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Insight into the Natural and Synthetic Factors Responsible for Cell Regeneration in Various Organs

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Abstract

Cell Regeneration is the key phenomenon liable for the smooth and healthy functioning of our body as it is responsible for replacing the damaged or aged cells. The research focusses on the factors and possible accelerators responsible for cell regeneration, both Natural and Synthetic. In this regard, we have studied the process of cell regeneration closely in individual organs like the bones, heart, skin, eyes, and liver. Our main research question revolves around the reasons that influence the resurgence of cells and also elements that fasten the process. The research highlights various biological events including involvement of growth factors and scientifically implemented techniques like biomodelled chemical substitutes and 3Dbioprinting that have been interpreted to be linked with the renewal of cells in our research.

The research efforts carried out in this article aims to further facilitate the Research and Development (R&D) initiatives of Jozbiz Technologies Pvt Ltd.

Keywords: hexagonal hydroxyapatite (HA), growth factors (GF), opacification.

1. Introduction

A saying goes like no life can proceed without regeneration and no death can ever occur if everything in this universe is regenerated. These are the two extremes between which all organisms seem to exist. The process of reproduction can be otherwise called as regeneration of organisms producing their own species. In this universe each and every organism regenerate.

Regeneration can be subcategorized into several kinds and one of the major one is reproduction specially focusing on the vegetative one. All organisms in this universe have the ability to synthesize molecules to generate additional units of any structure. There is a constant biochemical turnover allowing the additional units to adapt with their physiological changes as they continue to exist. These additional units should continue to multiply in

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order to successfully carry out the process of regeneration. The cells should unite together to form tissues which further forms tissues and finally end up forming organs.

Several organs found in various organism are often found to have the capability to regenerate naturally.

It is defined as the process of incorporating or merging man- made or synthetic material into a human for replacing natural tissues or organs. The primary function of this organ regeneration is restoring a particular function or a set of relevant functions providing the patient with a normal life. However, the process is still not fully understood. Even though it consists of tremendous therapeutical capability for humans. In this review paper, we chose to compile or outline the repair and regenerative capability of the organs such as: eyes, liver, skin, bone and cardiac tissues of humans and other organisms. In course of years, organ regeneration has evolved to be an encouraging and hopeful therapy that can cure diseases in humans and other organisms that cannot be healed by other methods or treatment procedures. It also achieved a superior post when compared to any other treatment utilizing exogenous sources in order to substitute the function and/or the structure of the organs that have been lost.

2. Results and discussion

Involvement of Biomodelled chemical substitutes in regeneration of the bone tissue:

Bone tissue encompasses a mineralized construction. Biomimetic composite substitute with a mineral constituent were used loosely for bone repair. The mineral element introduces structural integrity and osteoconductive features to the scaffold. Hexagonal hydroxyapatite (HA) is often used for the rationale that has the potential to simulate the natural minerals a part of bone. Besides, alternative inorganic phosphate such as calcium phosphate or bioglass were equally used because of their biocompatibility. Utilizing dioxane/water as a solvent, nano-HA/poly-l-lactide (PLLA) nanofibers composite scaffolds through TIPS (thermally iatrogenic section separation) technique were invented. The high expanse of the nanofibrous permits more the HA to be exposed, that is suitable for bone tissue regeneration.

In another study, HA was incorporated into electrospunnanofibers, then used a gelatin-apatite precipitate homogenized in Associate in Nursing organic solvent with polylactide-co-caprolactone (PLCL). For the length of the precipitation reaction, the Ca/P proportion was reserved to 1.67 to ensure ratio mineral fabrication. Simply rock bottom concentration of gelatin-apatite ends up in a growth in traditional strength. Lately, deposition methodology has been developed that decreases the mineralization time. To demonstrate the pliability of the technique, deposition has been effectively created on each electrospunPLLA fibers and phase-separated PLLA fibers. As a result, electrodeposition was confirmed to be a quick and operative methodology of mineralization of bone tissue scaffold. Collagen, within the style of injectable hydrogels, membranes, or sponges, extensively used for bone tissue regeneration.singly, as composite with inorganic phosphate structures like HA; many instances embody, collagen/HA/chitosan or collagen/HA/alginate hydrogels (Ansari, 2019).

Usage of 3DBioprinting in bone tissue regeneration:

3D printing employs 3D pictures of the bone trauma anatomy, sometimes noninheritable from computerized tomography (CT) scans, employing a hard software system, to fabricate a bone graft substitutes (BGS) structure that matches to a bony defect. The personalised bone graft substitute kind employs a 3D printer to regulate the BGS mechanical options and substantial values. The composition optimisation ensures related improved correspondence among the BGS and the patient's anatomy, allowing the regeneration. Replacements factory-made by titanium are very instrumental and most widely used. Metal plates are sometimes used to immobilize bone elements in jaw

operations. 3D printing is equally being studied for orthopaedic purposes: for cotyloid ruptures, mortise joint defects and more bone defects because of bone fracture, spurt fissure of spine, bone cancer and orbital ground repair. The tailored soft/spongy implant printed by Ti6Al4V bestowed outstanding chemical science options and characterized biological performances of biocompatibility, osteogenic property, and bone regeneration. Bioceramics and biopolymers like polyetheretherketone (PEEK) are presently being deviced in suitability to usage, and being studied at the pre-clinical stage. Research is being conducted on BMP-2-loaded polycaprolactone(PCL) /HA composite for the repair of animal tissue recession associated with bone and animal tissue tissue repair.

In a recent study, (Ansari, 2019) a mandibular bone bone was repaired via human amnionic fluid-derived somatic cell (hAFSC)-loaded hydrogel, a combination of PCL and tricalcium phosphate (TCP), and pluronicF12. The PCL/TCP and hAFSCs mixed with the colloidal solution of hydrogel, were reproduced during a kind I style with a PluronicF127 impermanent support . After induction of osteogenic differentiation for twenty eight days, the constructions with alizarin carmine S were stained; staining at the surface of the 3D bone constructions showed metallic element deposition within the hAFSC loaded hydrogel.

Cardiac tissue regenerative apparatus implemented by Growth Factors:

Angiogenesis is the phenomenon of generation of new blood vessels through differentiation of endothelial cells. From the medical purpose, the target is to stimulate vessel growth in patients with conditions characterised by lean blood flow, like anaemia heart diseases and peripheral vascular structure diseases.

As regards the latter side, the identification of growth factors that induce the angiogenic method aroused the interest within the use of those proteins for the induction of therapeutic ontogeny. Within the case of MI, angiogenic medical care with growth factors might salvage the anaemia tissue at early stages of infarct, by provision the tissue with new vessels. This method is crucial to forestall cardiopathy through the management of cardiomyocyte hypertrophy and ability. In fact, ontogeny is that the main growth factor-induced reparative mechanism and has been the mechanism most frequently investigated in experimental studies and clinical trials on slashed heart muscle repair. Most of those studies have dedicated their efforts toward the angiogenic and regenerative potential of vascular structure epithelial tissue protein (VEGF) and embryonic cell protein (FGF).

Mitigation of the anaemia injury within the internal organ tissue is also induced by antiapoptoticfactors, that exert doubtless cardioprotective effects. Hepatocyte protein (HGF) was initial known as a hepatocyte agent, with chemotactic and antiapoptotic actions in numerous cell sorts. In rats undergoing anemia and reperfusion, blood vessel administration of HGF reduced caspase-mediated cell death in cardiomyocytes and therefore the infarction size. Alternative antiapoptotic factors with therapeutic potential in internal organ regeneration embody platelet-derived protein (PDGF-BB) and supermolecule hormone hormone, IL-11, IL-33, and others (Rebouças et al., 2016).

Endogenous mechanisms mediate by progenitors and stem cells embody mobilization and orienting of bone marrow progenitors also as CSC activation. These cells might differentiate into new cardiomyocytes once the anaemia injury, however their range is reduced or they're insufficiently activated to provide important muscular regeneration. Some proteins show the potential to mobilize bone marrow progenitors to the internal organ lesion space or activate CSC. These properties is also therapeutically explored as regenerative mechanisms activated by growth factors or recombinant proteins, like the white cell colony stimulating issue (G-CSF), HGF, stromal cell-derived issue (SDF-1), and others. The paradigm of the guts as a very differentiated organ was contested supported the identification of mitogens able to induce adult cardiomyocytes to enter into the cell cycle. This method opens the likelihood to stimulate a brand new regeneration mechanism within the infarcted heart, resulting in the formation of a population of recent

cardiomyocytes capable of replacement the cell mass lost because of the anaemia injury. 3 living thing factors are known for his or her ability to activate receptors concerned in cardiomyocyte proliferation: acidic embryonic cell protein (FGF-1), neuregulin (NRG-1), and periostin. Treatment of infarcted rats with FGF-1 together with a mitogen-activating supermolecule enzyme (MAPK) p38 resulted in redoubled cardiomyocyte cell division and improved internal organ operation. Studies have incontestible improved internal organ operate in infarcted mice treated with daily injections of NRG-1.

Table 1. Mechanism of Growth Factor directed Cardiac tissue regeneration

Factor	Effects	Factor	Effects
VEGF	Formation of blood vessels	G-CSF	Prevention of cell death
FGF	Formation of blood vessels	Intermedin	Formation of blood vessels
HGF	Prevention of cell death	Angipoietin	Formation and stabilization of blood vessels
SDF-1	Hematopoietic stem cells orientation	Periostin	Increase in Cardiomyocytes
IGF-1	Stem cells'and antecedent cells' surviving ability and differentiation	Neuregulin-1	Increase in Cardiomyocytes
PDGF	Prevention of cell death	Erythropoietin	Prevention of cell death

Insight into Resurgence of skin cells:

The skin acts as a shield for the internal environment from the external one but in case of damaged or injured epidermis, it is able to thereafter regenerate due of the presence of stem cells. The skin is basically made up of three layers, starting with the uppermost and outermost layer is the epidermis, followed by the dermis which is made up of 95 % keratinocytes, further consisting of five layers, ranging from stratum basale to the stratum corneum. Then comes the layer next to the epidermis, the dermis, made up of connective tissue, hair follicles, and sweat glands followed by hypodermis, which is the is the deepest surface of the skin featuring loose connective tissue.

Keratinocytes are formed by basal cells at the basal cell layer as they migrate to the upper epidermal layers to form a dead cell on the surface of the skin which overtime shed away.

Growth factors, cytokines, chemokines, and other required cells coordinate in order to heal a normal wound, but a deeper or more severe injury might not be healed by the skin because of how complex and multiphase the whole process of cell regeneration is and ends up becoming a chronic injury which may further leave scars (Blanpain, 2010). Treating the chronic injuries requires continuous analysis and repetitive treatment and if left unattended or untreated can lead to much more severe infections. Thus, different strategies of stem-cell therapy have been proposed which have a potential to treat deeper injuries effectively and efficiently. Out of many solutions to heal these kind of skin damages, use of foreign compatible tissue is also one but depends highly on a healthy donor but also contains a lot of risks. According to researches, skin was the very first organ to be engineered that could be used for a patient. Since, tissue engineering and stem cell therapies are an evolving field, over the decade there has been numerous levels of

development and is still continuing to develop. Newer and advanced techniques are able to modify substitutes that hold the potential for a better testing.

Regenerative medicine is a field of medicine that focuses on finding ways to regenerate, repair, or replace cells, organs, and tissues that have been damaged. The synthesis and use of therapeutic stem cells, tissue engineering, and the creation of artificial organs are all examples of regenerative medicine.

According to studies (Martin, 1997) wound healing has been seen in foetal skin and appendages regeneration has been seen in adult skin. The models following this principle has taken this as a potential basis for further research and protocols. The initial affirmation from transplantation of bulge stem cells showed that stem cells can further differentiate into interfollicular epidermis, sebaceous gland and hair follicle lineages. Further studies (Takeo et al., 2015) showed that bulge stem cells contributed well enough for the regeneration of hair follicle but not for the maintenance of the interfollicular epidermis but meanwhile when there's some sort of injury, it shifted its function mainly towards the maintenance of the interfollicular epidermis to help healing the wound.

And observations later produced more such evidences like sebaceous-gland cells are maintained by progenitors located above the bulge, which express the Blimp1 protein during morphogenesis.Studies have shown that stem cell repair induce the major mechanism of secretion of paracrine factors which enhance wound healing. Similarly like the paracrine factors, mesenchymal stem cells(MSCs), also has the ability to promote healing by activating host cells. In one study, allogeneic MSCs generated from bone marrow were injected into cutaneous wounds in mice and found to produce keratinocyte-specific proteins and contribute to the creation of glandular structures after damage. Even though long-term engraftment wasn't as fruitful, MSC-treated wounds had a higher amount of released proangiogenic factors. Local injection of allogeneic MSCs has been demonstrated in our laboratory. Taken together, these findings imply that stem cell injection advantages are due to early cytokine release rather than long-term engraftment and differentiation.

The stem cell's dynamic microenvironment, or niche, is in charge of controlling their "stem-like" activity throughout life.

Adjacent cells (both stem and non-stem cells), signalling chemicals, matrix architecture, physical forces, oxygen tension, and other environmental variables make up a niche.

Following is a better breakdown of what these niches are and how they influence cell activity (Wong et al., 2012).

Table 2. The diverse types of cell niches

The Epidermis cells niche	The Dermal niche	The Adipose niche	Engineering niche
3 major stem cells population – a) Hair follicle Bulge b) Sebaceous gland c) Interfollicular epithelium	composed of – a) heterogeneous matrix of collagens b)elastin c)glycosaminoglycans interspersed with cells of various embryonic origin.	fat cells called adipocytes. Adipocytes are energy storing cells.	To emulate these dynamic microenvironments, tissue created systems will need to be increasingly scalable, adjustable, and customizable.

Epithelial stratification, hair folliculogenesis, and wound repair are all regulated by this protein.	This dermal unit contains at least three unique populations of progenitor cells that regulate expression of the transcription factor Sox2	Signalling pathways- VEGF PPARγ FGF2 MMPs PDGF	In order to examine perivascular stem cell niches in vitro, researchers constructed unique three-dimensional microfluidic devices.
Lineage tracing and gene mapping experiments have elucidated key components in epidermal homeostasis.	Skin-derived precursor (SKP) cells are thought to originate in part from the neural crest and have been shown to exit the dermal papilla niche and contribute to cutaneous repair.	Surface and structural proteins- CD29 CD44 CD73 CD90 CD105 CD166	Researchers have been able to create complicated three-dimensional habitats using bioengineering techniques in order to control stem cell fate.
Complex intraepithelial networks, signals from the dermis (e.g., periodic expression of BMP2 and BMP4) seems to regulate epithelial processes	perivascular sites in the dermis have been demonstrated to act as an MSC-like niche in human scalp skin.	harvested from human burn wounds and shown to engraft into cutaneous wounds in a rat model	Other researchers have discovered that oxygen tension, pH levels, and even wound electric fields can affect stem cell life, implying that the development of new sensor devices in the future will allow for even finer control of chemical microgradients within created niches.
Dermal stem cells have the potential to develop into functional epidermal melanocytes.	Fibroblasts have also been shown to preserve multilineage potential in vitro, suggesting that they may play a significant part in skin regeneration, but this has yet to be tested.	Multipotent cells have the potential to be used in a variety of skin-repair applications.	Current niche biology research has been conducted in culture systems or rodent models, with findings that will need to be rigorously verified in human tissues before being used in therapeutic settings.

Further studied have demonstrated that irreversibly committed progeny from an epithelial stem cell lineage may be "recycled" and used for the regenerative niche providing evidence of complexity of epidermal regeneration.		studies indicate that the ASC niche is closely associated with follicular and vascular homeostasis but further studies may define its role in skin homeostasis	

Optics and rebirth of cells that support vision:

The two most important organs: retina and lens, located at the front and back of the eye, plays a significant role in vision. The soluble proteins like denucleated fibres and crystallins are in charge of making the lens mostly transparent. The lens also consists of epithelial cells as a monolayer in its anterior side which repeatedly undergo the process of proliferation and differentiation forming fibres near its posterior side. The lens capsule responsible for covering the lens externally, is comprised of extracellular matrix. Light travels through the lens and gets focused on the retina which further performs the function of converting light into signals (Vigneswara et al., 2015). Opsins, a group of proteins are responsible for this entire process of light conversion. Later these light signals are transferred by means of the optic nerve finally reaching the brain which results in vision. A large number of cells types like cones, Muller cells, rods, horizontal cells, ganglion cells, amacrine cells, bipolar cells and pigment epithelial cells are contained in the retina. Mammalian lens do not have the ability to regenerate.

A most common eye disease leading to human blindness can result from opacification of cataract or the lens. Now a days lens opacification is treated by cataract surgery, a process of eliminating lens fibres leaving behind the lens capsule. The left-over epithelial cells present in the capsular bagfurther undergo the process of regeneration and differentiation producing new fibres. Sometimes, secondary cataract maybe produced from the cataract surgery by the process of EMT which is also known as epithelial to mesenchymal transition. TGF-b, a multifunctional growth factor regulates this entire process by mediating the process of epithelial cells differentiation producing elongated myofibroblast cells which further express a smooth muscle protein. A recent study also showed that secondary cataract formation can be delayed by a C5R antagonist.

However, lens regeneration is often found in lower vertebrates like newts which have the ability to regenerate the lens both as an adult or as a frog tadpole. The iris pigmented epithelial cells present in newts at the posterior side of their eye, undergo the process of trans differentiation forming lens epithelial cells which in coarse of time regenerate the lens. This process is associated with Pax6, FGF, Six3, Shh, Prox1, BMP, Wnt, and retinoic acid (Dietrich, Schrader, 2020). In frog tadpoles, trans differentiating cornea eventually bring lens regeneration using several transcriptional factors like Sox3, Otx2, Pax6, and Prox1. There have also been studies showing different signalling pathways participating in the regeneration process of amphibian lens. However, no studies till date showed evidence of retina regeneration in mammals post injury. An experiment unfolds that Müller glia cells show active response to damage in mammalian models while pigmented progenitor cells is responsible for carrying out the process of trans differentiation finally generating neuronal progenitor-like cells.

FGF and Wnt, the putative proliferation pathways were modified and manipulated in some studies to make the process of retina regeneration a most effective one. The most

dominant models for the process of retina regeneration have always been pre-, post-hatch chicks, amphibians and fishes. In amphibian retina, the regeneration process occurs when the normal development of retina is recapitulated by the retina pigmented epithelium through the process of trans differentiation (Grigoryan, 2018). However, in fishes, the regeneration of retina is usually accomplished when the residual progenitor cells are differentiated into rod photoreceptors, Müller glia then undergo the process of dedifferentiation giving rise to a progenitor-like state which further led to the rods and many other neuronal cell types regeneration. There are several other sources of cells which potentially assist the process of retina regeneration in fishes. These cells are mostly found in the ciliary marginal zone and the circumferential germinal zone.

Additionally, ability to regenerate retina was also observed in embryonic chicks when treated with growth factors. The pathways which crucially takes part in this regeneration process are BMP, FGF and Shh. The Müller glia present in post-hatch chicks have been reported to possess certain ability to carry on the process of retina regeneration. A study also unveiled that in vivo stem cells like iPSC and ESC via differentiation contribute in the process of retinal regeneration finally producing retinal neurons .

Developments in the liver cell regeneration arena:

Regeneration of liver as a response to liver injury can happen in two different ways. Either by the proliferation and regeneration of hepatocytes or from the reserve progenitor cell population when the hepatocytes can no longer regenerate the liver due to senescence or arrest. The main causes of liver injuries are due to drugs, toxins, resection or acute viral diseases.

Liver regeneration is a complex phenomenon that involves several intrahepatic and extra-hepatic constituents along with a huge number of signal molecules. Various extra hepatic factors like partial hepatectomy (PH), aging, platelets, hormones etc. affects the liver regeneration. Regeneration of liver after injuries are mainly achieved by the increase in the amount of organic tissues that result from the proliferation of hepatocytes. This process is highly controlled by the metabolic needs of the liver, it stops once the liver gets its appropriate body weight ratio. The molecule and cellular mechanisms behind liver regeneration is studied mainly using the two third partial hepatectomy in rodents. Later used genetically modified moles for more specific studies. Now global gene expression proliferation gives new discretion to the studies related to the liver regeneration.

The hepatocytes have the ability to re-enter the cell cycle for mitosis which helps in the liver homeostasis. Hepatocytes also show stem cell like characteristics. The hepatocytes are activated upon partial hepatectomy or liver injury which then extend towards the central area of liver lobule and replace the injured cells. The mature hepatocytes show high replication capacity and plasticity.

In hepatocyte mediated liver regeneration process Kupffer cells, hepatic stellate cells (HSC),liver sinusoidal endothelial cells, biliary epithelial cells (BECs) and extrahepatic cells interactions takes place. Also other factors such as blood flow stress, signals, hormones, immune factors, microbiota nerves etc influences this. The initiation and termination of regeneration depends on the regulation of various proliferation and antiproliferation factors (Cherian, Kang, 2006).

Increased blood flow triggers the urokinase plasminogen activator and matrix metalloproteinase to stimulate the breaking down of the extracellular matrix. This results in the release of hepatocyte growth factors (HGF) from ECM. Lipopolysaccharides are produced by inflammatory response binds with the TLR4 Receptor on Kupffer cells causing the release of tumor necrosis factor X (TNFX) and interleukin-6 (IL-6). In addition the HSCs and liver sinusoidal endothelial cells also can produce new HGF together with the growth factor and cytokinins such as epidermal growth factor (EGF) brought by the portal vein flow, liver mitogens reaches a high concentration in the designated site. Then

the HGF binds with receptor called C-Met, while TGF-x and EGF binds to their common receptor known as EGF binds to their common receptor known as EGF receptor (EGFR). This initiates various transduction pathways in hepatocytes. IL-6 can form an excited complex with IL-6R and gp 130 causing the activation of some pathways in hepatocytes thereby regulating apoptosis inhibiting nitric oxide synthase which in turn regulates the regeneration of liver.

All these pro-proliferation substance induced the sequence formation of complex between various cyclins and cyclin dependent kinases (CDK) that induces liver regeneration. Angiogenesis-2 plays an important role. Angiogenesis-2 is down regulated in initial stages of regeneration but then upregulated at the angiogenesis phase and there by regulates the vascular endothelial growth factors that promoter angiogenesis (DeLeve, 2013).

When the volume of the regenerated liver reaches the predetermined proportion termination of the liver regeneration gets activated. TGF-b act as the most significant hepatocyte proliferation inhibitor and termination signal in liver regeneration TGF-b initiates the termination of liver regeneration by regulatory DNA synthesis of cell proliferation. This together with some other negative feedback inhibitions causes the homeostasis of liver regeneration.

Hepatic progenitor cell mediated liver regeneration:

Hepatic progenitor cells (HPCs) serves as the hepatocyte reservoir when the mature hepatocytes fails to regenerate liver due to arrest. HPCs in rodents also known as hepatic oval cells, act as the bipotent progenitor cells. Under the stimulations, the quiescent HPCsproliferates and moves from the surrounding hepatic lobules to the hepatic cords and then differentiates into either hepatocytes or BECs and finally fuse to reconstruct the hepatic lobules. Also the HPCs can be considered as the dynamic stem cells that are capable of expressing different markers based on the lack of epithelial cell type and various pathological features of injury, thus differentiating into different cells. HPCs differentiate into hepatocytes in case of severe loss of hepatocytes whereas it becomes bile duct cells when cholestasis occurs (Al-Ghamdi et al., 2020). The Notch signals play a key role in BEC differentiation.

Factors influencing Liver regeneration:

1) Fibrosis:

The viral, alcoholic and autoimmune hepatitis can induce fibrosis change. The efficiency of HOCs to differentiate into mature hepatocytes is very low in alcoholic hepatitis patients. Liver fibrosis can be a reason for impaired liver regeneration. The liver with fibrosis can activate HSCs and HPCs to promote the regeneration of liver. Various pathological factors that lead to liver fibrosis can also stimulate the institution of liver regeneration.

2) Aging:

The aging liver would cause impaired liver function and poor liver regeneration after transplantation.

3) Platelet count:

From various studies it is found that low platelet count following partial hepatectomy (PH) or live liver transplantation can lead to post operative liver dysfunction and death. However the X granules produced by the platelets contains both pro-proliferation factors and anti-proliferation growth factors which shows multiple effect of platelets on liver regeneration.

4) Neural regulation and Hormones:

There is a direct feedback relationship between the lives and the brain via the autonomic nervous system. The hepatic branches of vagus nerves in rats produce vagus signals that can induce the liver regeneration. Nerve signals also induce the release of

serotonin in enterochromaffin cells after partial hepatectomy thereby facilitating liver regeneration indirectly.

5) Bile acids:

Bile acids act as an important signal regulates in the liver regeneration process; through multiple pathways.

3. Conclusion

The paper focuses on human fascination of animals' astonishing capacity to regenerate bodily parts following injury, and scientists have been drawn to study regeneration occurrences for generations. Much of the debate here is focused on how the goal of understanding the fundamental principles underlining organismal growth is fundamentally comparable to the study of regeneration. The paper has been written with rigorous and comprehensive findings of different research paper studies following Cell Regeneration of Eyes, Skin, Bone and Cardiac tissue and Liver. In a brief, research regarding regeneration of eyes is yet to accomplish something significant for human retina but few active responses has been seen in amphibians, fishes and chickens. Meanwhile, for Regeneration of bone and cardiac, discussion concerning use of 3dbioprinting and angiogenesis has been done with observations based on effects of different growth factors. Whereas, Skin regeneration discussion is based surrounding bulge and mesenchymal stem cells showing the capacity to heal. Regarding liver, the discussion sheds light on research that's been done with respect to intra and extra hepatic cells and signals, and the potential that new global gene expression and proliferation holds. As regards to scope and future of cell regeneration, progress has been made relating to regrowth and regenerative medicine and use of forefront advanced techniques following prime understanding of the molecular and structural biology will be the elementary focus for scientists for the upcoming researches.

References

Adolphe, Wainwright, 2005 – *Adolphe, C., Wainwright, B.* (2005). Pathways to improving skin regeneration. Expert Reviews in Molecular Medicine. 7(20). DOI: https://doi.org/10.1017/S1462399405009890

Al-Ghamdi et al., 2020 – *Al-Ghamdi, T.H., Atta, I.S., El-Refaei, M.* (2020). Role of interleukin 6 in liver cell regeneration after hemi-hepatectomy, correlation with liver enzymes and flow cytometric study. *Clinical and Experimental Hepatology*. 6(1). DOI: https://doi.org/10.5114/CEH.2020.93055

Amini et al., 2012 – *Amini, A.R., Laurencin, C.T., Nukavarapu, S.P.* (2012). Bone tissue engineering: Recent advances and challenges. *Critical Reviews in Biomedical Engineering*. 40(5). DOI: https://doi.org/10.1615/CritRevBiomedEng.v40.i5.10

Ansari, 2019 – *Ansari, M.* (2019). Bone tissue regeneration: biology, strategies and interface studies. *Progress in Biomaterials*. 8(4). DOI: https://doi.org/10.1007/s40204-019-00125-z

Atabay et al., 2018 – *Atabay, K.D., LoCascio, S.A., de Hoog, T., Reddien, P.W.* (2018). Self-organization and progenitor targeting generate stable patterns in planarian regeneration. *Science*. 360(6387). DOI: https://doi.org/10.1126/science.aap8179

Blanpain, 2010 – *Blanpain, C.* (2010). Stem cells: Skin regeneration and repair. Nature. 464(7289). DOI: https://doi.org/10.1038/464686a

Brand et al., 2007 – *Brand, S., Dambacher, J., Beigel, F., Zitzmann, K., Heeg, M.H.J., Weiss, T.S., Prüfer, T., Olszak, T., Steib, C.J., Storr, M., Göke, B., Diepolder, H., Bilzer, M., Thasler, W.E., Auernhammer, C.J.* (2007). IL-22-mediated liver cell regeneration is abrogated by SOCS-1/3 overexpression in vitro. *American Journal of*

Physiology – Gastrointestinal and Liver Physiology. 292(4). DOI: https://doi.org/10.1152/ajpgi.00239.2006

Chandika et al., 2020 – *Chandika, P., Heo, S.Y., Kim, T. H., Oh, G.W., Kim, G.H., Kim, M.S., Jung, W.K.* (2020). Recent advances in biological macromolecule based tissue-engineered composite scaffolds for cardiac tissue regeneration applications. *International Journal of Biological Macromolecules*. 164. DOI: https://doi.org/10.1016/j.ijbiomac.2020.08.054

Cherian, Kang, 2006 – *Cherian, M.G., Kang, Y.J.* (2006). Metallothionein and liver cell regeneration. Experimental Biology and Medicine. 231(2). DOI: https://doi.org/10.1177/153537020623100203

DeLeve, 2013 – *DeLeve, L.D.* (2013). Liver sinusoidal endothelial cells and liver regeneration. Journal of Clinical Investigation. 123(5). DOI: https://doi.org/10.1172/JCI66025

Dietrich, Schrader, 2020 – *Dietrich, J., Schrader, S. (*2020). Towards Lacrimal Gland Regeneration: Current Concepts and Experimental Approaches. *Current Eye Research*. 45(3). DOI: https://doi.org/10.1080/02713683.2019.1637438

Dimitriou et al., 2011 – *Dimitriou, R., Jones, E., McGonagle, D., Giannoudis, P.V.* (2011). Bone regeneration: Current concepts and future directions. *BMC Medicine*. 9. DOI: https://doi.org/10.1186/1741-7015-9-66

Duelen, Sampaolesi, 2017 – *Duelen, R., Sampaolesi, M.* (2017). Stem Cell Technology in Cardiac Regeneration: A Pluripotent Stem Cell Promise. *IEBioMedicine*. 16. DOI: https://doi.org/10.1016/j.ebiom.2017.01.029

Duncan et al., 2009 – *Duncan, A.W., Dorrell, C., Grompe, M.* (2009). Stem Cells and Liver Regeneration. *Gastroenterology*. 137(2). DOI: https://doi.org/10.1053/j.gastro.2009.05.044

Fujita et al., 2000 – *Fujita, M., Furukawa, H., Hattori, M., Todo, S., Ishida, Y., Nagashima, K.* (2000). Sequential observation of liver cell regeneration after massive hepatic necrosis in auxiliary partial orthotopic liver transplantation. *Modern Pathology*. 13(2). DOI: https://doi.org/10.1038/modpathol.3880029

Gonzalez de Torre et al., 2020 – *Gonzalez de Torre, I., Alonso, M., Rodriguez-Cabello, J.C.* (2020). Elastin-Based Materials: Promising Candidates for Cardiac Tissue Regeneration. *Frontiers in Bioengineering and Biotechnology*. 8. DOI: https://doi.org/10.3389/fbioe.2020.00657

González-Sastre et al., 2012 – *González-Sastre, A., MDolores, M., Saló, E.* (2012). Inhibitory smads and bone morphogenetic protein (BMP) modulate anterior photoreceptor cell number during planarian eye regeneration. I*nternational Journal of Developmental Biology*. 56(1–3). DOI: https://doi.org/10.1387/ijdb.123494ag

Grigoryan, 2018 – *Grigoryan, E.N.* (2018). Molecular Factors of the Maintenance and Activation of the Juvenile Phenotype of Cellular Sources for Eye Tissue Regeneration. *Biochemistry (Moscow)*. 83(11). DOI: https://doi.org/10.1134/S0006297918110032

Handberg-Thorsager, Saló, 2007 – *Handberg-Thorsager, M., Saló, E.* (2007). The planarian nanos-like gene Smednos is expressed in germline and eye precursor cells during development and regeneration. *Development Genes and Evolution*. 217(5). DOI: https://doi.org/10.1007/s00427-007-0146-3

Huang et al., 2020 – *Huang, X., Liu, X., Shang, Y., Qiao, F., Chen, G.* (2020). Current Trends in Research on Bone Regeneration: A Bibliometric Analysis. *BioMed Research International*. DOI: https://doi.org/10.1155/2020/8787394

Iaquinta et al., 2019 – *Iaquinta, M.R., Mazzoni, E., Bononi, I., Rotondo, J.C., Mazziotta, C., Montesi, M., Sprio, S., Tampieri, A., Tognon, M., Martini, F.* (2019). Adult Stem Cells for Bone Regeneration and Repair. *Frontiers in Cell and Developmental Biology*. 7. DOI: https://doi.org/10.3389/fcell.2019.00268

Li et al., 2020 – *Li, W., Li, L., Hui, L.* (2020). Cell Plasticity in Liver Regeneration. *Trends in Cell Biology*. 30(4). DOI: https://doi.org/10.1016/j.tcb.2020.01.007

Li, Hua, 2017 – *Li, N., Hua, J.* (2017). Immune cells in liver regeneration. *Oncotarget*. 8(2). DOI: https://doi.org/10.18632/oncotarget.12275

Lin et al., 2020 – *Lin, Y.H., Kang, L., Feng, W.H., Cheng, T.L., Tsai, W.C., Huang, H.T., Lee, H.C., Chen, C.H.* (2020). Effects of lipids and lipoproteins on mesenchymal stem cells used in cardiac tissue regeneration. *International Journal of Molecular Sciences*. 21(13). DOI: https://doi.org/10.3390/ijms21134770

LoCascio et al., 2017 – *LoCascio, S.A., Lapan, S.W., Reddien, P.W.* (2017). Eye Absence Does Not Regulate Planarian Stem Cells during Eye Regeneration. *Developmental Cell*. 40(4). DOI: https://doi.org/10.1016/j.devcel.2017.02.002

Marolt Presen et al., 2019 – *Marolt Presen, D., Traweger, A., Gimona, M., Redl, H.* (2019). Mesenchymal Stromal Cell-Based Bone Regeneration Therapies: From Cell Transplantation and Tissue Engineering to Therapeutic Secretomes and Extracellular Vesicles. *Frontiers in Bioengineering and Biotechnology*. 7. DOI: https://doi.org/10.3389/fbioe.2019.00352

Martin, 1997 – *Martin, P.* (1997). Wound healing – Aiming for perfect skin regeneration. *Science*. 276(5309). DOI: https://doi.org/10.1126/science.276.5309.75

Nourian Dehkordi et al., 2019 – *Nourian Dehkordi, A., Mirahmadi Babaheydari, F., Chehelgerdi, M., Raeisi Dehkordi, S.* (2019). Skin tissue engineering: Wound healing based on stem-cell-based therapeutic strategies. Stem Cell Research and Therapy. 10(1). DOI: https://doi.org/10.1186/s13287-019-1212-2

Radhakrishnan et al., 2014 – *Radhakrishnan, J., Krishnan, U.M., Sethuraman, S.* (2014). Hydrogel based injectable scaffolds for cardiac tissue regeneration. *Biotechnology Advances*. 32(2). DOI: https://doi.org/10.1016/j.biotechadv.2013.12.010

Rebouças et al., 2016 – *Rebouças, J. de S., Santos-Magalhães, N.S., Formiga, F.R.* (2016). Cardiac regeneration using growth factors: Advances and challenges. *Arquivos Brasileiros de Cardiologia*. 107(3). DOI: https://doi.org/10.5935/abc.20160097

Sadek, Olson, 2020 – *Sadek, H., Olson, E.N.* (2020). Toward the Goal of Human Heart Regeneration. *Cell Stem Cell*. 26(1). DOI: https://doi.org/10.1016/j.stem.2019.12.004

Shpichka et al., 2019 – *Shpichka, A., Butnaru, D., Bezrukov, E.A., Sukhanov, R.B., Atala, A., Burdukovskii, V., Zhang, Y., Timashev, P.* (2019). Skin tissue regeneration for burn injury. *Stem Cell Research and Therapy*. 10(1). DOI: https://doi.org/10.1186/s13287-019-1203-3

Smagul et al., 2020 – *Smagul, S., Kim, Y., Smagulova, A., Raziyeva, K., Nurkesh, A., Saparov, A.* (2020). Biomaterials loaded with growth factors/cytokines and stem cells for cardiac tissue regeneration. *International Journal of Molecular Sciences*. 21(17). DOI: https://doi.org/10.3390/ijms21175952

So et al., 2020 – *So, J., Kim, A., Lee, S. H., Shin, D.* (2020). Liver progenitor cell-driven liver regeneration. *Experimental and Molecular Medicine*. 52(8). DOI: https://doi.org/10.1038/s12276-020-0483-0

Takeo et al., 2015 – *Takeo, M., Lee, W., Ito, M.* (2015). Wound healing and skin regeneration. *Cold Spring Harbor Perspectives in Medicine*. 5(1). DOI: https://doi.org/10.1101/cshperspect.a023267

Vig et al., 2017 – *Vig, K., Chaudhari, A., Tripathi, S., Dixit, S., Sahu, R., Pillai, S., Dennis, V.A., Singh, S.R.* (2017). Advances in skin regeneration using tissue engineering. *International Journal of Molecular Sciences*. 18(4). DOI: https://doi.org/10.3390/ijms18040789

Vigneswara et al., 2015 – *Vigneswara, V., Esmaeili, M., Deer, L., Berry, M., Logan, A., Ahmed, Z.* (2015). Eye drop delivery of pigment epithelium-derived factor-34 promotes

retinal ganglion cell neuroprotection and axon regeneration. *Molecular and Cellular Neuroscience*. 68. DOI: https://doi.org/10.1016/j.mcn.2015.08.001

Wong et al., 2012 – *Wong, V.W., Levi, B., Rajadas, J., Longaker, M.T., Gurtner, G.C.* (2012). Stem cell niches for skin regeneration. *International Journal of Biomaterials*. DOI: https://doi.org/10.1155/2012/926059

Xu et al., 2020 – Xu, G.P., Zhang, X.F., Sun, L., Chen, E.M. (2020). Current and future uses of skeletal stem cells for bone regeneration. *World Journal of Stem Cell*s. 12(5). DOI: https://doi.org/10.4252/wjsc.v12.i5.339

Zhai et al., 2020 – *Zhai, M., Zhu, Y., Yang, M., Mao, C.* (2020). Human Mesenchymal Stem Cell Derived Exosomes Enhance Cell-Free Bone Regeneration by Altering Their miRNAs Profiles. *Advanced Science*. 7(19). DOI: https://doi.org/10.1002/advs.202001334