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# Regenerative Mice Provide Insights into Biomedical Tissue Regeneration

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**Tissue regeneration is a property that is commonly associated with non-mammalian organisms, but recent discoveries have revealed such characteristics in mice. The unique regenerative properties of MRL and *Acomys* mice, have provided insights into regenerative potentials for the biomedical advancing of myocardial regeneration and skin regeneration.. The two studies linked the existence of blastema like structures at the healing site of wounds and the lack of scar formation to the success of the tissue regeneration. Contributing differences between non-regenerators and regenerators aiding in regenerative capabilities include, cell cycle variation, collagen I and III ratios, and long-term cell proliferation. However, the mechanism for which the cell actually maintains the regenerative features remains unknown and needs further investigation.**

## Introduction

Tissue regeneration is a property that is commonly associated with non-mammalian organisms such as salamanders and sponges in which an appendage or region of the organism is lost and restored [2, 3]. This process of autotomy evolutionarily serves as a defense mechanism to escape predators, but recent discoveries have revealed characteristics of rare regenerators providing insights into biomedical tissue regeneration advancements. Rather than the previously mentioned stereotypical self-healers, unique regenerative characteristics have been discovered to exist among mammals particularly in the rodent class and rabbits[3]. It is the regenerative properties of particular mice in which the following review focuses. The Murphy Roths Large (MRL) mouse was found to posses similar regenerative capabilities of salamanders by having a blastema formation and basement membrane breakdown during the healing process. The MRL mouse also demonstrated complete healing of lipids, epithelial cells, cartilage, and regenerated partially lost digits, however, it could not heal the muscle of ear punch wounds [2, 3]. A study conducted by Lefervich and Heber-Katz found the MRL mouse to possess myocardial tissue regeneration without extensive scarring [1]. To understand how the MRL mouse is able to perform such extensive self-healing feats, Bedelbaeva et al. used the cell cycle of mammalian regenerative liver cells to study how the MRL mouse affects its regenerative abilities. It was found that cell cycle variation is present between non-healers and healers[2]. Furthermore, a more recent discovery by Seifert et al. demonstrated the distinctive skin regeneration capabilities of the mouse genus *Acomy*, commonly known as the African spiny mice. The African spiny mice utilize a shedding and healing process of their skin to aid as a survival mechanism[3]. A thorough analysis of the preceding studies will discuss the biological significance of the newly discovered regenerative properties used by the MRL and *Acomys* mice and also aim to understand the cellular mechanisms responsible for the regenerations.

## Dissimilarities between Non-healers and Healers

One difference between regenerators and non-regenerators is that the former are capable of producing a replicated functional tissue after injury were as the latter develops scar tissue. Scar formation, fibrosis, is a product of the production of a condensed network of collagen fibers in the extracellular matrix in response to a wound. On the other hand, non-scaring healing occurs because collagen fibers are loosely arranged in the extracellular matrix. Though the spatial orientation of collagen plays a role in fibrosis onset, the proportions of collagen I and collagen III also influence scarring of tissues. Regenerators tend to have higher collagen III levels with

 

respect to non-regenerators having low levels of collagen III in the extracellular matrix during wound healing[3]. This observation was made by Seifert et al. when studying the *Acomys* mice. The regenerative *Acomys* mice were compared to a non-regenerative *Mus* mouse in which both were inflicted with a small incision. During the healing process, it was found that the *Mus* mice had scar formation and low levels of collagen III in the extracellular matrix where as *Acomys* mice had no or little scar formation of the skin and high levels of collagen III[3].

Another contributing difference of regenerative capabilities is variations in the cell cycle at the G2/M phases. The G2 phase of the cell cycle corresponds to a division preparatory state while the M phase represents the mitotic process. Since mammalian liver cells undergo an acute degree of regeneration in which the cells experience a varying cell cycle between the G2 and M stages, Bedelbaeva et al. sought to determine whether the cells from MRL mice share a similar cell cycle variation strategy[2]. The study compared and contrasted a non-regenerative and regenerative mouse strains and found that there are differences between the proportion of cells in the G2 and M phases. A healer strain has increased numbers of cells in a G2/M arrest phase while a non-healer strain has a majority of cells in the G0/G1 phases[2]. The G0/G1 phases are associated with cell growth and maturation. A check and balance system is also present within the cell cycle in which the protein p21 is used as a strong G1 monitor, regulating the occurrence of cell maturation. Consequently, there is a deficiency in the number of p21 present in regenerative cells in which the low levels of p21 do not allow for cell maturation.

**Biological Significance of Regenerative Mice: MRL and Genus *Acomys***

The studies performed by Leferovich and Heber-Katz and Seifert et al. revealed biological implications of the regenerative capabilities of mice in myocardial regeneration and skin regeneration respectively. Both studies linked the existence of blastema like structures at the healing site and the lack of scar formation to the success of the tissue regeneration. The blastema is an undifferentiated group of cells that can proliferate rapidly [3] and mimics the behavior of stem cells. Leferovich and Heber-Katz, thus, linked their myocardial study of the MRL mouse to fetal development. Since the MRL mouse has a varied cell cycle during regeneration in which most cells are arrested in the G2/M phases, the cells are unable to grow and mature similar to the stem cells found in embryonic development. Leferovich and Heber-Katz, furthermore discovered a threshold in which fetal tissue wounds heal without scarring early in gestation but healing found after the transition into adulthood is accompanied by fibrosis [2]. The study examined the healing process of MRL mice and a non-regenerative mouse strain from a cryoinjury to the heart. It was found that scar formation was absent in MRL mice but present in the non-regenerative strain [2]. Until then there had been little evidence leading to the possibility of stem cells present within mature mammalian hearts, however, the healing tissue of the MRL mice was composed of proliferated cardiomyocytes meaning young undifferentiated cells are present in the heart [2].

More recently, Seifert et al. discovered African spiny mice to regenerate their skin by high cell proliferations and molecular pathways used in embryonic developments. Thus, it has been suggested that the healing process of these mice utilize a compartmentalized region of undifferentiated cells. This study examined the healing process of *Acomys* mice and the non-regenerative *Mus* mice from an ear punch wound to each mouse. It was found that the *Acomys* mice were able to regenerate the tissue without scarring while the *Mus* mice ultimately resulted in fibrosis. However, the *Mus* mice did not demonstrate a direct path toward scar formation but rather started the healing process in the same manner of the regenerative *Acomys* mice with the regeneration of cartilage. However, the differences lie within the ability of the cells to continue proliferation during the healing process in which the Mus mice lack [3].

**Discussion**

Tissue regeneration is biologically important because it can help expedite the treatment of patients needing transplants, reduce the immune's refusal of a transplant since it is the cells of the individual, and provide a deeper understanding to how the body heals. This in return will facilitate research for better treatment options. As the regenerative potential of the MRL and *Acomys* mice are in the early stages of development, the mechanisms for which molecular transduction signals is not fully understood. Further investigation should seek to determine how regenerative cells reduce scar formation by controlling the ratio of collagen I and III levels. This discovery may lead to the possibility of converting a non-regenerative tissue to a regenerative one.

**References**

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