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REGENERATION AND DEVELOPMENT MECHANISM IN ANIMALS

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ABSTRACT

As the cellular physiology is the outcome of enzymatic activity, so the enzymes must have developed before the cells. The first "*cell like*" structures with division power were known as *eobionts* or *Pre-cell*. It was noted that *eobionts* originated about 3800-4200 million years ago. The Protista (cells with distinct nucleus) gave rise to Eukaryotes that evolved into Protozoa, Metazoa and Metaphyta. The theories on natural selection mention that continued selection of more *eobionts* accompanied with the perfection of the membrane system probably led to the formation of the first cell. The first living cells were anaerobic and chemoheterotrophic evolved about 4200 million years ago. At cellular level, development in plants and animals shows quite similar. They share a common eukaryotic cell ancestor. The new scientific study suggests similarities may also extend to the earliest stages of plant and animal life, the formation of the *embryo* (embryogenesis). Growth or development means, the increase in cell size and number that take place during the life history of an organism. Whereas regeneration in plants and animals is the ability to recover from damage. As compared to animals, plants have evolved powerful regeneration abilities to recover from damage. In this review paper I have discussed regeneration and development mechanisms among animals.

KEYWORDS: *Regeneration, Development, Stem cells, Mechanism, Evolution.*

INTRODUCTION

Regeneration is a natural process that allows plants and animals to replace or restore damaged or missing cells, tissues, organs, and even entire body parts. Worlds scientist doing efforts on regeneration for its potential uses in medicine on treating a variety of injuries, diseases and aging processes. Regeneration capabilities are found in most or all animals. Whether regeneration is part of the development of an animal or a distinct phenomenon independent of development, similar to embryogenesis or metamorphosis (Mishel, 2011). Theories have been shown that the existence of regenerative capabilities found in adults and continues throughout the life of animals. The plant tissue culture relies on the fact that many plant cells have the ability to regenerate a whole plant (totipotency) (Vasil, 1972). As compared with animals, plants generally possess a high degree of developmental plasticity and display various types of tissue or organ regeneration. This regeneration capacity can be enhanced by exogenously supplied by plant hormones in *vitro* (Momoko *et al*., 2016). Evidence suggests that some forms of plant regeneration involve reprogramming of differentiated somatic cells. The studies on animal regeneration process itself is usually considered a distinct phenomenon as compared to development (Bely, 2010) or the mechanism underlying development (Brockes, 2008). Research on humans shows that these are specialized cells capable of cell renewal and can differentiate in different cell types of the human body. These abilities of stem cells are extremely useful for biomedical applications and regenerative medicine (Hussein, 2018). In animals' growth or development is defined as production of new cells. Development includes not only cell multiplication (hyperplasia) but also cell enlargement (hypertrophy) and incorporation of specific components from the environment (Owen, 2014). The development of every organism depends on several factors such as – environment, temperature, light, chemical factors, internal factors, genetic and non-genetic factors.

DISCUSSIONS

The ability of animals to regenerate missing parts is a dramatic and poorly understood aspect of biology (Elly & Peter, 2011). Biologist's questions about how and why tissue regeneration occurs and have captured the attention of regeneration mechanisms. Studies say that regenerative capacity differs greatly across organs and organisms. The epithelial cover of an injury can mature into a paracrine stimulator of regenerative growth, or stressed or dying cells can release signals that stimulate their replacement by the activity of progenitor cells

(Kenneth, 2010). Alexandra (2010) noted that the replacement of lost body parts is widespread and highly variable among animals. This variation remains a major challenge in biology, why and how regeneration evolves. Regeneration can replace a part, but never a whole, still biologists do not know what properties enable the cells in the territory to participate in regeneration (Richard, 1970). The Ancient Greeks were most certainly aware of animal regeneration from the work of scholars like Aristotle, and the phenomenon was often incorporated into their mythology. Some other famous examples of regeneration in Greek legends include stories of Hercules (Apollodorus, 1921) and Jason (Seaton, 1912) battling the multiheaded beast Hydra, which could grow two heads for every one sliced off. Meanwhile, ancient Indian legends depicted themes of regeneration as well. For instance, the multiheaded *Ravana* was said to regenerate after decapitation in the Sanskrit *epic* '*The Ramayana*' (Narayan, 1972). Panagiotis (2000) study shows that one way or another, all species possess the ability to regenerate damaged tissues. The degree of regeneration, however, varies considerably among tissues within a body and among species, with urodeles being the most spectacular. Such differences in regenerative capacity are indicative of a specific mechanism that controls the different types of regeneration. Studies have shown that the major cellular events, such as dedifferentiation and transdifferentiation, which allow complex organ and body part regeneration.

Mechanism of Regeneration and its types

Multicellular organisms use three mechanisms of regeneration: *compensatory hyperplasia*, *dedifferentiation/ transdetermination* of mature cells, and *activation* of stem cells (David, 2002). *Compensatory hyperplasia* is the proliferation of cells to restore tissue mass and integrity while maintaining most or all of their differentiated functions. Dedifferentiation is the loss of phenotypic specialization by differentiated cells to produce embryonic-like progenitor cells that retain none of their mature functional specializations. The *activation* of lineage-restricted stem cells set aside late in embryonic or fetal life is the most common mechanism by which adult mammalian tissues regenerate. The regenerative capacity is directly related to the presence of stem cells or progenitor cells, which are capable of proliferation and differentiation. Tissues maintain a high proliferative capacity (Arnaldo *et al.,* 2014). For tissue maintenance, stem and / or progenitor cells in many tissues and organs are thought to play an important role; however, we know little about their control and the process of tissue reconstitution (Atsushi, 2010).

In regeneration process the cells divide quickly into a large number of cells. Each cell undergoes changes to form various cell types and tissues. This sequential process of changes is known as development and the tissues form various body parts and organs. Not all organisms regenerate in the same way. In plants and in coelenterates such as the hydra and jelly fishes, missing parts are replaced by reorganization of pre-existing ones. Whereas the wound is healed, missing, and neighboring tissues reorganize themselves. This process of reorganization of wound, called morphallaxis, is the most efficient way of simple organisms to regenerate. Studies on regeneration show that it is very prominent among metazoans. Starfish, crayfish, reptiles, and amphibians also exhibit signs of tissue regeneration. In some animals such as the lizard, the shed limb regrows into the original organ. Regeneration processes can happen in many different ways using pluripotent stem cells. Some regeneration does not require stem cells. Mainly regeneration is of two main types:

1) ***Reparative regeneration:*** In this type multicellular organisms have the power only to repair certain damaged cells of the body. This common phenomenon observed in both invertebrates as well as the vertebrates.

2) ***Restorative regeneration:*** In this type multicellular organisms can redevelop the served body parts or the whole body can form from a body segment. It is commonly found in invertebrates. The power of restorative regeneration varies in different groups of organisms.

Mechanisms of regeneration

Multicellular organisms use three mechanisms of regeneration: compensatory hyperplasia, dedifferentiation/ transdetermination of mature cells, and activation of stem cells2-5. The regeneration-competent cells involved in each case exhibit different states of differentiation, but have two common features. First, they are not terminally differentiated and thus can respond to signals in the injury environment that promote re-entry into the cell cycle. Second, activation of the cells is invariably accompanied by the dissolution of surrounding ECM, uncoupling cell adhesion molecules (e.g., integrins) from ECM molecules. This uncoupling alters the actin cytoskeleton, activating signal transduction systems coupled to the cytoskeleton. At the same time, growth factors and other signaling molecules bound to ECM components are released and bind to transmembrane Mechanisms of regeneration Multicellular organisms use three mechanisms of regeneration: compensatory hyperplasia, dedifferentiation/ transdetermination of mature cells, and activation of stem cells2-5. The regeneration-competent cells involved in each case exhibit different states of differentiation, but have two common features. First, they are not terminally differentiated and thus can respond to signals in the injury environment that promote re-entry into the cell cycle. Second, activation of the cells is invariably accompanied by the dissolution of surrounding ECM, uncoupling cell adhesion molecules (e.g., integrins) from ECM molecules. This uncoupling alters the actin cytoskeleton, activating signal transduction systems coupled to the cytoskeleton. At the same time, growth factors and other signaling molecules bound to ECM components are released and bind to

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Regeneration in hydra

Hydra has the remarkable ability to regenerate after bisection or dissociation. Hydra regeneration offers a unique way to investigate ancestral molecular mechanisms leading to the establishment of organizer activity during animal development (Brigitte, 2006). Hydra, a primitive metazoan, has a simple body structure. The body column has a high capacity for regeneration of both the head and foot. Tissues are dynamics that take place in adult *hydra* and the regeneration is morphallactic and closely related to axial patterning processes (Hans, 2003). For over 218 years the simple polyp Hydra has been used as an experimental animal to biologists throughout the world. Regeneration of hydras is made possible by the amazing generative powers of totipotent interstitial cells. One important characteristic feature of regenerating in hydra is that it retains polarity (Nikunj Bhatt, 2014). Stanley's findings show that the gastrodermis of Hydra consists of four separate self-generating cell populations. The populations ate the ends support the tentacles or foot and budding region supports the development of buds.

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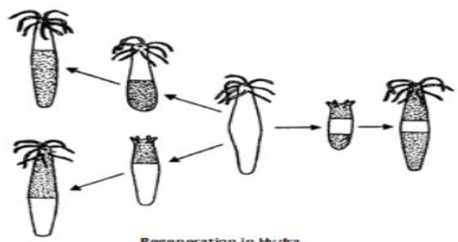
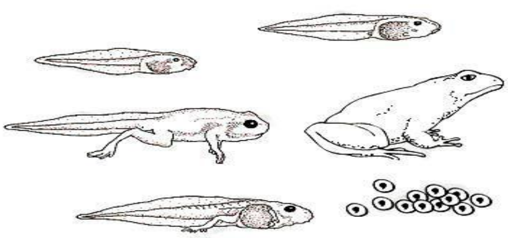
Trembley described how bisecting the animal will system- atically lead to regeneration of the missing part. In addition, regeneration may also occur even when the animal is fully dissociated up to the stage where the cells no longer form a tissue (Gierer et al., 1972). When a mixture of hydra single cells was centrifuged, a rapidreaggregation of thesecells was observed, with the formation of a new animal after a few days. Finally, besides the existenceof a permanent dynamic growth state in adult polyps, most hydra species reproduce throughout their lifetime both asexually by spontaneously budding and, under quite specific conditions, sexually by switching on the production of gametes.



Regeneration in Hydra

Molting, Metamorphosis and regeneration in arthropods

The crustaceans like lobsters, crabs, shrimps etc. to increase their size; they must molt or crawl out of their restrictive shells. Like a knight without his armor, these animals are extremely vulnerable during the early stages of molting before the new outer shell begins to harden (Marty, 1996). During molting the animal looks for a hiding place where it can safely wait for the new shell to finish forming and hardening. Molting is governed by hormones secreted by glands located in the eye stalks of crustaceans, and undergoes a period when they feed heavily and store fats. Hormonal changes cause the old shell to begin fracturing along strategic lines. The mechanism of molting is a well-defined inert structure that is secreted by, and strongly attached to the underlying epidermal cells. The epidermis may undergo a round of cell division and separates from the exoskeleton. A new exoskeleton is then secreted by the epidermis and is soft until the remains of the overlying old cuticle are shed at *ecdysis*. The new cuticle then expands and hardens (John Ewer, 2005). Likewise, metamorphosis is a biological process and is generally attributed to a subset of animals like insects and amphibians, but some fish and many marine invertebrates as well. Metamorphosis has selective advantage, this '*double life*' is easy to perceive: the young insect can exploit one habitat, the mature insect another (Snodgrass, 1954). Insect metamorphosis, whether complete or incomplete, is hormonally regulated. Animals prepare themselves physiologically for metamorphosis; however, studies have shown that the temperature is also an important factor for metamorphosis. Juvenile hormone (JH) plays an important role in insects' metamorphosis, whereas a vast body of work exists on the endocrine regulation of frog metamorphosis (Dodd, 1976). Hormones control the morphological and physiological transitions during metamorphosis, including limb elongation, gill and tail resorption, and remodeling of most other organs from the larval to adult versions. Of predominant importance are thyroid hormones (THs), which induce a gene regulation cascade leading to metamorphic changes (Shi, 1999).

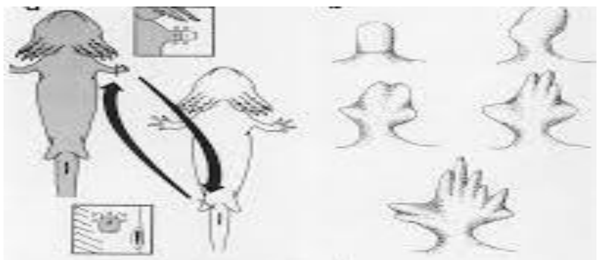


Regeneration fishes

Most of the species of vertebrates such as urodeles and fishes have exceptionally high regeneration abilities. Studies show that the teleost fish has a high ability to regenerate a variety of tissues and organs including scales, muscles, spinal cord and heart (Yuki, 2007). Fish fins can fully regenerate their missing structures in 10-14 days after amputation. It is noted that the epidermal cells migrate distally to recover the wound surface within a few hours. Studies have afforded extensive description of the process of regeneration goes through the following steps: (i) wound closure: (ii) epithelial wound healing and formation of a wound epidermis; (iii) the formation of a blastema at the distal end of the mesenchyme; and (iv) proliferation of blastema cells, their differentiation, and tissue reconstruction. The fish fin has been used for regeneration research (Broussonet, 1786), which has now spanned more than 200 years. It is said the fishes are the champions of regeneration among vertebrates, since they possess a striking potential to regenerate not only fins, but also scales, retina, spinal cord, and many internal organs including the heart and pancreas. Studies demonstrate that ray-finned possess a very high capacity to regenerate different tissues and organs when they are adults. Among fishes that exhibit robust regenerative capacities are neotropical electric fishes of South Africa. These fishes can regenerate injured brain and spinal cord tissues and restore amputated body parts repeatedly (Graciela, 2013).

The amphibian limbs

Among vertebrates, amphibians and fishes generally express a robust regeneration response to limb loss, whereas reptiles, birds and mammals have a more limited capacity to regenerate complex body structures (Brockes & Kumar, 2008). During evolutionary loss of regenerative ability in some groups, it remains an unsolved problem that attracts many biologists. Amphibians, such as salamander, display the highest regenerative ability among tetrapods. As such, they can fully regenerate their limbs, tail, jaws and retina via epimorphic regeneration leading to functional replacement with new tissue. Regenerating limbs of amphibians provide an important experimental model of complex organ replacement in a vertebrate. It was noted that anatomically and developmentally, such limbs are very similar to those of amniotes (Anthony, 2017). All amphibians regenerate both tails and legs as larvae, but anurans (frogs & toads) lose this ability as the animals undergo metamorphosis.



Regeneration of Horns and Antlers

The vertebrate horns and antlers are extraordinary mammalian organs that can fully regenerate annually. Horns in functional terms make sense. They serve possessors as effective weapons. Horns consist mainly of keratin, the protein that is the principal constituent of hair, nails, hooves, scales, feathers, claws and other tough structures derived from epidermal tissue. Horns and antlers differ significantly in their architecture. The antler renewal is stem cell-based epimorphic process and antler stem cells initiate the regeneration process. Stem cells are extraordinary in that they are capable of self-renewal and can differentiate into multiple cell types (Slack, 2018). It is known that the antler growth centre located in its tip (Li *et al.,* 2002). The rapid growth is mainly through the proliferation of cells resident in the reserve mesenchyme (Clark *et al.*, 2006).

Different animal groups and their regenerative parts		
Sr. No.	**Animal group & examples**	**Regenerated body parts**
(A) INVERTEBRATES		
1.	**Coelenterates**: (e.g. Hydra) **Flatworms**: (e.g. Planaria) **Sponges**: Sycon	Having fragmented body parts
2.	**Arthropoda**: (e.g. Insects, Spiders, Crustaceans)	Limbs
3.	**Annelida:** (e.g. Earthworm)	Body segments
4.	**Mollusca:** (e.g. Snail)	Parts of the head, foot, eye
5.	**Echinodermata:** (e.g. Starfish, Sea cucumber)	Arms
(B) VERTEBRATES		
1.	**Pisces:** (e.g. fishes)	Fins
2.	**Amphibia:** (e.g. Salamander)	Limbs, tail
3.	**Reptilia:** (e.g. Lizard)	Tail
4.	**Aves: (e.g.** Birds)	Beak
5.	**Mammals:** (e.g. Man)	Skin, body parts, Kidney, Liver (Only reparative regeneration)

Regeneration of skin and wound healing

Skin is the barrier between the internal and external environment and is the largest organ of the human body. The epidermis undergoes constant every 28 days, all the cells are turned over as the most superficial cells and replaced by new ones. Due to the presence of stem cells, the wounded epidermis is able to stimulate self-regeneration. Skin substitutes are upcoming alternatives to traditional wound healing strategies and tissue regeneration (Komal *et al.*, 2017). Studies show that constant regeneration of the skin is achieved due to stem cell differentiation within the epidermis and the hair follicle; thus, skin may serve as an excellent source of stem cells (Marzena *et al.*, 2011). The natural wound healing typically consists of three phases: Inflammation and Debridement, Repair and Maturation.

Cell differentiation

Cellular differentiation is the process in which a cell changes from one cell type to another. Differentiation occurs numerous times during development of a multicellular organism. The differentiation process alters the cell dramatically, its shape size, and energy requirements. Differentiation selects a subset of genetic information to be expressed at different stages of the differentiation process (Inn Chuan, 2019). Cell differentiation is sensitive to both mechanical and chemical stimulus from the environment.

Importance of stem cells

Stem cells are unspecialized cells of the human body. Stem cells are able to differentiate into any cell of an organism and have the ability of self-renewal. They exist both in embryos and adult cells, and have several steps of specialization (Wojciech *et al.,* 2019). Studies have shown that totipotent stem cells are able to divide and differentiate into cells of the whole organism. Totipotency has the highest differentiation potential and allows cells to form both embryo and extraembryonic structures. The function of stem cells is to enable the healing, growth, and replacement of cells that are lost each day. Stem cells have a restricted range of differentiation options. These cells are of following types: (i) *Mesenchymal stem cells* (present in bone marrow), (ii) *Neural cells* (rise to nerve cells), (iii) *Hematopoietic stem cells* (blood cells) and (iv) *Skin stem cells* (forms skin).

Control of regeneration

Biologists know that hormones play a role in influencing the normal course of growth during regeneration. Studies on the role of one class of regulatory genes called homeotic genes, may control patterns of development. However, still today the exact role of these genes in pattern formation remains unclear. Researchers finding the exact control mechanism for the regeneration of a lost limb in a salamander. But the experiments have confirmed its dependency upon *nerves, hormones* and *epithelial cover*. Experiments of C.S. Thornton (1960) has shown that the presence of the wound *epithelium* which covers the amputated surface is necessary for blastema formation. *Neural trophic factors* play an important role in regenerative processes. *Hormones* secreted in adrenal and pituitary glands have been found to influence the regenerative process considerably.

Tissue Engineering

Komal Vig *, Atul Chaudhari, Shweta Tripathi, Saurabh Dixit, Rajnish Sahu, Shreekumar Pillai, Vida A. Dennis and Shree R. Singh

CONCLUSION

It is tentatively concluded that whole-body regeneration as an ancestral character has been lost from most animals. Regeneration of appendages in some species is more likely to represent a derived character resulting from many specific adaptations. Regeneration shows significant differences between regeneration processes in adult animals and developmental processes. Regeneration is specific to distinct amputation. Stem cells are enabled to the healing, growth and replacement of cells that are lost each day. Cell differentiation has its specific role in regeneration. Overall, the whole mechanism of regeneration has been influenced through endocrine glands.

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