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Review

Future regenerative medicine developments and their therapeutic applications

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ABSTRACT

Although the currently available pharmacological assays can cure most pathological disorders, they have limited therapeutic value in relieving certain disorders like myocardial infarct, peripheral vascular disease, amputated limbs, or organ failure (e.g. renal failure). Pilot studies to overcome such problems using regenerative medicine (RM) delivered promising data. Comprehensive investigations of RM in zebrafish or reptilians are necessary for better understanding. However, the precise mechanisms remain poorly understood despite the tremendous amount of data obtained using the zebrafish model investigating the exact mechanisms behind their regenerative capability. Indeed, understanding such mechanisms and their application to humans can save millions of lives from dying due to potentially life-threatening events. Recent studies have launched a revolution in replacing damaged human organs via different approaches in the last few decades. The newly established branch of medicine (known as Regenerative Medicine aims to enhance natural repair mechanisms. This can be done through the application of several advanced broad-spectrum technologies such as organ transplantation, tissue engineering, and application of Scaffolds technology (support vascularization using an extracellular matrix), stem cell therapy, miRNA treatment, development of 3D mini-organs (organoids), and the construction of artificial tissues using nanomedicine and 3D bio-printers. Moreover, in the next few decades, revolutionary approaches in regenerative medicine will be applied based on artificial intelligence and wireless data exchange, soft intelligence biomaterials, nanorobotics, and even living robotics capable of self-repair. The present work presents a comprehensive overview that summarizes the new and future advances in the field of RM.

1. Introduction

Over the centuries, scientists have been interested to understand how can amphibians and reptilians regenerate their amputated limbs [1]. The regenerative capacity of many animal species as zebrafish is restricted to extremities and helps regenerate internal organs like injured heart muscles or hepatic tissues [2,3]. Although several adult mammalian organs like the heart, brain, and liver are incapable of functional self-recovery following injury, understanding the mechanisms and factors allowing reptilian fish. Even mammalian fetuses from self-renewable will start an evolutionary era in medicine that will save millions of lives of patients suffering from congestive heart failure and myocardial infarction (MI) due to the limited number of donors for heart transplantation [4,5]. However, despite the enormous size of available data aiming to understand such regenerative mechanisms, limited outcomes have been achieved from the pilot studies about their application in mammals. With the evolution of interdisciplinary medical sciences in the last decades, a new branch of medicine occurred,

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namely regenerative medicine (RM). It applies engineering and life sciences principles to heal or replace damaged tissues, promote organ renewal, restore lost functions, and continually bridge permanently emerging damages [6].

2. Examples of cardiac regeneration capacity

2.1. In zebrafish and amphibians

Heart regenerative capacity can be seen in zebrafish *(Danio rerio)* and amphibians like salamanders (*Cryptobranchoidea Salamandroidea*). They can completely regenerate their cardiac muscles even following resection of 20% of the heart. The structure and functionality of the newly formed heart muscles resemble the original muscular tissues [2,3]. However, the regenerative power of cardiomyocytes in zebrafish is not absolute. The injury size, cause of injury, and immune status influence the efficiency of the healing power. For instance, surgical resection of the ventricle of the zebrafish adult heart can be completely regenerated without fibrotic scarring within two months only if the amputated part is less than 20% of the total ventricular size, while cryoinjuries usually result in incomplete heart regeneration [7,8].

Researchers focus on zebrafish as an innovative natural biological model for understanding the mechanisms of RM. However, they are evolutionarily more distant from humans than other mammalian animal models. This attention is based on (1) its capability of regenerating most of its organs, such as the heart, following heart injury, (2) its short lifespan, and (3) its availability and low cost. Notably, the regeneration of cardiomyocytes in zebrafish does not require stem cells or cell re-differentiation but resembles wound healing. The heart bleeds for a few seconds before a fibrin clot is built when the cardiac tissue is injured. During the following days, the clot is gradually replaced by normal heart tissue synthesized by the proliferation of neighbor pre-existing cardiomyocytes and neovascularization [9]. However, it is not yet fully clear what signals are required for the heart regeneration process [10]. One of these principal proteins required for the signaling process is the cellular communication network factor 2a (CCN2a) encoded by *ccn2a* gene [11]. The presence and the possible role of other signalling and molecular pathways in the zebrafish cardiomyocyte regeneration process include hippo/YAP/TAZ, meis1, TGFβ-activin, hypoxia, Wnt/β-catenin, Insulin-like growth factor (IGF), Reactive Oxygen Species (Ros), monocyte/macrophage, CDK9/PTEFb, and miRNA need further investigation [12]. Heart transplantation is one of the limited available therapeutic options for MI patients. Additional future RM alternatives to heart transplantation include using cardiomyocyte stem cells to replace the damaged cell and reprogram fibroblasts into new functional cardiomyocytes [4,13]. Clinical trials targeted cardiac repair after myocardial infarction via promoting cardiomyocyte proliferation through stimulating cardiomyocyte cell cycle re-entry. Data analysis from pilot studies referred to limited success in stimulating the proliferation of terminally differentiated cardiomyocytes [14].

2.2. In mammals

On the contrary side to zebrafish, following Myocardial Infarction (MI) in humans, healing takes place through the formation of fibrotic scarring. Although the fibrous tissue preserves ventricular wall integrity, it leads to ventricular pathological re-modeling, irreversible and permanent cardiac damage, undermines pump function, and ultimately heart failure. Unfortunately, the prognosis of heart failure following myocardial infarction is usually poor as the available therapeutical approaches do not directly replenish the damaged myocytes [14].

However, some mammalian species possess myocardial regenerative capacity limited to their neonatal stage and disappear following birth. For instance, cardiomyocytes of mice fetuses and even one-day-old neonatal mice retain their mitotic capacity to regenerate damaged cells via the proliferation of pre-existing cardiomyocytes with minimal scar tissue formation. However, the capability of differentiated cardiomyocytes to proliferate arrests completely after the 7th day of life in parallel to the withdrawal of the cardiomyocytes cell cycle accompanied by their switch from hyperplasic to hypertrophic growth modus [8,15]. It is important to differentiate between heart growth before and after birth. Before birth, the growth is mainly via the proliferation of mononucleated cardiomyocytes. Therefore, after the first week of life, injured mice hearts will immediately react with a severe inflammatory process and the formation of massive scar tissue, which will interfere with the normal regenerative healing process and, consequently, normal heart performance [7].

Under certain circumstances, the hearts of adult mice undergo myocardial regeneration following MI. The decisive player in this process is a protein secreted by bone marrow-derived monocytes and macrophages called the Myeloid-derived growth factor (Mydgf) [16]. Such proteins may be used to stimulate cardiomyocytes regenerative ability as troponin I3 kinase, insulin-like growth factor 1, the nuclear lamina filament Lamin B2 (Lmnb2), and long noncoding RNAs (lncRNAs) as cardiomyocyte proliferation regulator (CPR) [16]. The inactivation of Lmnb2 upon birth is responsible for the loss of the regenerative power of cardiomyocytes and reduces the karyokinesis in human induced pluripotent stem cell-derived (iPS) cardiomyocytes. Modifying Lmnb2 expression in infant humans suffering from heart diseases showed promising effects as a therapeutic alternative [17]. Moreover, neonatal mice reactivation of cardiomyocyte proliferation can be suspended in response to immunosuppression due to the absence of interleukin-6 (IL-6), which complicates understanding of the whole healing mechanisms [7,8]. Additional factors such as the lympho-angiocrine signals (released by the lymphatic endothelial cells (LECs)) also play a role in cardiac renewal in neonatal mice. They influence both proliferation and survival of mice fetal cardiomyocytes to promote cardiac regeneration following myocardial infarction [18]. Other non-genetic factors also play a decisive role, such as postnatal overfeeding, resulting in short- and long-term cardiovascular dysfunction due to its epigenetic modulation of gene expression and their direct effect on gut microbiota.

Similarly, neonatal malnutrition affects the proliferation, differentiation, and regeneration of fetal mice cardiomyocytes [19]. In humans, the exact timing of cell proliferation arrest and the exact capacity of proliferation is still unknown. However, adult human cardiomyocytes do not completely lose their regenerative capability as 1% of the cells (at the age of 25 years) and 0.45% (at the age of 75) can be renewed annually. About half of human cardiomyocytes are renewed during the entire human life [20].

In addition to their hearts, mice can also regenerate their livers completely within only ten days, even after two-thirds partial hepatectomy. The liver can be regenerated through various mechanisms including hypertrophy, hyperplasia, dedifferentiation, and redifferentiation [21]. The information gained from studying rodents' fundamental hepatic and cardiac regenerative capacity was applied in RM to mammalian models like pigs, dogs, and sheep as a pilot stage in preclinical trials before applying it to humans [22,23]. Understanding the mice's regenerative mechanism can save thousands of lives of patients waiting for heart and liver transplantation worldwide [21].

3. Present approaches of RM

At the time, novel technologies were applied for restoring impaired organ functions expanded to encompass numerous strategies (Table 1), such as:

(1) enhancing the natural repair mechanisms (e.g. using growth factors and miRNA treatment). Although the growth factors and cytokines play a major regulatory role in cell division, differentiation, migration, and finally, cell apoptosis, uncontrolled release of kinetics following the administration of the growth

Table 1
A list of developed organoids from various body organs.

Organoid	Origin	References
Pancreatic organoid	Endoderm	[241]
Thyroid organoids	Endoderm	[242]
Adrenal gland organoids	Mesoderm	[243]
Pituitary organoids	Ectoderm	[244,245]
Mammary organoids	Ectoderm	[246]
Prostate gland organoids	Endoderm	[247,248]
Salivary gland organoids	Ectoderm	[249]
Testicular organoids	Mesoderm	[250]
Ovaries	Mesoderm	[251]
Fallopian tube, endometrium, and placental organoids	Mesoderm	[160,252, 253]
Hepatic and biliary tract organoids	Endoderm	[136,137, 254]
Intestine organoids	Endoderm	[255]
Stomach organoids	Endoderm	[256]
Oesophages organoids	Endoderm	[257]
Cardiovascular organoids	Mesoderm	[258]
Blood vesicles	Mesoderm	[259]
CNS organoids (Brain and neurons)	Neuroectoderm	[260,261]
Kidney organoids	Mesoderm	[262]
Bladder organoids	Mesoderm	[263]
Lung and airway organoids	Ectoderm	[264]
Retina and optic cup organoids	Neuroectoderm	[265,266]
Inner ear organoids	Ectoderm	[267]
Skin organoids	Ectoderm	[268]
Sweat glands	Ectoderm	[269]
Lacrimal gland organoids	Ectoderm	[270]
Oral organoids of the tooth, taste buds, and tongue organoids	Ectoderm	[249]
Bone organoids	Mesoderm	[271–273]
Bone marrow organoids	Mesoderm	[274,275]
Cartilage organoids	Mesoderm	[276]

factors may lead to severe complications [6,24]. In Old Egypt, honey was used to treat burns and wounds via enhancing natural repair mechanisms. Recently, additional medical applications of honey were reported for cartilage tissue engineering. The honey acts as a natural biomaterial scaffold or hydrogel, providing a favorable 3D microenvironment for tissue regeneration [25–27].

(2) Organ transplantation (e.g. heart, liver, kidney transplantation, or bone marrow transplantation and even hand and face transplantation) [28].

(3) Implantation of organs originating from genetically modified swine. Most recently, according to the data published by the NYU Langone Transplant Institute (New York University, USA), Montgomery and his team could implant a genetically modified swine kidney in a brain-dead human patient. The kidney was hooked outside the body to facilitate the monitoring and tissue sampling process. No rejection could be seen as the genetically modified pigs lost their ability to produce α-gal epitope (Galα1-3Galβ1-4GlcNAc-R) expressed in swine tissues and provoked the human immune system to reject the organs. A biocompatible xenograft-derived bone scaffold/bone graft could also be obtained from the modified porcine [29,30].

(4) With the advances in organoid technology, the production of mini-organs which resemble the structure and function of the native organs, provided a good alternative for organ transplantation [31].

(5) Gene therapy to repair concrete genetic defects with phenotypic consequences. This approach can be applied to correct hereditary abnormalities and pathological defects resulting from acquired diseases such as cancer (e.g. anti-cancer therapy by suicide genes), and even for the treatment of para- or tetraplegia. Experimental gene therapy could recently achieve revolutionary success in treating paralyzed mice subjected to a complete spinal cord crush [32].

(6) Tissue engineering using differentiated cells that maintained their proliferative capacity and were grown in the laboratories (e.g. skin grafting) and stem cell therapy using low antigenic allogeneic cells (e.g. human foreskin fibroblasts for wound-healing grafts). Their low antigenicity prevents the provocation of adverse immune reactions [6,33]. However, although low antigenic allogeneic cells overcome immune rejection of the implant, their application remains coupled with the risk of disease transmission contrary to the use of autologous grafts, which are much safer but the scarce supply of donor tissue limits their mass application. Modern tissue engineering technology develops mixtures of cells and bio-degradable scaffolds as skeletons for tissue formation [34–36].

(7) The use of bio-compatible materials to be integrated into the healing process, such as bioglass-based grafts, which fuse with the bones and enhance their healing [37].

(8) Biomechanics and prosthetics approach such as the design of synthetic bladder which mimics the biomechanical properties of native human bladders [38] or artificial intervertebral discs (IVD) to replace degenerated/injured discs through the use of biomaterials to simulate the height, neutral zone characteristics, and torsional biomechanical properties of the IVD. However, pilot trials of using prosthetic devices to treat IVD showed low success due to (a) technical difficulties in the production of durable artificial IVD which mimic the structure, function, mechanical properties, and size of the natural discs, (b) stability of the fixed IVD and their anchorage to the vertebral spines, and (c) the inflammatory reactions in response to the permanent friction and wear debris. A second alternative for IVD treatment is through the use of allografted discs. However, animal trials using this approach were also not promising due to the rapid development of progressive degeneration shortly after transplantation [34].

(9) Nanotechnology-based therapeutic approaches. Nanomaterials can provide rapid, effective, economical, and specific human and animal solutions [39,40]. Several nanomaterials (e.g. nanostructured titanium surfaces) were adopted for use in RM. They were developed to produce bone / dental implant surfaces/fibers that imitate bone structure and are now commonly used in bone regeneration. They provide optimal cell adhesion, maximal functionality, and minimal complications [41]. Moreover, linear nanostructures (e.g. Titanium inductively coupled deep plasma etching) were also developed to enhance endothelial cell proliferation [42]. In RM, nanoparticles represent a safer and more efficient alternative to viral vectors currently used for gene transfection [43].

(10) Through reprogramming the body cells to gain new characters and functions. Successful trials were carried out to convert mouse fibroblasts into cardiomyocyte-like cells through their treatment with cardiac-specific transcription factors such as Gata4, and Mef2c [4].

(11) Combinations of some of the previously mentioned approaches like combining nanomaterials with stem cell technology (e.g. stem cells labeled with silica NPs). NPs are increasingly used in RM due to their regulatory role in controlling stem cell behavior. They tract the SC in vivo, determine their origin, promote their differentiation, and enhance their migration, proliferation, and retention after transplantation (i.e. enhance cell homing at the injury site). Their ability to control overexpression/down-regulation of regulatory genes may be explained through their modulatory effect on the intracellular microenvironment, such as the pH value [43]. However, although the application of such combinations is promising, additional studies are urgently needed to evaluate the safety of this approach [44].

At present, different commercial FDA-approved regenerative medicine-based products are available. For instance: (a) biological

products (e.g. Carticel, autologous chondrocytes for the reconstruction of damaged cartilages and Cord blood, a stem and progenitor cells for the immunological reconstitution following myeloablative therapy), (b) Biopharmaceutical (e.g. Regranex, (platelet-derived growth factor (PDGF) used for foot ulcers in diabetics, and Infuse, Stryker's OP-1 (bone morphogenic proteins 2 and 7) bone graft for tibia fractures) and (c) cell-mediated factors (e.g. Dermagraft, for the treatment of diabetic foot ulcer) [6]. The present work aims to discuss different approaches applied in regenerative medicine and their possible application to replace and overcome the missing organ functionality after injury or congenital deformities. The present work also briefly describes promising future approaches in RM.

4. Enhancing new tissue formation to support natural repair mechanisms

4.1. Formation of 3D tissues (using Scaffolds technology)

Few materials are approved to support the 3D tissue formation. The used materials have to mimic the native extracellular matrix (ECM) to influence and direct the cell behavior to grow in a similar structure and function to the original ones [6]. Scaffolds are 3D polymer biomaterial building temporary structures/skeleton to support 3D cell proliferation and vascularization. The used biomaterials (1) provide a suitable base for 3D cell proliferation, (2) have adequate stability, (3) possess an optimal biodegradation rate, and (4) can be of natural origin (plant, insect or animal origin as collagen, fibrinogen, and hyaluronic acid), or synthetic (as synthetic polymers e.g. poly N-isopropyl acrylamide, poly-L-lactic acid, and poly lactic-co-glycolic acid) [45]. The polymers vary greatly in their characters. Therefore, it is important to know the exact characteristics of all used polymers to select the optimal one according to the purpose / clinical requirement. i.e. some polymers (e.g. PLG) initiate inflammatory response upon implantation, making them ideal for cancer immunotherapy to initiate inflammation-driven vascularization [46–48]. Other polymer scaffolds clearly promote expansion, making them ideal support for chondrocytes in cartilage repair (as the matrix-induced autologous chondrocyte implants) [6,49]. However, the wide use of the scaffolds in RM still faces many technical problems concerning the manufacturing process, provocation of inflammatory / immune responses, and the degradation rate of the used materials.

4.2. Enhancing neovascularization to support natural repair mechanisms

One of the main strategies to boost natural repair mechanisms is to enhance neovascularization to restore normal blood flow to ischemic tissues and the transplant/graft to guarantee a continuous supply of the grafts with oxygen and nutrients. The lack of sufficient active vascularization leads to necrosis of the grafts and the rejection of the transplant [50,51]. Angiogenesis is necessary for regenerating damaged / ischemic tissues such as nervous or cardiovascular tissues and even bones. In RM, many approaches are applied to stimulate angiogenesis and osteogenesis and to restore the vascularization process, such as (1) treatment with endothelial progenitor cells (EPCs) to improve the ischemic symptoms [52], and (2) via the administration of certain growth factors e.g. the vascular endothelial growth factors (VEGF), fibroblast growth factors (FGF), platelet-derived growth factor (PDGF), hypoxia-inducible factor 1α (HIF-1α), Placenta derived growth factor (PIGF), Angiopoietin 1, Ephrin-B2, transforming growth factor-β, keratinocyte growth factor (KGF), Insulin-like growth factor (IGF), hepatocyte growth factor (HGF), and Erythropoietin (EPO) [50,53–56]. These growth factors can be delivered using certain carriers or scaffolds to enhance granulation tissue formation, new tissue generation, and wound healing. VEGF-based treatment can even speed up wound healing in diabetic mice [50,57]. However, other approaches to support natural repair are also under development, such as enhancing DNA repair pathways. This tool is mainly used for the treatment of therapy-resistant neoplasm which usually possesses defective DNA repair pathways such as the downregulation of MMR genes (in colon cancer) or silencing of MGMT (in glioblastomas) [58].

5. Angiogenesis in RM

5.1. For the treatment of cardiovascular diseases

Cardiovascular diseases are the major cause of death worldwide claiming about 17.9 million deaths annually [59]. Several approaches were tested to regenerate infarcted heart muscles with minimal success due to the limited improvement of necrotic cardiac tissue following the re-enhancement of blood flow in the infarcted parts. This is attributed to the restricted regenerative capability of the heart muscle and the rapid formation of fibrotic non-contractile scars [60,61]. One of these RM approaches is through transplantation of myocardial cells, which could only improve heart function for a short period due to the poor retention of the cells [59]. As an alternative approach, it is now focused on administering exosomes to enhance the angiogenesis process. Exosomes are rich in miRNA and mRNA (which are potent regulators of gene expression). Their unique structure and function favor their therapeutic application for the regeneration of cardiac muscles following MI [62–64]. These trials are based on the reported association between cardiomyocytes and the production and release of MI-exosome. The influence of the expression level of miRNA-143 and miR-294 on angiogenesis is well documented [65,66].

A large number of miRNAs are now known to be involved in angiogenesis. Among the key miRNAs players are the MiR-126 (regulates the VEGF pathway and vessel permeability), miR-210 (regulates post-ischaemic neovascularisation), and miR-23–24–27 cluster (for the regulation of neovascularisation in MI mice, increases capillary density, and improves cardiac function) [59]. The use of intradermal MRG-110 injection enabled rapid wound health and activated the myofibroblasts at the injection site [67]. The administration of synthetic cholesterol-conjugated single-strand RNA analogs (miR-24 antagomirs) can improve cardiac function and vascularization following MI in experimental animals. Similarly, the suppression of miR-92a by antimir-92a can improve angiogenesis in experimental animals suffering from MI [68,69]. Running clinical trials delivered promising results for using multi-vessel intracoronary delivery of exosomes derived from cardiac progenitor cells for the regeneration of MI. They efficiently decrease the formation of fibrotic tissue, prevent apoptosis, initiate the regeneration process and restore normal physiological contractability [66,70].

In humans, accumulating shreds of evidence point to a crucial role of the protein Mydgf during cardiac repair via the enhancement of angiogenesis and inhibiting cardiomyocyte apoptosis. Recombinant human Mydgf mediates the proliferation of endothelial cells through MAPK-STAT3 signaling pathways. Although human Mydgf is expressed by monocytes, T and B lymphocytes, endothelial cells, and cardiomyocytes, the key question of whether Mydgf can promote the regeneration of human cardiomyocytes remains unknown [16,71,72]. In tissue culture studies, human c-kit positive cells isolated from the human myocardium were able for self-regeneration to produce new cardiomyocytes and coronary vessels in the laboratories [20].

5.2. Angiogenesis and cancer therapy

Angiogenesis is essential for tumor progress, proliferation, and metastasis [73]. The inhibition of tumor vascularization was successfully used in treating oral, prostatic, and renal cancers in pilot studies. Among the suggested approaches in cancer RM is the inhibition of the hypoxia-induced factor-1α (HIF-1α) responsible for the direct initiation of expression of the Hepatoma-derived growth factor (HDGF) and the vascular endothelial growth factor (VEGF). This will result, in turn, in the inhibition of endothelial cell proliferation [73,74]. However, the

control of cytokines on cell proliferation and apoptosis is usually impaired in cancer due to abnormal RNA stabilization, which leads to overexpression of cytokine and growth factor receptors encoding [24]. Using monoclonal antibodies to VEGF as a possible approach for cancer therapy showed promising results [75].

5.3. For regeneration of injured nerves

Regeneration of injured sciatic nerve could be achieved via using the natural material chitin coupled with nanoparticles and conductive hydrogel. The neuro-regenerative changes also included successful angiogenesis and Schwann cell adhesion [76].

6. Gene therapy/editing and the use of synthetic mRNA in RM

A lack of gene editing tools has long hampered the treatment of several inherited diseases. Gene therapy is a relatively new branch of RM that depends on introducing engineered viruses loaded with a copy of the therapeutic gene. The use of clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas 9)-based medication for this purpose is now a well-established tool. The used CRISPR is a family of DNA sequences present in the bacterial genome and originated from bacteriophages [77]. This approach was used for the treatment of (1) genetic disorders (e.g. primary immunodeficiencies and hemophilias), (2) tumor therapy (e.g. leukemias) [78], or (3) to enhance the regeneration of tissues that lost their ability to regenerate (e.g. nerve cells).

6.1. Gene therapy for the regeneration of damaged nerves

The absence of regenerative capability of severed axons makes nerve damage a serious event and usually results in permanent disabilities. However, the regeneration of the nervous tissues in RM can be achieved via the deletion of the suppressor of cytokine signaling 3 in nerve cells to enhance the healing and regeneration of injured nerve axons [79]. Clinical trials confirmed locomotor recovery and full resumption of mobility in all limbs in paralyzed mice subjected to a complete spinal cord crush. This could be achieved with cytokine stimulating JAK/-STAT3 signaling and axon regeneration following transduction of cortical motoneurons of the paralyzed mice using an Adeno-associated virus expressing hyper-IL-6 (hIL-6) [32]. This enabled, in turn, the expression and transneuronal delivery of hIL-6 at innervated neurons in the brain stem. As a result, the crushed corticospinal and raphespinal fibers could be healed and regenerated, and the mouse could resume its mobility [32]. The technique was also applied to restore the functionality of injured optic nerves by activating the transcription 3 (JAK/-STAT3) pathway in vivo. The activation of the pathway leads, in turn, to the delivery of IL-6- type cytokines as CNTF, LIF, and IL-6, in addition to the genetic reduction of the intrinsic STAT3 feedback inhibitor suppressor of cytokine signaling 3 to enhance the regeneration of the damaged nerve [79].

6.2. The use of synthetic mRNA in RM

The alternative approach to gene editing is now well established and was recently used to develop novel Covid 19 vaccines. This approach is based on the combined use of synthetic mRNA, or none coding RNA carried on nanoparticles (mainly lipid NP), lipid and polymer hybrids, dendrimers, and aptamers. It can be applied in (a) vaccine preparation e.g. against cancer and infectious diseases, (b) for restoring deficient proteins, (c) the production of pluripotent stem cells from somatic cells, and (d) in gene editing (Fig. 1) [80–83].

7. Stem cells (SCs) transplantation

Stem cells are undifferentiated cells that retain their capability of

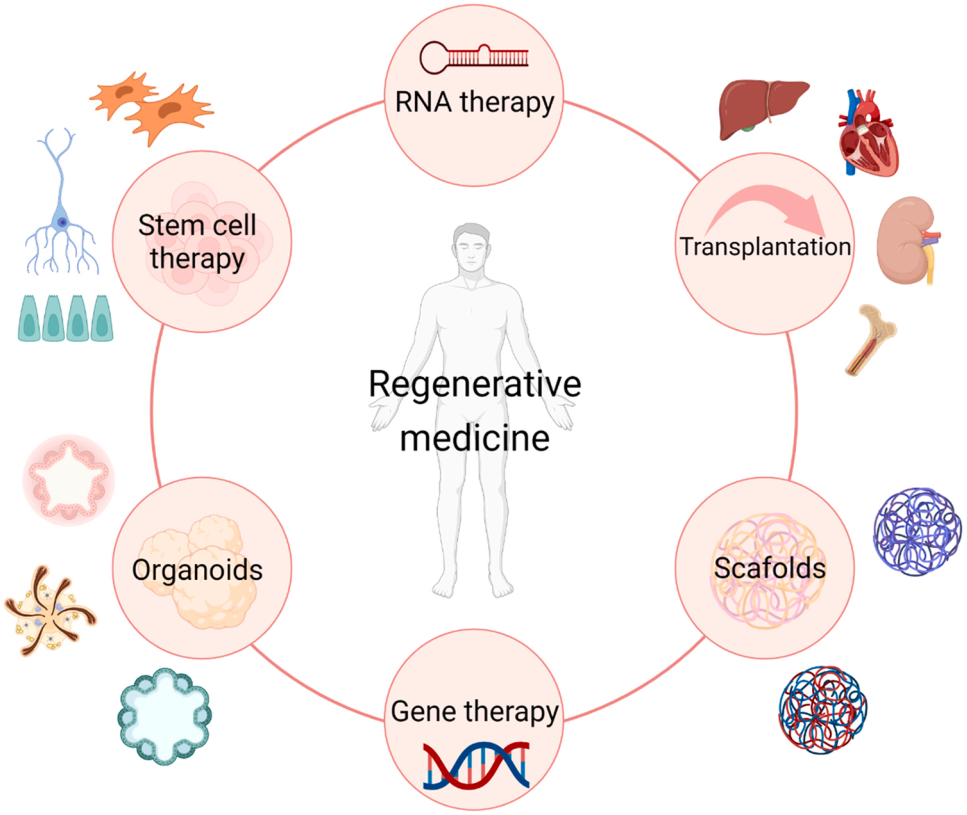

Fig. 1. Major technologies used in RM at present.

self-renewal and differentiation into specialized cells. Their therapeutic application aims to overcome the limited regenerative ability of damaged tissues/organs and to resume disturbed metabolic/functional disorders [84]. The therapeutic uses of stem cells to regenerate damaged organs started in the late 1990 s to treat cancer (e.g. leukemia and lymphoma). Pilot trials used autologous (stored/frozen person's own SCs) and allogeneic (compatible donor's SCs) transplants.

However, the modest results of using SCs obtained from the bone marrow directed the focus to search for resident stem cells in the heart. The differentiation of injected stem cells into cardiomyocytes and their integration into the myocardium was unsuccessful. The experiments failed due to immune rejection, poor engraftment, genetic instability, carcinogenicity (risk of building teratocarcinoma), and poor electrical coupling between the new and the host myocardial cells [59]. Several types of precursors originating from the original undifferentiated cardiac stem cell could be detected in human heart tissues like c-kit positive, cardiosphere-derived cells (CDCs), and islet-1 positive cells. Other stem cell types were also reported, including Sca-1 positive and cells with persistent expression of Abcg2, in addition to verapamil-sensitive side populations (SP) with stem cell-like activity [20].

Although allogeneic SCs are more available for wide usage, their transplantation will be recognized by the recipient CD8 +T cells and antigen-presenting cells, leading to their attack/ elimination by the immune system. The use of autologous SCs can avoid such disadvantages. However, they are usually available in limited amounts for therapeutic uses [84]. The concept of using self-tissues to overcome immunological mismatches leading to organ rejection is preferred [35]. To overcome the shortage in autologous SC, induced pluripotent stem cells (iPS) are used. The cells are obtained by reprogramming self-somatic cells to be converted to the pluripotent state. This conversion can be achieved by introducing certain transcription factors (e.g. OCT3/4, SOX2, KLF4, and C-MYC) to the genome. However, some obstacles remain to be solved, such as genetic instability. Retroviral transductions may also have carcinogenic effects (tumorigenesis) due to chromosomal alterations [85].

7.1. Classifications of stem cells and their therapeutic value in RM

There are two kinds of classification of stem cells. According to the developmental stage, the first approach is to divide them into embryonic stem cell (ESC) and adult stem cells (ASCs). The other approach is to divide them into totipotent stem cells (TSC), pluripotent stem cells (PSC), multipotent stem cells (MSC) and unipotent stem cells (USC) according to their developmental potential as shown in Table 2 [86,87].

In the last few years, some groups of stem cells were involved in RM proved their therapeutic value such as:

(A) Mesenchymal multipotent stem cells, which were used for the restoration of (1) diabetic foot, (2) musculoskeletal disorders and joint injuries, (3) acute and chronic renal disorders, and (4) several blood diseases. In addition, the utilization of the protective properties of MSCs against oxidative stress enabled their use to stop cell aging via the prevention of telomere shortening in target cells [88–92].

(B) Pluripotent stem cells (embryonic) provide unlimited raw materials for different cell types with high therapeutic value. They can be used for tissue transplantation, disease modeling, and drug screening purposes [52,93]. Several pilot studies tested human-derived induced pluripotent SC and human embryonic stem cell-derived cardiomyocytes to treat cardiovascular diseases. Their application could improve cardiac function following myocardial infarction and minimize fibrosis of scarred tissues. Meanwhile, human-derived mesenchymal SC (e.g. Adipose-derived MSCs) can also be used for the same purposes and their role in the treatment of peripheral vascular disease by enhancing therapeutic angiogenesis and vascular regeneration. They are clinically used to treat CNS diseases (e.g. Parkinson's and Alzheimer's diseases), diabetes mellitus, cardiovascular disorders, and rheumatic arthritis [43].

Table 2
The table summarizes the different subgroups and main classifications of the Stem according to previous reports [277–279].

SC are self-renewing and undifferentiated cells which are able to differentiate into several types of other functional cells. They can be divided into subgroups based on:					
According to their developmental stages:		According to their differentiation potential:			
Embryonic stem cells (ESCs): ESCs are the most studied type of stem cells. They originate from the pre-implantation blastocyst where they build the inner cell mass of the blastocyst. They can be induced to differentiate to all body cell types (almost).	Adult stem cells (ASCs): undifferentiated lineage-committed cells which are scattered in various body tissues and organs. They are postnatal derivatives of Embryonic stem cells. ASCs maintain their capability to co-express three (at least) out of the four transcription factors characteristic of Embryonic stem cells namely the OCT4, KLF4, and SOX2. They have the ability to renew themselves and simultaneously divide to produce at least one type of tissue-specific daughter cells in order to keep the normal turnover of the tissues in which they reside. ASCs can be divided into different subgroups including the mesenchymal SC (MSCs), neural SC (NSCs), hematopoietic SC (HSCs), and induced pluripotent SC (iPSCs).	totipotent stem cells (TSCs), The term (totipotent cells) is limited only to the first embryonic cells that occur as a result of the first couple of cell divisions of fertilized ova (first 1–3 days after fertilization; i.e. the Zygote and early Blastomeres). Therefore, Totipotent cells can differentiate into all cell types in a body or in the placental and extra-embryonic cells.	pluripotent stem cells (PSCs). (occur at the days 4–14 after oocyte fertilization). They are those cells that can differentiate into all cell types of the body.	multipotent stem cells (MSCs)/ progenitor cells: They have restricted differentiation power as they can only differentiate into some (more than one) cell type but not to all cell types of the body. They play a major role in healing process. Divided into different types according to their location e-g- brain's MSCs (divide to neural cells and glia) and haematopoietic SCs in the bone marrow (differentiate to blood cells). Similarly Adipose SCs, Dental pulp SCs, and Keratinocyte SCs.	Unipotent stem cells (USCs): the least potent group. They can differentiate into only a single lineage such as the muscle stem cells.

7.2. Examples of successful applications of stem cell transplantation in RM

Promising data could be obtained from pilot clinical studies investigating the therapeutic value of SC for the treatment of serious diseases as caner [94,95], cardiovascular diseases [96,97], immunodeficiency and metabolic disorders [98,99], neurodegenerative diseases [100–103], hepatic and renal disorders [104,105], diabetes type 1 and 2 [106–108], infertility [109,110], blindness [111,112], dentistry [113], joint diseases [88], wound healing [114], immune system disorders due to defects in NK cells [115,116], hepatic and renal failure [117–119] (Table 3, Fig. 2).

Table 3
Indications of stem cell transplantation in RM.

Indication	Examples	Reference
Cancer	Leukemia (Acute lymphocytic, Acute myelogenous and Chronic myelogenous forms), Myelodysplastic syndrome, Neuroblastoma Hodgkin's disease, Non–Hodgkin's lymphoma, and Burkitt's lymphoma. Glioma, Colon adenocarcinoma, Metastatic and primary lung cancers, Breast cancer, Hepatocellular carcinoma, Lymphomas, and Melanoma	[94,95],
Blood and cardiovascular disorders:	Anemia (Sickle-cell, Aplastic, Diamond– Blackfan, Fanconi's forms), Congenital cytopenia, Amegakaryocytic thrombocytopenia, Thalassemia Evan's syndrome, and cardiac diseases	[96,97],
Immunodeficiency disorders	Adenosine deaminase deficiency, Wiskott-Aldrich's syndrome, Duncan's disease, Ataxia-telangiectasia, digeorge's syndrome, Myelokathexis, Hypogammaglobulinemia, and Severe Combined immunodeficiency,	[98,99],
Congenital metabolic disorders	Adrenoleukodystrophy, Gunther's disease, Gaucher's disease, Hurler's syndrome, Hunter's syndrome, Krabbe's disease, Sanfilippo's syndrome, Tay-Sachs' disease	[98,99],
Neurodegenerative and nervous diseases	Spinal cord lesions, Lou Gehrig's disease, Alzheimer's Disease, Parkinson's disease, Multiple sclerosis (MS), Huntington's disease, stroke and cerebral ischemia, Amyotrophic lateral sclerosis, temporal lobe epilepsy, neonatal hypoxic-ischemic encephalopathy	[100–103],
Hepatic and renal disorders	Cirrhosis and kidney diseases	[104,105],
Newly diagnosed type 1 and 2 diabetics, and to treat the related complications	Such as diabetic foot, vascular complications, and problematic wound healing	[106–108],
Infertility and disorders of the male and female reproductive systems	Loss of spermatogonial SC as a result of pediatric gonadotoxic therapy. Hormonal disturbance of the ovaries.	[109,110],
Treatment of blindness and vision impairment	Corneal injuries	[111,112],
Dentistry	Tooth degeneration	[113],
Musclo-skeletal	Joint affection	[88],
Wound healing	Ulcers and diabetic foot	[114],
Primary immunodeficiencies associated with defects in NK cells		[115,116].
Hepatic failure	As a consequence of toxication or medication	[117,118].
Renal failure	As a consequence of toxication or medication	[119].

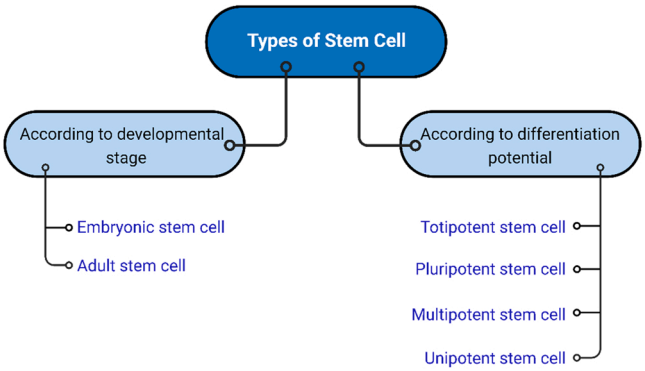

Fig. 2. Main types of stem cells based on their developmental stage and potetial of differentiation.

8. Application of organoid technology in RM

Organoids are complex 3D cell constructions arranged in clusters of miniature organ-like structures. They grow in vitro in suspension cultures to avoid direct physical contact with the bottom of the dish. Organoids are self-organized structures extracted from stem cells that contain fully differentiated functioning cell types resembling the structure and function of the native organs. They provide revolutionary personalized medicine and launch new horizons in cell therapy and drug screening [120,121]. Organoids can be established directly from various organs through the reprogramming of differentiated cells (induced pluripotent stem cells) or from pluripotent embryonic stem cells (Table 1). They can also be obtained from tissue biopsy samples containing resident adult stem cells [31]. For developing an organoid, the co-culture of various cell types representing a mixture of more than one of the three germ layers (endoderm, mesoderm, and ectoderm) may be required. Multistep pluripotent stem cell differentiation protocols are usually applied for this process [122].

Pilot studies indicated that combining induced pluripotent stem cell (iPSC)-derived organoids and the genome engineering/gene editing tools using CRISPR-Cas9 technology increases their development efficiency [123–125].

For instance, gene-modified immunotherapeutic organoids could be generated through gene editing in autologous MSC. The modified cells are then injected subcutaneously into a non-immunogenic matrix-based scaffold which helps the cells to survive and prevents their escape from the implantation site [126]. The immunotherapeutic organoids provide a new prospect for cancer immunotherapy and precision medicine and will write a new revolutionary chapter in drug screening and cell therapy [127]. They offer a dynamic tool to monitor the spatiotemporal process of early organ development during the embryonic stage. It offers efficient models for studying various developmental and degenerative disorders such as Alzheimer's disease, supplies researchers with an efficient preclinical platform to test, develop and evaluate personalized regenerative medicine, and, finally, it opens a new horizon for RM and replaces the growing need for organ transplantation [128] (Fig. 3). The organoids may also be used to prepare other therapeutic biological materials of non-human origin, such as providing snake venom for commercial purposes in mass production and lower costs. Venom glands constructed by the organoid development tools could secrete functionally active toxins [129].

8.1. Intestinal organoids

Chronic bowel diseases such as ulcerative colitis and Crohn's disease are long-standing diseases. The real cause of the disease remains unclear, although several infectious agents, none infectious factors, and even predisposing genetic factors are linked to the disease initiation [130–133]. However, with the progress in organoid development,

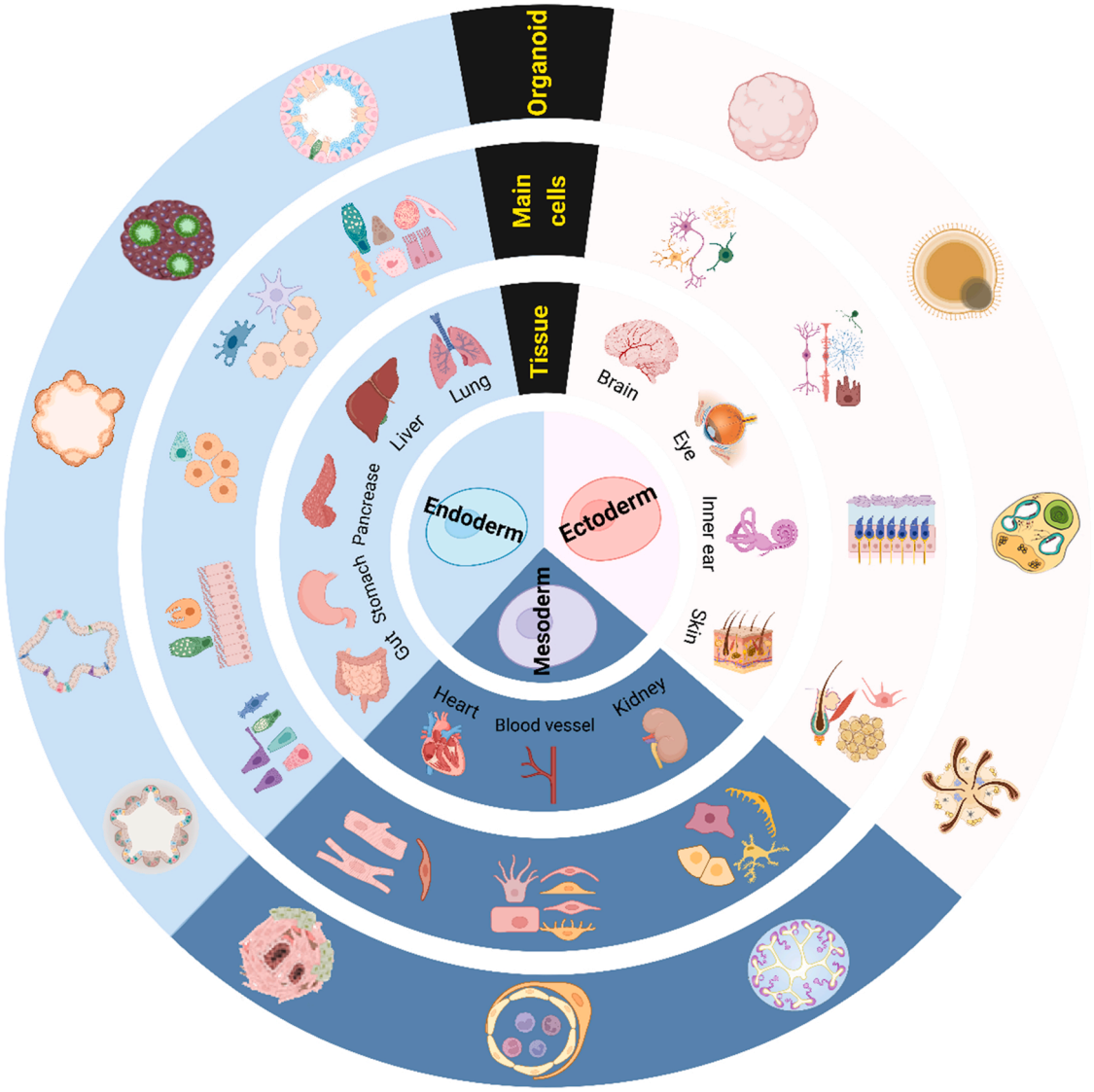

Fig. 3. Schematic diagram summerizes the different known types of organoids and their origin in the human body.

organoids extracted from the fetal intestine or adult small intestine stem cells could successfully repair the damaged tissues and reconstruct the crypt-villus structures upon their transplantation onto the colonic ulcers using an endoscopic cell delivery system in the animal model. In personalized RM, the use of self-organoids obtained from the crypts from adjacent intact areas to engraft the damaged tissues overcomes rejection of the graft by the immune system and provides for the first time an efficient therapeutic approach for these diseases [134].

8.2. Hepatic organoids

Due to the growing international demand for liver lobes in response to the increase in chronic liver disease and hepatocarcinoma associated with an obvious deficiency in liver lobe donors, the international demand to develop functional mini-liver in vitro is increasing [135]. The grown tissue using hepatic organoid technology included differentiated hepatic cells and vascular networks [136,137]. Successful implantation of hepatic organoids in mice resulted in the development of functional hepatic tissues and promoted the recovery of mice suffering from acute liver failure. The promising delivered data enables the treatment of liver cirrhosis in the near future [138].

8.3. Pancreas organoids

The lack of authentic disease models for studying diabetes represented a great obstacle to the complete understanding of the human pancreatic islets' physiological, pathological, and developmental conditions. Pancreas organoid technology enabled a better understanding of several pancreatic signaling pathways and enhanced the development of novel therapeutic concepts to completely cure metabolic disorders for the first time [139]. Implanted pancreatic organoids in the peritoneal cavity of immunodeficient mice grew and matured within 5 weeks and built a neovascularization network. The graft contained many beta cells, providing a direct revolutionary therapeutic approach for diabetes type I and II and other metabolic diseases [140,141]. Moreover, pancreas organoid technology provides a preclinical model for studying additional serious pancreatic health problems such as the highly aggressive pancreatic ductal adenocarcinoma [142–144].

8.4. Kidney organoids

The international demand for kidney transplantation is great. Pilot studies with renal organoids delivered promising success. The transplantation of hPSC-derived kidney organoids under the renal capsule of

immunodeficient mice resulted in their maturation, accompanied by the development of podocytes and the related glomerular vascularization connected with the pre-existing vascular networks. Glomerular perfusion could also be established [145,146].

8.5. Heart organoids

The advances in reprogramming specialized somatic cells to obtain induced pluripotent stem cells enabled the modeling of the human heart. They empowered the production of 3D personalized cardiomyocytes identical to the native phenotype [147]. It was reported that three different cell types could be observed within 24 h of hiPSC-derived cardiac organoid transplantation on the internal abdominal muscle of mice (cardiac progenitor cells, MSCs, and endothelial cells). The organoids were able to build an extensive neovascularization network and express physiological functions within the first month [148].

8.6. Lung and airway organoids

The development of lung organoids is important for future therapy of airway diseases, such as asthma and pulmonary cancer. However, mini-lung development still faces technical obstacles related to cell maturation, morphogenesis, and mesenchymal nature. The use of multiple microporous scaffolds provided some advantages in the production of lung organoids [149,150].

8.7. Brain organoids

Brain organoids generated from human pluripotent and induced neural stem cells became a novel model for studying neurogenerative diseases (e.g. brain ischemia) and infectious diseases (e.g. ZIKA virus-induced microcephaly in new borne babies) [151]. Immunodeficient mice were inoculated with thymus, brain, and bone marrow human organoids to obtain a suitable animal model for studying Zika virus infections in humans [152–154]. Transplanted human brain organoids in a mouse medial prefrontal cortex could grow, maturate and differentiate into different brain regions (e.g. cerebral cortex, the cerebellum, or the midbrain). Later on, mini-brains could be synthesized from a single organoid which can differentiate into different brain parts. Brain organoids showed a satisfactory degree of functionality [120]. They represent a future therapeutic option for treating cerebral diseases and provide new opportunities for testing and evaluating new drugs [151].

8.8. Retinal organoids

Transplanted retinal organoids in the subretinal space of mice could develop photoreceptors and get integrated into the host retina. However, their performance did not match the functional expectations. Improvements to the used protocol resulted in enhancing color vision during daylight [155,156]. However, with further maturation of the protocols, the visual functions and light sensitivity could be enhanced through the improvement of physical contact between the implanted organoids and the host inner retinal neurons and the expression of the phototransduction-related proteins [157]. At present, organoid technology has facilitated the development of a functional eye model in organotypic 3D configuration for the first time [158].

8.9. Organoids of the female reproductive tract

Constructing an experimental model of a female genital system is difficult due to its cellular heterogeneity and the complexity of the control mechanisms that regulate the reproductive system. The use of the animal model is not practical due to the anatomical and physiological differences, regulation and frequency of the estrous cycle, menstruation, litter size, and type of placenta among various mammals. The development of 3D organoid system from the human genital tract could resolve this issue and provide a functional model of the female genital tract [159]. At present, developed organoids cover all organs of the female reproductive system [159], such as fallopian tube organoids [160], endometrial organoids [161], and cervical and vaginal organoids [162,163]. They provide new therapeutic concepts for endometriosis and endometrial, ovarian, and cervical carcinoma [159]. Moreover, the development of mini-placenta represents a huge step in treating infertility and disorders related to pregnancy, conception, and stillbirth [164].

8.10. Other organoids

There are several additional types of organoids in the body. These include for example, skin organoids (which are derived from PSCs and can organize themselves to form skin-like structures of both skin progenitor cells and hair follicles that resemble the fetal skin [165]), gastrointestinal Organoids (which are derived from PSCs. They consist of three-dimensional structures build by epithelial and mesenchymal cells including esophagus organoids, Stomach organoids [166]) or Prostate organoids (which have a great medical value as they are used in the validation of preclinical anti-cancer drug and to predict their therapeutic efficiency [167].

9. The use of three-dimensional (3D) printers in RM

The new technology enables the computer-controlled fabrication of 3D living constructs on a moving platform. In clinical trials, 3D printers could successfully print bone fragments, cartilage, skin grafts, skeletal muscles, blood vessels, cardiac tissue, and heart valves. The application of 3D bioprinting is a very promising evolutionary approach in RM that might replace other approaches shortly [168–170].

10. Current challenges associated with regenerative medicines

Efficiency and safety issues are the most challenging aspects facing the application of innovative assays of RM when applied in treating various diseases [171]. For instance, stem cell therapy faces several challenges, including determining the best types of cells to be used and selecting the suitable therapeutic approach for every case. However, the key challenge in the therapeutic application of stem cell therapy is the development of a fast, easily operated and low-cost technique to isolate and purify the right cells from a multi-type cell mixture in the culture [172]. Similarly, several technical difficulties slow down wide range application of organoid technology despite the recent advances in this field. The challenges are mainly attributed to the differences in the structure between the organoids and their real organ, the difficulties in delivering the growth factors responsible for in vitro maturation of the organoids, the poor reproducibility for massive production, technical challenges facing culturing of organ mimicking organoids such as the unsuitable size of generated organoids for organ transplantation, and the limited maturity and cell diversity. It is also a great challenge to reduce cell variability in the culture. At present, all organoids generated under laboratory conditions cannot completely recapitulate the organs regarding cell types and maturation. Moreover, as iPSCs might be incompletely differentiated, they might show oncogenic potential with increased risk for the development of certain types of cancer such as teratomas [123,173].

Similarly, the use of nanoparticles in therapeutic and diagnostic protocols is restricted due to safety hazards [171]. In the meantime, it faces serious additional challenges such as improving the used nano-materials and their therapeutic properties. The continuous development and improvement of robust cell/material/gene delivery systems also represent a growing challenge for RM [174]. The lack of complete understanding of the mechanisms of interaction between the nano-materials and different stem cell lines and how they are metabolized complicates their wide application [172]. Currently, several researches

are running all over the world aiming to provide novel solutions to overcome these technical and life-threatened obstacles limiting the large-scale application of the RM assays.

11. Future aspects of regenerative medicine

In view of the shortcomings of the available therapeutic methods for regenerating vital organs, several research teams devoted themselves to developing novel therapeutic approaches to overcome the current strategies. This, in turn, will enable revolutionary advances in RM in the near future. The new approaches are mainly based on innovations in artificial intelligence, biomaterials, micro-robotics, and genome editing [175]. Several novel RM concepts have started to bear expected fruits and deliver promising results. In the present chapter, many of the future aspects of RM will be briefly discussed.

11.1. New future RM approaches to restore the functionality of injured nerves

The prognosis of nerve injuries is usually unsatisfactory. Currently, the gold standard for treating such injuries is autologous nerve grafting, which has several disadvantages concerning complications and the lack of donors. Therefore, several research teams focus on novel approaches for neurorehabilitation.

11.1.1. Using conductive hydrogels "molecular glue"

Electrically conductive biomaterials as hydrogels hold promise as they provide 3D-safe structures, can enhance nerve remyelination and are easily integrated in different shapes, sizes, and forms [76]. The new generation of conductive polymers (e.g. polypyrrole, polyaniline, and poly (3,4-ethylenedioxythiophene) are characterized by their high conductivity and biocompatibility [176]. However, further studies about the long-term safety of the used polymers, their degradability, and long-term changes in their mechanical and physical properties must be carried out before being widely applied to humans [76]. As an alternative, natural super-soft DNA hydrogels and super-elastic magnetic DNA hydrogel-based robots (DNA robots) were developed. They are self-assembly shape-adaptive which can build a network to trap magnetically driven navigational locomotion of inoculated stem cells in target sites. The network is characterized by the controlled release of trapped cells [177].

11.1.2. New future RM approaches to restore vision

There are several approaches under research for this purpose including the use of visual prostheses systems, signal amplifier electrodes, or DNA editing:

(i) The newly developed neural visual prosthesis supplied with a high-resolution digital camera (such as the Aurgus II Retinal Prosthesis System) enabled the replacement of older models which allow limited vision usually light and dark (Fig. 4). The system consists of a brain implant and an external digital camera connected through wireless radiofrequency (RF) telemetry to an additional unit to analyze the pictures and transform them into electrical signals before forwarding them to the brain. Other systems are also under development, such as the suprachoroidal prostheses system, intelligent retinal implant system, artificial silicon retina, and photovoltaic retinal implant bionic vision system. These systems delivered variable degrees of success and are still in need of further improvements [178]. Another approach was tested in a blind monkey to achieve the same goal, where the brain cortex was electrically stimulated via implanted electrodes on the surface of the brain to restore vision [179].

(ii) The second approach is through epigenetic reprogramming genomic DNA to recover youthful epigenetic information. This can be achieved by restoring youthful DNA methylation patterns and the youthful transcriptomes to promote axon regeneration after injury. In an animal model, the nerve cells of a blind mouse

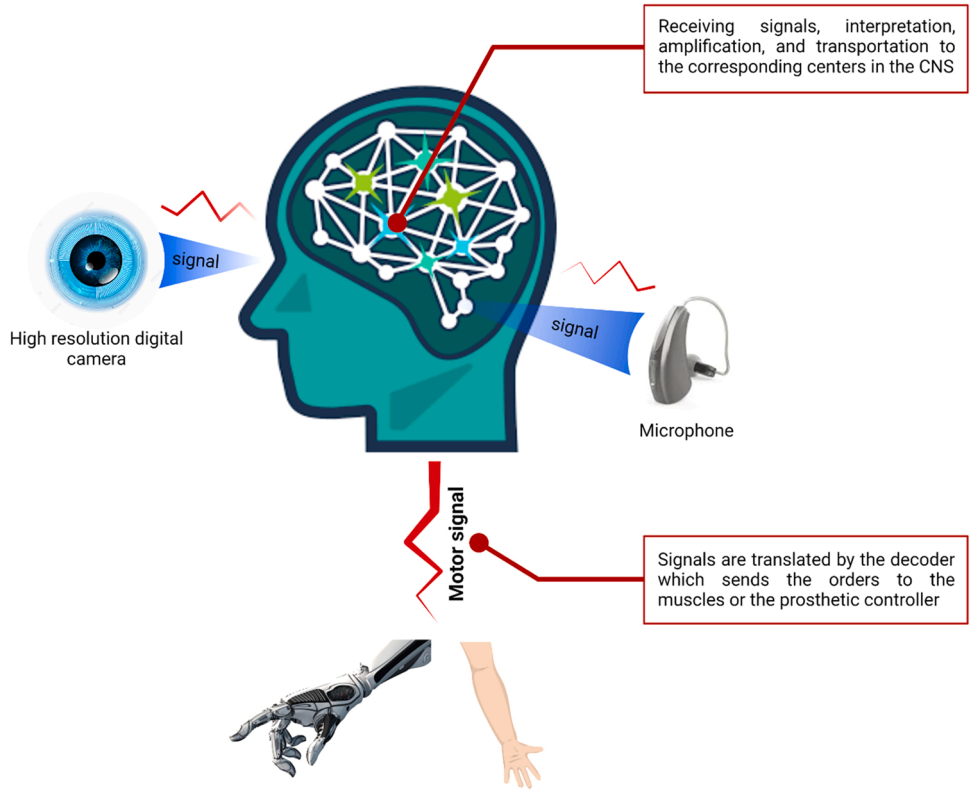

Fig. 4. Concepts of future implantation of electronic cheps to bridge function loss due to neuron damage.

could be reprogrammed to restore the regenerative power of the injured neurons and reverse vision loss via the activation of ectopic expression of OSK genes (*Oct4, Sox2,* and *Klf4*) to overcome neuron injury. This protocol was also applied to restore vision in a blind mouse induced by glaucoma [180].

11.1.3. New future RM approaches to restore hearing

Besides prostheses used to restore vision, auditory prostheses were also designed for hearing rehabilitation. The device consists of an external small microphone and processor implanted in a pocket behind the ear connected to an internal part surgically implanted in the auditory system. The embedded electrode bypasses the outer and middle ear and directly stimulates the acoustic nerves in the auditory system via electrical signals/ impulses (Fig. 4). Using artificial intelligence software, further improvements are still required to filter undesired noise from the surrounding [178].

11.1.4. Spinal cord electrodes

Rowald and his team (2022) recently implanted a multielectrode paddle in the dorsal roots of lumbosacral segments in three patients suffering from severe spinal cord injuries. The electrodes were responsible for epidural electrical stimulation of the spinal cord in association with specially developed software for the reproduction of the natural activation of desired motor neurons underlying every activity. With tablet-installed software to guide the lower limb muscles via preprogrammed orders, the implanted electrodes enabled neurorehabilitation and restored lost motor activities. The patients could successfully walk, cycle, and swim again without external help. This system may provide a better alternative to the electromechanical bionic limbs that mimic natural limbs' function [181].

11.1.5. Brain-controlled robotic limbs and soft body robots

Upon the brachial plexus injury, the upper limb becomes irreversibly paralyzed and insensible, which results in irreversible atrophy of the muscles and resorption of the neuromuscular junctions. New advances in the field of artificial intelligence and brain-machine interface systems enable the development of artificial lightweight robotic exoskeletons. Following amputation of the limb, it is replaced with a prosthesis system to restore hand functionality. The desired movement can be controlled through myoelectric systems receiving the signals directly from the brain. The system is based on the direct coupling of the coming signals from the brain to the micromotors implanted in the artificial robotic limbs through electrical impulses. The impulses are directed via special electrodes over certain healthy non-injured muscles (Fig. 4). In other cases, increased functional connections have been made in muscle units by dividing muscles into smaller segments and instrumenting these smaller units to control more degrees of freedom available in the limbs. [182].

The application of artificial intelligence in the field of RM extends to provide soft body robots that act as external supports such as intelligent haptic robotic gloves developed to help in post-stroke rehabilitation. The gloves restore hand movement control and recover functionality [183]. Similarly, powered ankle-foot orthosis supplied with artificial muscles, joints, and sensors can replace amputated ankles [184]. Wearable soft robotics can also be used in surgery, industrial, and educational purposes [185].

11.1.6. Brain-Computer Interface (BCI) system and the deep brain stimulation (DBS) systems (e.g. Neuralink Chips)

Novel neural prosthetics promise to improve lost motor and sensory functions. Among the promising motor and sensory neural prosthetics are microelectrode arrays for nerve regeneration (based on the Brain-Computer Interface system) and the deep brain stimulation system applied in the development of Neuralink Chips. The principle of the revolutionary Neuralink prosthetic depends on the implantation of electrodes (about 23 mm × 8 mm) in the brain to read the electrical signals produced in the CNS, and amplify them before being transmitted to the muscles or attached machines to respond in the form of movement or action. Further trials are running to develop wireless control mechanisms for the sensors via mobile applications. The applications of the Neuralink system can be adapted to the patient`s needs as visual or auditory prosthesis, prophylactic for disease prediction and physiological monitoring status, relieving pain, improving brain performance, or enabling the movement of the paralyzed exoskeleton and other robotics with mind [178].

11.1.7. Neuromorphic engineering and optogenetic technology (light-controlled gene expression)

The use of neuromorphic engineering (artificial electro-signaling) in treating psychological disorders such as depression and memory disorders might take place in the next few years [186,187]. The combined use of neuromorphic engineering with other advanced sciences reveals additional therapeutic strategies of RM (such as optogenetic technology) used to correct and control neuronal disorders such as Parkinson's disease. This technology is based on genetics, optics, and other branches of science [188]. Optogenetic technology enables us to write and read bioelectric information in living cells and to initiate the self-assembly of computational living tissues through switching (on and off) gene expression and cellular functions following exposure to light [189,190] where a viral vector manipulates the target genes to express light-sensitive proteins. The proteins can only be activated to modulate the cell response upon exposure to certain light wavelengths. The gene expression and its related functions can be switched on and off upon demand [188]. In parallel to optogenetics, light energy to correct locomotive disorders was also investigated. The concept depends on developing light-responsive shape-changing polymers that can change their shape similar to natural muscles when subjected to light stimuli. Running researches investigate a possible combination of these synthetic polymers with living cells (e.g. muscle cells) to support muscular performance for instance, the mechanical beating of cardiac muscles [191].

11.1.8. Nanorobotics in RM

Another aspect of future applications in the field of RM is the use of microscopic robots at the nano-level (nanorobotics) to perform the required tasks at the nanoscale. Their nano-size enables painless interference with minimal tissue damage (which means rapid recovery and less bleeding) [192,193]. However, one of the major obstacles in implantable robotics is their continuous need for energy supply for their work [194]. The use of external power sources has many restrictions, such as their relatively large size and weight, the need to regularly change/charge the battery, or the heating effect on the body which can denaturate body proteins and destroy the fine cell structures. Available batteries are also made of metals that are neither biocompatible nor biodegradable, rigid, and toxic substances that represent a great threat if leakage happens. They have a limited lifetime and must be regularly replaced by surgeries [195–205].

To overcome these obstacles, continuous research is currently running to develop alternative durable power supplies for medical implants [206]. For this reason, nanogenerators were developed to overcome the challenge of providing a durable, reliable power supply [206]. Such as triboelectric nanogenerators (TENGs) which are designed to harvest renewable mechanical local body energy from their surrounding environment and convert it into electricity [194] such as body heat, body motion, and vibration [193,206,207]. Pilot studies could successfully implant TENGs to restore bladder function, initiate muscular stimulation, and support the normal physiological performance of the nervous system (sensory and motor functions) [208–210]. They were also used to restore vision, hearing, and memory [211–216]. The advances in TENGs technology enabled the development of self-signaling pacemakers (that utilize the heart movement, blood flow, or the movement of respiratory muscles as energy sources). The application of

the prototype device showed promising results and might soon be available [217–221].

The medical application of TENGs extended to cover different branches of RM. For instance, they were used to support wound healing (wound dressing and self-powered electrical bandage) in none curable cases such as diabetic foot [214,222–224] and to stimulate bone regeneration through the enhancement of bone calcification [225]. However, although the use of robots has become increasingly common in RM, a major weak point of robots must be improved before their use can be generalized, namely their inability to carry out self-repair / regeneration when damaged. This disadvantage makes them fragile and sensitive to any damage, even minor ones. Therefore, the recent invention of biobots and xenobots could overcome this disadvantage whereas they are synthesized from living cells and can be defined as 'alive' or living robotics with the ability of decision-making and learning. This, in turn, leads to an ethical issue that must be solved first before proceeding with this concept [226,227]. The dynamic plasticity of the biological systems enables their adaptation to any environmental changes. The newly developed shape-changing artificial systems can mimic this property, are capable of editing their structure, and robustly operate mechanical robots [228]. Soft robots capable of self-regeneration via neural cellular automata are being proposed and designed from biological tissues (xenobots). The desired robots are supposed to reconfigure their morphology in response to any damage in their components. Such devices can be best described as synthetic living machines [106,229].

Moreover, as the implants contain software and require regular software updates or maintenance, the development of nano-devices that support wireless data transfer via Bluetooth or comparable tools are under development [230–233].

11.2. Improvement of metabolism and metabolic disorders (e.g. diabetes)

It is now known that all cells use electrical signals to perform their activities, including growth and differentiation. Therefore, the implantation of bioelectric circuits can support cellular metabolism and gene transcription [189,190]. Soft robotic-dependant approaches for treating metabolic disorders are still under development, in which macro-encapsulation devices are implanted to treat type I diabetes. The device comprises a highly conductive acrylic adhesive membrane-covered from both sides with 0.08 mm thermoplastic polyurethane layers. The capsules are refillable and controlled by implanted soft robotic [234].

Another approach for the treatment of diabetes is through the use of insulin pumps supported by artificial intelligence and controlled by mobile Apps. However, several technical problems still face commercially available insulin pumps such as insulin pump infusion set failures. New generation pumps are under development to optimize their performance [235].

11.3. Future RM approaches based on organoid technology

As previously mentioned, the *in Vitro* production of 3D organoids will cover the growing need for organ transplantation in the near future. Recent advances could design micro-physiological systems which represent 3D microfabricated tissue culture systems. They can mimic certain organs' physiological, anatomical, and functional properties (called Organ-on-a-chip technologies) [236]. The produced organs on a chip can be used to bioengineer damaged organs or correct developmental anomalies [237]. The technology aims to re-create the main key aspects of human physiology, including (1) the vascular network or epithelial interfaces of the target organs, (2) in addition to the parenchymal cells responsible for the functional properties of the organs, and (3) the coordination of systematic interaction of linked organs [238, 239]. One of the major advantages of this technology is the capability to develop new characters/properties of the cultured organs through re-modeling the organ physiological barriers through porous membranes [239]. The list of already produced organs on a chip includes liver on-a chip, Heart-on-a -chip, and Skin-on-a-chip systems. Linking several types of tissue together on a chip results in the production of (Body-on-a-Chip system) within a single device. Other advances in the field of biomaterials, nanotechnology, and gene therapy can also be integrated in such innovative systems [240]. The main present and future RM technologies are listed in Table 3.

12. Conclusion

Although regenerative medicine is relatively old, recent technological advances enabled a revolutionary improvement in this branch of medicine. Recent research on how some reptilians can renew their missed limbs or damaged organs provided important information and enriched our knowledge. Shortly, RM can save millions of lives by curing serious uncurable health problems such as diabetes, stroke, paralysis, and MI. It can also enable the replacement of lost limbs or correct congenital deformities. Approaches such as gene editing, 3D bioprinting, living robotics, soft nanorobotics, and combinations of these approaches based on artificial intelligence are expected to replace several classical therapeutic lines in a few years.

CRediT authorship contribution statement

Ahmed E Altyar: Conceptualization, Methodology, Data curation, Visualization, Investigation, Validation, Writing - original draft, Funding. **Amr El-Sayed**: Conceptualization, Methodology, Data curation, Visualization, Investigation, Validation, Writing - original draft. **Ahmed Abdeen**: Software, Visualization, Writing - review & editing. **Marina Piscopo**: Supervision, Writing - review & editing; **Shaker A. Mousa**: Supervision, Writing - review & editing. **Agnieszka Najda**: Supervision, Writing - review & editing. **Mohamed M Abdel-Daim**: Conceptualization, Methodology, Data curation, Visualization, Investigation, Validation, Supervision, Software, Writing - review & editing.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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