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Research Article

Hypothesis and Reflections on the Bases of Regeneration-Incompetence: Healing Through a Fibrotic Scarring Process

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Abstract

Introduction: Evolutionary divergence between regeneration competent and regeneration incompetent species reflects distinct tissue repair programs. While aquatic and semi aquatic vertebrates activate a highly coordinated regenerative cascade-involving rapid re-epithelialization, apical epidermal cap formation and blastema proliferation supported by mesenchymal cell plasticity, permissive immune modulation and efficient senescenT-cell clearance-mammalian wound repair is usually fibrotic. Aims: This review discusses current evidence and hypotheses explaining why mammals, despite retaining many regeneration associated genetic pathways, tend to follow a fibrotic healing program. Translational strategies to restore regenerative capacity are also explored.

Methods: This narrative synthesis integrates comparative evidence on wound re epithelialization, blastema biology, immune regulation, fibroblast activation and senescence associated constraints on tissue repair.

Results: In mammals, transforming growth factor beta and mechanical stress drive fibroblast to myofibroblast differentiation, collagen deposition, wound contraction and expansion of scar promoting lineages such as Engrailed 1 positive and paired related homeobox 1 expressing fibroblasts. Keratinocytes fail to generate a functional apical epidermal cap, while robust tumor suppressor activity and persistent senescenT-cells further restricT-cellular plasticity-prioritizing rapid wound closure and pathogen defense over structural restoration. The immune inflammatory response is a critical determinant of divergent outcomes: regeneration competent species mount a tightly regulated, pro resolving response with T-lymphocytes and regulatory T-cells fostering progenitor activation, whereas mammals exhibit prolonged, maladaptive immune activity that sustains fibrosis.

Conclusions: Many regeneration-related pathways remain conserved in mammals, but appear to be dormant. This suggests that regenerative repair may still be biologically accessible if the right epithelial, mesenchymal and immune signals can be restored. Approaches based on stem cells, biomaterial scaffolds and immune reprogramming may therefore help shift repair away from fibrosis and toward regeneration, addressing pressing unmet needs in wound care, fibrosis and organ transplantation.

Keywords: Epimorphic Regeneration; Regeneration in Vertebrates; Regeneration in Amniotes; Wound Healing; Tissue Repair; Fibrotic Scarring

Abbreviations

AEC: Apical Epidermal Cap; α-SMA: Alpha Smooth Muscle Actin; ARF: Alternative Reading Frame; BMP: Bone Morphogenetic Protein; DNA: Deoxyribonucleic Acid; EDA-: Extra Domain A-; EPF: Engrailed 1-Positive Fibroblast; ERK/MAPK: Extracellular Signal-Regulated Kinase / Mitogen-Activated Protein Kinase; FGF: Fibroblast Growth Factor; HIF1A: Hypoxia-Inducible Factor 1A; Hox: Homeobox Genes; IL-1: Interleukin 1; IL-10: Interleukin 10; Mdm2: Mouse Double Minute 2 Homolog; p16INK4a: Cyclin-Dependent Kinase Inhibitor 2A; PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha; pRB: Retinoblastoma Protein; Prrx1: Paired Related Homeobox 1; RNA: Ribonucleic Acid; SHH: Sonic Hedgehog Proteins; Smad: "Small" Worm Phenotype / "Mothers Against Decapentaplegic"; TAZ: Transcriptional Co-Activator with PDZ-Binding Motif; TGF-β: Transforming Growth Factor Beta; Tregs: Regulatory T-cells; TSG: Tumor Suppressor Genes; Wnt: Wingless/Integrated; YAP: Yes-Associated Protein.

Introduction

Regeneration is the biological capacity of certain living organisms to replace damaged, aged or missing tissues and organs [1]. This process has attracted scientist for more than two centuries, counting biologists, histologists and plastic surgeons. This is described as an evolutionary-imprinted, post-embryonic, complex and dynamic mechanism, variably represented in the animal kingdom. Thus, it may comprise rebuilding an organ like a salamander limb, the caudal fin of zebrafishes up to whole-body regeneration in hydra and planaria among others [2].

Robust regenerative process is more common in aquatic and semi-aquatic species than in terrestrial organisms [3]. In contrast, the most prevalent mechanism of injury repair in terrestrial vertebrates consists in fibrotic scarring [4]. Therefore, our inability to regenerate organs is likely a consequence of evolutionary changes as a response to environmental adaptations [4]. Successful organ regeneration entails complex and concertedly multifaceted events in which variegated cell populations and processes, as dedifferentiation, transdifferentiation, proliferation, migration, metabolic reprogramming and eventual differentiation - finely converge to properly rebuild an organ [5]. Morphogenesis is the coordinated reorganization of tissues to restore form and function, is the final stage of successful regeneration. This multistage process ensures that the rebuilt organ recapitulates topographic position, size, structure and color of the original counterpart through the interplay between genic and non-genic cues [5-7].

Mammals display increased physiological complexity, which may contribute to constraints on regenerative capacity [8]. Mammals exhibit the most sophisticated hierarchical organization of biological systems, exemplified by the length and interconnectedness of biochemical pathways, gene regulatory networks and their degree of integration and modularity [9]. Although mammals include the largest animal that ever lived with an evolutionary success in their anatomy, physiology and behavior, they traded the regenerative prowess for a rapid mechanism of wound healing response accounted by tissue fibrotic induration [10]. Researchers have theorized that "mammals do not have the luxury of spending the time required to regenerate structures epimorphically and that the more rapid tissue regenerative response is, a more effective substitute even though the final regenerate may not be as perfectly formed as it would have been if an epimorphic process had been operative" [11].

Decades of research using teleost fishes and urodele amphibians, organisms with notable regenerative capacity, have clarified key molecular pathways implicated in regeneration [12]. Many regeneration-associated molecular pathways are evolutionarily conserved, suggesting that mammals may retain latent regenerative mechanisms. A challenging task however, is to answer why these pathways are not activated when for instance, a limb is amputated [13]. Alike, whether or not terrestrial species still harbor the genes that in aquatic species allow for a broad regenerative response, is another pending subject. Alibardi proposed an evolutionary explanation: gene networks for regeneration became epigenetically repressed during terrestrial adaptation [10]. These years of continued efforts pursuing to open/expand the humans´ regenerative window, still fall short at the time of conclusively stating whether or not the main regeneration drivers are sheltered in regeneration-incompetent organisms [12,15]. If they are indeed, why are they overridden by an evolving fibrotic scar program? That non-regenerative organisms miss cues to activate dormant regeneration programs, is an alternative hypothesis put forward [16]. This field of biology remains plagued of challenging questions, countless unknowns and uncertain answers; but above all of these, it is enchanting.

With this review we aim to summarize current lines of thoughts within this fascinating biological capacity and comment the hypothetical frameworks that we and others deem as major phylogenetic and organismal constrains for amniotes regeneration incompetence.

Methodology

We conducted a comprehensive systematic review of articles published in the MEDLINE (PubMed), EMBASE, Scopus, Web of Science and Cochrane Central databases. The following keywords and search terms were employed: epimorphic regeneration, vertebrate regeneration, amniote regeneration, wound healing, tissue repair and fibrotic scarring. Studies were considered eligible if they met the following criteria: full-length articles published in English in peer-reviewed journals, with no restriction on publication date. The quality of the articles was independently assessed by the authors and studies suitability was identified according to their alignment with the study criteria. A final reference list was then compiled. The analysis of epimorphic regeneration was assumed from the perspective of lower vertebrate species as zebrafish, axolotls and newts; whereas the events in non-regenerating mammal's species characterized by a profibrotic scarring process, were based on the scenario of peripheral tissue wound healing by second intention and a hypothetical limb amputation in a human or a laboratory rodent. All compiled information was structured under four principal headings: (1) Introduction, (2) Conceptual frame of epimorphic regeneration, (3) Tissue repair in amniotes and (4) Concluding remarks and perspectives.

Epimorphic Regeneration: Main Events

Epimorphosis refers to the regeneration by localized cell proliferation that restores missing tissues. This type of regeneration is observed in higher order species and relies on the formation of a blastema as the highly proliferative regeneration unit, that typically contains cells transiting from an undifferentiated, to a fully differentiated and biologically competent state [2]. The regenerative process begins immediately after an appendage loss and consists of three phases: wound healing, blastema formation and regenerative outgrowth [16]. Successful regeneration in urodeles and zebrafish requires coordinated migration, dedifferentiation, proliferation and redifferentiation (Fig. 1) [17]. As mentioned, these events rely on the existence of soft, hydrated and permissive blastema environment for the incoming regeneration-supporting events [1].

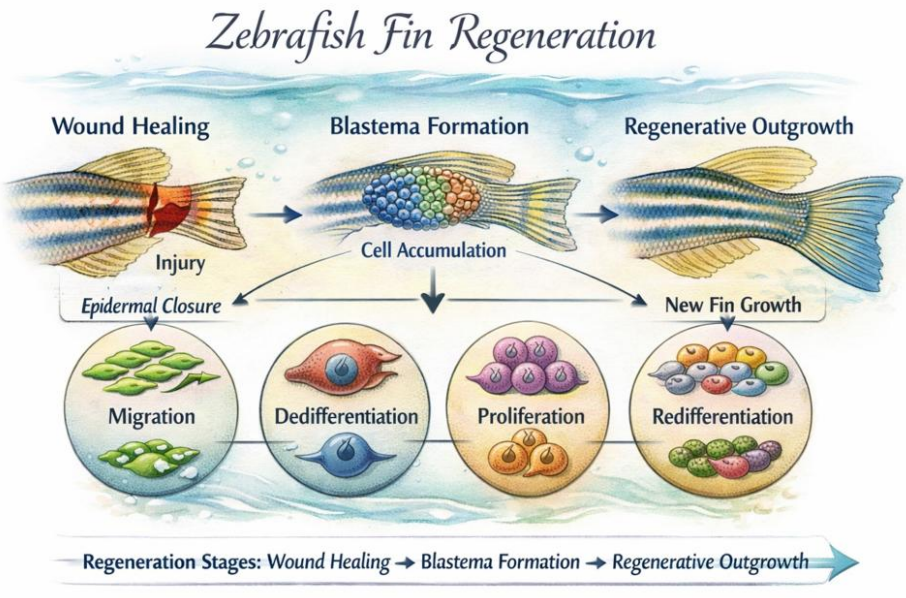

Figure 1: Fin regeneration following amputation. The image illustrates the sequential phases of regenerative healing in a competent species. After injury, rapid adjacent keratinocytes migrate, reepithelialize and protects the stump - initiating a signaling process addressed to distal mesenchymal cells. Consequently, these cells undergo dedifferentiation and proliferate to establish the blastema, a mass of mesenchymal progenitor cells. Progressive growth and redifferentiation restore tissue complexity, while patterning cues guide morphogenesis of skeletal, muscular and connective structures. The final stage depicts a fully regenerated fin, highlighting the remarkable capacity of this organism to replace damaged appendages without scarring.

The Critical Role of Epidermal Cells

Assuming the scenario of salamander's limb or zebrafish caudal fin, the primary response to injury is initiated by the recapitulation of the wound epidermis even before blastema full establishment, so that the wound typically re-epithelializes within 2 to 6 hours post amputation [7,18]. The process is based on the migration of nonmitotic epidermal basal cells through a fibrin clot in response to distal mesenchymal cells signals [19]. In correspondence, this epidermal layer, which lacks an underlying dermis or basement membrane, secretes paracrine factors that promote histolysis and dedifferentiation by releasing paracrine signals for the histolysis of internal tissues, the subsequent dedifferentiation and migration of cells in the mesenchymal compartment of the injury [20]. A variety of compelling approaches that somehow lead to epidermal ablation have demonstrated the relevance of the wound epidermis requirement for the blastema formation [21]. Most importantly, the experimental obstruction of wound reepithelialization is ensued by the advent of a scar tissue and the ultimate decline of salamander limb regeneration [22]. Later, the wound epidermal layer becomes stratified turning into the Apical Epidermal Cap (AEC) that has been compared to the apical ectodermal ridge in the embryonic limb bud [1,19,23]. Removal or blocking the AEC formation disrupts the limb regeneration program. Conversely, its ectopic grafting can induce limb outgrowths with cartilage and dermal composition [21]. Taken together, these findings indicated that wound re-epithelialization is essential for blastema formation, outgrowth and epimorphic regeneration [24,25]. Along with this process, the epidermal layer becomes innervated which contributes to dermal cells migration, proliferation and ultimately enhancing the epimorphic regeneration progression [19]. Insufficient nerve input impairs blastema formation; denervation during early blastema stages halts regeneration. Molecular signals originating from regenerating neural tissues, particularly the spinal cord and the brachial nerve, have been identified as essential primers of the regenerative process [26]. Of note, skin cells homeostasis is severely disturbed upon spinal cord injury in regeneration-restricted organisms, which is associated to an early and protracted disruption of the expression of gene networks involved in the wound healing phases [27,28].

Blastema Cells Population

Once the wound has been reepithelialized, the AEC releases priming factors that interact with the expanding blastema, triggering an intense proliferative activity as an indication of cell cycle re-entry [29]. The fact that blastema formation is mostly determined by cell proliferation waves was demonstrated sixty years ago by experiments based on blastema x-irradiation [30]. Again, the basal layer of the wound epithelium of the apical blastema regulates cells proliferation through the expression of oncogenes and tumor suppressor gene-derived proteins [31]. Consequently, blastema represents an example of finely tuned and balanced activity between the opposing activities of oncogenes and tumor-suppressors genes [31]. Recent lineage tracing studies define the blastema as a heterogenous population of cells with distinct origins and limited multipotency. Regarding the various hypotheses about the origin of blastema cells, some of them consider that blastema cells originate through the dedifferentiation of mature cells, trans differentiation of lineage-restricted progenitor cells and through the proliferation of undifferentiated progenitor cells [32]. In line with this, cells within the blastema transiently express pluripotency Yamanaka factors (Oct3/4, Sox2, Klf4 and c-Myc) in embryonic stem cells with well-known ability to reprogram somatic cells into pluripotent stem cells [33]. Studies have demonstrated that inhibition of Yamanaka factors, suppresses fin regeneration in zebrafish demonstrating their role in reprograming cells fate [34]. Yet, recent studies indicate that most blastema cells seem to derive from mesenchymal cells, dermal fibroblasts and fibroblast-like progenitor cells [19,23,35,36]. Some studies show that blastema signals can induce profound reprogramming events. Accordingly, when transplanting labelled intestinal blastemal cells into newts' limb blastema, they subsequently integrated into cartilage tissues and differentiated into chondrocytes. Likewise, the redifferentiation of retinal pigmented epithelial cells into the neurons that comprise the regenerated retina, is another illustrative example that blastema environment is rich in signals that enhance cellular plasticity/fate reprogramming [37]. Other evidences document however, that blastema environment-derived cues generate progenitor cells with restricted potential and conserving positional identity in a cell-type-specific manner [38,39]. Lineage-tracing studies confirm thaT-cells remain fate-restricted with no transdifferentiation during regeneration in the zebrafish fin [39]. Irrespective to the origin of blastema cells and their capability to commit broad transdifferentiation and fate reprogramming events, a recent thought-provoking observation is that Ribonucleic Acid (RNA) and proteins extracted from lizard blastema, inhibit the proliferation of aggressive breast and prostate human cancer cells overriding interspecies differences. This alluring finding has invigorated the search and identification of such tumor suppressor drivers [40].

Blastema Gene and Pathways

Identification and harnessing of the signaling networks involved in the regenerative morphogenesis, is an essential research

target given its futuristic medical translation [16]. Different gene expression transcriptional and proteomic profiling studies with blastema, have revealed the upregulation of numerous gene and protein classes associated with: pluripotency, proliferation, oncogenesis, mesenchymal identity, Deoxyribonucleic Acid (DNA) damage repair, RNA binding, survival, migration, morbidity, necrosis, embryo mortality, cell death and matrix metalloproteases secretion control [23,41,42]. The Greco and co-workers' transcriptomic study in lizards, an animal that regenerates the tail but not the limbs, identified differences in a universe of genes expressed in the regenerating tail, versus those in the scarring limb. For the authors, the stimulating environment and the paracrine release of specific signals from the injured tail, determine the selection and activation of regeneration or scarring-promoting genes networks [43]. Thus, it seems that sensing and reading the injury-derived signals is the trigger for the sequential activation of different gene programs, signaling pathways and epigenetic mechanisms. Among these, Extracellular Signal-Regulated Kinases/ Mitogen-Activated Protein Kinase (ERK/MAPK) pathway upregulation acts as an early and primary initiation factor for appendage regeneration [16,44]. A key feature of regeneration is faithful recapitulation of anatomical patterning (axis, size and shape) [16]. These mechanisms in which cellular identity memory is critical, seem to be determined by precise epigenetic patterns of chromatin organization and gene transcription [19,45]. A variety of developmental signaling pathways converge to regulate blastema formation, proliferation, outgrowth, cellular differentiation, positioning and overall morphogenesis [23,46]. These include skeletal patterning pathways of Bone Morphogenetic Proteins (BMP), Fibroblast Growth Factor (FGF), Wingless/integrated (Wnt) / β-catenin, Homeobox Genes (Hox), retinoic acid and Sonic Hedgehog Proteins (SHH) [46-49]. It was recently demonstrated the central role of the Hippo signaling pathway in zebrafish regenerative processes. This pathway, mostly represented through the transcriptional co-activators Yes-Associated Protein (YAP) and Transcription Adaptor putative Zinc finger (TAZ), is notorious for its contribution to organs shape and size [6]. All these morphogenesis pathways are activated in a spatiotemporally-regulated manner during blastema formation, playing a foremost role along the tissue regeneration process [50-52].

Metabolic Reprogramming of Blastema Cells

Metabolic plasticity and reprogramming characterize blastema regenerating cells. Metabolic alterations have shown to play an instructive role in regulating genetic programs that dictate fate decisions [53]. Glycolysis contributes to regeneration of the zebrafish larval tail and heart [54,55]. Injury sensing and cellular metabolic plasticity in zebrafish caudal fin regenerate, drive metabolic reprogramming toward glycolysis at the expense of mitochondrial oxidation, which contributes to reprogram mature osteoblast into pre-osteoblasts, facilitating their proliferation commitment [53]. Furthermore, up-regulation of glycolytic genes has also been described in Xenopus tails and adult zebrafish heart regeneration [56]. Enhancement of anaerobic glycolysis by paralleled repressed mitochondrial respiration is a conducive factor for cells dedifferentiation, reprogramming, preservation of stemness and self-renewal capabilities. Conversely, inhibiting glycolysis have shown to abort organs regeneration in different experimental models [57].

Nerves Input Contributes to Blastema Growth

The need for an adequate nervous cells input seems to be a widespread requisite in vertebrates regeneration [23]. As described for the apical epithelial cells, blastema formation and growth is also dependent on peripheral nervous system input, as limb denervation impairs blastema formation [58]. Nerves provide factors that support blastema cells survival. The administration of nerve-derived factors can initiate a regenerative response, bypassing nerve input requirement in limbs that had been rendered non-regenerative [48]. Remarkably, the influence of nervous input for cell proliferation is not restricted to the amputated limb, but occurs within a systemic context stimulating subsets of cells throughout the body. An ingenious experiment by Payzin-Dogru and co-workers, elegantly showed the existence of a systemic activation signal for cells distant from the amputated limb in axolotl, being this effect mediated by the sympathetic adrenergic system [59]. Once the regenerate has progressed and morphogenesis is apparent, the regenerate turns nerve-independent while conversely, angiogenesis begins to appear [60]. At this stage the blastema is considered complete and development of the patterned regenerate is ensued upon vascularization. The regenerated limb is initially a smaller replica of the original limb, but will continue to grow for about two months until eventually attaining the size of the original limb [61]. These biological processes are simplistically depicted in Fig. 2.

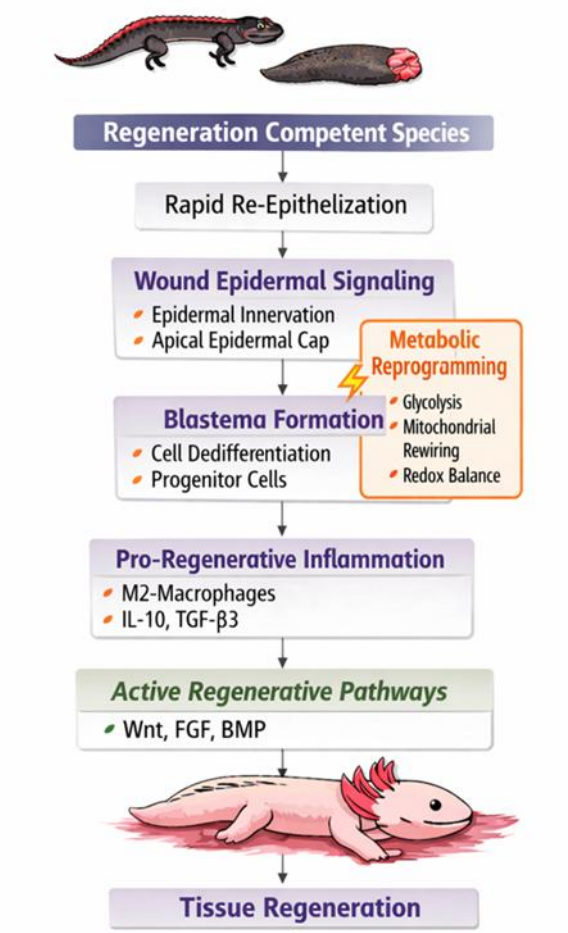

Figure 2: Simplified cascade of the main events integrated within the process of regeneration. The sequence begins with rapid re-epithelialization fostered by epidermal innervation with the formation of the AEC. Blastema progenitor cells proliferate, readjust their metabolic profile to glycolysis and accumulate beneath the cap, whereas the inflammatory reaction is dominated by infiltrating M2 counter-inflammatory macrophages and cytokines such as IL-10 and TGF-β3, which support blastema maintenance, growth and tissue remodeling. Activation of morphogenetic pathways including Wnt, FGF and BMP drives limb morphogenesis and pattern restoration. The process culminates in tissue regeneration, yielding a fully functional limb.

Damaged Tissue Repair in Regeneration-Incompetent Organisms

Forewords

Why regeneration evolutionarily became an attribute to selected organisms remains as one of the biggest, intriguing and defiant problems of biology. Comparable to the appearance of homeothermy, the loss of regeneration competency represents a profound turning point [10,62]. Terrestrial conquerors were evolutionarily assigned with an intrinsic fibrotic scarring formula that while not functionally faultless, is an emergency solution for a faster tissue repair and evade predators [63]. Although, most of these species have the ability to regenerate skin, heart, retina and spinal cord during early embryonic development, a gestational life transition toward an adult scarring healing program exists, so that regeneration ability switches off [15,64]. The key features distinguishing fetal wound regeneration from adult wound healing include minimal tissue inflammation, faster re-epithelialization and negligible contraction of the neo-dermis [65-68]. The molecular bases of this transition as the set of barriers that obstruct post-natal regeneration in mammals remain elusive [32,69]. Regenerative capacity constitutes a critical resource and its impairment is unlikely to be attributable to a unique determinantal factor [69]. This section examines hypothetical frameworks proposed to account for the evolutionary restriction of regenerative competence.

Meant to a Fibrotic Healing Program: Fibroblasts Activation and Scarring

The time difference between regenerating a salamander limb and an adult limb in a human is daunting. According to Brockes and Kumar, it would take the human body 15 years to regenerate an adult arm, representing a long-time course that might not

be undertaken by such a complex species [70,71]. Hence, increase in overall body size is one the several evolutionary innovations that may impair regeneration [72]. Under physiological conditions, the wound-healing cascade can be regarded as an emergency reparative mechanism designed to achieve hemostasis, mitigate microbial infiltration and re-establish epidermal barrier integrity to safeguard intravascular plasma volume and electrolyte homeostasis [20,67]. Notably, it was evolutionarily organized through as a series of well-scheduled and physiologically sounding phases that overlap and include hemostasis, inflammation, granulation tissue formation along with progressive epithelial resurfacing and tissue remodeling (Fig. 3) [73].

Figure 3: Main trajectory events in the scarring repair process in regeneration-incompetent species. Tissue injury initiates with bleeding, the clot formation and the release of damage signals. The fibrin-rich clot serves as a temporary barrier against infection and provides a provisional matrix for incoming cells like the primary wave of infiltrating and anchoring fibroblasts. Inflammation is initiated with complement activation and the infiltration of neutrophils and macrophages which, in addition to remove debris, contribute to control bacterial invasion and the general choreography of tissue response via the secretion of cytokines. Following neutrophils, M1 subclass macrophages amplify the inflammatory phase which predisposes toward pro-fibrotic signaling, laying the groundwork for scar formation. In the meantime, the invading fibroblasts contribute to eliminate and replace fibrin scaffold, secrete collagen III and fibronectin accumulate, contributing to the formation of a new and contractile matrix in which TGF-β1 predominates as a pro-fibrotic cytokine. Local loops of matrix secretion, fibroblasts activation and TGF-β secretion, contribute to define the scar phenotype. At this point, granulation tissue is emerging with an extracellular matrix and angiogenic sprouts, amplified by growth factors secreted by M2 subclass macrophages. Over time, the scar becomes mature and remodeled by a cascade of finely-tuned proteases, collagen material undergoes cross-linking, matrix continues in a contractile process and excessive vessels regress. The mature scar is permanent, structurally rigid and functionally inferior to the original tissue.

The hypothesis that wound healing is governed by a cellularly imprinted program-one that is both genetically encoded and epigenetically reinforced, finds compelling support in the inspiring work of Michael Longaker and colleagues. In this study, wounded adult sheep skin was transplanted into a fetal environment, a context otherwise characterized by scarless regenerative healing. Remarkably, the transplanted adult tissue repaired itself through fibrotic scarring, rather than adopting the regenerative phenotype typical of the fetal milieu. This observation suggests that adult dermal tissue retains an intrinsic "scar program," a form of biological memory that persists irrespective of extrinsic environmental cues [74]. Other studies have demonstrated however, that postnatal myocardial tissue retains the capacity to re-engage an embryonic regenerative phenotype. Pharmacological reduction of extracellular matrix stiffness showed to restore regenerative potential in the heart after birth, whereas these effects are not merely mechanical but orchestrated by a transcriptional reprogramming. This evidence again underscores the role of intrinsic gene regulatory networks in determining the repair outcome [75]. Comparative analyses across amniote species, reveal that fibroblastic mesodermal cells host substantial intrinsic differences depending on the regenerative competence. In non-regenerative amniotes, including mammals and birds, fibroblastic cells have undergone evolutionary and developmental changes that restrict their capacity to activate regenerative cascades. Instead, these cells predominantly engage in fibrotic repair, ultimately sacrificing functional tissue architecture for rapid wound closure. This divergence underscores cellular and molecular determinants that govern species-specific healing strategies and provide a framework for understanding the evolutionary constraints on regenerative biology [69]. A widely accepted and enduring hypothetical construct to explain regeneration failure, is that those incompetent species are preconditioned since the fetal period, to implement a fibroblast activation driver that supersedes regeneration leading to a fibrotic scar, in which these cells differentiate into contractile myofibroblasts-provided with alpha Smooth Muscle Actin (α-SMA)-rich stress fibers. This process is operated by the master pro-fibrotic cytokine Transforming Growth Factor Beta (TGF-β) and influenced by extracellular matrix-generated mechanical tension, rendering a collagenous stiff bed, devoid of dermal appendages that ultimately become contracted [76,77]. Contraction is accordingly interpreted as an ancient prosurvival mechanism of vertebrates that through tensile forces, accelerates wound closure with minimal energy expenditure [78]. In humans and pigs, contraction of circular wounds contributes to 50% of wound area closure, while in rodents, this mechanism accounts for ~90% of closure [79]. Another outcome of the TGF-β/Smad receptors/fibroblasts activation cascade, is the deposition of fibronectin Extra Domain A- (EDA-), which amplifies myofibroblast differentiation and TGF-β activation [80]. Robust evidences supporting this hypothesis derive from three adult mammalian injury models, wherein regenerative outcomes were achieved by reducing the activity of pro-fibrotic fibroblast subpopulations. These findings suggest that the postnatal decline in regenerative capacity is mechanistically linked to a myofibroblast-mediated scar program [67]. Consistent with Yannas and colleagues, there is an evolutionarily embedded survival mechanism mediated by mesodermal cell populations, that prioritizes fibrotic tissue repair with contractile remodeling, accounting for the principal constraint for regenerative capacity [67,81]. However and challenging to this interpretation, is the fact that axolotls' dermal excisional wounds contract to approximately the same degree as human skin, even with relatively fewer myofibroblasts and less α-SMA positive cells [63].

Fibroblasts are a heterogenous assortment of mesenchymal subpopulations homing the dermis, having different embryonic/developmental origin, regional specificity, varied activation phenotypes, tissue-repair abilities and lineage-specific transcriptomic profiles [82-84]. There are major cellular differences between regeneration-competent and regeneration incompetent mammals′ skin fibroblast [85]. For instance, mammals cells do not recall the embryonic developmental program [86], their dedifferentiation capabilities are largely more restricted as they do not return to a fully pluripotent state, neither to an early progenitor state within their developmental history. They are also unable to induce and instruct epidermal cells to create a specialized layer like the AEC. Thus, amniotes mesodermal cells fail to provide the necessary signals to initiate a regenerative response [69,87,88]. A major hallmark of fibroblastic cells in amniotes is the existence of scar-promoting subpopulations that become expanded following a trauma and are tagged by the expression of gene products involved in the scar formation process. These include Engrailed-1 positive expressing fibroblasts [89] and the paired related homeobox 1 (Prrx1) lineage expressing gene, detected in papillary and reticular dermis and responsible for extracellular matrix deposition [90]. The Engrailed 1-Positive Fibroblast (EPF) intrinsic scarring abilities are broadly documented including its mechanical role in conveying fascial matrix connective tissue to plug the wound area [91-94]. Mounting evidences demonstrate that its functional ablation both *in-vitro* and *in-vivo* turns to a scarless, pro-regenerative phenotype by down-regulating scar-related genes [95-97]. Notably, supporting this evidence is the observation that EPFs emerge during a developmental window when the skin's response to injury transitions from a regenerative, scar-free mode to one characterized by scarring [92]. These scar-prone cells are abundant in deep dermis of regeneration-incompetent mammals showing an increased propensity to express α-SMA and retain a memory of being in a

mechanically stressed microenvironment, thereby amplifying their ability to become myofibroblasts [82,97-99]. These findings support the notion that amniotes mesodermal cells harbor a repertoire of genes whose injury-induced expression, suppresses residual endogenous regenerative pathways and impose the postnatal fibrotic scarring program [92].

Epithelial Response Differences. Inability to Induce a Paracrine Active Epithelial Cap

Another argument used to explain regeneration-incompetence, is that amniotes are incapable of inducing a specialized epidermal coat, as a main signaling center to promote blastema growth and drive regeneration [100]. Although mesenchymal-epithelial interactions play a critical role in regulating the repair process in multiple species, via autocrine/paracrine signalers [101], paramount differences exist in skin and epidermal cells complexity between regeneration-competent and incompetent counterparts. These differences span and characterize the re-epithelialization process in each of both realms. First, the acute re-epithelialization response deployed in hours in regenerative vertebrates after a limb or a fin amputation, contrasts with that of regeneration-incompetent organisms that may take 2 or 3 weeks even when for both scenarios, epithelialization is dependent on the centripetal migration of the keratinocytes from the wound margins [102]. Another difference is that re-epithelialization in regeneration-incompetent organisms requires the reconstitution of a basement membrane at the dermal-epidermal junction, as a major matrix for keratinocytes anchorage, migration and polarity [103]. Upon the AEC control, cells of the mesenchymal compartment underlying the wound epidermis lose their differentiated identity and proliferate. Conversely in amniotes, keratinocytes modulate fibroblasts via TGF-β and Interleukin 1 (IL-1) paracrine signaling pathways, leading fibroblastic mesenchymal cells to differentiate into myofibroblasts with an enhanced capacity to build up a fibrotic scar [36,104]. Despite all these differences, compelling evidences demonstrate that moist retentive dressings enhance complex wounds re-epithelialization in amniotes like humans [102], a response that may be reminiscent of the disappeared blastema humid microenvironment [105].

The Role of Tumor Suppressor Gene in Regeneration-Incompetent Organisms

In complex, non-regenerative adult vertebrates, cellular populations are characterized by diminished turnover, predominance of quiescenT-cell populations, limited proliferative reactivation and constrained phenotypic plasticity; while these processes are tightly governed by Tumor Suppressor Genes (TSG) [106]. Therefore, TSG act as critical pieces to safeguard genomic stability, cells populations homeostasis, developmental tissue formation and ultimately prevent malignant transformation. The pervasiveness of TSG function also extends to the context of tissue regeneration [107], so that the repertory of their suppressor activities may contribute to explain the differences in regeneration capabilities along the evolutionary tree [108]. As elegantly reviewed by Pomerantz and Blau, highly and poorly regenerative organisms exhibit differences in the activity of their TSG machinery. They proposed that in a context-specific manner, some TSG exhibit "regeneration suppressor" activities, although they remain as critical guardians of the regeneration quality by preventing oncogenesis [107]. Accordingly, it can be inferred that the functional threshold of TSG is comparatively elevated or more prominently represented in amniotes than in regeneration-competent organisms. There are two main tumor-suppressor signaling pathways, p53/p21 and p16INK4a/Retinoblastoma Protein (pRB), which drive cell arrest, senescence and that control tissue regeneration [109]. p53, the guardian of the genome, serves as a pivotal regulator of cell fate decisions. Inhibition of p53 activity promotes progenitor cell expansion, facilitates dedifferentiation of terminally differentiated cells and enables epithelial-to-mesenchymal transition reprogramming [110]. In salamander limb regeneration, p53 down-regulation promotes the dedifferentiation process in postmitotic, differentiated tissues to give rise to blastema formation and growth [106]. Alternative Reading Frame (ARF) is one of the most important TSG that stabilizes and activates p53 by binding and sequestering mouse double minute 2 homolog (Mdm2), restricting cell proliferation [111]. Hesse and co-authors provided the first *in-vivo* experimental demonstration that a single TSG activity can negatively impact on solid tissues regeneration [112]. In zebrafish, ARF overexpression was shown to associate with Mdm2, stabilize p53 and induce cell cycle arrest-thereby revealing a potential barrier for epimorphic regenerative processes in amniotes [113]. Inactivation of TSG could translate in amplified regenerative capacity, nonetheless with the consequential risks of cancer development [112].

Amniotes Cellular Senescence May Contribute to Regeneration Incompetence

An alternative conceptual framework posits thaT-cellular senescence, together with the accumulation of senescenT-cell populations in amniotes, constitutes a barrier to regenerative capacity [114]. Cellular senescence, potentially arising from the epigenetic repression of growth-promoting genes and proliferative signaling pathways, coupled with the activation of differentiation-associated programs, undermines regenerative competence [115]. SenescenT-cells enter a state of permanent arrest and secrete cytokines, growth factors and enzymes that remodel the extracellular matrix. Through these secretions, they

accumulate into expanding societies that interfere with tissue repair [116,117]. In amniotes, the heightened incidence of cellular senescence has been linked to a progressive decline in regenerative capacity. A seminal study by Yun and colleagues demonstrated that, while tissue repair deteriorates with age in mammals, certain organisms such as salamanders retain the ability to regenerate tissues throughout their lifespan, sustaining multiple regenerative episodes. Notably, although senescenT-cells were detected during salamander limb regeneration, they were rapidly and efficiently eliminated from the regenerating tissue. Similarly, senescenT-cells experimentally implanted into a salamander amputation stump were also swiftly cleared [114]. Because the number of senescenT-cells does not increase with aging or repeated amputations in salamanders, the authors proposed that efficient macrophage-mediated clearance of senescenT-cells, may underlie the sustained regenerative capacity of these organisms despite advancing age [114]. Salamanders, also lack the traditional signs of age-related decay [118]. By contrast, mammals accumulate senescenT-cell populations which may exponentially increase as described in the skin of aging baboons [119]. A longitudinal study of lens regeneration in Japanese newts, spanning 16 years and encompassing 19 successive regenerative cycles, revealed that regenerated lenses were structurally indistinguishable from the originals. Furthermore, transcriptomic analyses showed no differences in gene expression profiles between young and aged specimens. Remarkably, by the conclusion of the study, the animals were at least 30 years old representing a geriatric cohort within this species, in contrast to the age-related decline in regenerative capacity observed in amniotes [120]. Additionally, a phenomenon resembling rejuvenation has also been documented in salamander skin [118]. Preservation of DNA replication fidelity and telomere length is essential to averT-cellular senescence and sustain proliferative potential. In zebrafish, telomerase activity has been detected across all ages and its expression levels correlate with the species' lifelong regenerative capacity in heart and fin tissues [121]. Contrarywise, telomerase expression is postnatally suppressed in human and mouse tissues, with the exception of those with high turnover, reinforcing the association between telomerase activity and repair reserves [122]. A zebrafish null mutant for the gene encoding for the enzyme telomerase reverse transcriptase, leads to premature aging in several organs. In telomerase-null fish, cardiac regeneration is inhibited and a fibrotic scar remains following ventricular cryoinjury [123]. This inability appears to be due to a proliferative arrest and the onset of a senescence program [124]. Globally, telomere attrition is associated with diminished or lost regenerative capacity, whereas sustained telomerase activity has been documented in highly regenerative vertebrate species. These findings advise that active telomere extension may contribute to the maintenance of regenerative abilities [125].

Differences in Signaling Translation Pathways

We posit that the role of the Wnt signaling pathway constitutes a fundamental ingredient of the tissue repair mechanism with evolutionary divergent roles (Fig. 4). Unlike mammals, in regenerative organisms the pathway is induced rapidly, intensely and sustained following an injury and throughout life, aligning with their lifelong regenerative capacity [126]. As a consequence, progenitor cell pools are expanded, thereby sustaining their proliferative potential and ensuring a continuous supply of undifferentiated cells for tissue regrowth. Conversely, inhibition of Wnt signaling completely abolishes blastema formation and regenerative capacity [127]. In regeneration-incompetent species, Wnt activation is transient, insufficient or dysregulated, promoting cellular differentiation, restricting plasticity and driving fibroblast activation with consequent matrix deposition. Its inhibition is associated with regenerative outcomes [128,129]. Topical administration of a pharmacological Wnt inhibitor was shown to attenuate fibrosis, as evidenced by reduced numbers of α-SMA-positive myofibroblasts and diminished collagen type I deposition. Wnt inhibition also facilitated restoration of skin architecture [128]. Mechanistic links have been established between Wnt, TGF-β, fibroblast activation, extracellular matrix accumulation and fibrosis [130,131]. Activation of Wnt signaling has also been implicated in the transdifferentiation of adipocytes into myofibroblasts, a process that contributes to the development of cutaneous fibrosis [132]. In summary, Wnt/β-catenin signaling in amniotes supports development and wound healing, but restricts regenerative capacity by enforcing lineage commitment to fibrosis [133].

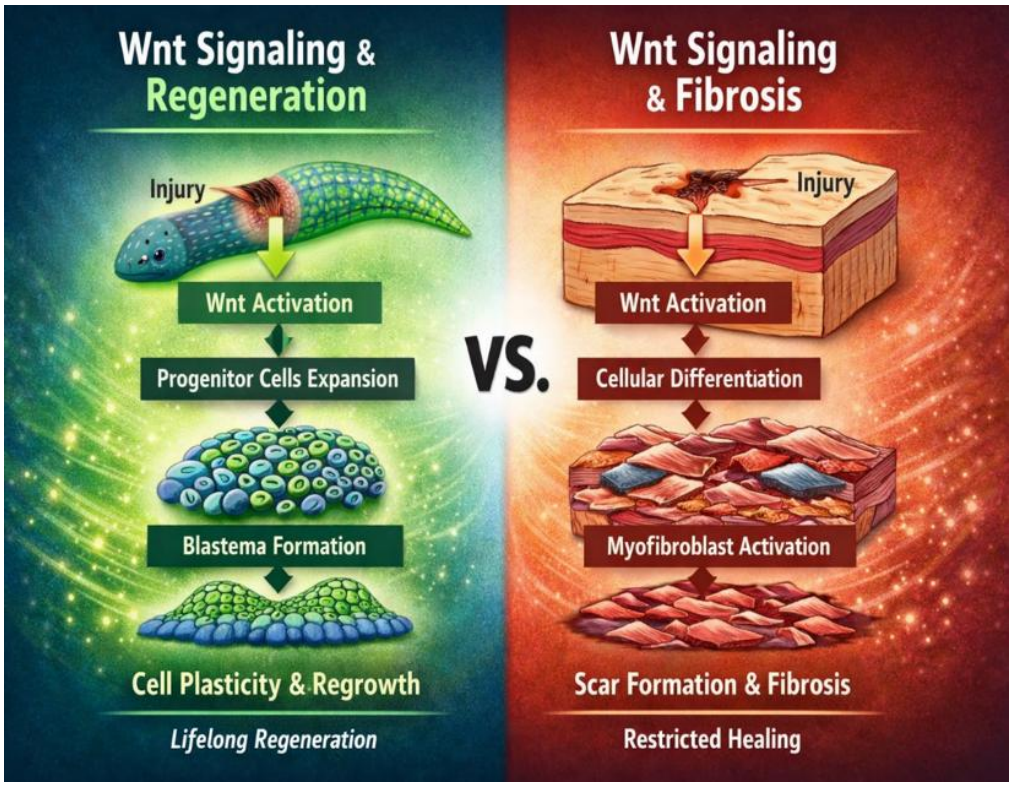

Figure 4: Evolutionary divergence in Wnt pathway activity. In regeneration-competent organisms (e.g., amphibians), Wnt signaling is rapidly and persistently induced, sustaining progenitor cell expansion, broad cellular plasticity and blastema formation that culminate in complete tissue regrowth. In contrast, in mammals, Wnt activation is transient or dysregulated, promoting lineage commitment and fibroblast differentiation into α-SMA-positive myofibroblasts, leading to extracellular matrix accumulation, collagen type I deposition and fibrotic scar formation. Mechanistic links between Wnt and TGF-β1 signaling further reinforce fibroblast activation and extracellular matrix deposition. This pathway acts as a pivotal determinant of regenerative plasticity versus fibrotic repair, highlighting its dual role as both a driver of lifelong regeneration in competent species and a restrictor of regenerative capacity in amniotes.

Metabolic Reprograming is Another Restrictive Point

Metabolic reprogramming and oxygen sensing are interconnected events set forth as an integral response to tissue injury. Both appear to deploy a crucial role in sustaining cell proliferation, dedifferentiation and epigenetic reprogramming at the site of injury [57]. However, regeneration-competent organisms exhibit a broad and flexible metabolic reprogramming plasticity that contrasts with that of non-regenerating organisms. Thus, we posit that as for the Wnt signaling pathway, metabolic reprogramming may be an additional limiting factor in regeneration competence in amniotes. In species like zebrafish or salamanders, injury triggers a shift toward glycolysis leading to mitochondrial remodeling which enables dedifferentiation and a robust blastema formation; whereas non-regenerating species show limited or incomplete metabolic adaptation [134,135]. In mammals for instance, glycolysis is very transient and cells acutely revert to oxidative metabolism, which somehow lead to fibrosis and scar formation. This suboptimal metabolic plasticity is associated to fibroblast activation via TGF-β1 signaling [136]. In regenerative competent species substantial upregulation of the peroxisome Proliferator-activated receptor Gamma Coactivator 1 alpha (PGC-1α) gene has been observed, fostering mitochondrial biogenesis, stem cell fate regulation and antioxidant defense, which are critical for sustaining the intense energy demands of regeneration. In contrast, substantial downregulation of this gene is evident in both *in-vitro* and *in-vivo* fibrosis models [137]. PGC-1α plays a pivotal role in stem cell regulation and directing lineage fate decisions promoting tissue regeneration [138].

Hypoxia-mediated signaling pathways constitute another pivotal regulatory mechanism in wound healing and tissue regeneration, predominantly through the induction of cellular dedifferentiation and metabolic reprogramming [139]. Oxygen-sensing ability appears as an evolutionary imprinted species-specific mechanism. Reduced oxygen availability, coupled with impaired regulation of Hypoxia-Inducible Factor 1A (HIF1A), permits epigenetic, metabolic and biochemical processes to

converge, thereby activating regenerative pathways [7]. As a matter of fact, hypoxia is highlighted as a key feature of blastema microenvironment in regeneration-competent organisms. Early blastema is an avascular structure and the local expression of a known anti-angiogenic factor (pigment epithelium-derived factor), correlates with a successful regenerative response [140]. Conversely, angiogenesis is one of the earliest and most energic events during wound healing, specially by second intention in most terrestrial vertebrates [141]. Within this context, a hypoxic gradient arises between the vascularized wound margins and the avascular wound core. The ensuing transient lactate accumulation serves as a potent angiogenic stimulus, while simultaneously promoting extracellular matrix deposition through the recruitment and activation of local fibroblasts [142]. In such context, lactate accumulation enhances TGF-β1 signaling and directly promotes the fibroblast-to-myofibroblast transition [143]. In regeneration-competent species, transient TGF-β activity facilitates mature cells reversion to progenitor states and generates a permissive environment for dedifferentiated cells to migrate and proliferate [144]. Contrariwise, within the wound environment in amniotes, TGF-β seems to be the proximal cytokine in driving fibrosis [145]. Experimental elevation of oxygen tension has been shown to delay the regenerative response. In contrast, the pro-angiogenic milieu of granulation tissue in full-thickness cutaneous wounds, drives excessive neovascularization, ultimately culminating in scar formation [146]. Thus, the evidence suggests that the angiogenesis/oxygen/hypoxia cascade is a potential evolutionary target responsible for restricted regenerative capabilities in mammals [147].

There is a Divergent Pattern of Immune-Inflammatory Reaction

Although the idea that a progressive immune system complexity is inversely related to regenerative capacity is not a proven law, this is a strong hypothetical evolutionary framework [148]. Successful tissue regeneration critically depends on both the magnitude and phenotypic composition of recruited immune cells, as well as the timely resolution of the inflammatory response [148]. In general terms, regeneration-competent species exhibit immune and inflammatory responses that are transient, tightly regulated, with an immunosuppressive inflammatory pattern that is quickly resolved, allowing for creating a permissive environment for regeneration. For instance, the lower immunocompetence in embryos and neonates correlates with higher regeneration capacity [149]. By the contrary, a persistent or unresolved inflammation disrupts blastema patterning and ultimately impairs regeneration [150]. The acquisition of increasingly sophisticated immunological mechanisms is assumed to impose constraints on the cellular and molecular processes required for regenerative potential. In mammalian systems, it is broadly hypothesized that adaptive immunity evolved under selective pressures, prioritizing pathogen defense and immune surveillance, but with trade-offs in tissue plasticity and regenerative potential [151]. Regeneration-incompetent species regularly display prolonged, dysregulated inflammation that predisposes to fibrosis and scarring [152]. This notion has solid validation from clinical findings as chronic inflammation is a well-established driver of fibrotic phenotypes and persistent inflammatory signaling leads to fibroblast activation and myofibroblast differentiation, which ultimately underlies fibrosis [153]. In mammals, inflammation is protective when acute and resolved, but can become maladaptive when persistent, excessive or coupled to fibrotic remodeling [154]. Nevertheless, compelling evidences document that reducing inflammation alone is insufficient to induce a regenerative response, suggesting that amniotes scar formation derives from a more proximal intrinsic program where inflammation is included [155].

Macrophages are essential components of the regeneration of organs and appendages. Their targeted depletion during tissue repair from salamander to mammals, highlights their essential role as orchestrators of regeneration and tissue repair [149]. Macrophage polarization is central to tissue regeneration: a rapid shift from pro-inflammatory M1 macrophages to reparative M2 enables scar-free healing, while delayed or excessive M1 activity leads to fibrosis and impaired regeneration [156]. It has been proposed the existence of two main qualitatively and quantitatively different populations of tissue resident macrophages: embryonic and adult-derived. These two different types of macrophages, explain the correlation between the higher regenerative capacity and the immunosuppressive response in neonatal cardiac regeneration in mice. On the contrary, non-regenerating adults, contain monocyte-derived macrophages that promote differentiation of fibroblast and proliferation of stromal cells, increasing the production of extracellular matrix and therefore causing fibrosis [157-159]. This observation provides a compelling counterexample: in fetal and neonatal mammals, a more contained inflammatory response in various tissues is associated with reduced fibrosis and enhanced repair. Crucially, this indicates that the problem is not inflammation per se, but rather its intensity, duration and regulation.

T-lymphocytes represent a critical immunological determinant of tissue repair, yet their functional outcomes diverge markedly between regeneration-competent and regeneration-incompetent species. In organisms such as salamanders and zebrafish, T-cells

facilitate regenerative processes by modulating the inflammatory milieu, secreting reparative cytokines and supporting progenitor cell activation, thereby enabling restoration of tissue architecture and function. By contrast, in mammals-including humans, T-cell responses are frequently characterized by sustained pro-inflammatory signaling and fibroblast activation, culminating in fibrotic scar formation rather than true regeneration. This dichotomy underscores the context-dependent nature of adaptive immune regulation in tissue injury and highlights T-lymphocytes as both potential mediators of regenerative success and barriers to repair [160,161]. Regulatory T-cells (Tregs) are a unique subset of T-cells vital for maintaining immune balance, preventing autoimmune diseases and controlling immune responses. These cells are recognized for their role in suppressing excessive immune-inflammatory reactions and promoting repair and regeneration following tissue injury [162]. Yet their functional impact diverges across species with differing regenerative capacities. In regeneration-competent organisms, Tregs contribute to successful tissue restoration by attenuating excessive inflammation, secreting anti-inflammatory cytokines such as interleukin 10 (IL-10) and fostering a permissive niche for progenitor cell activation and differentiation. By contrast, in regeneration-incompetent species, including mammals, Treg activity is often insufficient to counterbalance pro-inflammatory effector T-cell responses, resulting in prolonged immune activation, fibroblast recruitment and deposition of extracellular matrix that culminates in fibrotic scarring rather than true regeneration. This comparative dichotomy underscores the pivotal role of Tregs, highlights their potential as therapeutic targets to reprogram maladaptive immune responses and enhance regenerative outcomes in species otherwise constrained by scarring [163]. In conclusion, the fate of injured tissues is dictated by the character of the immune-inflammatory response (Fig. 5). Regeneration-competent species mount a tightly regulated, pro-resolving program in which specialized subsets of immune cells actively suppress excessive inflammation and foster progenitor activation, enabling scar-free restoration. In contrast, non-regenerative species often sustain prolonged effector responses that drive fibroblast recruitment and extracellular matrix deposition, culminating in fibrotic scarring. These differences highlight that regeneration depends not on immune silence, but on the precise reprogramming of inflammatory pathways toward constructive, pro-regenerative phenotypes [164].

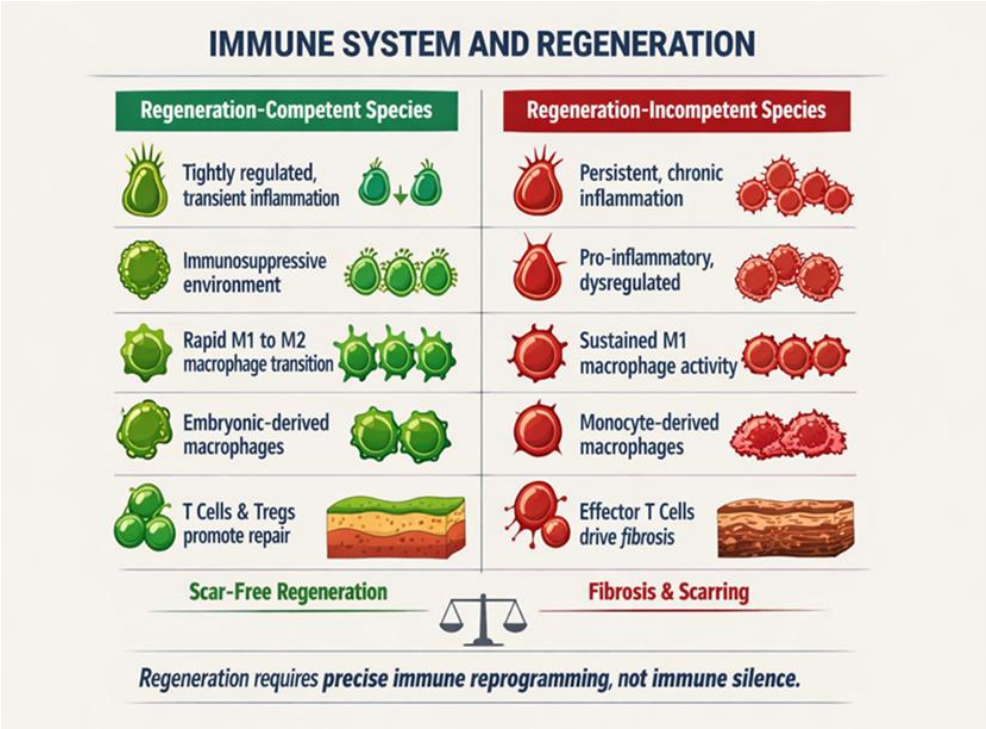

Figure 5: Immune regulation as a determinant of regenerative versus fibrotic outcomes. The schematic contrasts immune responses in regeneration-competent species (green) with those in regeneration-incompetent species (red). Regeneration-competent organisms exhibit tightly regulated, transient inflammation, an immunosuppressive milieu, rapid M1→M2 macrophage transition, embryonic-derived macrophages and reparative T-cell/Treg activity, culminating in scar-free regeneration. In contrast, regeneration-incompetent organisms display persistent inflammation, dysregulated pro-inflammatory signaling, sustained M1 macrophage activity, monocyte-derived macrophages and effector T-cell-driven fibrosis, leading to fibrosis and scarring. The figure emphasizes that successful regeneration requires precise immune reprogramming rather than immune silence.

Concluding Remarks and Perspectives

The evolutionary divergence between regeneration-competent and regeneration-incompetent species, reflects a profound shift in the orchestration of tissue repair. In amphibians and fish, injury initiates a highly coordinated sequence of events as rapid re-epithelialization, AEC formation and blastema proliferation-supported by fibroblast plasticity, permissive immune modulation and efficient clearance of senescen cells. Amniotes have evolved a repair paradigm dominated by fibrotic scarring, in which fibroblasts are predisposed to differentiate into contractile myofibroblasts under the influence of TGF-β and mechanical stress. Collagen deposition, wound contraction and the expansion of scar-promoting fibroblast lineages such as Engrailed-1 and Prrx1 entrench this trajectory, while keratinocytes fail to generate a functional AEC, reinforcing fibrosis. The prominent tumor suppressor activity and the persistence of senescenT-cells further restricT-cellular plasticity, reflecting an evolutionary prioritization of rapid wound closure and pathogen defense over structural restoration. The immune-inflammatory response emerges as a central determinant of these divergent outcomes. In regeneration-competent species, T-lymphocytes and regulatory subsets actively resolve inflammation, secrete reparative cytokines and establish a niche conducive to progenitor activation. In mammals, however, immune activity is often prolonged and maladaptive, sustaining effector responses that drive fibroblast recruitment and extracellular matrix deposition (Table 1). Accordingly, the immune system may act as both a facilitator of regenerative success and a barrier to repair, depending on its regulation.

Feature	Regeneration Competent	Regeneration Incompetent
Blastema onset	Formation of a blastema is central, a mass of proliferating progenitor cells driving regrowth	No blastema forms, wound healing relies on scar tissue deposition instead of regenerative outgrowth
Role of epidermis	Wound epidermis actively signals regeneration, secreting growth factors, enzymes and signalers that contribute to organize blastema	Epidermis mainly acts as a barrier; signals are insufficient to trigger regeneration. Signals prime fibroblasts to myofibroblast transition
Fibroblast biology	Fibroblasts remain plastic, can dedifferentiate and contribute to blastema cells	Fibroblasts become pro-fibrotic, depositing extracellular matrix and promoting scarring
Tumor suppressor genes	Tumor suppressor activity is modulated; regeneration requires temporary relaxation of anti-proliferative checkpoints	Strong tumor suppressor activity prevents uncontrolled proliferation, but also limits regenerative potential
Wnt signaling pathway	Wnt signaling is robustly activated, guiding cell fate, proliferation and patterning during regeneration	Wnt signaling is weaker or deregulated, insufficient to sustain regenerative programs
Metabolic reprogramming	High metabolic plasticity; cells switch to glycolysis and anabolic metabolism to fuel rapid growth	Limited metabolic reprogramming; cells remain in oxidative phosphorylation state, restricting regenerative expansion
Inflammation role	Controlled, transient inflammation supports regeneration by recruiting immune cells that release pro-regenerative signals	Chronic or excessive inflammation leads to fibrosis and scarring, blocking regenerative pathways

Table 1: Summary of the major biological divergences between regeneration-competent and regeneration incompetent organisms.

From a translational perspective, the recognition that many regeneration-associated pathways remain conserved yet silenced in mammals, offers a tantalizing opportunity. Stem cell-based tissue engineering approaches that recreate embryonic limb bud analogues, transplanted to amputation sites, may provide a conceptual strategy to reawaken regeneration-dormant programs. The urgency of this pursuit is underscored by pressing clinical needs: millions affected by different types of skin ulcers, over 100 million individuals burdened by skin fibrosis and more than 105,000 awaiting organ transplantation in the United States alone. Current therapies remain inadequate, failing to replicate the complexity of native tissues or prevent fibrotic remodeling. In conclusion, the dichotomy between regeneration and scarring reflects a complex interplay of fibroblast plasticity, epithelial

signaling, immune modulation, all presumably derived from an evolutionary-imprinted unique program. Future therapeutic strategies aimed at reawakening latent regenerative programs may also involve broadening the plasticity of mesenchymal cells, enhancing their metabolic reprogramming toward a "Warburg-like" phenotype, attenuating the activation of intrinsic profibrotic signaling cascades and reprogramming the inflammatory milieu. Several therapeutic approaches are now converging on these pathways. Small-molecule inhibitors can be designed to modulate specific pro-fibrotic signals. Biologics, including neutralizing antibodies and ligand traps, offer another way to adjust cytokine activity more selectively. Cell-based strategies, such as Tregs and engineered macrophages, may provide a more adaptive form of control. Biomaterials are also becoming increasingly useful because they allow localized and time-dependent delivery of signals that support a regenerative environment. Conclusively, the horizon of regenerative medicine thus points toward a future where human tissues recover not merely with survival, but with restoration, fulfilling the long-imagined promise of reclaiming our regenerative birthright. Achieving a scar-free healing for instance, would revolutionize clinical practice, reduce morbidity and meet up with the aspiration to restore the regenerative prowess.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Co-pilot AI was used to generate the infographics included within this narrative, all derived from academic text inputs.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

Conceptualization, J.B.-A. and A.T.-C.; formal analysis, G.P.-F., D.C.-C, A.G.-O., J.R.F-M., G.G.-N., L.W.; Resources, J.B.-A., G.G.-N., LW.; Writing and original draft preparation J.B.-A., A.T.-C., G.P.-F., D.C.-C., A.G.-O., J.R.F-M., D.G-B., G.G.-N., L.W. S.F-P., Y.N-F. Writing review and editing, J.B.-A, A.T.-C.; G.P.-F., D.C.-C., A.G.-O., J.R.F-M., D.G-B., G.G.-N., L.W., S.F-P., Y.N-F. Project administration, J.B.-A and A.G.-O.

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