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REVIEW ARTICLE

COMPARATIVE CARDIAC REGENERATION: ZEBRAFISH VS. HUMAN HEART REPAIR MECHANISMS

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Abstract

Zebrafish(Danio rerio) can regenerate their hearts, completely after being injured, they have become an important model organism for research on cardiovascular regeneration. Through the proliferation and dedifferentiation of cardiomyocytes, and additional contributions of other cell types such as epicardial cells, endothelial cells, and fibroblasts.Zebrafish may repair significant cardiac injury, in contrast to mammals or humans whose hearts have limited regeneration capacity. Wnt/β-catenin, Notch and Hippo signaling are some of the molecular pathways involved in this regeneration process that coordinate the reactivation of cardiomyocytes, proliferation, and the development of new blood vessels. Comparative studies show how Zebrafish and mammals differ greatly in their ability to repair the heart, highlighting how Zebrafish research may help or guide us in regenerative medicine treatments for human heart disease. This analysis looks at the molecular and cellular processes that underlie the betterment of human life threatened by heart surgeries.

Introduction:-

Heart disease is the leading cause of death worldwide, accounting for an estimated 17.9 million deaths per year[1]. Despite scientific and technical advances, cardiovascular procedures such as surgery and transplants remain dangerous and have a low success rate. However, a small freshwater fish known as the Zebrafish (Danio rerio) may hold the key to transforming the way we treat cardiovascular disease. Because of their extraordinary capacity to fully rebuild their hearts following injury, Zebrafish have emerged as an important model organism for cardiovascular regeneration research. Zebrafish are extraordinary. “These fish appear to be able to repair anything, including fins, heart cells, spinal tissue, cartilage, and ligaments. They have a broad range of restorative abilities”[2].

One of the most remarkable characteristics of Zebrafish is their capacity to completely mend their hearts following damage that would be fatal in other species. This includes serious injury, such as chopping off up to 20% of the heart or removing the entire organ.

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Cardiomyocytes, which are responsible for heart muscle contraction, proliferate and dedifferentiate, allowing this regeneration process to occur. Unlike mammals and humans, which have limited regenerative capacity in the heart, Zebrafish can efficiently replace damaged tissue with freshly produced cardiomyocytes. [3,4]

However, the process of heart regeneration in Zebrafish is more than just the proliferation of cardiomyocytes. Other cell types, including epicardial cells, endothelial cells, and fibroblasts, are also important in the repair of major heart damage.

These cells work together to coordinate their activity and communicate via numerous chemical pathways, which initiate the regeneration process. Wnt/β-catenin, Notch and Hippo signaling pathways play important roles in mammalian heart regeneration. [5]

Wnt (Wingless-related integration site) /β-catenin (a protein which helps to stick together and communicate with other) signaling is an essential biochemical route that controls a number of developmental processes such as tissue regeneration, differentiation and cell proliferation. When this route is in its traditional form, Wnt proteins bind to cell surface receptors, stabilizing and accumulating β-catenin in the cytoplasm. [6]

After that, the β-catenin moves into the nucleus, where it triggers the transcription of target genes that govern decisions about cell fate and regenerative reactions.

The Notch and Hippo pathway

The Notch and Hippo pathways are both critical signaling channels that control cell fate, development and tissue homeostasis in multicellular animals, although they do it in different ways. Both these pathways are present in embryonic development and adult tissues

The Notch pathway

The Notch signaling pathway governs activities such as cell development, proliferation, and apoptosis.This route works via a receptor-ligand interaction.

- **Activation:** Activation occurs when a target cell's Notch receptor interacts to a neighboring cell's ligand (e.g. Delta or Jagged). This binding initiates a cleavage event that releases the Notch receptor's intracellular domain.
- **Intercellular effect:** Notch's released intracellular domain (NICD) translocates to the nucleus, where it interacts with transcription factors to regulate gene expression in a variety of cellular processes, including differentiation, proliferation and death.

The Hippo pathway

This pathway is important for embryonic development, stem cell maintenance, and regulating tissue boundaries. Hippo Pathway controls cell growth, proliferation, and apoptosis. It affects cell cycle progression and cell division in context-dependent ways to control organ growth and tissue homeostasis.

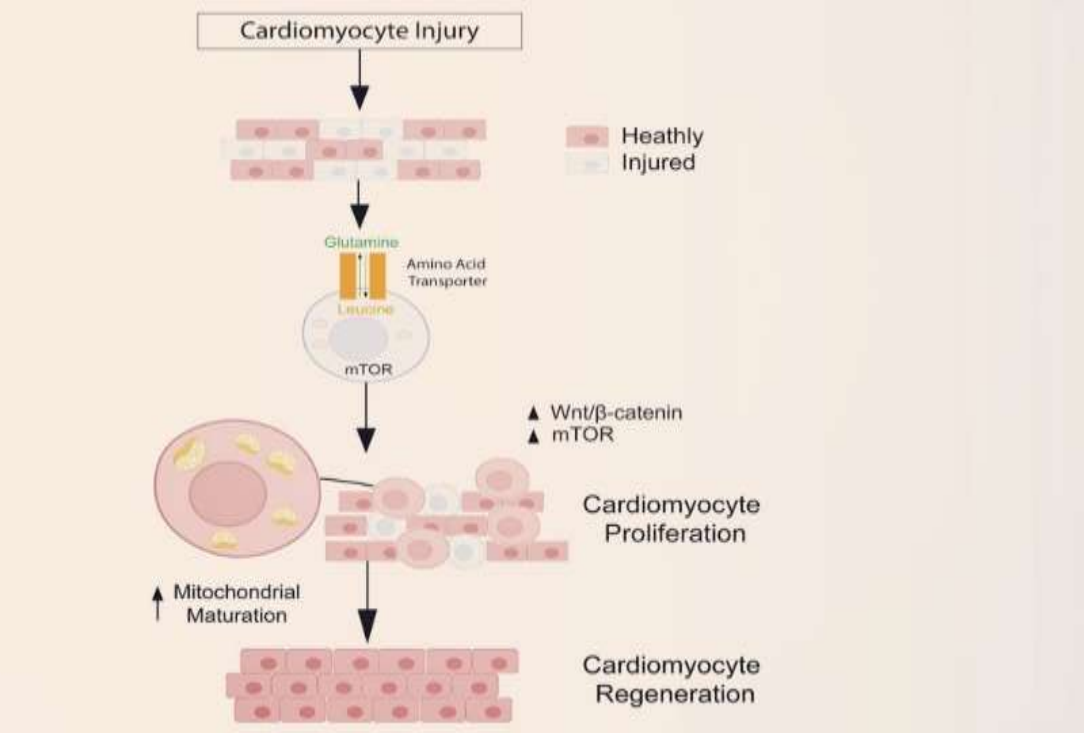
• Core components:

The system is driven by a kinase cascade involving numerous proteins, most notably MST1/2 (Mammalian Ste20-like kinases), LATS1/2 (Large Tumor Suppressor Kinases) and YAP/TAZ (Yes-associated protein and Transcriptional co-activator with PDZ-binding motif), which operate downstream effectors.

• Activation and effects;

The Hippo pathway activates MST and LATS kinases, which phosphorylate YAP/TAZ and prevent it from accessing the nucleus. When the Hippocampus is inactive, YAP/TAZ are dephosphorylated, allowing them to enter the nucleus and increase gene expression, which drives cell proliferation and survival.

Scientists have learned a lot about how the heart regenerates and how it differs from mammals by examining molecular and cellular mechanisms in Zebrafish. This comparative study has revealed major variations in the regenerative capacity of Zebrafish and mammals, giving a potential foundation for creating new treatments for heart disease. The process is as follows,



1.Cardiomyocyte Injury
Cardiomyocytes, the heart's muscle cells, are injured to start the cycle.The diagram depicts a combination of healthy cells (pink) and wounded cells (white), which indicate harm.

In humans, injuries often result in scar formation, however in some creatures, such as zebrafish, regeneration happens naturally.

2. Amino Acid Transport and Activation of mTOR
After damage, cardiomyocytes transport certain amino acids (glutamine and leucine) through an amino acid transporter.These amino acids activate mTOR (mechanistic target of rapamycin), a vital regulator of cell growth, metabolism and regeneration. [7] Activation of mTOR increases pathways for cell proliferation and repair.

3. Wnt/β-catenin and mTOR pathways are activated.
mTOR and Wnt/β-catenin signaling are activated.These pathways drive cell cycle re-entry in cardiomyocytes, facilitating cell division and tissue healing.Mammals adult hearts are mostly dormant, but efforts are being done to trigger these pathways for heart regeneration.

4. Cardiomyocyte Proliferation
mTOR activation and Wnt signaling lead to cardiomyocyte proliferation.This stage replaces lost or injured cells, preventing the formation of fibrotic scars in humans.Improving this mechanism could improve heart attack healing.

5. Mitochondrial maturation.
New cardiomyocytes undergo mitochondrial maturation, leading to increased energy output. Mitochondria provide ATP (energy) to support cardiac muscle function.Proper mitochondrial function strengthens and functionalizes newly generated cardiomyocytes.

6. Cardiomyocyte Regeneration
After proliferation and mitochondrial maturation, the damaged heart tissue is recovered.Instead of scar tissue, functioning cardiomyocytes regenerate, allowing normal cardiac function to be restored.

In zebrafish, this process occurs naturally, but in humans, research is being conducted to activate these processes for therapeutic heart repair.

The Zebrafish study has consequences that go beyond simply figuring out how to repair broken hearts. As it is genetically similar It could potentially serve as a model for human regenerative medicine therapy for various disorders. For example, Zebrafish are a good model for studying tissue regeneration due to their ability to regenerate other organs such as the spinal cord and fins. Zebrafish research could have an impact on the larger field of regenerative medicine, ultimately enhancing human health and welfare.

The sinus venosus, atrium, ventricle, and bulbous arteriosus are the four linear chambers of the adult Zebrafish heart. Although the Zebrafish heart's basic structure is different from that of the human heart's four chambers, important anatomical and functional parallels make the Zebrafish heart a valuable model for researching human cardiovascular biology[8].

Pacemaker activity and sinus venosus:
The sinus venosus is the principal pacemaker region in the Zebrafish heart, triggering the electrical impulses that cause the heartbeat. This is analogous to the sinoatrial (SA) node in the human heart, which likewise produces electrical impulses that control the heart's rhythm. Pacemaker cells in these locations can depolarize spontaneously in both species, resulting in rhythmic heart contractions.

Functional Parallels Between the atrium and the ventricle:
Zebrafish atriums and ventricles function similarly to those in the human heart. The atrium takes blood from the venous system (sinus venosus) and pumps it to the ventricle, where it enters the systemic circulation. In humans, the right atrium pumps blood into the right ventricle, which then transports it to the lungs for oxygenation, whereas the left atrium circulates oxygenated blood throughout the body. In Zebrafish, blood is oxygenated through the gills rather than the lungs, but the essential function of pumping blood from the atrium to the ventricle is unchanged.

The bulbus arteriosus and the ventricles:
The Zebrafish ventricle is a muscular chamber that pumps blood, just like the human heart. In order to maintain smooth blood flow, the bulbous arteriosus, which serves as a pressure buffer, receives blood from the ventricle of Zebrafish. The aorta receives blood from the left ventricle, which then distributes it throughout the body. Despite the absence of a direct aortic structure, Zebrafish and other animals carry out the identical function of maintaining blood flow.

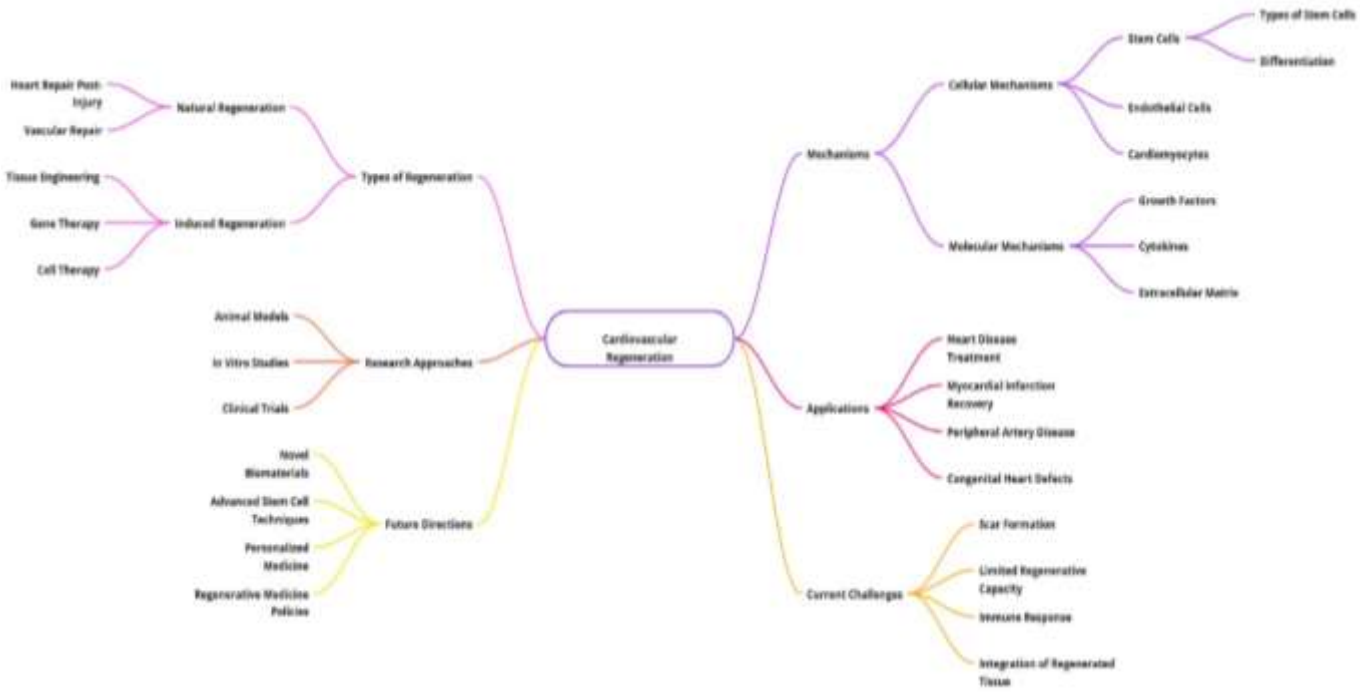
Cardiac function and circulation: parallels in blood flow.
The overall purpose of the Zebrafish heart is to pump blood through the circulatory system, much like the human heart, although the paths change slightly. In both species, the heart circulates deoxygenated blood through the atrium and the ventricle before oxygenating it in the lungs or gills.

In Zebrafish, blood flows from the body to the sinus venosus, atrium, ventricle, and bulbous arteriosus, where it is distributed to gills and other tissues.

The Human blood travels to the right atrium, the right ventricle, and the lungs for oxygenation after leaving the body. After passing through the left atrium and the left ventricle, the oxygenated blood continues via the aorta to the rest of the body.

The complex pulmonary and systemic circulatory separation present in the human heart is absent from the Zebrafish heart; yet, both hearts are crucial for maintaining constant and effective blood flow to meet the physiological demands of the organism.

Regeneration: Zebrafish's Unique Advantage and Implicationsfor Human Cardiac Repair
One of the most remarkable features of the Zebrafish heart is its ability to mend after injury. This regenerative power contrasts with the human heart's limited regenerative potential, which has aroused the interest of researchers studying heart failure and other cardiac disorders.



Zebrafish have regenerative capacity:

Zebrafish have a remarkable ability to repair torn heart tissue. Following injury, such as the removal of a part of the ventricle, Zebrafish cardiomyocytes (heart muscle cells) can multiply and replace missing tissue. This procedure involves the migration of epicardial cells into the injured area, which promotes cardiomyocyte development. Fibroblasts and endothelial cells also help to form new blood vessels, ensuring that the regenerated tissue is well-vascularized and functional.

Limitations and Potentials of Human Heart Regeneration:

In contrast, the human heart has extremely little regenerating ability following injury. Cardiomyocytes in humans seldom re-enter the cell cycle after birth and any heart injury causes fibrosis and scar tissue rather than functional muscle regeneration. However, research into Zebrafish heart regeneration sheds light on prospective ways for improving human heart repair. Researchers are looking for ways to stimulate cardiomyocyte proliferation or use stem cell therapy to replicate some of the healing mechanisms identified in Zebrafish.

Cardiac physiology includes temperature sensitivity and heart rate:

Both Zebrafish and humans adjust their heart rates in response to the changing environmental conditions. While Zebrafish are ectothermic, which means their heart rate is strongly influenced by water temperature, the human heart rate fluctuates in reaction to temperature, exercise, and stress. [9,10]Because of the transparency of their embryos, Zebrafish heart rhythms may be easily measured in real-time, making them an excellent model for studying how environmental changes affect cardiac function.

Conclusion:-

The Zebrafish's exceptional regenerative potential gives light on the molecular and cellular processes that participate in heart regeneration. Understanding these systems could lead to the development of new treatments for human heart disease and other tissue-damaging illnesses. As we understand more about the mysteries of Zebrafish regeneration, we come closer to a time when cardiac surgeries and other invasive treatments may be unneeded to maintain a healthy heart and reduce the chance of mortality. As a result, the mortality rate decreases. However, further research is needed to overcome the challenges of turning these insights into practical, effective treatments for humans.

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