

Why Do Human Tissues Differ in Regenerative Capacity? A Critical Synthesis of Single-Factor and Multifactorial Explanations

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Abstract: Human tissues differ in their ability to replace cells and repair structures after damage. Some tissues rely on almost constant cell renewal like the blood and intestinal epithelium tissues. Other tissues, like heart tissue, suffer from almost complete cell loss after damage. This paper critically assesses the evidence to argue if there is one singular biological factor that accounts for the varying degrees of the regenerative potential of human tissues, or if the evidence supports a more complex, context-dependent situation. The analysis includes the following types of research: clinical and observational studies, analysis of ex vivo human tissues, and mechanistic animal models. This paper focuses on the evidence for each argument. Six major explanations were evaluated: resident stem or progenitor cells and their behavior; parenchymal cells and their post-mitotic state; the level of tissue vasculature and access to metabolic resources; immune and extracellular-matrix tissue milieu; the developmental stage of the tissue; and positional and/or injury geometry. Each of these concepts has explanatory value in some situations, but none can account for all of the phenomena: post-mitotic cells do not explain why some tissues, like cartilage, experience loss of cellular structure; tissue vascularization is necessary but not sufficient to explain the phenomenon; and the regeneration of some tissues requires macrophages, but in some cases that does not prevent the formation of scar. The synthesis argues that many factors act in combination at higher levels rather than a single dominant factor. In this context, cell differentiation imposes a limit on the outcome of regeneration while progenitor cells and their environment determine whether this limit is reached. The developmental stage of the tissues and the geometry of the injury further affect the outcome. This argument implies that there is limited value in pursuing regenerative medicine interventions based on single cell pathways.

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I. INTRODUCTION

There are noticeable differences in the recovery of different human tissues post-injury. For example, the small intestine renews itself approximately every three to five days by crypt-resident stem cell division. The hematopoietic system replaces hundreds of billions of blood cells each day. Meanwhile, the adult human heart replaces less than 1 percent of its cardiomyocytes each year, and the neurons of the central nervous system do not regenerate after injury to their axons (Barker et al., 2007; Bergmann et al., 2009; Fliedner et al., 2002; Silver & Miller, 2004). In addition to the tissues at these extremes, there are intermediate tissues, including the liver, which can restore its full mass after resection of up to two-thirds of its mass in a few weeks, and skeletal muscle, which has an efficient satellite cell-based regeneration. The articular cartilage tends to be unable to self-repair after injury (Chen et al., 1991; Ismail et al., 2022;

Xu et al., 2015). There is a noticeable impact on regenerative medicine and organ transplantation from the differences in recovery that exist. There is also a dedicated focus of research for the mechanisms behind regeneration and its restriction to understand the nature of recovery.

A problem often found in this literature is attributing single causal factors to regeneration outcomes. For example, some people argue it's the dedicated stem cell population while others argue it's the post-mitotic state of parenchymal cells, the local immune response, or even the retention of embryonic developmental programs. At one point or another, each of these factors has been proposed as the most important contributor. Since each of these factors has proven to predict regeneration in specific tissues, it is relatively easy to construct a compelling argument for each of them in isolation.

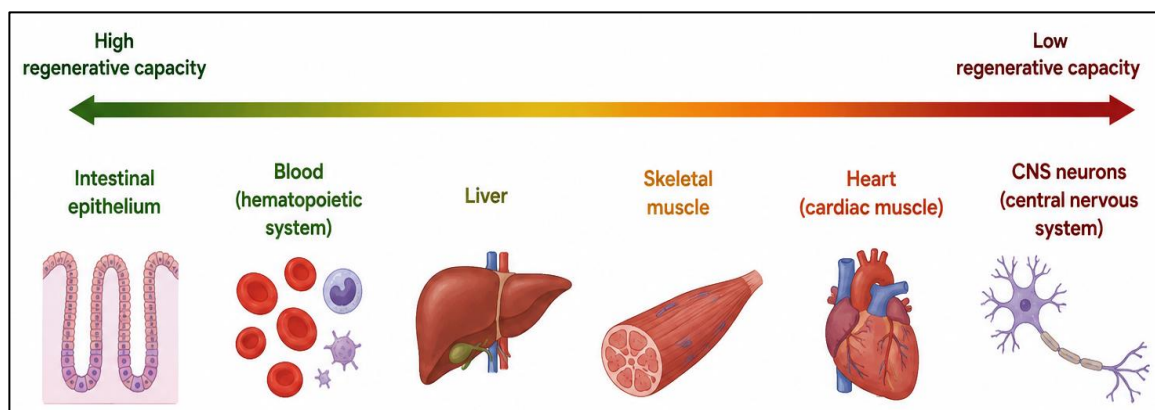


Fig 1 Variation in Regenerative Capacity Across Human Tissues

II. DEFINING AND MEASURING REGENERATIVE CAPACITY

Analyzing regenerative capacity across different tissues is not an apples to apples comparison. The literature distinguishes many processes and phenomena that fall under the term "regeneration," which leads to much of the confusion. Replacement of cells is the process of restoring lost cells of the same type, and this is what is studied with the turnover of cardiomyocytes (Bergmann et al., 2009). The replacement of cells does not necessarily include the restoration of cells in the proper spatial configuration which is a separate criterion of tissue architecture restoration. This is satisfied with the renewal of the intestinal crypts, but is accomplished by the regeneration of the liver with an imperfect restoration of the original architecture because mass and function are restored by a combination of hepatocyte hypertrophy and hyperplasia (Michalopoulos, 2010). Despite incomplete restoration of the architecture, functional restoration can occur with the compensation of the remaining organ, like the kidney or the liver, which emphasizes the importance of functional recovery, even if it results in an altered organ structure. Epimorphic regeneration is the most difficult of the categories where a complex proliferative blastema is formed to regenerate and reconstruct a multi-tissue structure in the correct geometry, of which only the distal fingertip is considered a clear example in humans (Schultz et al., 2025).

These distinctions matter because a tissue can score very differently on regenerative capacity depending on which outcome is measured. Articular cartilage is often defined as non-regenerative because of its low cellular turnover. However, chondrocytes in articular cartilage are not always post-mitotic. In fact, lack of vascular access, the presence of a dense extracellular matrix and the low cellularity of articular cartilage combined generate a self-repair impairment in articular cartilage (Ismail et al., 2022). Skin, on the other hand, achieves effective wound closure and barrier restoration in most cases, and in that respect heals well, but adult human skin does not regenerate the original dermal structural organization, nor does it regenerate hair follicles or glandular structures. Instead, it forms scar tissue. From a functional perspective, this is an adequate outcome. However, it is significantly dissimilar to the scarless skin regeneration that occurs in early gestation

human fetal tissue (Walmsley et al., 2015a; Zheng et al., 2016). Definitions of outcomes vary. Consequently, in this paper, the regenerative potential of tissues is compared across a variety of outcomes such as cellular, architectural and functional recovery and epimorphic regeneration.

A methodological concern includes the source of evidence. Much of what is known regarding the topic of mammalian regeneration is due to studies conducted on rodent models, particularly mice. The reason is that these models can be genetically altered and injury can be introduced where in a human, this is ethically and practically not possible. Data regarding humans is starting to accumulate in regards to cardiomyocyte turnover using radiocarbon birth-dating, hepatocyte regrowth using longitudinal computed tomography, and satellite cell frequency using biopsy and xenotransplantation (Bergmann et al., 2009; Chen et al., 1991; Xu et al., 2015). This paper presents these data over mouse, salamander, and spiny mouse models. In the absence of data regarding human models, the paper presents results from mouse models. It draws cautious conclusions regarding human regeneration considering the time of postnatal development and severity of injuries and the physiology of the immune system for mouse models are not comparable to humans.

III. RESIDENT STEM AND PROGENITOR CELL AVAILABILITY

The best candidate explanation for the existence of tissue regeneration capacity is a self-renewing, dedicated stem or progenitor population in a given tissue. This explanation is highly intuitive and is well supported by several human tissue systems. One of these systems is the small intestine. Cells located at the base of the crypts of the intestinal epithelium and expressing the protein Lgr5, are capable of self-renewal and creating the entire lineage of the epithelium. During the process of continuous regeneration, a cycle of self-renewal and differentiation of intestinal epithelium to replace outgrowth enterocytes takes approximately three to five days (Barker et al., 2007). The hematopoietic system is similar to the intestine. Like intestinal epithelium that sustains itself by the continuous replacement of differentiated enterocytes, the daily production of blood cells is maintained by hematopoietic stem cells located in the marrow. Similar to blood cells, the

production of blood cells can be increased with loss of blood due to hemorrhage or chemotherapy-induced myelosuppression as well as transplantation (Fliedner et al., 2002; Morrison & Scadden, 2014). Regeneration of skeletal muscle relies upon PAX7 positive satellite cells that occur at a consistent frequency (2-4/mm) throughout muscle of the trunk, limbs and head of adult human musculature. Under physiological conditions, satellite cells are in a quiescent state. Injury induces satellite cells to proliferate, differentiate and fuse into damaged myofibers. The resulting repair can restore the muscle to its histologically uninjured form (Xu et al., 2015).

If the presence of progenitor cells determined regenerative capacity, then there should be a positive correlation between the abundance of progenitor cells within a tissue and the degree of tissue regeneration. However, this is not always the case. The regenerative potential of the liver is a good example of this. In most cases, hepatocytes are quiescent and the liver does not retain an obvious cycling progenitor cell compartment, similar to the crypt in the intestine. Remarkably, in a rodent model of two thirds partial hepatectomy, most of the differentiated hepatocytes in the remaining tissue enter the cell cycle in a coordinated manner in response to cytokine, growth-factor, and hemodynamic signaling. Pro-regenerative cytokines such as tumor necrosis factor and interleukin-6 and growth factors such as hepatocyte growth factor, acting through the MET receptor and epidermal growth factor receptor ligands, together with hemodynamic cues, induce this response. Rodent liver regeneration takes approximately one to two weeks, while regeneration in human living donors occurs over a comparable multi-week timescale (Michalopoulos, 2010). The restorative regeneration of the human liver has been studied using volumetric imaging. Non-cirrhotic livers undergoing significant resections in one reported study increased in volume by 28.4% $\pm$ 9.5% at 3 months and 48.4% $\pm$ 17.8% at 6 months post-surgery (Chen et al., 1991). Thus, considerable regeneration of the liver can occur in the absence of a dedicated progenitor cell compartment.

Cartilage has the opposite counter-example to collagen. Unlike collagen, chondrocytes are postmitotic but do not regenerate due to the phenomenon of matrix embedding. Matrix embedding consists of the active discouraging of conditions for proliferation of cellular repair. Chondrocytes are scattered throughout a dense extracellular matrix, and the matrix that defines the mechanical properties of cartilage also impedes chondrocyte migration, hence growth factor and nutrient delivery thus ensuring no regenerative response is mounted by chondrocytes (Ismail et al., 2022). The contrasting examples of the liver and cartilages suggest that the presence of progenitor cells is not always necessary, for example the liver, and not always sufficient for regeneration, as in the case of the cartilages. In such cases, the surrounding context of the matrix dictates the extent to which the progenitor cell activity can be productive for repair.

Another issue occurs with cross-species tissue comparisons that have similar progenitor systems but have a large discrepancy in the outcome of regenerative ability. Laboratory housed mice and African spiny mice have different healing outcomes to identical ear punch wounds. In mice, healing results in fibrotic scarring, whereas in spiny mice healing results in almost complete epimorphic regeneration, including the restoration of hair follicles, skin, and cartilage tissues (Gawriluk et al., 2016; Simkin et al., 2024). Because progenitor cells are similar in both species, disparities in regenerative ability cannot be explained by cell types. These differences can be explained by how the progenitor cells are influenced by and respond to instructive signals. This will be addressed further in Section 6. Based on the current evidence, progenitor availability is clearly an important factor, yet is an incomplete factor regarding regenerative ability. It is evident that regenerative ability correlates with rapid cell renewal systems such as the epithelium. However, regenerating progenitor cells of the liver and the inability to regenerate cartilage are examples of regenerative ability and demonstrate the inability to regenerate cartilage. The regenerative ability of mice and spiny mice also illustrates this.

IV. TERMINAL DIFFERENTIATION AND CELL-CYCLE RE-ENTRY CAPACITY

A second major candidate explanation centers around the main functional cells of the tissue, which permanently exit the cell cycle in a state known as post-mitotic. This account is most developed for the mammalian heart. In case of the mammalian heart, cardiomyocytes undergo intense proliferation during fetal development. However, the majority of these cells undergo permanent withdrawal from the cell cycle, after which there is a final round of DNA synthesis. This may result in binucleation or polyploidization and is followed by a switch to an oxidative metabolism, maturation of sarcomeres and stiffening of the extracellular matrix. This phenomenon is cited as irreversible for adult cardiomyocytes (Lázár et al., 2017). Radiocarbon birth-dating of genomic DNA (which employs the spike in atmospheric carbon-14 following nuclear weapons tests as a proxy for date of cell birth) has shown the adult human heart replaces cardiomyocytes at a rate of approximately one percent per year in young adulthood, dropping to well under half of a percent per year in the elderly (Bergmann et al. 2009; Lázár et al. 2017). This rate is not sufficient for regrowth of cardiomyocytes lost in myocardial infarction. Myocardial infarctions are repaired by the formation of scar tissue.

The mechanistic cause of postnatal cardiomyocyte cell-cycle arrest is not fully understood, and the uncertainty is useful in the context of this argument. Some hypotheses include a postnatal shift to oxidative metabolism that increases mitochondrial production of reactive oxygen species and triggers a DNA-damage response, activation of the Hippo-YAP signaling pathway, changes in the neuregulin-ERBB2 signaling pathway, and changes to pericentrin, a centrosomal protein, that results in a failure to couple centriole duplication to cytokinesis. It should be

noted that a molecular atlas of postnatal mouse cardiac development reported that oxidative DNA damage does not fully correlate with cardiomyocyte cell-cycle withdrawal in humans and therefore, cannot fully explain the loss of regenerative potential. This reflects a broader trend in the literature, in which single mechanisms proposed are genuine necessary contributors, yet remain insufficient explanations. It is also worth considering that there is a neonatal mouse cardiac regeneration period that exists for a short time after birth. During this time, the apex of the heart is able to be repaired after resection and cardiomyocyte proliferation restores the tissue before the first postnatal week. This data, along with the other data cited, shows that the post-mitotic state of cardiomyocytes is not an inherent, fixed state and, in fact, is a developmentally acquired and actively maintained state. Thus, it is reasonable to conclude that no single molecular cause has been identified that is both necessary and sufficient.

If terminal differentiation and cell-cycle exit were universal, tissue-specific explanations for poor regenerative capacity, cartilage, in which chondrocyte proliferation is very low, should exhibit poor regenerative capacity similarly to cardiac muscle. However, the evidence in Section 3 shows that quiescence is more likely due to the matrix and vascular constraints for chondrocytes. This evidence is shown through the proliferation of chondrocytes in culture and through clinically relevant therapies that utilize autologous chondrocyte implantation that do not exist for terminally differentiated adult cardiomyocytes (Ismail et al., 2022). Unlike chondrocytes, hepatocytes are differentiated and have functional maturity, but differ from cardiomyocytes in that they still have high capacity for proliferation. Hepatocytes enter DNA synthesis after a partial hepatectomy (Michalopoulos, 2010). From what we observe in the liver, heart, and the cartilage, terminal differentiation is not a state with consistent regeneration that can be applied easily to different tissues. Different tissues have evolved different and partially overlapping programs that couple differentiation and cell-cycle status, and the mechanism of cardiac binucleation-linked differentiation and cell-cycle exit is a program specific to cardiac muscle.

Failure to regenerate terminally differentiated cells is also observed in the nervous system. In the nervous system, post-mitotic adult neurons cannot be induced to re-enter the cell cycle without triggering apoptosis or neoplastic transformation unlike cardiomyocytes. Central axon regeneration is limited not only by the status of the adult neural cell cycle, but also by the external and glial cell environment. The juxtaposition of cardiac and central nervous system regeneration failure suggests that even where post-mitotic status is an important barrier, it operates alongside environmental determinants rather than instead of them. In these cases, an unregenerative environment, in addition to cell-cycle arrest, determines the final outcome.

V. VASCULARIZATION AND METABOLIC ACCESS

A third candidate factor is the physical and metabolic accessibility of the injury site. This includes whether the site can accommodate an adequate supply of cells, oxygen, nutrients and signaling molecules to support a regenerative response. Once again, articular cartilage is an excellent example. This tissue is avascular, aneural and alymphatic, relying entirely on diffusion through its dense extracellular matrix for nutrient transport. This diffusion-limited metabolism contributes to low chondrocyte density and turnover, while vascularized tissues can mount a more effective inflammatory and repair response. Injured avascular tissue responds even slower due to the inability of growth factors or progenitor cells to reach the injury site. Ismail et al. (2022) have demonstrated that it is difficult to stimulate a repair response in articular cartilage. Clinical trials that contain drilling or microfracturing to breach subchondral bone for cartilage defects demonstrate that, to produce any repair response, tissue vascular access is necessary, but is not sufficient to reproduce the native tissue structure and functionality.

Bone can be a good example for us to learn from because it does something that cartilage cannot; it has regeneration potential beyond repair: The healing of a fractured bone and the tip of a regenerating finger in rodents and humans occur through processes that depend on a particular dynamic pattern of tissue oxygenation. The first phase after the injury is an initial hypoxic phase, and the phase following that is a period of active neovascularization required for the differentiation of bone cells and the growth of new bone to occur by the process of appositional bone growth (Sammarco et al., 2014). This provides a reason for the limitation of the digit tip regeneration; amputations that are distal to a critical anatomical limit regenerate a close approximation of the original digit tip, whereas more proximal amputations that eliminate the niche do not regenerate bone, but the skin, connective tissue, and nail regenerate normally at both levels of amputation (Sensate & Marques-Souza, 2019). Vascular niche, access, and position information all inform the process together.

Although the existence of vascular access is essential for regeneration, it is much more accurately described as a necessary, permissive condition rather than a sufficient explanation. Although the heart has a rich supply of blood vessels, cardiomyocyte turnover is almost nonexistent. The blood vessels do not break the cell-intrinsic barrier to the re-entry of cardiomyocytes into the cell cycle. Adult human skin is also richly vascularized, and vascular ingrowth (angiogenesis) is one of the key components of the healing process of cutaneous wounds, and yet, adult human skin heals by fibrosis as opposed to architectural regeneration. Thus, vascular supply needs to be considered as a component of a larger system. Vascularization creates the potential for a regenerative response, but does not determine if the cells present are competent to proliferate, or if the environmental signals will direct the cells to regeneration rather than scarring.

VI. THE IMMUNE AND EXTRACELLULAR-MATRIX ENVIRONMENT

The most interesting theoretical evidence relates to the local immune response and extracellular matrix, which influence if an injury heals by regeneration or by fibrotic scar formation. This evidence is particularly well suited to test necessity and sufficiency because it primarily comes from comparative and loss-of-function studies and not just correlation, even though the best of these studies have been performed on animals and not humans.

Regarding necessity, macrophage depletion studies provide direct evidence of necessity. One example is an amphibian vertebrate, the axolotl, which can regenerate the entire amputated limb throughout its adult life. In this species, systemic macrophage depletion during the first days post-amputation eliminates the regeneration of the amputated limb. Instead, the axolotl heals the amputation site with extensive fibrosis instead of regenerating the amputated limb. Regeneration is restored only when macrophages are allowed to replenish post-amputation before experimentation (Godwin et al., 2013). The axolotl's macrophages are necessary for healing by regeneration. In a second example, macrophages are necessary for regeneration in the spiny mouse. Like the axolotl, the spiny mouse is capable of regenerating tissues after injury; however, it is a mammalian species. The loss of macrophages during the injury response in the spiny mouse also inhibits the regeneration of tissues, thus demonstrating macrophage involvement is necessary for regeneration in a mammalian species and not an epiphenomenon of a distantly related amphibian lineage (Gawriluk et al., 2016; Simkin et al., 2017).

House mice have an inflammatory response that is very similar to spiny mice. They also recruit macrophages during injury. Still, scarring occurs on house mouse injuries, despite the presence of macrophages. Additional studies on macrophage phenotypes in ear injury showed that spiny mice macrophages secrete specific factors, including vascular endothelial growth factor C and lactotransferrin. These activated macrophages also promote a pro-regenerative phenotype of fibroblasts in cultured cells from both species. There is also a role of spiny mice macrophages in the formation of the blastema via lymphangiogenesis. There are however, no such factors secreted by macrophages in house mice under the same injury conditions (Simkin et al., 2024). Spiny mouse macrophages have factors that can promote a regenerative phenotype of fibroblasts of both species within injury culture. House mouse macrophages do not secrete these factors, and this difference shows that the relevant variable is not simply macrophage presence, but the macrophage activation program. This difference is important because the distinction between the two species is related to the macrophage activation program, a property of the responding immune cells that is different across species and injury contexts. So, macrophages are necessary but not sufficient for regeneration, but there is a requirement of a

more refined aspect (macrophage activation state) of macrophages that is context-dependent and species-related.

Just like cellular components, the extracellular matrix (ECM) can be permissive and, under certain circumstances, inhibitory to regeneration. The peripheral nervous system (PNS) holds a clear advantage over the central nervous system (CNS) following an injury. After an injury, Schwann cells are able to dedifferentiate, proliferate and synthesize a basal lamina which aids in the regeneration of axons with laminin in the PNS. This process allows PNS injuries to achieve a large degree of, though seldom complete, functional reinnervation (Höke, 2006). Unfortunately, in the CNS, astrocytes and other glial cells respond to injury by forming a glial scar containing matrix components that inhibit axon regrowth. This inhibitory environment has long been considered an important reason for failed CNS axon regeneration (Silver & Miller, 2004). Recent evidence, however, argues against a purely matrix-centered position. It states that the failure to stimulate the intrinsic growth of axons is the major limiting factor to regeneration, and it has been argued that CNS-directed therapies target a necessary but non-limiting factor (Cregg et al., 2014; Shafqat et al., 2023). This statement captures an important trend: an extracellular factor should not be considered the primary limiting factor for regeneration when cell-intrinsic competence remains limiting.

The immune and matrix environment behaves as a modulatory rather than an independently sufficient factor. It's necessary for regeneration to occur in multiple tissue systems. The inhibitory matrix and pro-fibrotic macrophage polarization can lead to scarring and cause otherwise regenerative injuries to heal by scarring. In the systems studied, the immune and matrix environment do not appear to be sufficient to overcome the unfavorable state of a post-mitotic cardiomyocyte or a mature neuron.

VII. DEVELOPMENTAL STAGE AND THE FETAL-TO-ADULT TRANSITION

The ontogenetic timing of injury shows that many human and animal tissues can regenerate in an embryonic state and then can no longer do so in an adult state. An example in humans is the healing of skin wounds. Early in human fetal development, a dermal wound heals by the restoration of the architecture of the dermis along with hair follicles and complete organization of the extracellular matrix. Conversely, later in fetal development, skin wounds heal via the deposition of fibrosis scar that is identical to adult scar. In humans, this skin wound healing transition occurs at the second-to-third trimester. In mice, it occurs at a defined embryonic day. It is an intrinsic feature of skin because scarless healing fetal skin, when transplanted to an adult immunocompromised host, loses its scarless healing property, whereas a scar-forming adult skin, when transplanted to a fetal host, heals scar-forming (Walmsley et al., 2015b; Zheng et al., 2016). Possible reasons for this transition may be differences in the pattern of expression of the transforming growth factor beta isoforms. It may also be differences in a more transient and less severe inflammatory

response in fetal wounds, and differences in adult and fetal fibroblasts (Zheng et al., 2016).

There exists a different, yet comparative, developmental window within the mammalian heart. Within the first postnatal week of neonatal mice, apical resection of the heart promotes cardiomyocyte proliferation and the regeneration of lost tissue (Lázár et al. 2017). However, the same injury performed after the postnatal cell cycle exit and binucleation of cardiomyocytes results in fibrotic scarring, demonstrating the non-regenerative state is not gradual, but rather occurs within a narrow developmental window. Within this window, there is a loss of regenerative capacity. As this evidence was derived through the use of rodent models, the temporal bounds of this window in humans is unknown. However, it is known within the neonatal rodent models, a cell cycle exit occurs in a different timeframe than in humans, so it is possible that this loss of regenerative capacity may occur differently in humans. Regardless of the differences in the timing of cell cycle exit in different species, it is clear that cardiomyocyte regeneration is developmentally regulated and time limited in all species (Bergmann et al., 2009).

Developmental stage functions more as a modifier to other factors already mentioned than as an independent explanation. The maturation of skin from a fetal to an adult stage correlated to changes in inflammatory signaling and the production of fibroblast matrix. This places maturing skin as a distinct point in time for the immune and extracellular-matrix factors discussed in Section 6, and the maturing of the neonatal cardiac window aligns with the acquisition of the binucleation-linked cell-cycle arrest discussed in Section 4. Thus, the developmental stage should not be considered the sixth independent factor. It should rather be the time scale along which the other factors (matrix composition, inflammatory, and cell-cycle control) are integrated. This new perspective will help the paper's overall argument, because it demonstrates that even a factor with a strong and consistent correlation across tissues (regenerative competence is observed to be more dominant in the early stages of development, both in the skin and the heart) is more appropriately explained by the integration of more precise, tissue-specific mechanisms, rather than by a single, omnibus biological switch.

VIII. POSITIONAL INFORMATION AND INJURY GEOMETRY

A fifth body of evidence, primarily from studies on digit- and fingertip-tip regeneration, demonstrates that regenerative outcomes in a single tissue and in a single organism can be dependent on the specific site and geometry of the injury. This also holds true in the regenerative competence of the tissue. In both the mouse model of digit-tip amputation and in comparable cases of digit-tip amputations in humans, distal amputations that only remove the terminal portion of the digit allow for regeneration of a digit that closely approximates normal, with restoration of the nail and the architecture of the skin, as well as the restoration of the fingerprint pattern in

humans. In contrast, amputations that remove a more proximal portion of a digit result in a complete failure of the regeneration of the bone of the digit, while the skin and the other soft tissues, including the nail, regenerated with equivalent fidelity (Schultz et al., 2025; Sensiata & Marques-Souza, 2019). This amputation site-dependent regrowth of the skeletal structures is attributed to the removal, at more proximal sites of amputation, of a periosteal progenitor cell population and a Wnt-signaling zone that is required for the regrowth of the skeletal structures. Distal amputations leave the signaling center and the progenitor population active, while proximal amputations that remove these sites deny the regrowth of skeletal structures in a decomposition-competent environment (Sensiata & Marques-Souza, 2019).

There are two predominant points that arise from this finding that impact the larger point being made within this paper. The first point that arises states that regenerative capacity is not always a fixed property of named tissue types (digit or bone). It can be a case of a spatially graded property where removing or leaving in-tact a structure that carries positional information or positional memory will determine the outcome, rather than the cell-intrinsic, vascular, or immune factors that have been discussed in the previous sections. The second point that this finding adds is that a single injury event can result in regeneration of one component of a composite structure (skin, nail, connective tissue) and regenerative failure of an adjacent component of the same structure (bone) in the same individual. It is hard to explain this due to regeneration not fitting a cell-intrinsic, vascular, and immune factor, if the overall inflammatory tone of the individual is the same (vascularity, dominant progenitor cell, etc.). Positional information therefore accounts for a distinct axis of explanation, separate from cell type, vascularization, and immune state, and it is a definite limitation of single-factor accounts of regeneration capacity that it is not considered within those accounts.

An example of how positional and contextual factors interact with clinical management is the case of the fingertip. A region of the body and a facility that retains and preserves wound-fluid composition, hydration, and gas exchange shows that, within humans, the distal fingertip amputation heals by regenerating the nail bed and restoring the dermal architecture and fingerprint pattern, while premature surgical closure, or a dried wound bed, results in scarring and failure of regeneration (Schultz et al., 2025). This supports the notion that, in the only known case of human epimorphic regeneration, the outcome of regeneration is not automatically achieved and requires an active preservation of the microenvironment of the wound. This supports the main idea of the research article that regeneration is the fulfillment of several independent, necessary conditions, rather than the loss of a restrictive property.

IX. EVOLUTIONARY AND COMPARATIVE CONTEXT

The poor regenerative aptitude of most adult mammals, compared to salamanders and teleost fish, may be explained by a single evolutionary or phylogenetic factor (e.g. the evolution of adaptive immunity, homeothermy, or a particular body size or lifespan). The comparative evidence suggests that phylogeny cannot explain the gap on its own. However, it is necessary to understand the findings cited above.

The evidence that regenerative capacity is not a constant fixed throughout the phylogenetic tree, but may be acquired or lost within closely related groups, is seen in the example of the spiny mouse and laboratory house mouse. They are both within the same mammalian order and are separated by a comparatively short evolutionary distance, yet one shows extensive regeneration and the other none (Gawriluk et al., 2016). This exemplifies that a mammalian lineage is not committed to being regeneration incompetent because there are species that can regenerate, while their close relative is mammalian and lacks complex regeneration. The principle difference of the two groups is not due to the evolutionary or developmental lineage across non-regenerating mammals but rather due to the immune and macrophage response (Simkin et al., 2017).

Although it does not take center-stage, phylogenetic context is important. It provides the population of mechanisms which compose a lineage-specific regenerative phenotype. Salamanders have hematopoiesis occurring in the liver and the spleen, rather than the bone marrow. Concomitantly, the source of pro-regenerative macrophages and the bone-marrow-and-spleen derived monocytes that are recruited to wounds during mammalian tissue repair differ. So, even with a conserved requirement of macrophage recruitment to the injury site, lineage-specific hematopoiesis will dictate the structure of macrophages and other cell types involved in the tissue repair process (Godwin et al., 2013). This pattern agrees with the overall conclusion of the paper. The mechanisms available to a lineage are limited by evolutionary history; for example, the location of hematopoiesis in a lineage may be in the bone marrow or in the liver and spleen, but evolutionary history does not dictate the outcome of regeneration. Where evolutionary history should be placed within the regeneration framework is as a constraint on the mechanisms of regeneration rather than a separate, multicastal explanation for variation in regeneration potential across species and tissues.

➤ *Aging, Cellular Senescence and Stem Cell Exhaustion*

The sixth proposed factor, aging-associated cellular senescence and stem cell exhaustion, is unique from the first five factors in that it accounts primarily for changes that occur in regenerative capacity in a tissue across a human lifespan rather than accounting for differences between tissues. Cellular senescence occurs when cells enter a stable cycle arrest state as a result of various forms of damage, including damaged DNA, shortened telomeres, oxidative stress and even incessant activation of certain genes.

Senescent cells also produce a senescence-associated secretory phenotype which negatively affects neighboring cells and therefore the overall tissue regeneration. (Hernandez-Segura et al., 2018) It has been shown that there is a positive correlation between the aging process and the loss of regenerative potential, or exhaustion, in multiple tissue-specific stem cell populations such as mesenchymal stromal cells, hematopoietic stem cells, and skeletal muscle satellite cells, all of which have been characterized by increased senescent cell accumulation in the tissue.

There is a considerable amount of supportive evidence to explain why decline in regenerative capacity is age-related, within a specific tissue, for example describing the differences in regeneration of skeletal muscle between an old and a young individual. These muscle regeneration differences are associated with senescence and the depletion of satellite cell functional reserve. However, gaps in aging and senescence accommodate the most concerning area of this paper, and the primary reason for this gap, is that when comparing regenerative capacity across all tissues, the order and position of these tissues is constant throughout the lifespan: in an old individual, cartilage is poorly regenerative in comparison to the liver; however, an elderly individual's liver maintains a high level of regenerative capacity in comparison to young individual's cartilage or the myocardium. Aging related-senescence is accountable for the changing levels of regenerative capacity within a tissue across an individual's lifespan. However, it is limited to explaining why some tissues have vastly different levels of regenerative capacity in comparison to other tissues. This gap is established well before the onset of major cause and effect relationships, such as senescence, which typically occur in the early adulthood age range.

➤ *Synthesis: Evaluating Candidate Factors Against Necessity, Sufficiency and Generality*

Building on the previous sections, none of the six candidate factors explored in this paper explains significant variation in the human capacity for regeneration, although each is a significant, context-specific contributor. Stem or progenitor cells correlates to regenerative potential in some tissues. However, they are not always required (e.g., significant liver regeneration occurs through the facultative proliferation of fully differentiated hepatocytes as opposed to a dedicated hepatic progenitor cell lineage), and they are not always sufficient (e.g., failure of cartilage regeneration occurs in the presence of a population of resident chondrocytes, while spiny mice and house mice possess populations of Fibroblasts and an immune system, respectively, yet scar rather than regenerate). A post-mitotic, terminally differentiated state is a well-documented and cell-intrinsic barrier to regeneration of cardiomyocytes and central neurons, but the reasons for the arrest of the cell cycle in cardiomyocytes are incomplete, and the environmental constraints over the proliferative activity of cartilage chondrocytes are much more important. Limiting factors such as vascularization and metabolic access are needed since marrow-stimulating procedures restore vascular access to cartilage and allow for at least some degree of cartilage repair. Adequate vascularization of both

the heart and the skin, however, is not sufficient to support regeneration.

Rationale behind necessity and implausibility of macrophage absence in mice Macrophage-depletion studies in axolotls and spiny mice present the most compelling mechanistic evidence of necessity in the current literature. This is also the case with the comparison of spiny mice and house mice, which shows that macrophage absence is not sufficient. Rather, the qualitative polarization state of the macrophage response is the more proximal determinant, and this state behaves jointly with the matrix and neuron-intrinsic growth competence, as the renewed focus on glial-scar-directed therapies in the central nervous system illustrates. It must be qualified that the developmental stage (Section 7) presents strong, reproducible correlational evidence across two very different tissues (skin and heart), however, it mechanistically functions more as a reorganization of the cell cycle, matrix, and inflammatory factors previously discussed, as a temporal process, rather than functioning as an independent causal axis. The remaining factors; positional information and injury

geometry, aging and senescence, communication of nervous and immune systems, wound, and developmental contexts, explain within-tissue decline over the lifespan in detail. However, they do not explain the between-tissue differences that drives the research.

A recurring pattern is that the strongest evidence of necessity comes from loss-of-function studies that are controlled (macrophage depletion studies, amputation of digits at specific levels, fetal to adult tissue transplantation). In contrast, evidence for sufficiency is quite scant and, where it is available, tends to disprove and/or negate single-factor accounts by showing that under the given conditions (macrophages in house mice, vascular access in cartilage repair, chondroitinase treatment in spinal cord injury), merely providing the candidate factor is not sufficient to result in full or complete regeneration. This asymmetric pattern has considerable evidential weight. It suggests that the regeneration of tissue is a complex endovascular system in which many factors must be satisfied in order to result in complete tissue regeneration.

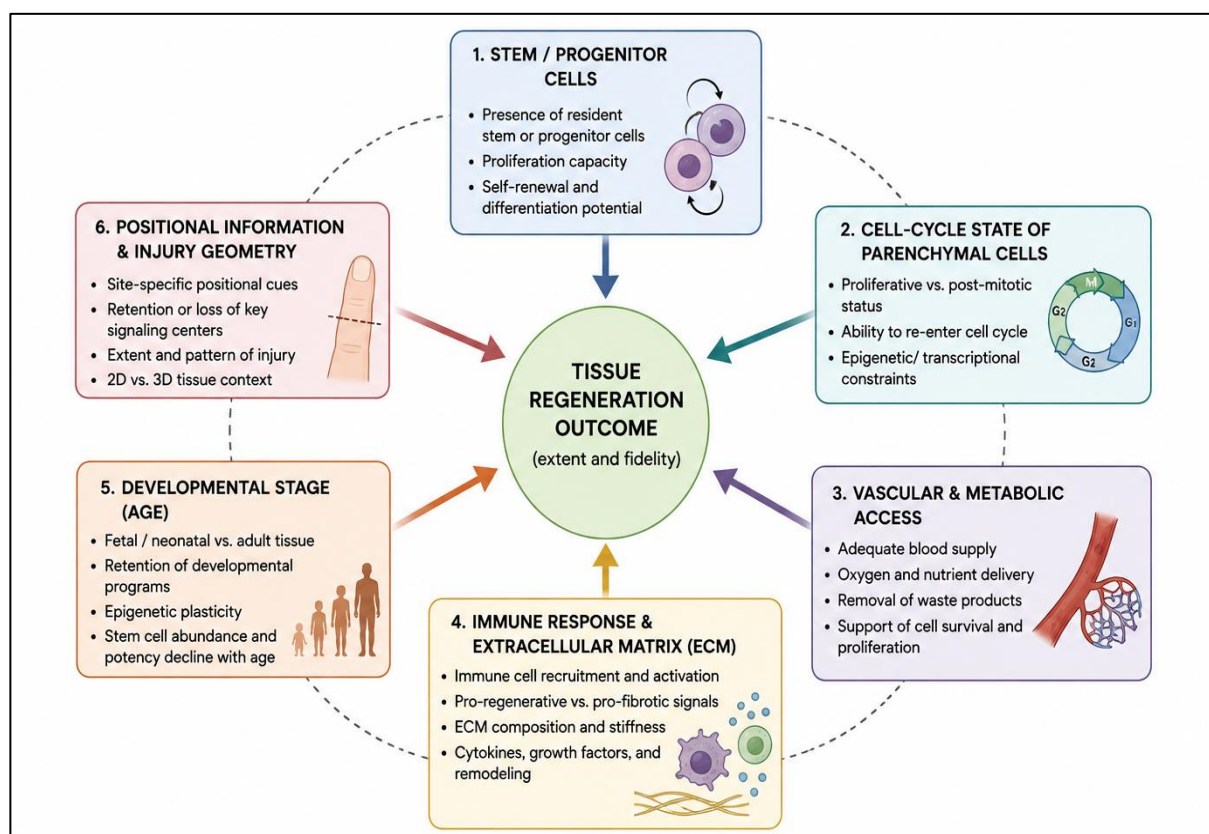


Fig 1 Multiple Interacting Determinants of Tissue Regeneration

X. TOWARD A HIERARCHICAL, CONTEXT-DEPENDENT ACCOUNT

The evidence studied in this paper is more amenable to a hierarchical, context-dependent model of regenerative capacity as opposed to any single-factor solution. In this model, the terminal differentiation of a tissue's principal functional cell type along with its cell-cycle state imposes an upper limit on the biologically achievable outcomes of

regeneration. For example, a tissue composed primarily of cells that have undergone a terminal cell-cycle exit with binuclearization, similar to adult cardiac myocytes, cannot regenerate by replacement, despite having a favorable vascular, immune, or extracellular matrix environment. Conversely, tissues comprised of cells retaining facultative or obligate proliferation (like liver cells), or with a dedicated progenitor pool (like small intestine or skeletal muscle), are capable of extensive regeneration.

Within a cell-intrinsic limit on tissue repair, the actual achieved limit is due to vascular and metabolic factors, as well as the immune response and the extracellular matrix, that work together in an integrated system. These factors determine the supply of energy and proteins, the immune response, and the condition and Signaling in the extracellular matrix. Evidence from cartilage and digits shows that, together, these factors must allow sufficient energy turnover and matrix remodeling. Spiny mice and axolotls show that the immune system, if it is in a pro-fibrotic state, must instead be in a pro-regenerative state. Finally, evidence from the peripheral nervous system shows that the extracellular matrix must be permissive to cell migration and axon extension. The factors of developmental stage and injury geometry influence the combined tissue and environmental factors at the second tier. In these factors, a favorable environment is found at the time and site of an injury. The same skin, at an earlier stage of development, is found to have a more favorable environment at the second tier (less and more transient inflammation, different behavior of fibroblasts), as the skin is found after the fetal-to-adult transition. The same digit, amputated at a more distal level, retains a progenitor and signaling structure, which a more proximal amputation removes.

This framework accommodates the evidence presented in the different sections of the paper in a hierarchical manner, and therefore, does not require a single mechanism to carry the burden of explanation that the evidence does not support. This also creates a testable hypothesis. The hypothesis states that, in comparison to trying to control a universal switch, interventions aimed at improving regenerative outcomes should be more successful when specific tissues are targeted at the tier where the tissue under investigation is currently limited (for example, restoring vasculature for cartilage regeneration or modulating macrophage polarization for healing in mammalian tissue). The finding in this literature that single-pathway manipulations result in the regeneration of some, but not all, aspects of tissue architecture and functions, and that these interventions are effective in some, but not all, cases, is supportive.

XI. LIMITATIONS OF THE EVIDENCE BASE

Some limitations of this paper should be mentioned in order to understand the proper context of the conclusions. First, the primary sources for the molecular core of the immune-environment and developmental evidence supporting the insights in this paper are based on studies of rodents, amphibians, or other animals. This is mostly how the data were collected due to ethical issues and the challenges of working with humans. For example, cardiac regeneration, in the case of humans, is mostly described as comparable to that of rodents when cardiomyocyte turnover is described as occurring. However, we cannot be certain that the same quantitative measures would apply to humans. It is generally accepted that these differences would be present when comparing humans and other animals, or when considering how the duration of the developmental window

may vary or the rate of cellular turnover. For instance, the developmental discontinuity of scarless wound healing may occur as early as the second or third trimester.

Compared to the adult, scar-forming equivalent, the postnatal skin of humans is lacking in antimicrobial peptides and otherwise highly regenerative. Compared to most adult animals, such scarless human skin is both architecturally and functionally more regenerative. While most adult animals have scarring skin, the fetal and neonatal human skin is structurally and functionally more regenerative in nature. This is attributed to the postnatal loss of regenerative potential. Nonetheless, as predicated by a functional definition of regeneration, scars heal postnatal and adult humans, even if architectural regeneration is largely absent, resembling scar formation.

The debate over the cardiac turnover rate highlights a larger epistemological issue. Different methods used to analyze the same tissue generally yield orders of magnitude discrepancies. Temporal methods used to identify cells' birth dates using radiocarbon dating differ from histological methods used to identify cells' synthesis of DNA or apoptosis. The discrepancies can be attributed to the different markers used to identify cells, the assumptions of the mathematical models of turnover, and the sensitivity of assays like the TUNEL method of apoptosis to certain artifacts. This paper uses the radiocarbon dating method to identify cell's birth dates due to its relative epistemological strength, but the presence of serious discrepancies indicates that when quantifying the turnover of human tissue, one should adopt a more relative, rather than absolute, approach.

Other important systems of human tissues that exhibit distinct patterns of regeneration, such as the epidermis, the corneal epithelium, the kidney, skeletal bone beyond the digit-tip model, and the endometrium, were not examined in comparable detail. It is therefore possible that studying these systems would allow for the identification of additional factors or would provide a better understanding the extent to which the factors examined in this paper apply. The six factors examined in this paper were those that appeared most frequently in the literature and in the systems for which the strongest and most direct human and comparative evidence is available. This does not reflect a complete or exhaustive examination of every factor that could possibly be relevant to the study of regeneration.

XII. CONCLUSION

The evidence reviewed does not support a single biological factor that consistently explains variations in the regenerative capacity of human tissues. Six of the major explanations assessed included resident stem or progenitor cells, the post-mitotic state of all differentiated cells, damage-related tissue and organ vascular/metabolic access, the immune and extracellular matrix environment, the stage of development, and positional and injury-related information. All of the explanations have relative merit and some are necessary in particular contexts; however, all of the explanations fail the generality test when considering the

range of tissues. Stem cell availability cannot explain why the liver has the ability for substantial facultative regeneration and why the cartilage cannot regardless of resident cells; the post-mitotic state is documented to be a cell intrinsic factor in cardiac cells, but does not apply the same way to the cartilaginous tissues where extrinsic factors dominate the post-mitotic and other barriers. Vascular access is a necessary, but not sufficient, factor as the restoration of heart and skin parenchyma is poor, despite a rich vascular bed. The immune and extracellular matrix environment is necessary in numerous systems, however, the outcome of reconstituting spiny mice with house mouse tissue suggests that having an active and organized environment is more important than just having the environment. Developmental stage correlates with regenerative capacity, however, the reorganization of the immune, matrix, and cell cycle factors over time explains this. Finally, positional information shows that tissues with the same systemic environment have different regenerative capacities to explain the outcome.

The predominant trend I observed in this synthesis is a hierarchy and context-dependency. Cell-intrinsic differentiation state suggests the upper limit of what a particular tissue's constituent cells can do biologically. In a given case, a given individual of a particular injury, environmental, developmental and spatial factors will jointly determine if a given cell extends to its upper limit. As no individual factor is sufficient to do so, and because the joint requirement of multiple, independently necessary and sufficient conditions is observed across all tissue systems investigated in this paper, where sufficient evidence of control of interventions is available, it is justified to conclude that human regenerative potential is multifactorial and context-dependent, rather than dominated by any single factor. This conclusion has a direct implication to regenerative medicine. It suggests that if a single-pathway strategy such as reactivating cardiomyocyte proliferation or dissolving the glial scar is followed, it is not likely that full tissue regeneration will be achieved, given the multiple (intrinsic, vascular, immune, and positional) constraints that may need to be satisfied, and the most promising translation-oriented strategies identified in this literature, such as the combined signaling of progenitors and pro-regenerative macrophages, are the strategies that span multiple levels of this hierarchy.

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