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REVIEWARTICLE

FUNCTION OF MATRIX METALLOPROTEINASES (MMPs) IN TISSUE REGENERATION: A COMPREHENSIVE REVIEW IN AQUATIC ORGANISMS

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ABSTRACT

The process of regenerating organs that have been lost or damaged is fascinating hence it involves several cellular activities that come together to build a new structure. All creatures can regenerate to some extent; however, some have the astonishing ability of regeneration, while others have a limited capability and lose it with maturity. Having regenerative powers in adults is an argument in support of the hypothesis that development continues throughout an animal's life span. There are numerous physiological and pathological processes in which matrix metalloproteases (MMPs) play a fundamental regulatory part in synthesizing, remodeling, and destroying extracellular matrix (ECM) components. Catalytic and hemopexin domains are found at the C-terminal end of these proteins, as well as signaling peptides and propertied, which all include zinc ion binding sites. Numerous cell types may secrete or localize MMPs to their membranes in order to generate them. Enzymes such as MMPs are critical for reshaping the extracellular matrix by destroying specific components and encouraging the growth and differentiation of cells along the progression of apoptosis and angiogenesis. While in healthy mature tissue, they are unnoticeable until there is an abnormality, such as an accident, illness, or pregnancy. The present study aims to comprehend the function of matrix metalloproteinases (MMPs) in the regeneration of body organs and tissues in aquatic organisms, emphasizing the regulatory function of MMPs in the synthesis, remodeling, and degradation of extracellular matrix (ECM) components that are essential for cellular processes like growth, differentiation, and apoptosis. The review highlights recent discoveries that shed light on the ways in which MMPs aid in the regeneration of aquatic organisms after injuries or abnormalities.

Keywords: Matrix metalloproteases, Regeneration, wound healing, Blastema formation, Aquatic animal models

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INTRODUCTION

Biologists have long examined the phenomena of regeneration, which is the restoration of missing body components in animals and plants (Zeng *et al*., 2018). Planarians (flatworms), which can regenerate their complete body from minute tissue fragments, and the Hydra, which can restore their entire head after amputation of a tentacle are two examples of organisms with exceptional regeneration abilities (Fuchs, 2015). More known creatures, such as salamanders and insects also been shown to have extraordinary limb-regeneration capabilities (Levin, 2021). Most animals have restricted their regeneration but the basic ability to regenerate of gut or skin's epithelial lining, the capability to restore muscle fibers following damage, and the ability to continually replenish blood cells have remained (Elchaninov *et al*., 2021).

Matrix metalloproteinases, often known as MMPs, are found to be involved in regeneration and wound healing processes (Dolmatov, 2021). MMPs are the enzymes that belong to the Meta zinc superfamily. This family also contains several additional endopeptidases, such as serralysins, asatacins, adamalysins, leishmanolysins, snapalysins, and pappalysins (Beroun *et al*., 2019; Muri *et al*.,2019). The purpose of this review is to examine the function that MMPs play in regeneration. Therefore, different research works are reviewed from the last 15 years and data is gathered to highlight the aspects of MMPs role in regeneration processes in different marine animal models.

Both in human wound healing and newt limb regeneration, MMPs direct the remodeling of wounded tissue. Inflammation is the earliest sign of wound healing in mammals after injury to the incisor-dental epithelial layer (Patruno *et al*., 2018). The production of cytokines

and growth factors by platelets, macrophages, and neutrophils as well as epithelial and stromal cells is high during this period (Huet *et al*., 2019). The mobility of leukocytes and the destruction of collagen in wounded tissue are stimulated by the production of MMPs by a variety of cell types, including macrophages, epithelial cells, stromal and inflammatory cells. More MMPs have a role in re-epithelializing wounds after inflammation in the first few days (Singh *et al*., 2019). They promote cell migration to the site of damage by degrading the extracellular matrix (ECM) components around the injured area. Angiogenesis is the process by which MMPs repair the injured tissue barrier in order to prevent fluid loss or bacterial infection in the future (Huet *et al*., 2019; Peng *et al*., 2021). Collagen synthesis is also seen in the later phases of wound healing. The overproduction of transforming growth factor β (TGF-β) leads to excessive collagen synthesis, which impedes muscle regeneration in the most severe cases (Patruno *et al*., 2018).

Wound healing in amphibians is different from that of mammals, however, MMPs are also present to carry out their specialized functions. Following the amputation of a newt's leg, there is an immediate increase in the activity of MMPs in order to expeditiously construct an apical epithelial cap (AEC) to cover the stump, therefore it reduces the risk of further tissue damage, contamination, or inflammatory response (Guirado and George, 2021; Taghiyar *et al*., 2018). Following AEC creation, the amputation site's peripheral cells undergo dedifferentiation and are subsequently transformed into a multipotent state (Dwaraka *et al*.,2019). A blastema, also called a regeneration bud, is formed as a consequence of migrating fibroblasts. In newts, many MMPs have been linked to the production of blastema and limb regeneration (Suzuki *et al*., 2019).

Regeneration Mechanism: In 1901, Morgan postulated two primary forms of regeneration, depending on whether or not active, cell propagation is necessary, and this classification is still extensively employed by current biologists (Sasidharan and Sanchez Alvarado, 2021). Morphallaxis is a kind of regeneration that does not involve the division of cells to restore a lost body part; the restoration is exclusively based on the modification of pre-existing cells and tissues (Duncan *et al*., 2020).

Epimorphosis is a term used to describe a form of regeneration that necessitates an increase in the number of cells. Epimorphic regeneration could be further classified into two major groups depending on whether a regenerative blastema is present (Seifert and Muneoka, 2018). In the case of amputation or damage, the blastema (a specialized structure with two cell partitions: epithelium on the outside and mesenchyme-like cells on the inside) is formed. Differentiation of the blastema cells will lead to regeneration. Blastemal regeneration may be seen in flatworms, regenerating their whole bodies, and vertebrates regenerating their limbs or tails (Storer *et al*., 2020). There are many diverse methods to create and organize blastema, however, the blastema itself has remarkably similar structures in numerous species (Darnet *et al*., 2019). It has been shown that under certain circumstances in planarian regeneration, stem cells known as neoblasts migrate toward the wound, and proliferate then differentiate into daughter cells, resulting in blastema development as shown in Figure 1 (Sasidharan and Sanchez Alvarado, 2021).After amputation, regeneration of a vertebrate's leg normally starts with the dedifferentiation of differentiated cells in the residual tissues, followed by their proliferation and re-differentiation into the original or other cell types (a process known as 'Transdifferentiation', which happens when a cell type other than the original is developed). Different approaches can be used to induce non-blastemal epimorphic regeneration as well. Parts of residual tissue can be transdifferentiated to fill up the gaps in the missing structure (Ben Khadra *et al*., 2018; Fornshell, 2019).

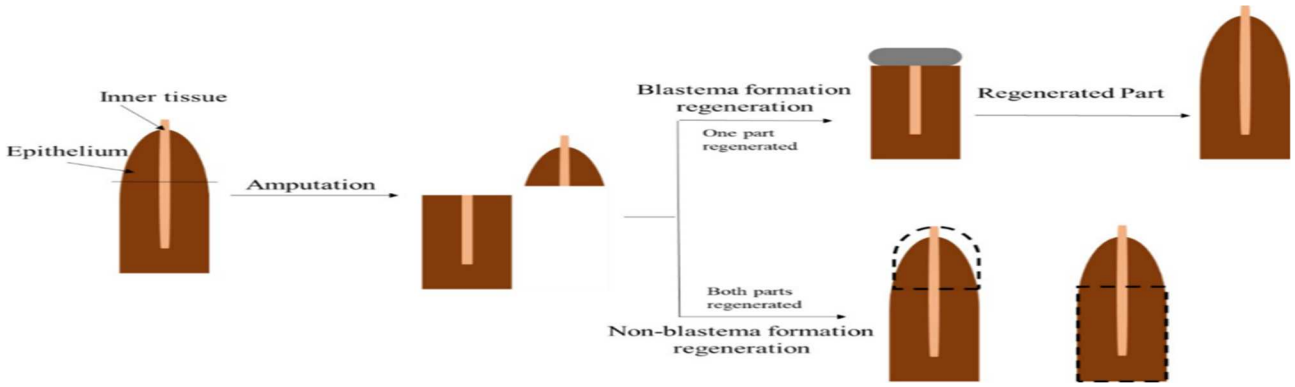


Figure 1:- Modes of regeneration. In vertebrates, regenerations occur through the blastemal formation and only one part is regenerated while the other part is discarded. In another mode of regeneration, invertebrates like a hydra, and planaria regenerate without blastema formation and both parts regenerates.

Role of MMPS In Regeneration: Some of the components of the ECM may be degraded by the MMPs, during both physiological and pathological activities (Geranmayeh *et al*.,2019; Haubruck *et al*., 2018). Several proteinases may extracellularly trigger MMPs, which are typically released as zymogens. In vitro, experiments have demonstrated that plasmin may directly activate proMMP-1, proMMP-3, proMMP-9, and proMMP-10, as well as proMMP-13 (Gifford and Itoh, 2019; Taskina and Kharintseva, 2019). When plasmin is stimulated, MT1-MMP hydrolyzes proMMP-2, which activates it. The positive feedback mechanisms in many tissues include several additional active MMPs that further activate the proMMPs (Gifford and Itoh, 2019).

The breakdown of extracellular matrix (ECM) components by matrix metalloproteinases (MMPs) is essential for tissue remodeling. Targeting different ECM proteins including collagen, elastin, and proteoglycans, MMPs enable regulated tissue reorganization throughout immunological response, development, and wound healing. For aquatic creatures to maintain tissue homeostasis and react to external stresses like infections or injuries, MMPs' control of ECM turnover is essential in (Figure2).

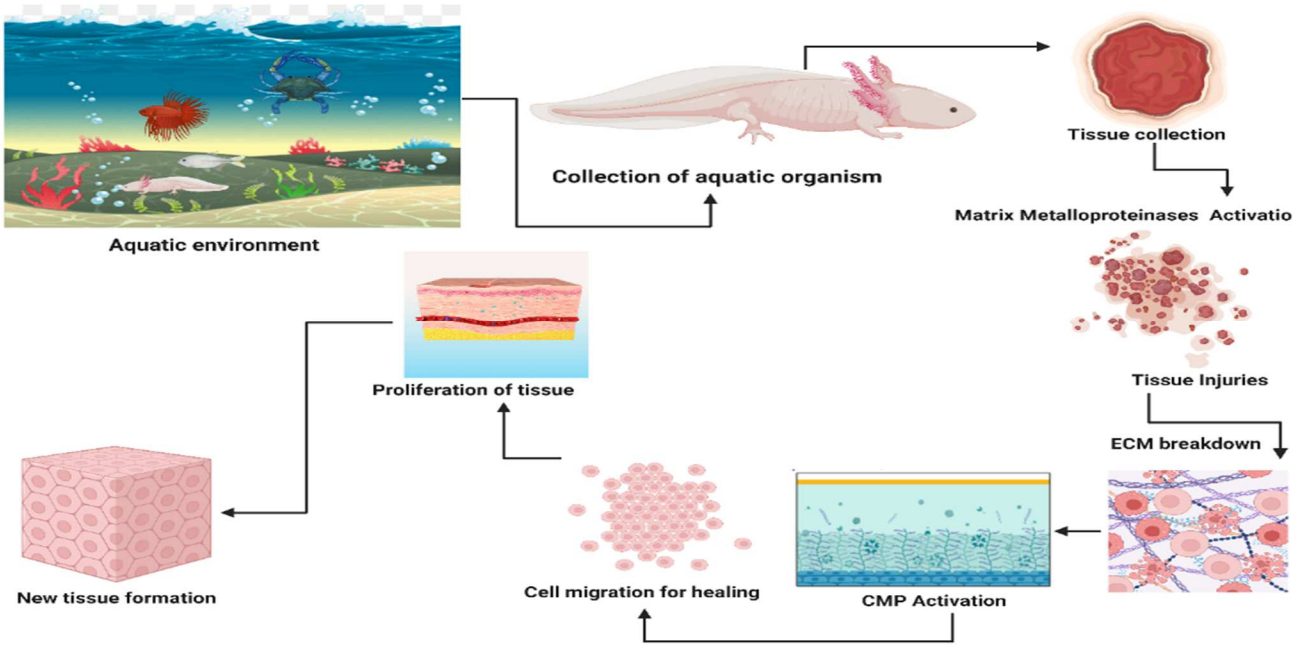


Figure2:- MMPs aid tissue repair and immunity. Matrix Metalloproteinases (MMPs) mediate extracellular matrix (ECM) remodeling by degrading ECM components, facilitating tissue restructuring, cell migration, and immune response regulation.

There are certain tissue inhibitors of metalloproteases (TIMPs) that control MMP activity in the human body. TIMP-1 is one of four members of the TIMP family presently known to exist (which is produced by connective tissue cells and macrophages). Additionally, TIMP-1 can resist all kinds of collagenase, stromelysin, and gelatinase (Behm *et al*., 2021). MMPs alone or in conjunction with the plasminogen/plasmin system may degrade extracellular matrix components. Having this degrading ability is essential for cell migration and tissue remodeling, which are engaged in a wide range of physiological and pathological functions as mentioned in Figure 3 (Behm *et al*., 2021; Guirado and George, 2021).

These processes are comparable because both need progressive parameters, such as proliferation, migration, and differentiation of skeletal muscle precursors. To understand how metalloproteases interact with muscle, it is important to understand how skeletal muscle satellite cells fuse to generate myofibers that are terminally differentiated, contractile, and highly patterned. MMPs have long been thought to play a role in myogenesis, and several of the specific proteases involved have been discovered (Kok and Barton, 2021). MMPs are a broad family of multifunctional zinc ion-dependent endopeptidases that have been preserved throughout evolution. They are essential for the hydrolysis of cell-surface and extracellular matrix components. The breakdown of fibrillary collagen in tadpole tails during metamorphosis was facilitated by the first member of the MMP family, which was identified in 1962. Since then, MMPs have been found in a variety of organisms, including humans and bacteria, but the quantity of MMP genes varies by species (Wu *et al*., 2024).

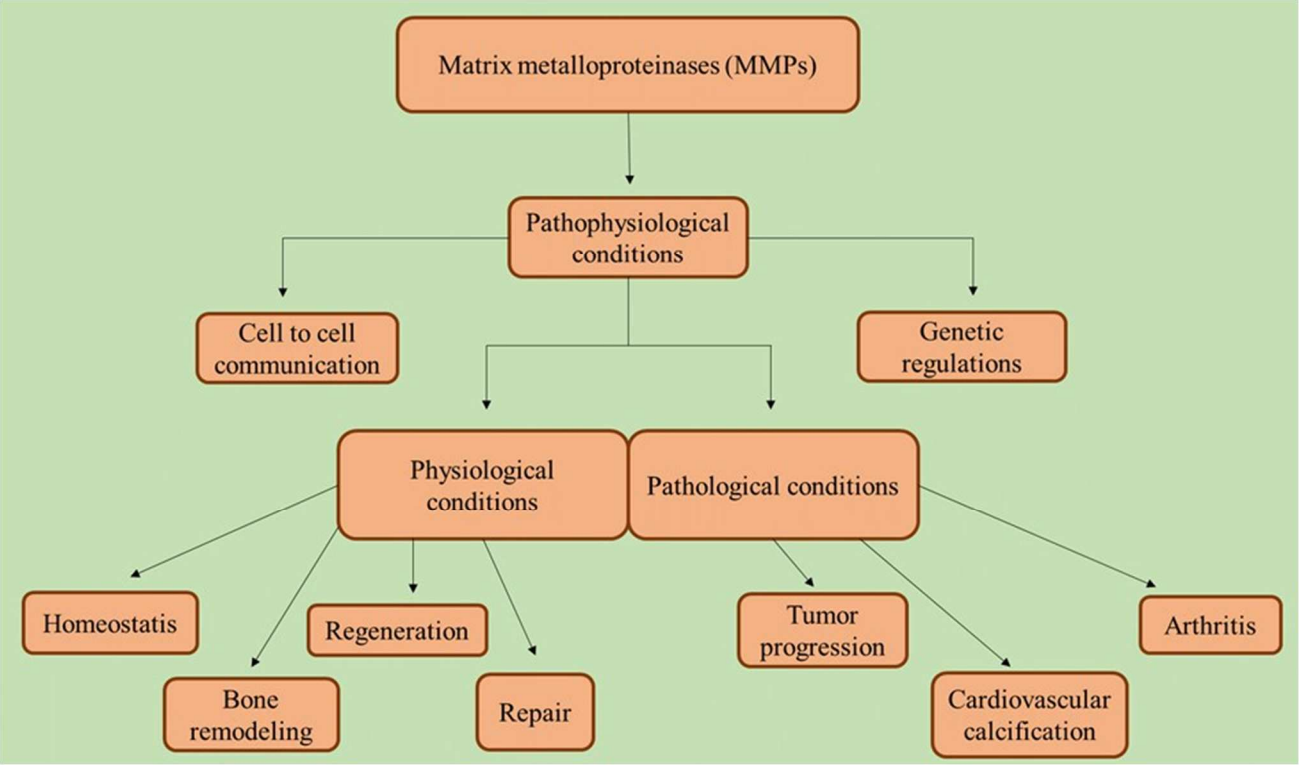


Figure3:- Role of MMPs in pathophysiological conditions. During physiological conditions, MMPs maintain the homeostatic conditions of cells and help in regeneration, repair, and bone remodeling mechanisms. While in pathological conditions MMPs are found to be involved in tumor progression, cardiovascular calcification, and Arthritis (Osteoarthritis and Rheumatoid Arthritis).

The matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) found in echinoderms, one of the oldest families of invertebrates, are very diverse. The lytic activity of echinoderm MMPs against collagen type I and gelatin suggests that these proteins play essential roles in asexual reproduction, regeneration, and development. Additionally, echinoderms have a large number of genes that encode TIMPs and TIMP-like proteins, which have distinctive structural characteristics such as conservatively positioned cysteine residues and NTR domains. Their growing functional importance in echinoderm physiology is probably reflected in the TIMP genes' frequent duplication and divergence (Dolmatov *et al*., 2021).

According to a recent discovery on photo-damage, prolonged exposure to sunlight causes an increase in matrix metalloproteinases (MMPs), which degrade collagen and cause skin aging and damage. One important target for halting skin aging is MMPs. In addition to highlighting current studies on MMP inhibitors that successfully block MMPs and aid in shielding the skin from UV damage, it describes how MMP inhibitors lessen the effects of photo-aging (Li *et al*., 2024). Matrix metalloproteases (MMPs) are enzymes that break down the extracellular matrix and are essential for many physiological and pathological functions. Each member of the 23-protein MMP family has a distinct substrate selectivity and function in both healthy and pathological processes (Fingleton, 2007). These 23 enzymes have been categorized into six groups based on their main structures, cellular location, and substrate selectivity (Cui, *et al*., 2017).

Role of MMPs in regeneration across different aquatic invertebrates

Planaria: Planarian flatworms are well-known for their remarkable potential for regeneration (Duncan *et al*., 2020). Chopping one worm into little bits will result in a dish full of newly-regenerated tiny worms within days, much as in Sorcerer's Apprentice (Mouton, Wudarski, Grudniewska, and Berezikov, 2018). A new experimental model for studying how and why tissues regenerate has been found as an experimental model in recent years with the aim that this will assist us in improving the healing of tissue in our bodies (Rink, 2013).

One of Planarians' greatest assets is its population of pluripotent stem cells, which has the capability of both internal and external responses (such as food availability) in order to control its growth, development, and response to injury (Baranov *et al.*, 2020; Reddien, 2022). Planarians also "regrow," decreasing proportionately over time when they are

starved, but animals regain their original size when food is resumed (Ivankovic *et al*., 2019). Additionally, neoblasts play a critical part in the planarian's ability to regenerate (Yang *et al*., 2022). There are two key periods of proliferation for neoblasts following injury: 6 hours and 48 hours (Tewari*et al*., 2018). A considerable increase in cell proliferation occurs throughout the body 6 hours after the first mitotic peak is reached by any kind of tissue damage. In response to amputation, the 48-hour peak in mitosis is more localized than the first peak (Dingwall and King, 2016). Two unique stem cell response programs are shown by these two peaks, each arising in response to a different kind of tissue perturbation. From the perspective of homeostasis and regeneration, MMPs were shown to be involved in pathways that regulate stem cell proliferation (Cote *et al*., 2019).

Planarians are an appropriate model for studying how the extracellular environment impacts cell activity in vivo because of their readily accessible stem cell population and remarkable regeneration potential (Isolani *et al.*, 2013). The role of planarian MMP genes in tissue homeostasis and regeneration is studied using RNA interference (RNAi). Planarians that have had their mmp1 inhibited show substantial changes in tissue architecture and a reduction in cell death. According to these findings, mmp1 regulates tissue turnover by influencing postmitotic cell survival. Mmp1 has no effect on the body's capacity to rejuvenate, which is surprising. Inhibition of MT-MMPA changes tissue integrity and slows blastema formation but does not influence stem cell proliferation. The findings of the researchers also revealed that the activity of this protease impacts cell migration and anoikis, which are both essential for the maintenance of tissue homeostasis and the regeneration of tissue. Planarian stem cells' function is highly reliant on the milieu in which they are located. This study provides evidence that certain MMPs are involved in maintaining tissue homeostasis and regeneration. The planarian model gives insight into how specific proteases act in adult tissues by studying MMPs.

***Hydra*:** The tiniest freshwater body in terms of understanding regeneration, Hydra is one of the greatest models available. Hydra has the ability to regenerate its entire body from any fragment that has more than a few hundred cells, even just 1/50th of the size of the Hydra, they can regenerate into new (Page-McCaw, 2008). They have a morphallactic regeneration process in which cells and structures are reconfigured to take on new identities even in the absence of cell proliferation (Wang *et al*., 2022). When it comes to healing in Hydra, tissue remodeling has never been more apparent (Farooq *et al*.,2021). MMP is required in the regeneration process in Hydra, and inactivation of MMP via antisense technology or MMP inhibition shows that they cannot induce regeneration of their head or foot after surgical amputation (Suzuki *et al*., 2019).

Extracellular Matrix may be cleaved by recombinant MMP in hydra vitro, which is lost and subsequently reconstituted during normal regeneration (Fanjul-Fernández *et al*.,2010). In regeneration sites, MMP seems to have a direct role in the remodelling of the ECM. These findings show that both newt limb regeneration and regeneration of vertebrate MMPs may have similar activities (Yang *et al*., 1999). MMP's expression pattern shows that it serves an extra purpose. MMP expression is increased at amputation sites, as would be predicted given its role in regeneration. However, it is also found in large concentrations in the complete animal's tentacles and feet, namely in the endoderm (Vogg *et al*., 2019).

Vertebrate and MMPs Role In Regeneration

Axolotl: Axolotl belongs to the family Ambystomatidae (Vieira *et al*., 2020) and is one of 30 salamanders species in the Ambystoma genus (Mescher and Neff, 2006). They are closely related to the tiger salamander and are known for their neotenic characteristics, axolotls reach sexual maturity without undergoing complete metamorphosis, retaining aquatic gill structures throughout their lives (retained as aquatic larval). This neoteny allows researchers to study the regenerative processes in axolotls without the complications associated with metamorphosis (Vieira *et al*., 2020). The axolotl is a commonly utilized organism for studying epimorphic regeneration, an intricate process that initiates by developing a specific structure called blastemal (Londono *et al*., 2018). They exhibit an extraordinary capacity to regenerate a wide range of tissues, including the heart, brain, gills, jaw, tail, and limbs. Among these, the limbs have been extensively utilized for studying regeneration for many centuries (Farkas and Monaghan, 2015; Nowoshilow *et al*., 2018). This unique regenerative capacity has made axolotls a valuable model organism for investigating the underlying mechanisms of tissue regeneration.

As mentioned above, the regeneration of axolotl limbs has been the most studied and well-defined regeneration process to date and, can regenerate whole limbs regardless of where the injury occurs along the limb axis (Vieira *et al*., 2020). Healing begins with injury, but not all injuries will result in the production of new tissue, such as an injury to the side of one's body, such as an amputation (Vieira *et al*., 2019). An epithelium migrates across the wound site within a few hours, but the duration varies according to the animal's age (Kumar and Brockes, 2012) and initiates the formation of an epithelial cap (AEC) by nerve fibers that penetrate the wound epithelium and create specific communication pathways between the nerve and the wound epithelium in the days after the wound has healed (McCusker *et al*., 2015).

Salamanders: All salamanders are capable of regenerating complex structures, including limbs, tails, ocular tissues, and significant portions of the central and peripheral nervous system and heart (Joven and Simon, 2018; Tanaka, 2016). Several salamander species, including the axolotl and three distinct newt species, are often used in regeneration investigations (*Notophthalmus viridescens*, Eastern red-spotted newt; *Cynops phyrrogaster*, Japanese fire-belly newt; and *Pleurodeles waltl*, *Iberian ribbed* newt). Within these animals, although the natural regeneration abilities are similar, but not identical (Joven *et al*., 2019). For instance, newts regenerate a greater number of body components than axolotls do. Newts' ability to regenerate their eye lenses over the course of their entire lives serves as an example of this. First two weeks after hatching, axolotls' lenses regenerate but are lost subsequently (Sousounis *et al*.,2014). Although lens regeneration declines with age and the number of lens removal/regeneration cycles in Cynops, this is not the case in other species (Eguchi *et al*., 2011). Injury-induced reversal of terminal differentiation in newt regeneration is another distinctive feature. In newts, iris-pigmented epithelial cells dedifferentiate and proliferate, and a fraction of these cells are subsequently transdifferentiated into a new lens (Eguchi *et al*., 2011; Sousounis *et al*., 2014).

Zebra fish: They are common throughout the river basins in East India since1970s. Streisinger and his colleagues employed them for the first time as an experimental model system to study vertebrate development using genetic analysis (Gemberling *et al*., 2013). Zebrafish have been a significant tool for studying embryogenesis throughout the years. Small genome, quick outward development, and amenability to mutagenesis are some of the benefits of zebrafish for this application. The generation period is also comparatively low. Scientists have identified important factors in a broad variety of developmental processes, from early germ layer patterns to how tissues formed from these layers develop form and functions (Pierpont *et al*., 2018; Tokarz *et al.*, 2013). In recent years, zebrafish have been increasingly used to study a wide range of biological topics, including behavior, stem cells, and illness (Hoshijima *et al*.,2016; Wolman and Granato, 2012).

All tissues have an extracellular matrix (ECM) that is responsible for wound healing. Macrophages, which may be found in the wound, release growth factors and cytokines, which stimulate ECM synthesis, results in the formation of a a patch like growth that covers the wound (Amit *et al*., 2016). Fibronectin and collagen are two of the most important components of the ECM, and their deposition leads to scar tissue following amputation in animals (Sanchez-Iranzo *et al*., 2018). Matrix metalloproteinases (MMPs) are proteolytic enzymes that modify matrix proteins to protect healing organs and move cells to replace damaged tissue. When a wound is healed in zebrafish after bleeding, the amputation of the caudal fin, the quantity of fibrin and fibronectin reduces, which prevents scarring. This occurs because MMPs are involved in the healing process (Lebedeva *et al*.,2020).

To determine the involvement of MMP-2 and MMP-9 in these processes Plucking adult male zebrafish of their scales resulted in the discovery of several newly-formed scales that had regenerated in their corresponding scale pocket. A gelatinolytic activity test, a hydroxyproline assay, and an mmp-9 in situ hybridization were some of the methods used to conduct the research (Vrieze *et al*., 2011).

Tilapia: Thus, Tilapia zillii (Gervais, 1848) and red belly are known as cichlid which belongs subfamily (Pseudocrenilabrinae) however it is native to Africa but now a day it has been distributed widely in Europe and America including Asia and Australia however it can be found more than fifty-six countries likewise food fish or as forage and also for the commercial aquarium trade. These fish exceed 139.3 in total length and the maximum body depth would be 35.91 (Khaefi *et al.*,2014).Tilapia fish have the quality to tolerate fluctuations in temperature along the rapid growth, omnivores and high fecundity however adaptively ever such variable environmental conditions (Martin *et al*., 2010).

Tilapia has great regenerative potential, particularly for tissue regeneration and wound healing. According to studies, tilapia skin collagen promotes fibroblast proliferation, decreases inflammation, and aids in tissue regeneration including blood vessels, sebaceous glands, and hair follicles, thereby accelerating wound healing (Harun *et al*., 2023). Based on previous studies, tilapia is a great model for researching osteogenesis due to their ability to repair bone tissue, specifically in their opercula (gill coverings). Understanding how growth factors and signaling channels interact in this regeneration process is essential to comprehending vertebrate bone healing processes (Buglass *et al*., 2020). Additionally, research indicates that tilapia may recover their liver following a partial hepatectomy. This regeneration is a useful model for researching liver repair processes in vertebrates since it is characterized by a sharp rise in hepatocyte proliferation and the activation of growth factors like hepatocyte growth factor (HGF) (McGruer *et al*., 2019). The caudal Fins of tilapia can regenerate after being amputated. In this process, mesenchymal and epithelial cells proliferate and MMPs are activated, which remodels the ECM during regeneration (Schmidt, 2013).

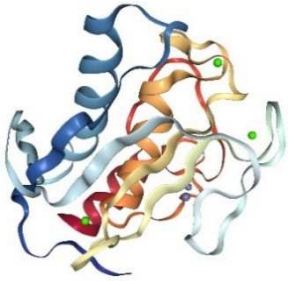
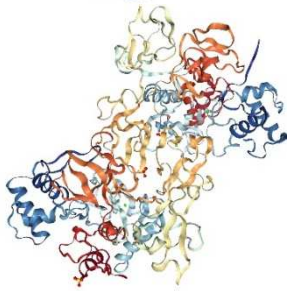
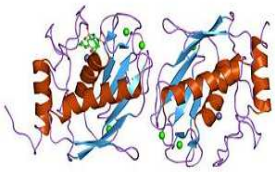
Sailfin molly: Several animal species have an inherent ability to regrow lost body parts through post-embryonic development. Epimorphic regeneration's once-in-a-lifetime ability to regenerate an organ declines with increasing evolutionary distance (Patel *et al*.,2019).

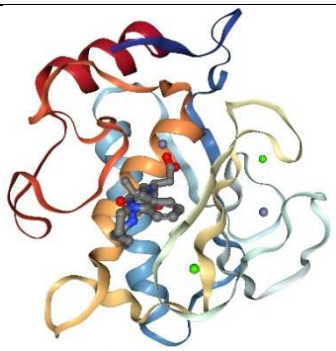
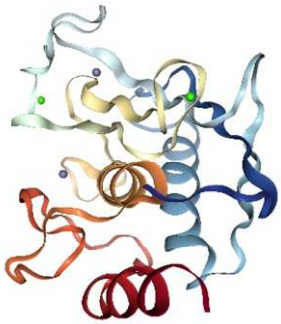
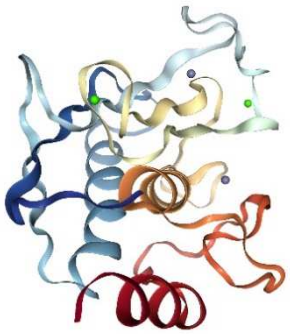
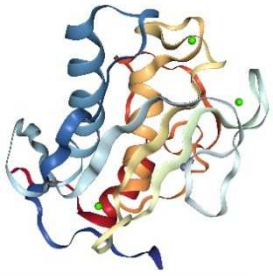
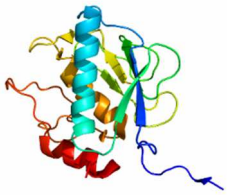
Because of its extraordinary ability to regenerate several complex organs, it has emerged as an ideal model for studying epimorphosis in vertebrates (Daponte *et al*.,2021). The capacity to regenerate following fin damage has been recorded in *Salaria pavo, Tilapia melanopleura, Cyprinus carpio, Carassius auratus*, the zebrafish, *Danio rerio*, and *Poecilia latipinna* (Patel *et al*., 2019).

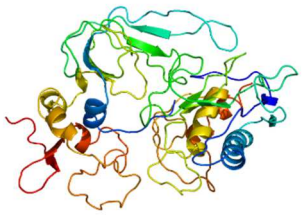
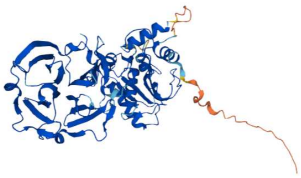
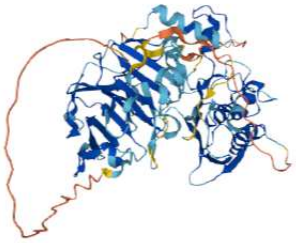
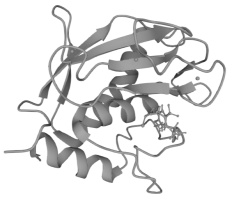
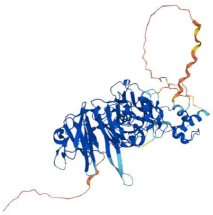
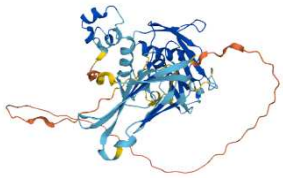
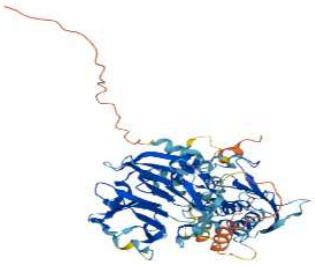
Caudal fin regeneration after the damage has been examined extensively since it is very easy to perform invasive treatments on it. As a model system, the caudal fin has been around for about 230 years. *Poecilia latipinna's* caudal fin anatomy is extremely similar to that of the zebrafish. According to Rajaram *et al*., the structure's morphology and histology have been thoroughly examined (Rajaram *et al*.,2016). As a further example, the process of regeneration of *P. latipinna* caudal fins has been documented by Murawala and colleagues, although in a stage-specific way. As a result, the present work aimed to characterize the diurnal dynamics of cellular activities connected with the regeneration of *P. latipinna's* caudal fin. It was found that in *P. latipinna*, the caudal fin that had been amputated grew back to its original size 25 days after the procedure had been completed. Photos of the regenerate's morphology were taken every day between 0 and 25 days of age (dpa). The morphometric data were also used to determine the growth rate of the regeneration.

As far away from the lesion as 65 µm, amputation stimulates cell growth in connective tissue (Sehring and Weidinger, 2020). The Proliferation of cells occurs at a variety of speeds during regeneration. As a result, BrdU staining was used to examine the regeneration process' highly proliferative stages. Alcian blue-alizarin red staining was also used to observe skeletal morphogenesis. The skeletal patterning during the regeneration of the caudal fin has been documented (Pfefferli and Jazwinska, 2015).

Table 1:-Different types of matrix metalloproteinases (MMPs) involved in the regeneration processes of aquatic organisms.

Enzyme	Structure	Function	Reference
MMP1		Breakdown interstitial collagens (Type I, II & III)	(Deshmukh, 2020)
MMP2		Degrades type IV collagen + endometrial menstrual breakdown + regulation of vascularization + the inflammatory response	(Solga *et al*., 2019)
MMP3		degrades collagen types II, III, IV, IX, andX, proteoglycans, fibronectin, laminin, and elastin + Activates MMP-1, MMP-7, and MMP-9	(Ravindra *et al*., 2018)

MMP7		Degrade gelatins, fibronectin, proteoglycan and casein types I, II, IV, and V.	(Cerofolini, Fragai, and Luchinat, 2019)
MMP8		Degrades type I, II and III collagens	(Decock *et al.*, 2015)
MMP9		Regulates pathological remodelling processes that involve inflammation and fibrosis	(Vandooren, Van den Steen, and Opdenakker, 2013)
MMP12		Regulates inflammatory responses	(Collison, 2018)
MMP13		Wound healing, tissue remodelling, cartilage degradation, bone development, bone mineralization and ossification	(Smith *et al.*, 2020)

MMP14		Regulates ageing process	(Gutiérrez-Fernández *et al*., 2015)
MMP18		Degradation of fibrin and type IV collagen	(Boguszewska-Czubara, Budzynska, Skalicka-Wozniak, and Kurzepa, 2019)
MMP19		Cell proliferation migration, angiogenesis and adhesion	(Mehana, Khafaga, and El-Blehi, 2019)
MMP20		Tooth development	(Kim *et al*., 2020)
MMP21		Embryogenesis	(Napoli *et al*., 2020)
MMP23		To induce cell death, degrade the extracellular matrix, activate chemokines and other cytokines, and cleave the cell surface receptors.	(Laronha and Caldeira, 2020)
MMP28		Tissue homeostasis and wound repair	(Napoli *et al*., 2020)

Echinoderms and MMPs in regenerative processes

Holothurians: Holothuroidea, or sea cucumbers, belong to the Echinodermata class. Various protuberances protrude from their elongated, worm-like bodies. Holothurians, like other echinoderms, are only found in the ocean (Kamyab *et al*.,2020). They can be found all across the seas, from the shallow intertidal zones to depths of more than 5000 meters. However, there are a few species of holothurians that can be found in the water column as well as those that can swim (Smirnov, 2014; Sotelo-Casas *et al*.,2015). Holothurians can regenerate themselves quite quickly (Kamyab *et al*., 2020). Small body parts like tentacles and tube feet can be regenerated and wounds healed on the skin. Holothurians can regenerate any damage to their internal organs, even the gonad (Dolmatov *et al*.,2019). Because they can divide into two or three pieces, they are able to regenerate huge sections of the body (I Yu Dolmatov, 2020).

Regeneration in holothurians is commonly related to research on the repair of internal organs as these animals have a distinctive autotomy known as evisceration (García-Arrarás *et al*.,2018). The internal organs (viscera) of holothurians may be ejected in the event of environmental degradation (Dolmatov *et al*.,2021). In some holothurian species, evisceration occurs only at certain times of the year (Tuwo *et al*., 2019). Evisceration's purpose and reasons are still a mystery (Okada and Kondo, 2019). When a predator attacks, parasites invade and reproduce, or waste materials accumulate in tissues, the ejection of viscera occurs (Ramón *et al*.,2022). It is also possible to live in harsh environments through evisceration. Some examples of environmental stress that lead to evisceration include oxygen depletion, polluted water, and rising temperatures (Ding *et al*., 2019).

Brittle stars: Brittle stars (class: Ophiuroidea) are the most diverse group of echinoderms comprising over 2000 species with a lobal distribution (Czarkwiani *et al*., 2016)..Adult brittle stars are able to regenerate their entire arms, making them an appealing system for studying regeneration of adult structures. Brittle star arms are complex structures composed of various tissue types organized in repetitive segments, here referred to as metameric units. Each such unit contains five different skeletal elements-the dermal oral, aboral and lateral shields (or plates), spines, and the internal vertebral ossicles-in addition to a set of two pairs of intervertebral muscles, intervertebral ligaments, and a pair of podia on each side. The radial water canal, the brittle stars (class: Ophiuroidea) are the most diverse group of echinoderms comprising over 2000 species with a global distribution (Czarkwiani *et al*., 2016).. Adult brittle stars are able to regenerate their entire arms, making them an appealing system for studying regeneration of adult structures. Brittle star arms are complex structures composed of various tissue types organized in repetitive segments, here referred to as metameric units. Each such unit contains five different skeletal elements-the dermal oral, aboral and lateral shields (or plates), spines, and the in ternal vertebral ossicles-in addition to a set of two pairs of intervertebral muscles, intervertebral ligaments, and a pair of podia on each side. The radial water canal, the Brittle stars (class: Ophiuroidea) are the most diverse group of echinoderms comprising over 2000 species with a global distribution (Czarkwiani *et al*., 2016). Adult brittle stars are able to regenerate their entire arms, making them an appealing system for studying regeneration of adult structures. Brittle star arms are complex structures composed of various tissue types organized in repetitive segments, here referred to as metameric units. Each such unit contains five different skeletal elements-the dermal oral, aboral and lateral shields (or plates), spines, and the internal vertebral ossicles-in addition to a set of two pairs of intervertebral muscles, intervertebral ligaments, and a pair of podia on each side. The radial water canal, the Brittle stars (class: Ophiuroidea) are the most diverse echinoderm group, with more than 2000 species found worldwide. In order to better understand adult regeneration, brittle stars may regrow their whole limbs (Czarkwiani *et al*.,2016). There are several kinds of tissue in the brittle star arms, which are grouped into metameric units, which are called metameric units (Clark *et al*., 2018). Each of these units has two pairs of intervertebral muscles and ligaments, two pairs of podia on each side, and two sets of intervertebral muscles and ligaments on each side of the body (Tomholt *et al*., 2020). Additionally, radial nerve cords and peripheral sensory neurons may be found in the arm segments (Czarkwiani *et al*., 2013). Several aspects of regeneration in this class have been studied using the burrowing brittle star. The regeneration rates of these animals have been shown to vary widely in several investigations. This is likely due to changes in animal size, traumatic vs self-amputation, the length of the amputated limb, or the most important function needed at the time (e.g., separation of sensory structures or development of arm for mobility and feeding) (Czarkwiani *et al*., 2016). This wide range of variation serves as a reminder of the animals' capacity to regenerate in a flexible manner. According to Ben Khadra and colleagues (Ben Khadra *et al*., 2018), the early stages of repair and regeneration in two ophiuroid species are best described by histology investigations. Genes that are activated during regeneration have been discovered by recent molecular research (Mahar and Cavalli, 2018). Alx1, a transcription factor well-known for its function in regulating gene networks related to skeletogenesis in sea urchins and sea cucumbers, is one of the mesodermal genes that is produced during embryonic regeneration of the arms and skeleton in A. filiformis (Ben-Tabou de-Leon, 2022). Notably,

transcription factors belonging to the Cart/Alx3/Alx4 family have a role in vertebrate skeletal development (Czarkwiani *et al*., 2021). Echinoderm arm regeneration in the brittle star Amphiura filiformis is becoming an established experimental paradigm for cellular and molecular echinoderm regeneration research (Piovani *et al*., 2021). Collagen is the primary extracellular matrix (ECM) component of connective tissue, which is engaged in the regeneration process of this species. However, little is known about the ECM's participation in this process (Halper, 2021).

Collagen genes are expressed differently in different structures at intermediate and late stages compared to early stages and distal undifferentiated arm-tip at late stages; some collagen genes are not expressed at any stage considered regenerative, indicating their potential for varying spatial and temporal contributions to ECM deposition and maturation throughout the regeneration process. It is possible that laminin and ficolin have a role in the regeneration of the neurological and skeletal systems since they are expressed at the tip of the spines, in both the epidermis and dermis, and in the radial nerve cord at various regenerative phases. There is no observable expression pattern for the specified TIMP at any of the phases of the study (Ferrario *et al*., 2016).

Sea urchin: The genome of the purple sea urchin *Strongylocentrotus purpuratus* was recently sequenced, revealing the existence of at least 26 potential MMP genes (Angerer *et al*., 2006). No orthologs can be assigned to either the vertebrate or sea urchin MMPs since they seem to have duplicated independently, as was the case with the Drosophila MMPs. There might be as many as nine membrane-type MMP family members, which is comparable to the four MT-MMPs and three GPI-anchored MMPs seen in vertebrates (Miller *et al*., 2010). In the early phases of development, 19 of the 26 MMPs are expressed (Nuttall *et al*., 2004). The sea urchin genome is anticipated to have 10 TIMP genes, which is more than double the amount of TIMP genes that are present in vertebrates (Khor *et al*., 2019). *Paracentrotus lividus* has a hatching enzyme that is quite similar to two of these novel sea urchin MMPs. The hatching enzyme, also known as envelysin, was first identified based on its function of dissolving the fertilization envelope in order to allow the developing embryo to emerge from the ECM of the mother egg (Dolmatov *et al*., 2021). Since hatching enzyme seems to be delivered from cell nuclei to egg ECM through the cell membrane's outermost layer, it's one of the earliest zygotic genes to be expressed. Its expression is very restricted, occurring only in roughly two-thirds of embryos and disappearing just before hatching (Briggs *et al*., 2018; Fu *et al.*, 2019). Considering the sea urchin's enormous number of MMP genes, additional highly specialized MMPs may have developed in the sea urchin (Davey *et al*., 2021).

Crustaceans and MMPs in regeneration

***Crabs*:** The hard shell of crustaceans makes it possible for these animals to grow very quickly (Hopkins, 2001). They must moult their exoskeletons to grow larger, and then extend a new, flexible exoskeleton that has developed underneath the old one (Kaleka *et al*., 2019). The intermolt cycle is the period of time between moults. Variables such as the season, nutritional health, and whether or not the animal is regenerating a limb influence the amount of time it takes for the cycle to complete (Islam, 2019).

Many crustaceans have the ability to regenerate. When a fiddler crab loses a leg to damage or predation, it can regrow the whole limb in a single intermolt cycle owing to the reflexive autotomy reflex (Chang and Mykles, 2011; Vogt, 2022). All walking limbs have an autotomy at their root. When an injury occurs, the autotomy reaction guarantees that the leg will be cast off at a predefined location between the coxa and the basiischium at the base of the leg (Rahman *et al.*, 2020). Pre-determined loss ensures the most effective and rapid regeneration possible (Alksne *et al.*, 2020). After an autotomy, there are two stages to the regeneration of limbs (Emberts *et al*.,2019). The first phase, known as basal growth, occurs shortly after the amputation of a limb. It is possible for basal growth to take place at any stage throughout the moulting process (Corona *et al*., 2020; Emberts *et al*., 2019). Animals go through a second period of maturation known as proecdysial growth as they prepare for ecdysis (Emberts *et al*., 2019).

An autotomy membrane is used to close the hole left by the removal of a limb (AM). Crabs' AM is a complicated double membrane that extends the full length of the coxa (Ren *et al*., 2021). In addition to the long pedal nerve, the area is also served by a few blood sinuses. No other tissues cross the AM during autotomy, resulting in little tissue injury. A preformed autotomy fracture plane severance occurs, and the nerve stub is pulled back into the coxal stump (Haszprunar *et al*.,, 2022). A part of the AM bulges outward during autotomy in order to close the opening. The severed nerve's sheath is still linked to the AM's proximal part (Darnell *et al*., 2018). As the blastema develops, this tether helps to protect the nerve from receding too deep into the stump. An empty limb shell will regrow in the absence of the pedal nerve. In arthropod limb regeneration, the pedal nerve seems to be essential for muscle growth (Suzuki *et al*., 2019).

Conclusion: The review aims to provide a comprehensive synthesis of existing literature, offering valuable information for researchers in the field. By compiling and analyzing diverse data sources, this work contributes to advancing our understanding of MMPs' multifaceted roles in different aquatic models, particularly in regeneration, and presents new

perspectives for future research. According to recent research, MMPs promote vital regeneration processes in addition to aiding in degeneration. As evidenced by zebrafish, where MMPs are increased during fin regeneration, this dual role implies that MMPs can promote recovery and regeneration in a variety of tissues under particular regulatory circumstances. MMPs also have a role in tissue and limb regeneration in other aquatic animals, including amphibians, which supports their potential as regenerative medicine treatment targets. Adult animals are unable of re-growing amputated limbs, considerable portions of heart muscle, or healing from serious injuries to the brain or spinal cord. MMPs serve a critical role in the remodeling of the extracellular matrix and in the migration of skeletal muscle satellite cells. Throughout the progression of fibrosis, the production of scar tissue in injured skeletal muscle and other organs and tissues relies on a balance between collagen deposition and breakdown. MMPs initiate the destruction of collagen and other extracellular matrix components. MMPs may also promote muscle cell migration, proliferation, and differentiation in sick and injured skeletal muscles. Researchers are now looking at novel cellular and molecular therapeutics to change the pathogens that lead to skeletal muscle damage and healing, as well as dystrophic muscle. Additionally, the use of MMPs has to deal with the issue of identifying the proper dosage and the ability to maintain it. Gene therapy and mixing degradable polymers have both been proposed as ways to extend the lifespan of MMPs. In order to degrade fibrotic tissue and enhance cell migration, proliferation, and differentiation, it may be necessary for researchers to investigate techniques to boost MMP expression. When it comes to damaged tissue and diseased tissue, higher MMP expression has been shown to be deleterious. Multiple studies have linked high MMP expression to tumour development, metastasis, and inadequate ECM remodeling in diseased tissues. A significant portion of the next ten years will be spent trying to figure out how certain MMPs interact with other ECM molecules (such as collagen, fibronectin, and laminin) and cellular proteins (such as actin, neurofilament, and myogenin) in order to determine whether or not they should be promoted or inhibited in order to impact tissue remodeling correctly.

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