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## INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/13722  
DOI URL: <http://dx.doi.org/10.21474/IJAR01/13722>



### REVIEW ARTICLE

#### REVIEW ON TAIL REGENERATION MECHANISM OF *XENOPUS LAEVIS* AND *CLINOTARSUS CURTIPES* AS A THERAPEUTIC MODEL FOR REGENERATIVE MEDICINE

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#### Manuscript Info

##### Manuscript History

Received: 11 September 2021  
Final Accepted: 14 October 2021  
Published: November 2021

##### Keywords:

*Clinotarsus curtipes*, *Xenopus laevis*, Regenerative capability, Reactive oxygen species, TRKA signalling, Myeloid Lineage.

#### Abstract

The augmentation of regenerative capability is a powerful method for pursuing the regulation of degeneration, traumatic injury, and cancer. The tadpole, *Clinotarsus curtipes*, and *Xenopus laevis* is significant model system for addressing the fundamental regeneration mechanism that enables understanding the key aspects of regeneration medicine. The selected creatures *Clinotarsus curtipes* and *Xenopus laevis* could able to obtain both tissue regeneration and scar-free healing during the larval stage in spite of its predominant loss of such ability during the metamorphic process. Such transient capability associated with the evolutionary correlation with humans creates *Clinotarsus curtipes* and *Xenopus* a very good attractive model for uncovering the functional regeneration mechanisms. The study analyzed the existing literature on change in the levels of ROS that is required for the proper wnt-signaling in every regeneration system. Apart from that, the paper provided a comprehensive review on the histopathological view, regeneration signals like TGF $\beta$ , FGF, BMP, Wnt, etc for successful regeneration. Factors that affect tail regeneration like O<sub>2</sub> influx, epigenetics, and HDAC activity have also been provided. Significant other such criteria like the role of TRKA signaling, profiling, and intracellular protein expression followed by its corresponding challenges adds value to the paper. The study presents an overview of *Xenopus* and *Clinotarsus curtipes* as a model organism for the research and highlighted the new insights.

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#### 1. Introduction:-

The tail of the tadpole is capable to regenerate its tail that includes notochord, vasculature, epidermis, spinal cord, and muscle. From the past decade, several researchers identified multiple molecular mechanisms that regulate tail regeneration like BMP, Notch TGF- $\beta$ , and Wnt-FGF.

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Generally, amphibians are employed in the study of tail regeneration. Urodeles have the capability to regenerate the tails for their entire lives. But, the anurans do it for a limited period at the tadpole stage, since the tail of anuran is not permanent for their entire life [1]. *Clinotarsus curtipes* is a Malabar or bi-colored frog belonging to Western Ghats, India. Besides, the tadpole of *Clinotarsus curtipes* is black, as well as they are formed in slow-moving streams and forest regions. This species can also be brownish or greyish, without or with black dots. They have a parotoid gland for secreting white viscous fluid; also they are structurally equivalent to the granular glands compared to other amphibians. From the study [2] it was observed that these tadpoles with longer larval period possess new strategies for counteracting the predation pressure. Further, *Clinotarsus curtipes* tadpoles are equipped with the physiological suit as a cutaneous gland, parotoid glands in reddish-brown on the dorsal side as well as supra caudal gland in the tail base. This study [3] described the anti-bacterial, characterization as well as isolation activities from *Clinotarsus curtipes*. From the structural analysis, the study depicted that, the peptides have a higher sequence of homology. And a detailed analysis of primary, as well as secondary structure, mechanism, and biological activates, would be useful for designing and developing new peptides-based anti-infective

Even though several types of research were performed utilizing salamanders as well as newts, the tail regeneration of tadpole (*Xenopus* larva) is considered to be a more beneficial model system for the analysis of molecular mechanisms[4]. Further, the tail of *Xenopus* is transparent and also suitable for cellular level observations [5]. The molecular studies utilizing the tadpoles were simplified by recent advancements in the genetic techniques and genetic sources that include (EST) Expressed Sequenced Tags, Trans-genesis as well as micro array [6].

Notochord, located at the center of the larval tail is the major structure of the *Xenopus*. Further, it incorporated vacuolated cells that are surrounded by collagenous sheath [7]. A pair of sensory ganglions, as well as a spinal cord, are situated at the dorsal side of the notochord [8]. And the bilateral muscle masses cover the spinal cord as well as the central notochord [9]. The ventral and dorsal fins are situated at the midline of the tail and the arteries and major veins are placed in mesenchymal space [10]. Moreover, tadpoles regenerate the majority of the tail after the amputation during the larval life until the process of metamorphosis. But some tadpole populations may lose the ability of tail regeneration in the refractory period between the 45th and 47th stages. At stages 48 to 50, the regeneration of the reproducible tail was performed within 2 weeks.

The main contribution of the paper is to analyze the regenerative capability of *Xenopus laevis* which is a significant model system for addressing the fundamental regeneration mechanism and the key aspects of regeneration medicine. The paper focused on the prevailing studies on change in the levels of ROS, regeneration signals for successful regeneration. The paper also analyzed the factors responsible for tail regeneration and other such criteria intracellular protein expression criteria. Followed by that the review article presented the existing challenges on the understanding of tail regeneration of *Xenopus laevis*.

The paper is organized as follows. The initial section of the paper deals with the introduction regarding the significance of the tail regeneration capability of *Xenopus laevis*. The following sections deliberated the important process involved in this mechanism. A separate section was framed to provide the prevailing challenges in revealing the concepts of the tail regenerative process. The review is finalized with a comprehensive conclusion in the *Xenopus laevis* research on tail regeneration.

## 2. CLINOTARSUS CURTIPES

In the species *Clinotarsus curtipes*, this study [11] observed that, the development of *Clinotarsus curtipes* was similar to post-embryonic development in the mammals, which displays increased ROS levels. Besides, scavenging of reactive oxygen species with anti-oxidant has depicted an unexpected result of transforming to pro-oxidant as well as new thyroid hormone memetics with significant impact on the neurotransmitter function. Further, the

development of *Clinotarsus curtipes* is valuable in investigating the role of reactive oxygen species in the post-embryonic development.

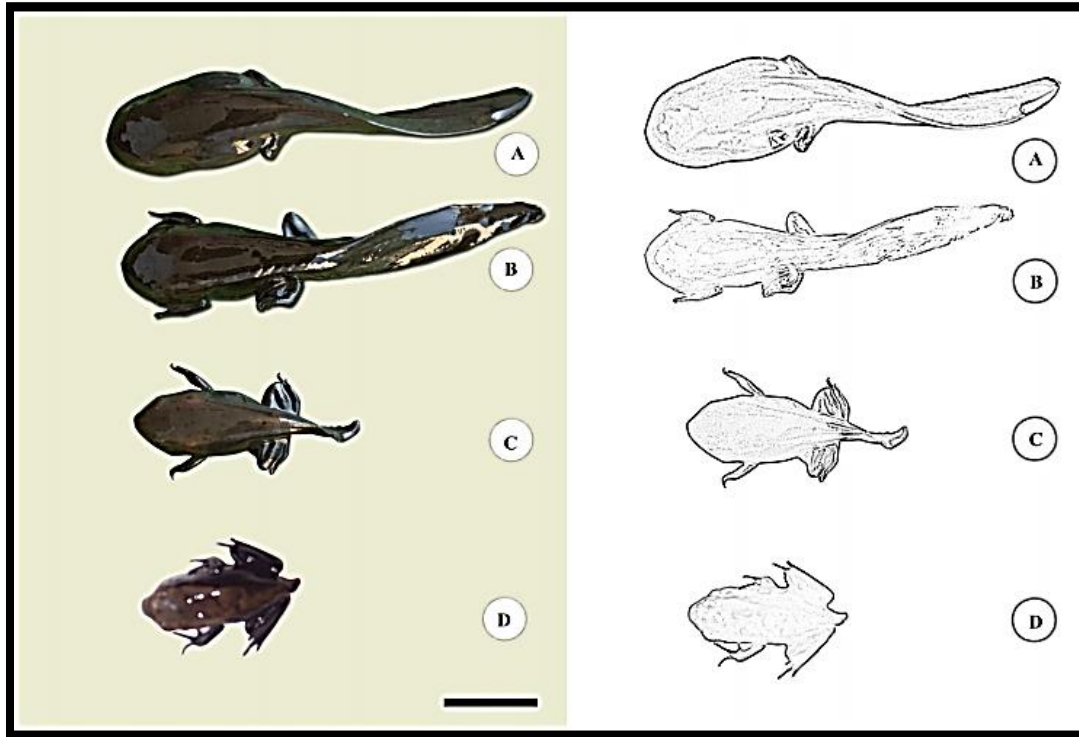


Figure 1. Critical stages in *Clinotarsus curtipes*

The figure 1 depicted the critical stages in *Clinotarsus curtipes* on the basis of morphological index as well as external morphology. From this figure, it has been understood that, the tadpoles developed the hind limbs with toes as well as well differentiated and also fully-functional tail. In this stage, the study observed that, muscle bundles were intact and prominent. Besides, majority of melanocytes were found to be situated in epidermis.

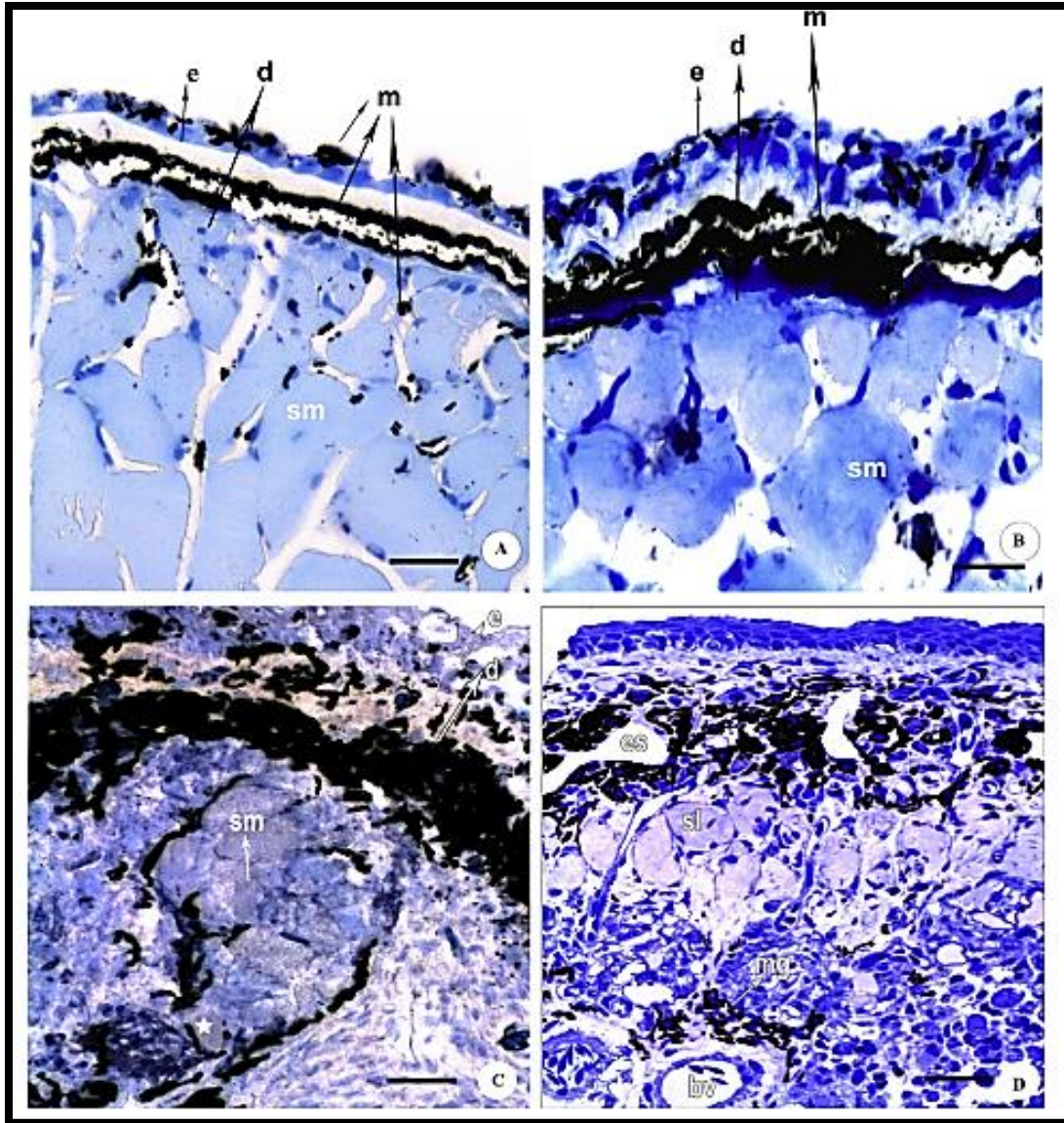


Figure 2. Tail sections of *Clinotarsuscurtipes*

The figure 2 depicted the tail portions of *Clinotarsuscurtipes*, which is embedded in paraffin as well as stained with the Nile blue sulphate. From figure 2, it has been understood that, A and B represented epidermis, melanocytes, skeletal muscles and dermis, whereas, C indicated melanin at deeper location. And finally D represented a semi thin portion of tail, which was showing sarcolytes, empty space, and blood vessel and migrating melanocytes.

### 3. THE *XENOPUS* LARVAL TAIL MODEL

*Xenopus* tadpoles are able to regenerate the tails including all associated tissues like muscles, major blood vessels, and spinal cord as mentioned in Figure 3. But some tadpole populations may lose the ability of tail regeneration in the refractory period between the 45th and 47th stages. Here, as mentioned in Figure 4, there are three phases in regeneration such as, at the first phase, the initial wound closes and the inflammatory response phase occurs at 0 to 1 DPA (days post-amputation), at the second phase, blastema like regenerative bud forms at 1 to 2 DPA, and a third phase, the outgrowth, as well as the regeneration phase, starts at 2 to 3 DPA [6]. Even though the new tail cannot



regain its originality and reveals some variations in muscles, axonal, and vasculature organization. Further, the regenerated tail is completely functional at 7 DPA.

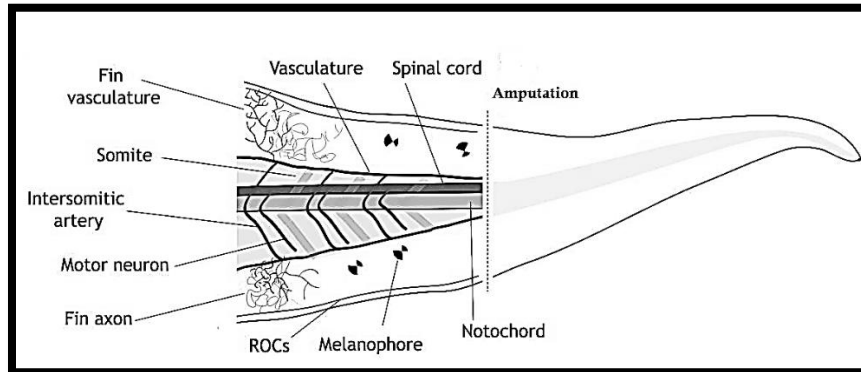


Figure 3. Complete tail of tadpole consisting of somatic muscle, melanophores, vasculature, epidermal cells, notochord, ROCs (re-organization cells). Depiction of tail components that are spinal cord, from where the axons exit through the spinal ganglia for innervating the fin. Moreover, the motor neurons outspread axons over the intersomitic boundaries. The tail regeneration was investigated after amputation that is generally performed at the location from halfway to a two-thirds way of the total length of the tail [12]

The studies of tadpole appendage regeneration were experimental in promoting the understandings of molecular mechanisms that are required for initiating the regenerative program. Further, the earlier assessments of the regeneration drivers are concentrated on the signaling pathways. The studies have confirmed that the developmental pathways like BMP (bone morphogenetic protein), notch, FGF (Fibroblast growth factor), Wnt, SSH (sonic hedgehog), and TGFβ (transforming growth factor β) were re-activated during the regeneration of the tail.

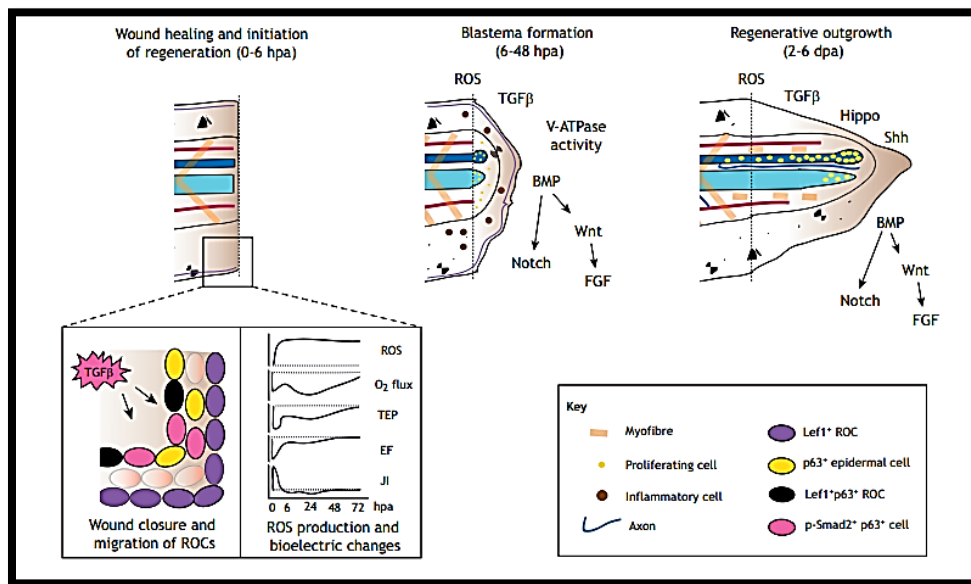


Figure 4. Regeneration stages of tadpole tail are depicted. Here, the injury induces healing of the wound followed by initiation of the regeneration at 0 to 6 HPA (hours post-amputation), that needs bio-electric variations and up-regulation of the signaling molecules, including TFGβ and ROS (transforming growth factor β and reactive oxygen species). The signaling of TGFβ is required for the healing of wounds by the epidermal cells (p63+). Also,

Lef1+ROCs could also express the p63, which contributes to the formation of epithelial cells around the wound for initiation of the regeneration. From 6 to 48 HPA, the formation of blastema occurs that contains the proliferating cells as well as the regenerative structure of the notochord and spinal cord [12].

Then, the regenerative outgrowth begins from 2 days post-amputation that coincides with the innervation of neuronal axons from spinal cord as well as outgrowth of vasculature, notochord and spinal cord. Additionally, the Myofibres are degenerated and they are replaced by strong Myofibres that are originated from the satellite cells (pax7)[13]. The Melanophores are originated during the regeneration from corresponding melanophore precursors. Also, some signalling pathways are implicated in the regeneration are represented along regenerating tail [12].

#### 4. REACTIVE OXYGEN SPECIES (ROS)

The ROS like HO• (Hydroxyl radical), O<sub>2</sub><sup>-</sup> (superoxide anion), as well as H<sub>2</sub>O<sub>2</sub> (Hydrogen peroxide), incorporated non-radical and radical oxygen species that have been formed by partial reduction of the oxygen [14]. Moreover, the cellular reactive oxygen species may arise from the interactions with the exogenous source like xenobiotic compounds. ROS overwhelms the cellular anti-oxidant defense systems through an increase or decrease in anti-oxidant levels, oxidative stress will occur [15].

The data represents that the tadpole tail regeneration requires sustained production of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) or closely-related reactive oxygen species (ROS), particularly during the first seventy-two hours after amputation. Moreover, the reactive oxygen species are more likely to have the pleiotropic effects on the cellular physiology that includes signaling, proliferation, motility as well as metabolism. In the study [16], the author focussed on cell proliferation as well as Wnt-signaling, because of their earlier established role during the regeneration of tail. The Wnt-Signaling pathways are referred to a group of STP (signal transduction pathways) that begins with the proteins which passes signals into cell via the cell surface receptors [7]. The term Wnt is created from the terms Wingless and Int 1. Therefore, this study suggested that the increased production of the ROS acts as an important part in facilitating the Wnt-signaling and allows initiating the regeneration program.

#### 5. HISTOLOGY

The study [17] presented a histological evidence of the regeneration of tail in reptiles that could be used for the investigation of *Xenopus* tail regeneration. Here, the regenerated tail was looked externally different from original tail. In lepidosaurs, the regenerated tail of radially organized around the endoskeleton, whereas the amphibians regenerate the tail with dorsal ventral axis. Moreover, the regenerated tail was lacking in skeletal muscles and was featured with newly established blood vessels as well as axons. Furthermore, the study [18], it has revealed the restorations of mesenchymal cells, muscle bundles, blood vessels, nerve cord and notochord. However, regenerated muscle has failed to organize in regularized patches as the original tail.

#### 6. REGENERATION SIGNALS

Using the traditional advantages of tadpoles, others provide predominant lineage data on origin of cells, makes up the regenerate tissues. The transcriptome analyses of the regenerating tissues pursue to find the cellular process as well as the genes that enable successful regeneration.

##### *Transform Growth Factor-β (TGFβ) signalling*

Generally, wound healing is the primary step in the process of regeneration, and for a successful regeneration, formation of epithelial cells is predominant process. In recent years, it has been stated that TGFβ signalling (Transform growth factor β) plays a vital role in the process of wound healing.

### ***Fibroblast Growth Factor (FGF) signalling***

The significance for the Fibroblast growth factor signalling (FGF) has been functionally described for the regeneration of limb. From the demonstration, a correlation between the FGF 10 expression in mesenchyme cells followed by the observation of regeneration capability.

### ***Bone Morphogenetic Proteins (BMP) signalling***

It has been depicted, blocking the Bone morphogenetic protein pathways by overexpressing dominant the-ve BMP receptor or Noggin that leads to the inhibition of the tadpole tail as well as the hindlimb regeneration. In recent years, it has been depicted that Smad1 has been specifically activated in bud regeneration.

### ***Wnt Signalling***

Recently, various studies have shown a role for Wnt signalling pathway at the time of regeneration. Further, the Wnt signalling can also be blocked by the over-expression of Dkk-1 (Dickkopf-1) by utilizing HS-Dkk-1 (heat-inducible transgene). Over-expressing the heat-inducible transgene at the start of regeneration is adequate for inhibiting the regeneration of limb and tail in *Xenopus*.

### ***Notch signalling pathway***

Earlier, it has been depicted that the bone morphogenetic proteins activated the Notch during the development of tail. The notch signalling has found to be significant in notochord and spinal cord generation, whereas the formation of muscles has been directly simulated by Bone morphogenetic proteins. Therefore, this suggested a conservation of molecular relation between the 2 pathways in the development of embryos and regeneration.

### ***Retinoic acid signalling***

After the treatment of hindlimb with the retinoic palmitate at the time of regeneration, histological analysis was seen in the augmentation of earlier regenerative events, that were interpreted as an extensive stump tissue de-differentiation. Further, it has been discovered that the retinoids can proximalize the regenerative limbs that leads in the duplicating the limb elements.

## **7. FACTORS AFFECTING TAIL REGENERATION**

### ***Extracellular O<sub>2</sub> influx correlates with the regulation efficiency***

*Xenopus laevis* has a fascinating age dependent refractory-period that permits for investigating the simulating as well as the limited factors without changing the regeneration model. Considering this advantage, the study [19] investigated the oxygen flux magnitude difference within refractory period (6 & 24 HPA). Primarily, the study verified that the amputation in refractory period weakens the regeneration. Finally, the study integrated the HIF-1 $\alpha$  cues, ROS and O<sub>2</sub> roles during regeneration, thereby enabling in-depth redox activity analyses during demanding process [19]. Thus, the redox-state functions acts as predominant targets for the translational medicines.

- ***Role of epigenetics***

For better understanding about the epigenetic modulations during the regeneration of *Xenopus* tail, the study [20] examined about the requirements of HDAC activities during the 1st and 2nd waves of the myeloid differentiation and the contribution towards the ability of regeneration. The tadpoles form diverse development stages covering the 1st and 2nd wave has been incubated. Here, during the incubation of first (1, 3,6,12 Hours post-amputation), was adequate to weaken the ability of regeneration, whereas incubation after the first (1,3,6,12 HPA), the ability of regeneration has been rescued. Thus, the study has concluded that the epigenetic mechanisms could control the

behaviours of myeloid cells on tissue injuries and the HDAC inhibitors can be utilized for the regeneration of tissues in translational studies[21].

- **HDAC activity**

The study [20] provided information about epigenetic control of the immune mechanisms that were involved during the regeneration of tadpole tail. Further, the study depicted that, the 1<sup>st</sup> 24 HPA incorporated the 1<sup>st</sup> wave of the myeloid differentiation, which were critical for epigenetically modulating the ability of *Xenopus* tail regeneration. Moreover, during developmental window, the activities of HDAC has found to be significant for establishing myeloid cell movements in bud regeneration, that contributed mainly for modulating the behaviours of monocytes, neutrophils as well as the myeloid markers like mmp7, Spib, MPOX and LURP. This study also concentrated on the spatial and temporal profiling of the lipid mediated pathways during regeneration of tail. From this, the outcomes supported a role for epigenetic control of the inflammatory responses during the organ and tissue regeneration that positively impacts the translational methods for regenerative medicines.

## **8. ROLE OF MYELOID LINEAGE IN TAIL REGENERATION**

The positive impact of Myeloid Lineage (ML) is in the regeneration as well the tissue repair. Particularly, the study [22] suggested that ML induced activation and rapid solution for the inflammatory process had a greater influence in the regeneration outcomes. This study primarily determined the predominant role of myeloid lineage for the tail-regeneration in regeneration incompetent tadpoles. The study [23] revealed that during the tail amputation, ML dependent apoptosis occurs that enhances the tissue remodelling causing relocalization of cells for the regenerating cell proliferation. Here, these cellular mechanisms have failed to be executed in the regeneration incompetent tadpoles. Also, the study demonstrated that the factor regeneration-incompetency has been characterized by the inflammatory myeloid-cells, whereas the regeneration competency was related with reparative myeloid-cells. Further, the immune suppressing drugs are employed for the restoration of ML-regulated cellular process for treating regeneration incompetent tadpoles. Collectively, this study reveals the impacts of differential activation of ML on creating regeneration permissive environment that could be utilized in framing strategies for the regenerative medicines. The increased activation of ML has less impact on the potential of regeneration when compared with the impacts of clodronate mediated ML cell depletion. The outcomes of the study suggested that the already reported metabolic gene like slc2A3 and pkm, etc. were enriched in reparative ML[23]. Overall, the study used early stage *Xenopus* tadpole having constrained immune cells for observing the necessary functions of ML lineage and inflammation in the origin of favourable environment of regeneration.

## **9. ROLE OF TRKA SIGNALING IN TAIL REGENERATION**

The Neurotrophic signalling controls the behaviour of nerve cells in physiological development, even though its role in the process of regeneration hasn't been thoroughly investigated. The Tropomyosin receptor kinase-A is referred to high-affinity factor for the nerve growth. The study [24] analysed the role of neurotrophic signalling in the *Xenopus* tail regeneration. After amputation and at the time of regeneration, the neurotrophin ligand genes (bDNF and ngf) has been expressed followed by up-regulation. Furthermore, the NGF receptor gene (Trk A) was expressed for the regeneration bud formation. This regeneration bud is a predominant structure emerging from tail stump after the amputation[24]. Here, the length of regenerated tail has been significantly reduced by pan-Trk kinase inhibitor K252a, suggested that the signalling of Trk-A has been involved in the elongation of regeneration tail. During the embryonic development of *Xenopus laevis*, expression of Trk-A has been identified in dorsal mesoderm as well as in notochord at gastrula stage and neurula stage. Moreover, gastrulation causes knockdown followed by axis length shortening. Therefore, these outcomes suggested that the Trk-A signalling in the tadpole tail regeneration performs a predominant role in elongation of tail during *Xenopus* regeneration and the elongation of body axis during embryogenesis.



## 10. PROTEIN EXPRESSION

The molecular-mechanisms that govern the regeneration of vertebrate appendage are poorly understood. Further, revealing these mechanisms will lead to some novel therapies that are aimed at[12]. This study has explored the regeneration of tadpole tail.

- *Expression profiling and intracellular metabolic processes analysis*

The main aim of the study[25] was to calculate the variations in gene expression during the regeneration of tadpole tail. Particularly, the study required to develop a gene-expression dataset to act as a resource in finding genes as well as the processes that are involved in the tail regeneration.

Further, *Xenopus tropicalis* is said to be a potent model for revealing the genetic mechanisms of the regeneration of vertebrate appendages. Also, the study has suggested a novel and significant microarray-dataset for analysing the gene expression during the regeneration of vertebrate appendages.

## 11. CHALLENGES

The existing challenges mainly deals with the regulation of ROS levels as well as the identification of downstream targets of the ROS production, promotes proliferation of cells, metabolic re-programming growth factor signalling.

The ability for studying the non-regenerative and regenerative phases within similar species makes the tadpole as beneficial model for tackling the reasons for regenerative process modification in accordance with age. Even though the presence of refractory period is not documented, the *Xenopus* tadpoles confirmed the absence of certain pro-regenerative microorganisms while refractory period.

At cellular levels, the regeneration organizing cells failed to move to the site of amputation [26]. Several studies of refractory period implicated the significance of the inflammatory process while the process of tail regeneration[27][28]. Also, in the regeneration competent tadpoles, the inflammatory cells have been recruited to the site of wound over the first 6 HPA, whereas the studies of tadpoles that demonstrated an importance of the inflammation associated genes while the earlier regeneration phase[23]. As the immunosuppression improves regeneration in these animals, the inappropriate activations of immune system might spoil the tail regeneration. Presence of bacteria as well the downstream NF-KB pathway activation are suggested by the study[15] for promoting regeneration in refractory period.

## 12. CONCLUSION

Generally, *Clinotarsus curtipes* and *Xenopus laevis* (tadpoles) have higher regenerative potential. This study on the tail regeneration of *Clinotarsus curtipes* and *Xenopus* has given us a comprehensive understanding of molecular as well as morphological processes. Further, *Clinotarsus curtipes* and *Xenopus laevis* tadpole is a potent model system, the fundamental regeneration mechanisms has been addressed. In recent years, these processes have revealed the interesting molecular details regarding the repair of complex appendage injury. Moreover, the study of tadpole tail regeneration has also been facilitated by developing chemical as well as molecular-biology technology that could be utilized in manipulating the molecular pathways. From the extensive study outcomes, it has been suggested that the endogenous bio-electric event were also incorporated in control of regeneration. The recent data analysis has begun to show the molecular details of ions that regulates the earlier phases of regeneration of tail. Thus, the rapid accumulated knowledge about molecular pathways in regeneration of *Clinotarsus curtipes* and *Xenopus* tail gives a complete understanding of the vertebrate appendages regeneration that can be leveraged in the therapeutic development for augmentation of human regenerative repairs.

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