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ADVANCES IN BIOTECHNOLOGY FOR CELLULAR AND TISSUE REGENERATION: CHALLENGES AND PERSPECTIVES IN HUMAN DISEASE TREATMENT

AVANÇOS EM BIOTECNOLOGIA PARA A REGENERAÇÃO CELULAR E TECIDUAL: DESAFIOS E PERSPECTIVAS NO TRATAMENTO DE DOENÇAS HUMANAS

AVANCES EN BIOTECNOLOGÍA PARA LA REGENERACIÓN CELULAR Y TEJIDUAL: DESAFÍOS Y PERSPECTIVAS EN EL TRATAMIENTO DE ENFERMEDADES HUMANAS

Isabele Pagani Pavan[1], Giulia Maria Giacinti[1], Flávio dos Santos Alvarenga[1], Isabelle Mendonça Martins[1], Camilly Victoria Campanharo[1], Matheus Correia Casotti[1], Iúri Drumond Louro[1], Débora Dummer Meira[1]

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ABSTRACT

Biotechnology constitutes a realm of inquiry that extends its benefits across diverse domains of knowledge, ranging from agricultural sciences to clinical applications. This field leverages technology to address challenges frequently entailing living organisms. Of current significance is the endeavor to elucidate the process of animal regeneration, particularly within the human species, given its burgeoning potential as an ally in the treatment and cure of various maladies. Recognizing the societal importance of this subject, the present article seeks to expound upon contemporary biotechnological advancements facilitating the exploration of cellular and tissue regeneration for the treatment of human diseases. To this end, a comprehensive review of articles delineating the current landscape was conducted, involving a comparative analysis of regenerative activity across species, with a specific focus on humans. Evidentially, the use of biomaterials in tissue regeneration assumes paramount importance, albeit not without the formidable challenge posed by the inflammatory process. Stem cells, conversely, present themselves as promising entities in the realm of regeneration. However, their interaction within the host organism necessitates further scrutiny to attain a more nuanced understanding. Despite strides made in the field of regenerative medicine, the lack of comprehensive comprehension regarding the properties of biomaterials and their responses within the human body constrains their clinical applicability. Nevertheless, an auspicious future is envisioned, marked by advancements in biomaterials and a heightened understanding of interactions within the human body, thereby fostering the development of more efficacious treatments for a myriad of diseases.

KEYWORDS: Animal Regeneration. Regenerative Medicine. Biocompatible Materials.

RESUMO

A biotecnologia constitui um domínio de investigação que estende seus benefícios por diversas áreas do conhecimento, indo desde as ciências agrícolas até aplicações clínicas. Este campo utiliza tecnologia para enfrentar desafios frequentemente relacionados a organismos vivos. De significância atual está o esforço para elucidar o processo de regeneração animal, especialmente dentro da espécie humana, dada sua crescente potencialidade como aliada no tratamento e cura de diversas enfermidades. Reconhecendo a importância societária desse tema, o presente artigo busca explicar os avanços biotecnológicos contemporâneos que facilitam a exploração da regeneração celular e tecidual para o tratamento de doenças humanas. Para isso, foi realizada uma revisão abrangente de artigos delineando o cenário atual, envolvendo uma análise comparativa da atividade regenerativa entre espécies, com foco específico em humanos. Evidentemente, o uso de biomateriais na regeneração de tecidos assume importância primordial, embora não sem o desafio formidável imposto pelo processo inflamatório. As células-tronco, por outro lado, apresentam-se como entidades promissoras no campo da regeneração. No entanto, sua interação dentro do organismo hospedeiro exige uma investigação mais aprofundada para alcançar uma compreensão mais matizada. Apesar dos avanços na medicina regenerativa, a falta de compreensão abrangente sobre as propriedades dos biomateriais e suas respostas dentro do corpo humano limita sua aplicabilidade clínica. No

[1] Universidade Federal do Espírito Santo - UFES.

entanto, vislumbra-se um futuro auspicioso, marcado por avanços em biomateriais e uma compreensão aprimorada das interações dentro do corpo humano, promovendo assim o desenvolvimento de tratamentos mais eficazes para diversas doenças.

PALAVRAS-CHAVE: Regeneração Animal. Medicina Regenerativa. Materiais biocompatíveis.

RESUMEN
La biotecnología es un campo de investigación que beneficia diversas áreas del conocimiento, desde las ciencias agrarias hasta las aplicaciones clínicas, utilizando tecnologías para abordar problemas que a menudo involucran organismos vivos. Un gran interés en este campo en la actualidad es dilucidar el proceso de regeneración animal, especialmente en los humanos, ya que se ha convertido en un aliado potencial en la cura y tratamiento de diversas enfermedades. Dada la importancia de este tema para la sociedad, este artículo tiene como objetivo discutir los avances biotecnológicos actuales que ayudan a aprovechar el potencial de la regeneración celular y tisular en el tratamiento de enfermedades humanas. Con este fin, se realizó una compilación de artículos que describen el escenario actual, analizando comparativamente la actividad regenerativa entre especies y humanos. A partir de la exposición, fue posible constatar que el uso de biomateriales en la regeneración tisular es crucial, pero el proceso inflamatorio representa un gran desafío. Las células madre, por otro lado, parecen ser prometedoras en el campo de la regeneración; sin embargo, su interacción en el organismo huésped necesita un estudio más profundo para una mejor comprensión. A pesar del progreso en la medicina regenerativa, la falta de comprensión sobre las propiedades de los biomateriales y sus respuestas en el cuerpo limitan su aplicación clínica. No obstante, se espera un futuro prometedor con avances en biomateriales y una comprensión más profunda de las interacciones en el cuerpo humano, promoviendo tratamientos más efectivos para diversas enfermedades.

PALABRAS CLAVE: Regeneración Animal. Medicina regenerativa. Materiales biocompatibles.

INTRODUCTION

The environment to which an organism is subjected undergoes constant changes, stemming from physical, chemical, or biological alterations that often prove detrimental to the physiology of the organism in question. Accordingly, certain taxa exhibit mechanisms capable of reconstructing, repairing, or even regenerating areas that have been damaged and lost a certain degree of functionality - methods that may be associated with evolutionary adaptations for survival. Among these organisms, planarians possess a superior regenerative capacity when considering their entirety, primarily due to the presence of adult stem cells, known as neoblasts (Pearson, 2022). However, tissue and organ regeneration prove to be a complex strategy for the systems composing the human organism (Rehman *et al.,* 2023). In this context, elucidating mechanisms related to regenerative models observed in basal animals can aid in comprehending the long-term process (Henrot *et al.,* 2023).

The regenerative process relies on a series of phases, including cellular proliferation and differentiation. These stages are influenced by extensive cellular movement and standardization to facilitate subsequent conversion into tissues and organs (Da Silva Filho *et al.,* 2022). It is a highly specialized process that, in adulthood, is more prevalent in other classes of the Animalia Kingdom than in humans. Thus, with the aim of harnessing regenerative properties in healthcare treatments, Human Cell Regeneration research areas have grown since the beginning of the century.

Regenerative medicine is a specialized field that explores the use and regenerative potential of stem cells, biomaterials, and organ and tissue engineering, encompassing related areas of study such as gene therapy (Deguchi *et al.,* 2023). This research field is aligned with the development of effective techniques for implementing artificial tissues that act as substitutes for damaged ones. Its relevance extends from the quest to formulate 3D bio-printing for corneal functional regeneration, given the limitations of corneal transplantation (Jia *et al.,* 2023), to endeavors applying bioengineering techniques in cardiac regeneration, as cardiac tissue ranks among the lowest in regenerative capacities among human tissues (Häneke; Sahara, 2022; Vu *et al.,* 2022).

With this purpose, studies combining this biological process with new technologies gain momentum, contributing to advances in regenerative medicine (Garcìa-Perdomo *et al.,* 2022). In the long term, efforts aim to promote the well-being of patients in need of transplants or to restore damaged and/or diseased organs and tissues (Petrosyan *et al.,* 2022). To achieve this, it is essential to amalgamate knowledge from cellular therapy, tissue engineering, and organ regeneration with available technologies such as nanotechnology and 3D bio-printing (Galliot *et al.,* 2017; Lumelsky, 2021). Consequently, innovative techniques and promising biomaterials for use in human regeneration gain prominence, such as the use of genomic editing tools in conjunction with stem cell studies (Häneke, 2022), as well as genetic editing techniques like CRISPR-Cas (De Sio, Imperador, 2023), and the development of lithium-doped bioactive ceramics (Easterling, Engbrecht, Crespi, 2019) or the utilization of marine collagen for bone regeneration (Farmani *et al.,* 2022).

For decades, the primary focus of regenerative medicine was the study of long bone stem cells and how these could aid in understanding the mechanism of cellular regeneration in humans, driven by the undifferentiated nature of these cells. However, Jeyaraman et al., 2023, indicated, in animal studies, a potential superior efficacy of mesenchymal stromal cells derived from the mandible compared to those derived from long bones, concerning cell proliferation and regeneration. Nevertheless, such evidence must still be studied *in vivo* to substantiate the benefits.

Understanding the described current scenario and seeking to optimize knowledge regarding the interconnection of biotechnology and regeneration, this article delves into the conformity between animal regeneration processes and regenerative methods applicable to humans, aiming to update the panorama regarding regeneration knowledge, concurrently with the use of biotechnology, with the objective of enhancing medicine as a whole.

2 METHODOLOGY

This article is focusing on updating the overall panorama of the relationship between biotechnology and tissue regeneration, especially in humans. To achieve this, a narrative literature review was conducted by searching for articles on the PubMed online database platform. Englishlanguage articles were selected using the descriptors: Animal Regeneration, Regenerative Medicine, and Biotechnology. Regarding exclusion criteria, articles published before 2022 were eliminated, as the focus of this article is to discuss the current state of the topic. At the end of the search, a total of 111 articles were obtained, of which only those presenting a direct correlation between animal regeneration and clinical applications in regenerative medicine, with a special focus on those addressing an integrative view with the use of new biotechnologies, were analyzed and filtered. Thus, 45 articles were properly used for the development of this work.

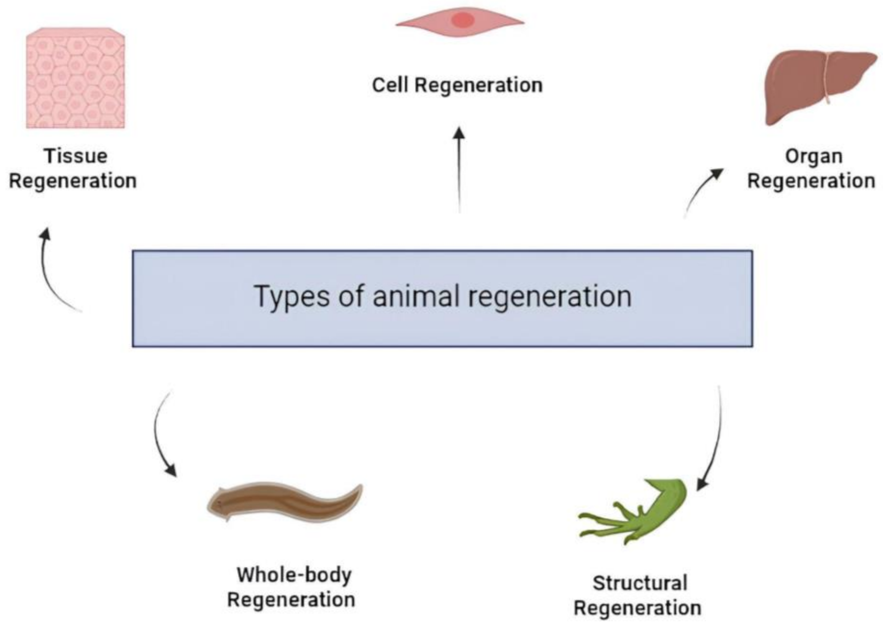
3 RESULTS AND DISCUSSION

3.1 Animal regeneration

The capacity for cellular and tissue regeneration is ubiquitous across all phyla of the Animal Kingdom. However, this ability is not evenly distributed among taxa. Remarkably, as cells and tissues become more differentiated in an organism, their tendency to regenerate large areas of organs and tissues decreases (Galliot *et al.,* 2017). The specificity crucial in cells of tissues in more complex animals is inversely proportional to their regenerative capacity. Therefore, exploring the genetics involved, coupled with evolutionarily conserved inhibitory signals, may aid in understanding these processes (Chen; Poss, 2017; Cigliola *et al.,* 2020).

The Animal Kingdom presents five main types of regenerative processes, involving different organelles and biochemical pathways: cellular, tissue, organ, structure, and whole-body regeneration as shown in Figure 1. In invertebrates such as hydra, planarians, and nematodes, the ease with which they apply whole-body regeneration is noteworthy (Coffman, 2019; Easterling *et al.,* 2019).

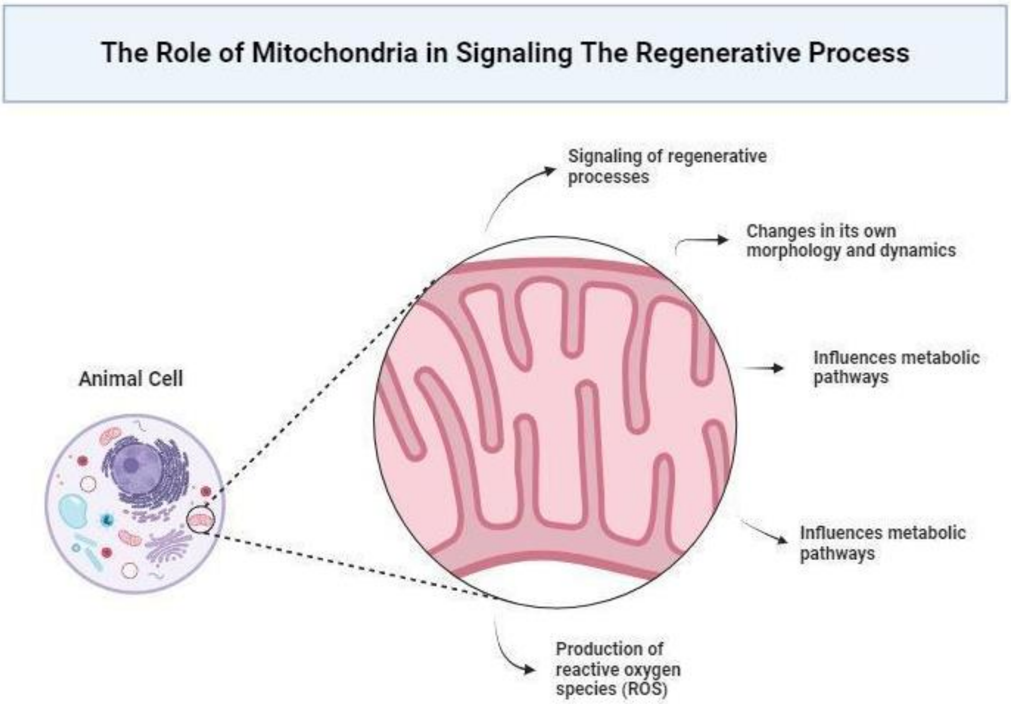
Figure 1 - Scale of cell regeneration: from a single cell to whole body.



Source: created with Biorender, 2024.

Furthermore, the pursuit of a deeper understanding of regenerative processes has been propelled by the consistent use of animal models in various studies in this field. Among nematodes, the species *Caenorhabditis elegans* (C. *elegans)* stands out as an organism frequently employed in *in vivo* research due to its syncytial epidermis and the ease of manipulating its neurons. In cases of epidermal injury, an increase in reactive oxygen species (ROS) concentration has been observed in this model, accompanied by events such as mitochondrial fragmentation, actin polymerization, and subsequent wound healing. Additionally, the presence of neuronal injuries in these organisms exhibits mitochondrial translocation to the affected area, essential for promoting cellular regeneration as shown in Figure 2 (Zhao *et al.,* 2023).

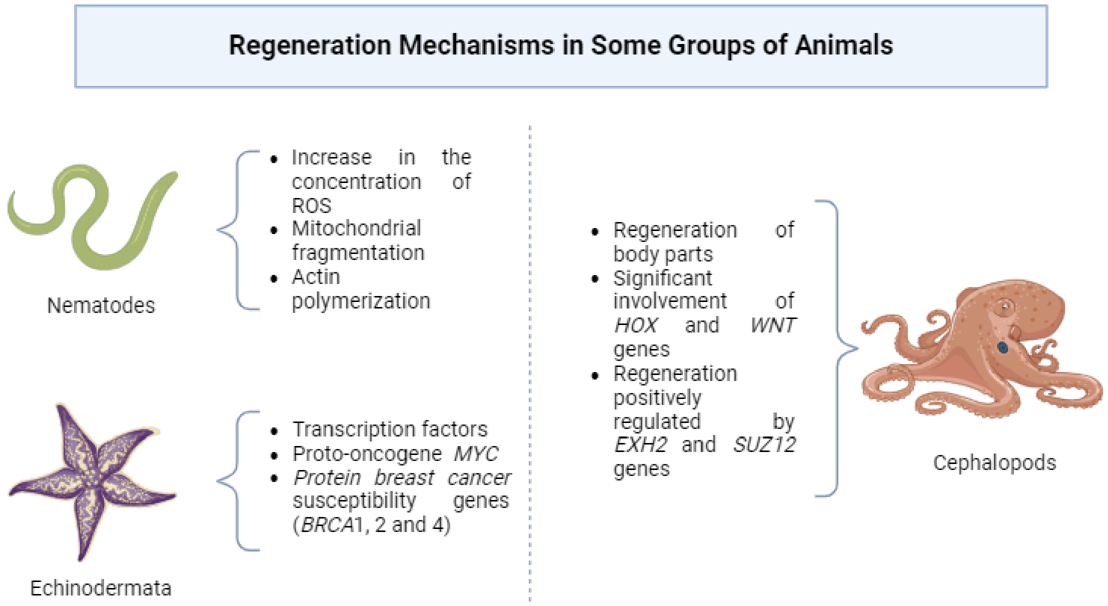
Figure 2 - The role of mitochondria in signaling the regenerative process



Source: created with Biorender, 2024.

Other groups, such as cephalopods, exhibit regeneration of body parts such as muscles, fins, nerves of the central and peripheral nervous systems, cornea, etc. Additionally, research indicates the significant involvement of genes *HOX* and *WNT*, present in various metazoans as shown in Figure 3. These genes allow the growth of appendages in embryos of *Sepia officinalis* and *Sepia bandensis*. Moreover, regeneration is positively regulated by genes *EXH2* and *SUZ12*, influencing blastema formation (De Sio; Imperadore, 2023). Besides understanding genetic regulation, comparing the epigenome of cephalopods with that of other organisms may elucidate new treatments (De Sio; Imperadore, 2023).

Figure 3 - Regeneration mechanisms in some animal groups.



Source: created with Biorender, 2024.

Some other invertebrates also assist in potential future approaches to treating degenerative diseases. This is the case with echinoderms (Figure 3), which, despite their pentaradial architecture, share with chordates the existence of radial glial cells responsible for neuronal migration during embryonic development. Their conservation across evolutionary scales allows for molecular, functional, and morphological comparisons between taxonomic groups, offering an interesting path to investigate for possible future treatments. They perform various relevant functions, such as phagocytosis, secretion, support of the neuroepithelium, progenitor cells, and plasticity. Their regenerative capacity is attributed to numerous transcription factors, such as the proto-oncogene *MYC*, crucial in cellular healing, and the Protein Breast Cancer Susceptibility (*BRCA*) genes, which, when inactivated, allow radial glial cells to function as progenitors (Figure 3) (Mashanov *et al.,* 2023).

In fish and amphibians, regeneration also occurs frequently. However, advancing in evolutionary scale, other vertebrates show a significant reduction in their regenerative capacity, especially mammals and birds. Even reptiles, which can regenerate some body parts like the tail, jaw, teeth, and spinal cord, have regenerative capacity varying according to body size, age, growth pattern, healing, reinnervation, and angiogenesis (Coffman, 2019; Khyeam, 2021; Haddadi; Mousavi, 2020).

Considering evolution, amniotes, over time, became more dependent on higher oxygen levels for survival. This process led to an expanded imbalance between reactive species and antioxidants in the body. Furthermore, throughout development, they maintained a limited number of pluripotent stem cells. Despite the relatively low regenerative capacity of most chordates, these organisms are widely used in *in vivo* studies, such as small rodents. The use of these animals stands out for associated advantages, including wider availability, practicality, ease of handling, lower demand for pre and post-procedural care, and also genetic manipulability (Zhao *et al.,* 2023).

From *in vivo* experiments with these animals, advances are noted in the literature. Studies with mice indicate that axons have high regenerative capacity post-spinal cord injury. Transcriptomics of corticospinal tract neurons demonstrated that they can undergo dedifferentiation to an embryonic state. Clarifying these characteristics can provide advancements in neural transplant areas (Zheng; Tuszynski, 2023). A specific genus of mice is relevant in in vivo experiments. This is the *Acomys* genus, which exhibits an incredible regenerative ability for severe skin wounds and internal injuries. Additionally, there are reports of regeneration after ischemic and visceral injuries in the kidneys, heart, muscles, and spinal cord. This genus is an exception, as the high level of regenerative complexity is not observed in other mammals (Okamura *et al.,* 2023).

Other rodents, such as rabbits and rats, have been used in studies with platelet-rich fibrin (PRF) to improve dental and medical treatment. PRF draws researchers' attention for its assistance in tissue and wound regeneration, as well as the treatment of cardiovascular diseases. Currently, cardiac fibrosis is treated with stents, coronary artery bypass grafting, and transplants. One alternative could be the use of pluripotent stem cells. However, a significant challenge is their low reproducibility in clinical trials, which can be enhanced with *in vivo* studies (Zhao *et al.,* 2023; Mourão *et al.,* 2023). These animals are not only used in cardiovascular studies but also in the treatment of osteoarthritis, soft tissue injuries,

3.2 Biology of regeneration: unraveling the importance of synthetic, systems, and omics biology

Understanding the complexity inherent in the field of regeneration biology prompts an exploration of how synthetic biology, systems biology, and omics can enhance our understanding of human regenerative processes. The omics fields, such as genomics and metabolomics, serve as potential tools to construct an understanding of how synthetic biology is crucial in developing biomaterials applicable in medical and pharmaceutical sciences. This includes applications in bio-printing, a technique aiming to position cells in the extracellular matrix to design artificial organs with new anatomical arrangements. This modernization of transplants aims to reduce the risk of rejection by the donor's immune system (Davies; Cachat, 2016; Matai *et al.,* 2020; Yan *et al.,* 2023). Additionally, synthetic biology enables the understanding of synthetic oscillators and morphogenetic events, aiming at personalizing cells and organs to advance the field of tissue engineering (Davies; Cachat, 2016; Matai *et al.,* 2020). To achieve this, studies on stem cells are necessary to understand the predictable reprogramming of their cellular fate and how they differentiate into specific types (Davies; Cachat, 2016; Matai *et al.,* 2020). To support this area, the use of technologies that enhance the field of bioregeneration is crucial. In this case, data sciences and bioinformatics are branches that can elucidate the mechanisms of action of autotherapies in human tissues (Lumelsky, 2021).

Therefore, it is observed that stem cell niches, when injured, can alter their regulatory landscapes, acquiring, in certain situations, the conforming capacity to induce embryonic homeostasis states. This results in a pro-regenerative microenvironment capable of activating, proliferating, and differentiating stem and progenitor cells, allowing them to form new functional tissues (Lumelsky, 2021).

In order to better understand these regulatory landscapes, also known as epigenetic landscapes, which refer to the modulation of gene expression when exposed to the environment without altering the genetic code, synthetic genetic circuits and transcription factors are constructed to control functions inside and outside the cell. Through these circuits, environmental variations can be detected, triggering a response to produce new proteins or alter their expression patterns (Vogel *et al.,* 2019). This action is exemplified by Chuong *et al.* (2012), who used hair follicles and feathers to study new insights into how the functional activities of stem cells are associated not only with their intrinsic mechanisms but also with external environments, as well as how stem cell conformations are correlated with the different possible tissue molds that will be originated.

Thus, the importance of understanding the epigenetic mechanisms of gene regulation involved in regeneration is emphasized, including transcription factors and cis-regulatory elements, during the adaptive and maladaptive periods, which can be applied in cases of acute kidney injury (Gerhardt *et al.,* 2023). Another technique worth mentioning is single-cell analysis, which also aims to elucidate the cellular fate of stem cells, how environmental signals influence lineage development, and how environmental factors antagonize or act on neighboring cells. In this sense, the technique provides the ability to track the fate of a lineage for subsequent interpretations and decision-making, including information on cellular ancestry, lineage development, and how stem cells are converted into specific tissue groups.

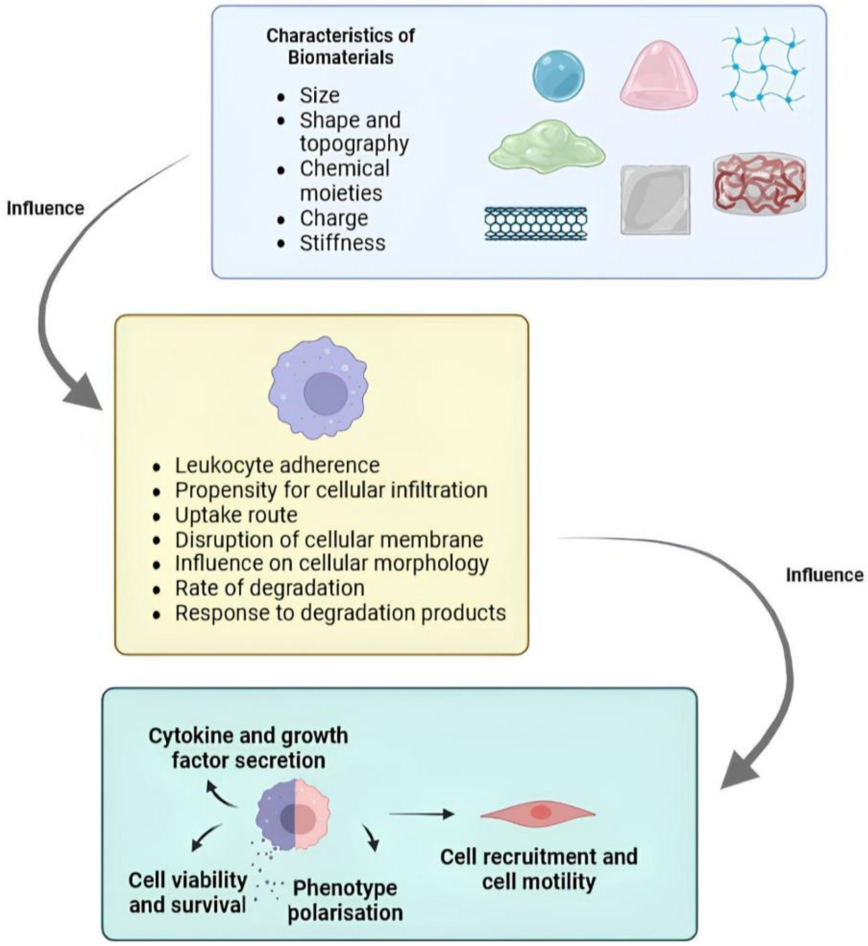
Moreover, cells of interest can be studied through genetic markings with TAGs (transposons, CRISPR arrays, reporter genes, DNA barcodes, CRISPR arrays), in conjunction with mathematical models of cell differentiation using interrelated parameters. These parameters include pseudotime, cell state velocities, and diffusion deviation (Haghverdi; Ludwig, 2022). All the aforementioned information is relevant to contribute to research in tissue engineering areas, aiming to replace damaged tissues and diseases, as well as elucidating the molecular bases of differentiation and subsequent cellular fate to provide relevant information for tissue engineering research (Vogel *et al.,* 2019).

3.3 Biotechnology applied to regeneration

Given the aforementioned content, regeneration is a prevalent phenomenon across the animal kingdom at various levels. Some animals can regenerate tissues, limbs, or even entire organs (Chen; Zhou; Feng, 2022; Walczyńska; Zhu; Liang, 2023). Consequently, research has been directed towards understanding regeneration applied to humans. Regeneration involves the restoration of key structural proteins in the extracellular matrix (ECM) to maintain normal cellular processes. Biotechnology applied to regeneration goes beyond producing ECM components; instead, it utilizes porous biodegradable three-dimensional frameworks to mimic the structure and functions of the natural ECM (Corduff, 2023; Dhania *et al.,* 2022). These are employed in regenerative medicine, tissue engineering, and biomaterials. They interact with living tissues in a biocompatible, non-immunogenic manner, with structures suitable for hosting cells, facilitating cell proliferation, and tissue regeneration (Fadilah *et al.,* 2023).

One of the main challenges in the therapeutic use of biomaterials is inflammation, given that they are extracorporeal. To mitigate inflammation, understanding the properties of biomaterials and the immune responses they can modulate is crucial (as shown in Figure 4). Prolonged inflammation can lead to delayed healing and, consequently, biomaterial rejection. In this context, the choice of biomaterial must be carefully considered to minimize this process, ensuring the body accepts the biomaterial (Linchar; Lavelle, 2022).

Figure 4 - Biomaterial properties dictate immune response and efficacy.



Source: Adapted from Linchar and Lavelle, 2022. Created with Biorender, 2024.

Biomaterials can be natural or synthetic. Natural biomaterials are derived from other living systems, such as bacteria, plants, fungi, and animals. They are biocompatible, biodegradable, and possess the ability to remodel damaged structures/tissues in vivo. On the other hand, synthetic biomaterials are easily reproducible polymers, highly available, and can be chemically modified.

Regardless of their origin, they are expected to be incorporated into the biological system without adverse effects, such as inflammation. Table 1 below lists the most commonly used biomaterials in the medical field (Chen; Agrawal; Thankam, 2022).

Frame 1: Main natural and synthetic biomaterials.

Type	Natural Biomaterials	Synthetic Biomaterials
Examples	Collagen, Gelatin, Chitosan, Silk, Hyaluronic Acid, Fibrin	Polyethylene Glycol (PEG), Poly(lactic-co-glycolic acid) (PLGA), PVC
Properties	Biocompatible, Biodegradable, Tissue Remodeling Capability	Reproducible, Chemically Modifiable, High Availability
Applications	Tissue Engineering, Wound Healing, Drug Delivery	Implants, Drug Delivery, Scaffolds for Tissue Engineering
Considerations	Derived from living organisms, Mimic natural tissue properties	Controlled fabrication, Tailored for specific applications
Challenges	Potential allergenicity, Variability in sourcing	Inflammatory response, Long-term effects not yet fully understood

Source: Adapted from Chen, Agrawal & Thankam (2022)

Stem cells are also widely employed as biomaterials in regenerative medicine, as they possess innate regenerative potential to restore the function and structure of damaged or diseased tissues. Adult stem/progenitor cells, located in niches within adult tissues and organs, can be hematopoietic, mesenchymal, endothelial progenitors, neural, and have the advantage of being mobilized to distant sites of injury to participate in tissue repair and regeneration as shown in Figure 5 (Safina; Embree, 2022).

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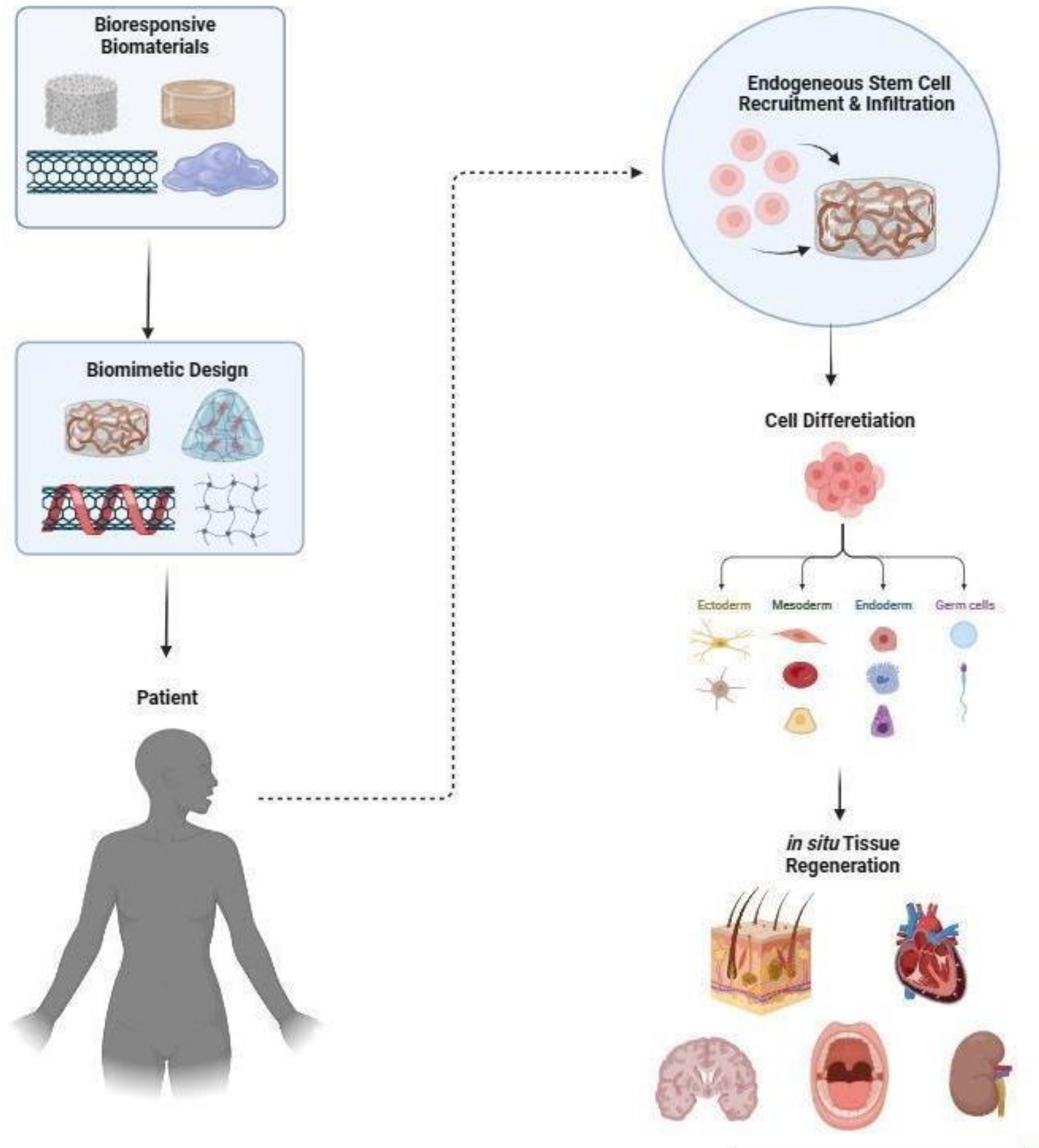
Figure 5 - Biomaterials utilizing endogenous stem cells *in situ* tissue regeneration.



Fig, 5 - This figure illustrates the innovative approach of employing biomaterials to harness the potential of endogenous stem cells for *in situ* tissue regeneration. The biomaterials act as scaffolds, providing a conducive environment for the activation, proliferation, and differentiation of existing stem cells within the damaged tissue. This strategy aims to stimulate the natural regenerative capacity of the body without the need for exogenous stem cell transplantation. The depiction showcases the interaction between the biomaterial and endogenous stem cells, highlighting the key steps in the process. The biomaterial, designed to mimic the extracellular matrix, promotes cell adhesion, migration, and tissue remodeling. This *in situ* regenerative approach holds significant promise for various medical applications, including wound healing, tissue repair, and regenerative medicine.

Source: Created with Biorender, 2024

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In the context of the diverse biotechnological applications in regeneration, there is a growing focus on continuous research involving new biomaterials. Additionally, the application of this technology is carefully examined for each specific tissue or organ, as illustrated by the utilization of fish skin for connective tissue regeneration (Esmaeili *et al.,* 2023). However, there remains a limited understanding of the biocompatibility of biomaterials within the host system, and significant challenges are posed by inflammatory and immune responses. Consequently, the utilization of these materials is constrained, and a lack of awareness among medical professionals about the applications of new products often leads to a preference for traditional methods over regenerative medicine treatments.

Therefore, studies considering the properties of biomaterials, their inflammatory response, and clinical requirements are imperative. Despite these challenges, the future outlook for regenerative medicine products is promising, and biotechnologies for regeneration may progressively gain commercial traction and widespread adoption, potentially revolutionizing the treatment of numerous diseases (Chen; Agrawal; Thankam, 2022; Beheshtizadeh *et al.,* 2022).

4 CONSIDERATIONS

The loss of regenerative capacity throughout evolutionary scales has notably made room for other characteristics that proved more suitable for species maintenance, aiming to meet the demand for tissue specialization. Currently, through the use of model species, biotechnological tools such as omics, along with *in silico*, *in situ*, and *in vivo* studies, research to answer how and which cellular, metabolic, and embryonic mechanisms led to this alteration in regenerative capacity has been advancing. By combining evolutionary studies with new omic data to elucidate what remains of ancestral regenerative processes, a more comprehensive understanding of the enduring mechanisms can be achieved, seeking new treatments for various pathologies.

It is also understood that biomaterials, whether natural or synthetic, have been essential in tissue regeneration, but inflammation poses a crucial challenge. Stem cells hold promise for regeneration, but there is a need to better understand their interactions within the host organism. The application of these technologies is restricted due to a lack of comprehension of their properties and inflammatory responses, leading traditional methods to still be preferred in clinical practice.

Regenerative medicine has made significant strides, with constant studies on new biomaterials and their specific applications, such as the use of fish skin for connective tissue regeneration. However, challenges persist, primarily regarding the biocompatibility, inflammatory response, and clinical acceptance of these materials. The need for more in-depth studies considering the properties of biomaterials and their responses in the organism is evident for the continuous progress of this field. In summary, despite current limitations and challenges, the future of regenerative medicine is promising. With the refinement of biomaterials, a more detailed understanding of host interactions, and the development of more tissue or organ-specific technologies, significant advancement in treating various diseases is expected. Finally, evolution reduced regenerative capacity in favor of more adaptive specializations; however, modern scientific research, combining biotechnology and evolutionary studies, has unveiled ancestral regenerative mechanisms to advance the treatment of human diseases.

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