels remain low until day 14 and the levels are upregulated between day 14 and day 18	*Myf5*, *MyoD* and myogenin are high on day four and five and decrease on day six
Myh3 levels are still upregulated from day 18 to day 28	
Increase of FAP cells in the endomysials spaces between myofibers (more noticeable)	Increase of FAP cells in the endomysials spaces between myofibers (less noticeable)
Wnt6 levels do not change from days 7-14	*Wnt6* levels are downregulated from days 7-10
Wnt6 levels are upregulated from days 18-28	*Wnt6* levels are upregulated from days 18-28
Wnt7a levels are upregulated	*Wnt7a* levels are downregulated or do not change
Wnt2 expression increases between days 7-10 (less noticeable)	*Wnt2* expression increases between days 7-10 (more noticeable)
Wnt2 levels stabilize until day 28	*Wnt2* levels keep increasing until day 18 and decrease on day 21
Can regenerate the muscle multiple times sequentially	loses its ability the more it must regenerate

3.5 Kidney Regeneration

Nowadays, chronic kidney disease is one of the as a leading public health problem worldwide, leading to more deaths than breast or prostate cancers in America. 13,4% of adult worldwide present a chronic kidney disease (Lv and Zhang 2019).

Until today, the scientific community was not able to show that *Acomys cahirinus* is able to regenerate the kidney after damage. Nevertheless, this animal shows a resistance to damage of the kidney after damage by uretal obstruction or ischemia.

3.5.1 Damage by Unilateral Uretal Obstruction

One way to induce kidney damage in animal models is by obstruction of the urethra. Recently *Acomys* was used as a model to study kidney regeneration.

After the obstruction the kidney starts to swell and the tubular dilatation starts to increase, reaching its peak in day seven, this happens in both *Acomys* and *Mus*. However, the weight and the anatomic structure of the kidney remain the same in *Acomys*, while *Mus* had a rapidly decline of kidney weight. *Acomys'* E-cadherin (*Cdh1*) levels remain the same, showing that there is no change in the anatomic structure of the tubules as the loss of *Cdh1* leads to a defective tubular structure (Okamura et al. 2018, 2021; Zheng et al. 2016). On the other hand, *Mus*' *Cdh1* levels progressively declined (Okamura et al. 2018, 2021).

After three weeks, *Acomys* did not have any significant change in the collagen levels, suggesting that there is no fibrosis, while in *Mus* the collagen levels increased rapidly (Table 7). There is also no interstitial matrix fibrosis, and the Interstitial fibrosis and tubular atrophy (IFTA) scores are low compared to *Mus*. However, the levels of *Acomys' Acta2* myofibroblasts, which secrete collagen-rich matrix during injuries, and F4/80+ macrophages, which is characteristic of chronic inflammation and tissue fibrosis, are increased compared to the uninjured kidney however, *Mus* has higher levels (Okamura et al. 2018, 2021; Grgic et al. 2014; Duffield 2014).

In both *Acomys* and *Mus*, there is an upregulation of kidney injury markers (*Timp1, Sox9, Vcam1, Serpine1*) and a downregulation of genes that affect ions transport (*Aqp3, Slc26a7, Slc12a1, Slc4a1*) after day two. In *Acomys*, there is an upregulation of genes responsible for the regulation of cell cycle activity (*Cenpa, Mybl2, Dnmt1, Foxm1, Znf367*), angiogenesis and persistence of nephron progenitors (*Igf2* and *H19*). *Mus*, however, upregulates profibrotic, myofibroblast-inducing factors (*Tgfb3*, *Dkk3*, *Runx1*, *Gli3*, *Nkd2*) and inflammatory mediators (*Atf3*, *Nfil3*, *Nfkb2*, *Relb*, *Nfkbid*, *Nfkbie*, *Ciita*) (Okamura et al. 2021).

Cdh6 is a nephron progenitor gene that is upregulated in the kidney development and is expressed mainly in zones transitioning from mesenchymal to epithelial (Cho et al. 1998; Mah et al. 2000). Throughout the *Acomys*' proximal tubular network *Cdh6* is upregulated and expressed in mosaic patches and increased five fold in day fourteen, while in *Mus Cdh6* is only in small subsets in the tubules (Okamura et al. 2021).

Table 7- Comparison of kidney regeneration when the urethra is obstructed in *Acomys* and in *Mus*.

Acomys	***Mus***
Kidney starts to swell and tubular dilatation increases, reaching its peak in day seven	Kidney starts to swell and tubular dilatation increases, reaching its peak in day seven
Weight and the anatomic structure of the kidney remain the same	Weight and the anatomic structure of the kidney decline
Cdh1 levels remain the same	*Cdh1* levels decline
No significant change in collagen levels	Collagen levels increased rapidly
No interstitial matrix fibrosis and the IFTA scores are lower	Interstitial matrix fibrosis and the IFTA scores are higher
Acta2 myofibroblasts levels are increased compared to the uninjured kidney	*Acta2* myofibroblasts levels are increased compared to the uninjured kidney
Upregulation of kidney injury markers (*Timp1*, *Sox9*, *Vcam1*, *Serpine1*) after day two	Upregulation of kidney injury markers (*Timp1*, *Sox9*, *Vcam1*, *Serpine1*) after day two
Downregulation of genes that affect ions transport (*Aqp3*, *Slc26a7*, *Slc12a1*, *Slc4a1*) after day two	Downregulation of genes that affect ions transport (*Aqp3*, *Slc26a7*, *Slc12a1*, *Slc4a1*) after day two
Upregulation of genes responsible for the regulation of cell cycle activity (*Cenpa*, *Mybl2*, *Dnmt1*, *Foxm1*, *Znf367*),	Upregulation of profibrotic, myofibroblast-inducing factors (*Tgfb3*, *Dkk3*, *Runx1*, *Gli3*, *Nkd2*) and

angiogenesis and persistence of nephron progenitors (*Igf2* and *H19*)	inflammatory mediators (*Atf3*, *Nfil3*, *Nfkb2*, *Relb*, *Nfkbid*, *Nfkbie*, *Ciita*)
Throughout the proximal tubular network *Cdh6* is upregulated and expressed in mosaic patches and increased five-fold in day 14	*Cdh6* is only in small subsets in the tubules

3.5.2 Damage by Unilateral Ischemia-Reperfusion Injury

Another model to induce an injury in the kidney is by induction of ischemia with the clamping of vascular pedicle. *Acomys* were also submitted to this surgery to study the regeneration of the kidney. 24 hours after the ischemia, there is an increase of blood urea nitrogen (BUN) in both species. *Acomys* BUN levels are slightly higher than *Mus*, but it returns to normal by day 16 while *Mus* BUN levels keep on increasing. The ischemia also causes a severe injury in the tubular epithelium, but there is no fibrosis, and the kidney weight remains the same in *Acomys*. In contrast, *Mus* lost almost 40% of the kidney weight. *Acomys* injury is healed by day 14 as *Cdh1* levels return to baseline after its depletion in day seven while in *Mus Cdh1* levels keep on declining (Okamura et al. 2018, 2021).

By day 14, *Mus* tubules are atrophic as its membrane laminin is progressevely shrinking and thickening, while in *Acomys* the membrane structure are similar to the uninjured kidney (Okamura et al. 2021).

Eventhought there is no fibrosis in *Acomys*, Acta2 myofibroblasts levels increased, but plateau after one week and reduce significantly at day 14, in contrast to the progressive increase that happens in *Mus*. Moreover, the F4/80+ macrophage infiltration also increases, although in *Acomys* it is lower. (Okamura et al. 2021).

There is a big number of necrotic debris and tubular casts with polymorphonuclear cells and other nucleated cells in the tubular network. However, while in *Acomys* approximately 48 hours after injury the debris is cleared and tubular structures start to develop, in *Mus* the debris remains in the tubular network. The tubular structures forming in *Acomys* are still unorganized and have flattened epithelial cells which means they are still in a dedifferentiated state. In day seven, the tubular structure are already defined, have open lumens and their epithelial cells are mature (Okamura et al. 2018, 2021).

Nevertheless, despite *Acomys* show a resistance to injury in the kidney after both obstruction and ischemia, it was not shown that this animal has the capacity of regenerate the kidney after injury (Table 8).

Table 8- Comparison of kidney regeneration after ischemia in *Acomys* and in *Mus*.

Acomys	***Mus***
Increase of BUN levels after 24 hours	Increase of BUN levels after 24 hours
BUN levels return to normal by day 16	BUN levels keep on increasing
The tubular epithelium is severely injured	The tubular epithelium is severely injured
No fibrosis, and the kidney weight remains the same	Almost 40% of the kidney weight was lost
Cdh1 levels deplete in day seven and return to baseline by day 14	*Cdh1* levels deplete in day seven and keep on declining
The membrane structure is similar to the uninjured kidney	Tubules are atrophic as its membrane laminin is progressevely shrinking and thickening by day 14
Acta2 myofibroblasts levels increased, but plateau after one week and reduce significantly at day 14	*Acta2* myofibroblasts levels progressively increase
F4/80+ macrophage infiltration also increases	F4/80+ macrophage infiltration also increases
Increase of necrotic debris and tubular casts with polymorphonuclear cells and other nucleated cells in the tubular network	Increase of necrotic debris and tubular casts with polymorphonuclear cells and other nucleated cells in the tubular network
Approximately 48 hours after the debris is cleared and tubular structures start to develop	Debris remains in the tubular network

In day seven the tubular structure is already defined, has open lumens and the epithelial cells are mature	

3.6 Neural Tissue and Spinal Cord Regeneration

Spinal cord injury leads to paralysis, which greatly affects humans and knowing mechanisms that lead to spinal cord regeneration would be fantastic for humans. *Acomys* can regenerate both the spinal cord and neural tissue so it can be used as a model for these studies.

There are cells called Neuronal Stem Cells (NSCs) that can generate new neurons. Moreover, they are self-renewable and quiescent and influence brain plasticity throughout life. These cells can be found mainly in two niches: the Subventricular Zone (SVZ) and the Dentate gyrus (DG), but there are more niches (Palmer, Takahashi, and Gage 1997). The NSCs in the SVZ generate neuroblasts which will migrate through the olfatory bulbs and then differentiate into olfatory neurons (Mirzadeh et al. 2008) while the ones in the DG generate immature neurons that will differentiate into DG neurons (Sun et al. 2015).

BrdU staining of four to six- month-old *Acomys* showed that *Acomys'* SVZ is packed with NSCs ventrally between the caudate putamen and the lateral septal nucleus, whereas the same region in two- to three-month-old *Mus* have less NSCs. It also showed that the fields where the cells proliferate have approximately twice cells per field comparing with *Mus*. The proliferation can be showed by Ki67 staining. Aside the NSCs the SVZ is also packed with immature neurons, stained by DCX (Maden et al. 2021). DCX is a protein NSCs expressed when they start dividing and the immature neurons still express it until the 3rd week (Brown et al. 2003). In the DG the results are similar (Maden et al. 2021).

Sox2, *Notch1*, *Shh* and *Noggin* are more upregulated in the cortex of *Acomys* than in *Mus* (Maden et al. 2021). *Sox2* is important for the maintenance of the number of NSCs, and its loss leads to a depletion of NSCs (Miyagi et al. 2008). *Notch1* promotes NSCs proliferation and regulates the cell fate as does *Shh* (Imayoshi and Kageyama 2014; Balordi and Fishell 2007). *Noggin* inhibits BMPs which in turn inhibit the formation of new neurons, or neurogenesis (Brooker et al. 2017).

The ability to regenerate spinal cord in *Acomys* was also recently studied. Two weeks after completing spinal cord transection at T8, *Acomys* starts to recover its motor functions and has a Basso mouse scale (BMS), which reflects mice's locomotor function, score of 2 while *Mus'* score remains 0. Eight weeks after injury, *Acomys'* BMS score is 4, which means that the initial weight support is re-established. On the other hand, *Mus* were not able to re-establish initial weight support and the BMS score remained between 0 and 1 (Nogueira-Rodrigues et al. 2022).

As *Acomys* heals, the spinal cord connects with the rostral and caudal boundaries of the injury site by forming a bridging tissue while in *Mus* the original borders are not respected (Nogueira-Rodrigues et al. 2022).

Acomys wound has an increased number of axons that express bIII-tubulin which penetrate and span the new tissue. In contrast, *Mus* only have bIII-tubulin-positive axons far from the wound. Moreover, there is a significantly high number of regenerating neurons, compared to *Mus*, that can only grow until the border lesion. There are few neurons that cross the border which are already myelinated, which means the regeneration includes myelination (Nogueira-Rodrigues et al. 2022). The bridging tissue in *Acomys* is penetrated by superior cervical ganglion 10 (SCG10)-positive sensorial axons, in *Mus* they are accumulated at the caudal border of the injury (Nogueira-Rodrigues et al. 2022). SCG10 is a protein expressed by the nervous system during development (Menon and Gupton 2016). Moreover, axons containing descending serotonin (5-HT) are regenerated through the *Acomys* lesion while in *Mus* they accumulated in the lesion border. There is also more 5-HT staining in *Acomys* than in *Mus* (Nogueira-Rodrigues et al. 2022).

12 weeks after the injury, bilateral axons are sprouting caudally to the injury site, which does not happen in *Mus*. These axons are in the corticospinal tract which is involved in voluntary motor function and have a pattern of axon arborization where collaterals are ventrally directed caudally to the injury site (Nogueira-Rodrigues et al. 2022).

Synaptic connectivity is re-established in *Acomys* as pre-synaptic vesicular glutamate transporter 1 (vGlut1)-positive/eGFP-positive buttons are present, eventhough their density is low. The presence of vGlut1/eGFP buttons means that synapses have been formed. This can also be seen as *Acomys* can conduct compound action potentials (CAPs) throughout the injury site. However, there is no vGlut1/eGFP buttons in *Mus* and they cannot conduct CAPs (Nogueira-Rodrigues et al. 2022).

Acomys have more neurogenesis specific genes upregulated than genes involved in wound healing, which are mostly downregulated. There are also upregulated several growth factors or their transcriptional activators, neural stem cell genes or their transcription factors, genes involved in axonal guidence, *Tgfβ1* and *Wnt* signaling molecules and gene that induces cell death (Streeter et al. 2020).

There is a decrease of collagen IV expression and an increase of MBP expression (Streeter et al. 2020) which is important for the production of myelin (CAROL et al. 1990). Collagen IV is part of the dermal-epidermal junction and it separates endothelial cells from epithelial cells (Velez and

Howard 2012). The decrease of collagen expression explains the lack of fibrosis in *Acomys*. *Mus* has collagen I depositions in the injury site and has fibrotic scaring (Streeter et al. 2020).

Keratan (KSPG) and heparan (HSPG) sulfate proteoglycans are key enzymes in major ECM glycosaminoglycans biosynthetic pathways, whose levels are altered in the *Acomys* injury site. There is an upregulation of b-1,3-N-acetylglucosaminyltransferase 7 (b3gnt7), which is important for the KSPG synthesis, and a downregulation of N-deacetylase-N-sulfotransferase 3 and 4 (Ndst3 and Ndst4), which are involved in post-synthesis modification of HSPG and of b-1,3-N-acetylgalactosaminyltransferase 1 (b3galnt1), which is involved in glycosphingolipids biosynthesis. In addition, KSPG deposition increased 30-fold in injured *Acomys* rostrally and caudally to the lesion site and HSGP deposition decreased (Nogueira-Rodrigues et al. 2022).

Expression of chondroitin sulfate proteoglycans (CSPGs), which also participate in ECM glycosaminoglycans biosynthesis, are also changed. The usual positions for sulphuration in glycosaminoglycan chains of CSPGs are positions 4 (C4) and 6 (C6). C4s inhibits axonal growth, while C6s regulates positively regeneration and plasticity (Hang Wang et al. 2008; Lin et al. 2011; Nogueira-Rodrigues et al. 2022). The *Acomys* injury site has an upregulation of C6S-sulfotransferase Chst15 expression while there is no change in C4 regulation (Nogueira-Rodrigues et al. 2022).

Astrocytes are present in both species and there is no significant difference between A1 astrocytes and A2 astrocytes observed between *Acomys* and *Mus*. However, pan-reactive astrocytes are decreased in *Acomys* (Nogueira-Rodrigues et al. 2022). A1 astrocytes and A2 astrocytes are types of reactive astrocytes that appear after ischemia or neuroinflammation. While A1 astrocytes are responsible for upregulating genes that damages synapses, A2 astrocytes upregulate neurotrophic factors (Liddelow et al. 2017). Pan-reactive astrocytes are a mixture of A1 and A2 astrocytes (Escartin et al. 2021). *Acomys* astrocytes are organized next to the spinal lesion in a network and their interface is surrounded by microglia and leukocytes, while *Mus* astrocytes are concentrated in the injury's epicenter (Table 9) (Streeter et al. 2020).

The morphology of the *Acomys* DG and hippocampus is similar to the morphology of a gerbil. Studying *Acomys* brain is very important to undergo several degenerative diseases, such as Parkinson and Alzheimer diseases. Recently an atlas of the *Acomys cahirninus* brain was developed by our group (Vitorino et al. 2022). This tool allows the exact knowledge of all the brain, allowing direct targeting of structures. A brain atlas is an excellent tool for neuronal studies and to allow *Acomys* to be used as a model for the study of regeneration in neurodegenerative diseases.

In summary, *Acomys* can regenerate and regain its ability to move and support itself in their backpaws

Table 9- Comparison of neural tissue and spinal cord regeneration in *Acomys* and in *Mus*

Acomys	***Mus***
SVZ and DG are packed with NSCs ventrally between the caudate putamen and the lateral septal nucleus	SVZ and DG have NSCs ventrally between the caudate putamen and the lateral septal nucleus
SVZ and DG are packed with immature neurons	SVZ and DG are packed with immature neurons
Sox2, Notch1, Shh and *Noggin* are upregulated in the cortex	*Sox2, Notch1, Shh* and *Noggin* are upregulated in the cortex
Two weeks after complete spinal cord transection at T8, starts to recover its motor functions and has a BMS score of 2	Two weeks after complete spinal cord transection at T8, there is no recover of its motor functions and has a BMS score of 0
Eight weeks after injury, BMS score is 4 and initial weight support is re-established	Eight weeks after injury, BMS score is 0 or 1 and initial weight support is not re-established
Spinal cord connects with the rostral and caudal boundaries of the injury site by forming a bridging tissue	Original borders are not respected
Increased number of axons that express bIII-tubulin which penetrate and span the new tissue in the wound	bIII-tubulin-positive axons far from the wound
High number of regenerating neurons	Low number of regenerating neurons that can only grow until the border lesion
Bridging tissue is penetrated by SCG10-positive sensorial axons	SCG10-positive sensorial axons are accumulated at the caudal border of the injury

Axons containing descending 5-HT are regenerated through the lesion	Axons containing descending 5-HT are accumulated in the lesion border
12 weeks after the injury, bilateral axons are sprouting caudally to the injury site	12 weeks after the injury, no bilateral axon is sprouting
Synaptic connectivity is re-established	Synaptic connectivity is not re-established
Neurogenesis specific genes are upregulated	
Genes involved in wound healing are mostly downregulated	
Upregulation of several growth factors or their transcriptional activators, neural stem cell genes or their transcription factors, genes involved in axonal guidence, *Tgfβ1* and *Wnt* signaling molecules and gene that induces cell death	
Decrease of collagen IV expression and an increase of MBP expression	Collagen I depositions in the injury site and has fibrotic scaring
Upregulation of b3gnt7 and downregulation of Ndst3 and Ndst4	
KSPG deposition increased 30-fold rostrally and caudally to the lesion site and HSGP deposition decreased	
Upregulation of C6S-sulfotransferase Chst15 expression while there is no change in C4 regulation	
Astrocytes are present and there is no significant difference between A1 astrocytes and A2 astrocytes	Astrocytes are present and there is no significant difference between A1 astrocytes and A2 astrocytes
Pan-reactive astrocytes are decreased	

Astrocytes are organized next to the spinal lesion in a network and their interface is surrounded by microglia and leukocytes	Astrocytes are concentrated in the injury’s epicenter

4 Discussion

In the last decade, regeneration in *Acomys* was described by several research group showing its ability to regenerate skin, ear, muscle and spinal cord and a resistance to heart and kidney injury. Nevertheless, it is possible to find in literature some divergent reports between the research groups on the time that *Acomys* takes to regenerate skin or ear holes (Maden 2018; Brant et al. 2019; Matias Santos et al. 2016; Gawriluk et al. 2016). This might be due to different laboratory conditions or because the way the injury was made was not the same. Moreover, eventhough the mice are the same species, they are different wild type individuals between studies, which can also change the regeneration time.

Eventhought there is no definitive answer as to why *Acomys* is able to regenerate scarlessly or show a resistance to injury in case of heart or kidney injury, most studies agree that *Acomys'* reduced inflammatory response is one of the main factors for this. Because of this, some studies have focused on the mechanism of the inflammatory response when *Acomys* are regenerating ear punches. This studies have shown that, if the mechanism is changed, the wound heals with a scar (Brewer et al. 2021; Simkin et al. 2017).

Acomys' and *Mus'* monocytes, lymphocytes, neutrophils and eosinophils have similar profiles and their basal percentages in the blood are similar between both species. When there is an injury, *Mus* shows a higher accumulation of immune cells than *Acomys*. However, macrophages in *Acomys* produce more reactive oxygen species (ROS) (Simkin et al. 2017). This difference in macrophage response might mean that macrophages are important for scarless regeneration.

To confirm this, it was studied what would happen if the number of macrophages decreased in *Acomys* by injecting them with clodronate liposomes (Clo-Lipo). While the mice that were not injected with Clo-Lipo were able to close completely an ear punch 34 days after it was made, Clo-Lipo-injected mice only started closing the wound by day 20. Moreover, most of the Clo-Lipo-injected mice still had the wound open on day 53 and the ear punch completely closed on day 70 (Figure 5) (Simkin et al. 2017).

There is also the theory that *Acomys* can regenerate because fibrosis does not happen. Seifert et al. 2012 proposed that *Acomys* could regenerate without fibrosis due to the absence of myofibroblasts (MF). As it was described in the ear regeneration previously, *Acomys* do have MF until week three and after the MF disappear the wound closes and there is formation of blood vessels. However, if

MF do not disappear, *Acomys'* wound healing will be similar to *Mus* (Brewer et al. 2021). *Acomys* MF seem to have a unique phenotype. Brewer et al. 2021 used *Tgfβ1* treatment in *Acomys'* dermal fibroblasts (DF) to study this. *Acomys* DFs express Acta2 and has short F-actin filaments under control conditions that do not change with Tgfβ1 exposure, which does not happen in *Mus*. However, SMAD2, SMAD3, and p38 in *Acomys'* DFs phosphorylate in response to Tgfβ1 treatment, meaning that *Acomys* has the same response as *Mus*, when fibrokine signals are sensed. This shows that while there is MF formation in *Acomys*, there is also a resistance against cellular phenotypes associated with it (Brewer et al. 2021).

After Tgfβ1 treatment, *Acomys* had an upregulation of *Serpine1*, which promotes fibrokine activity and is one of Tgfβ1 targets in mouse and humans. Moreover, there was also a downregulation of signalling pathways that are fibrotic (*Pdgfb*, *Tgfr2*, *Vegfd*, *Bmp4*, and *Hgf*) or their transcriptional regulators (*Klf15*, and *Dlx3*) and an upregulation of genes and pathways that help regeneration, angiogenesis and might be anti-inflammatory (*Lif*, *Cyr61*, *Wnt11*, *Il18*, and *Ctgf*), connective tissue growth factor (*Ctgf*) being one of the most significantly upregulated of the group. This implies that there is an activation of Hippo-Yap signalling, since is one of its targets. In addition, when levels for *Mst1* and *Lats2*, which are inhibitors of Hippo-Yap signalling, were studied, they were downregulated while *Yap1* levels were the same, on contrary to what happened in *Mus* (Brewer et al. 2021). Because of these data, Brewer et al. 2021 theorised that Hippo-Yap signalling regulation might help in regeneration. Both species DFs show high nuclear/cytoplasmic (N/C) ratios of Yap at subconfluent density on low N/C ratios at hyperconfluent density. However, when exposed to Tgfβ1, nuclear Yap in *Acomys* DFs is maintained, while in *Mus* Yap migrates to the cytoplasm. In addition, in *Acomys* there is little Yap phosphorylation after Tgfβ1 treatment in contrast to the large amount of phosphorylated Yap in *Mus*, although *Acomys* Yap 1 and 2 have more than 90% of similarity to mouse Yap and the phosphorylation sites are conserved (Brewer et al. 2021).

Verteporfin (VP) treatment inhibits Yap signalling and slows down *Acomys* regeneration. To study the importance of Yap signalling in the blastema formation and in differentiation events after the closure of the wound, Brewer et al. 2021 treated animals with VP in the early phase of wound healing and in the late phase. In the early phase of wound healin, VP exposure caused Acta2+/Myh11- MFs numbers to increase and a decrease of angiogenesis, as already described. On the other hand, in the late phase, VP exposure caused a disruption of the tissue organisation, loss or reprogramming of adipose and melanocyte progenitors and a reduced cartilage regeneration.

This data can prove that Yap signalling is indeed important for the formation of the blastema and tissue patterning and cell fate during later phases of healing (Brewer et al. 2021).

The Hydra is the oldest regeneration study model. Both Wnt signaling and apoptosis are essencial for the regenerative capacity of Hydra (A. S. Mehta and Singh 2019). When Hydras' head is amputated *Wnt*3 is upregulated one hour and a half later. *Wnt11* expression is very restricted and there is also a weak expression of *Wnt9* and *Wnt10c*. Three hours after the amputation, there is also an upregulation of *Wnt1* and *Wnt16* and six hours after an upregulation of *Wnt9*, *Wnt10a* and *Wnt7* (Lengfeld et al. 2009). The initial upregulation of *Wnt3* is likely due to apoptotic cells that have *Wnt3a*-positive speckles and are very important for the head regeneration as the inhibition of apoptosis decreases the *Wnt3* signalling and inhibits the regeneration (Chera et al. 2009). Beside Hydra, other regeneration models, including *Acomys* also have an upregulation of *Wnt* pathways. For example, Zebrafish has an upregulation of *Wnt10a* and *Wnt5a* and just like Hydra, when the *Wnt* pathway is inhibited there is no regeneration (Stoick-Cooper et al. 2007). This can mean that the regulation of *Wnt* signalling might be a conserved regeneration mechanism.

Xenopus larvae, just like *Acomys*, have a small immune response when their limbs are amputated, and this is thought to be the reason for their ability to regenerate limbs. However, *Xenopus* lose their regenerative ability when metamorphosis occurs as their immune system matures (Zielins et al. 2016). Larvae at development stage 53 are still able to regenerate most of the limb but not the whole limb, while larvae at development stage 57 cannot regenerate. In both stages, there is an increase of macrophages and neutrophils in the first six hours after the amputation and start to decrease after one day. On day five there are still macrophages and neutrophils in stage 57 limbs. Interestingly, while there is a persistent expression of genes involved in inflammatory regulation, cell reprograming is not affected, which usually happens in earlier development stages (Mescher, Neff, and King 2013).

The rabbit (*Oryctolagus cuniculus*) is also capable of regenerate ear punches. If the diameter is 4mm or 8 mm, *O. cuniculus* has the hole completely healed by day 85. After closing the hole, the tissue is uniformly distributed in the ventral and dorsal compartments. Just like in *Acomys*, *O. cuniculus* formed a new cartilage and dermis that is similar to the uninjured ones and new sebaceous glands and hair follicles (Gawriluk et al. 2016).

Some mammals, like mice and human infants, are able to regenerate the tips of digits after amputation. Neufels and Zhao theorised that the regrowth of bone in mice is dependent of the nail regrowth which happens thanks to canonical Wnt signalling (Neufeld and Zhao 1995, Takeo et al. 2013). Leucine-rich repeat-containing G protein-coupled receptor 6 expression is also important for digit regeneration as it is a nail stem cells marker and it is needed to give rise to the blastema and are probably involved in formation of new bone (Lehoczky and Tabin 2015).

Figure 5- Comparison of 4mm ear punch closure in *Acomys* injected with Clo-Lipo (up) and controls (down) at days 10, 15, 20, 34, 60 and 70. The control ears close the wound 34 days after wound (yellow arrow) while in deficient of macrophages condition, the ear only closes after 70 days (red arrow). Adapted from (Simkin et al. 2017)

In summary, *Acomys* is an important animal model that has been used in the last decade to study animal regeneration, since it was already shown that it is able to regenerate several organs and tissues such as skin, ear, muscle and spinal cord. Moreover, it is not able to regenerate heart or kidney, however these organs are more resistant to injury compared with mice. It is suggested that this regenerative capacity is due to a milder immune system. Nevertheless, a lot of information is missing about regeneration and *Acomys* can be used as an animal model to gain more knowledge about mammalian regeneration.

5 Conclusion

Acomys are able to completely regenerate various tissues and resist death after injury probably because of their reduced immune response, evolved MFs and the Hippo-Yap signalling.

Studying *Acomys* ability to regenerate multiple tissues without scars and regain function and its' mechanism could help us understand why adult humans are not able to regenerate most of the tissues and find a way to regain this ability.

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