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ELEMENTS OF REGENERATIVE MEDICINE IN GENERAL SURGERY: NEW OPPORTUNITIES

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Abstract: This article reviews the current status, opportunities, challenges, and prospects of regenerative medicine (RM) elements in general surgery. The introduction discusses the concept of regenerative medicine, its importance, and its integration into general surgery. The research methodology section explains the data collection method based on literature review, empirical experiments, and clinical studies. The main part analyzes in detail how regenerative approaches such as cell therapy, biomaterials, and 3D bioprinting technologies, wave therapy, growth factors, and exoinvasive components can be applied in general surgery. The analysis and results section discusses initial clinical experiences, limitations, and achievements. The article concludes with a conclusion and future directions.

Keywords: Regenerative medicine; general surgery; cell therapy; tissue engineering; biomaterials; 3D bioprinting; growth factors; translational medicine

Introduction

Surgery is a clinical and procedural discipline that deals with the repair, removal, or reconstruction of diseased, injured, or lost tissues and organs. Historically, general surgery has undergone major changes, including operations involving the gastrointestinal, hepatic, biliary, endocrine, and regional soft tissue. The reconstructive techniques used in many surgeries at the last stage—transplantation, plastic, graft, and flaps—can often be associated with reduced biocompatibility, immunological compromise, compromised vascularity, and neurovascular integration. Regenerative medicine (RM) is a new interdisciplinary field that combines cell therapy, gene therapy, biomaterials, molecular signaling, and tissue engineering techniques to regenerate, renew, or repair human cells, tissues, or organs. RT is defined in terms of content as "regenerative methods that are established using autologous or allo-cellular/tissue elements generated within the body or in the laboratory."

The application of RT elements in general surgery is attractive for a number of reasons:

1) Autologous cells may not be immunogenic per se, which reduces the need for immunosuppression.

2) Tissue microvascularization and neovascularization can be improved by RT methods.

3) The possibility of creating anatomical structures of complex shapes using 3D bioprinting, biomaterials, and structural scaffolds.

4) The possibility of improving surgical outcomes by using additional regenerative elements (e.g., cell placement, local delivery of growth factors) during the surgical steps.

However, there are a number of challenges and obstacles to the application of RT to general surgery: cell sources and expansion, cell migration and integration, immunological balance, biocompatibility of biomaterials, vascularization and nerve regeneration, as well as translational and regulatory aspects. The aim of this article is to review how elements of RT can be applied to general surgery, analyze existing experiences, and outline prospects for the future.

Research methodology

This article is a mini-theoretical (narrative) review article based on a literature review and was based on the following methodological steps:

1. Literature search and collection

A search was conducted in PubMed, Web of Science, Google Scholar databases using the keywords "regenerative medicine general surgery", "tissue engineering surgery", "stem cell surgery", "biomaterials surgical repair", etc. Clinical trials, randomized trials, translational studies, review articles and conference abstracts were also selected.

Selection criteria: articles published in the last 15 years, articles in English and Russian, studies related to the application of RT in general surgery or surgery.

2. Data sorting and synthesis

Each article was analyzed as follows: research objective, RT components used, animal or clinical model used, results, limitations and authors' suggestions. Relevant data were collected in tabular form: cell type, biomaterial or scaffold type, modifications, integration, functional outcomes (tissue regeneration, vascularization, functional integration), and challenges.

3. Observational analysis

The similarities and differences between studies in key areas (e.g. cell therapy, biomaterials, 3D-bioprinting) were identified. New opportunities and knowledge gaps were identified. Possible directions for future work were suggested.

4. Conclusions and suggestions

The information obtained from the studies was summarized and the opportunities that RT elements can create in general surgery were analyzed. Suggestions and perspectives were given based on the problems and limitations. It should be noted that this article does not provide new experimental data, as it is based only on a literature review. However, a synthesis of knowledge in the field and directions are presented.

Below are discussed in detail the main directions and tasks of applying elements of regenerative medicine in general surgery.

1. Cell therapy

1.1 Mesenchymal stem cells (MSC)

Mesenchymal stem cells (MSC — Mesenchymal Stem Cells) are the most studied cell type in the field of RT. They can be easily obtained from bone marrow, adipose tissue, umbilical cord, osteoclastic tissue, and are characterized by low immunogenicity.

MSC are used in surgery with the following strategies:

Faster and better wound healing — stimulating regeneration by filling tissue defects after surgery with MSC-bound scaffolds.

Defect filling in the liver and biliary tract — supporting tissue regeneration by introducing MSC cells into liver resection sites or into wounds where the biliary tract has been created.

Restoration of internal organ parenchyma - for example, using cell regeneration with MSCs in defects in the pancreatic, stomach, or intestinal wall.

Immunomodulation and inflammation suppression — MSCs can reduce inflammatory activity through cytokine secretion and shift the wound environment toward regenerative. Some animal studies have shown promising results with the use of MSCs. For example, in animal models of general surgery, tissue repair has been observed to be improved by seeding intestinal defects with MSCs on a scaffold. However, clinical trials are still limited.

1.2 Induced pluripotent stem cells (iPSC) and pluripotent cells iPSCs are cells that have been genetically reprogrammed from adult cells and are able to differentiate into different tissue types. This application theoretically opens up great possibilities for the creation of complex organs or cell types. However, the safety, controlled differentiation, oncological risk and immunogenicity of iPSCs remain unresolved issues. In general surgery, iPSCs have the potential to be used for: Generating organ tissues in the laboratory and then implanting them (e.g. liver, pancreas or intestinal segments). Differentiating and using specific cell types, such as hepatocytes or intestinal epithelial cells, from iPSCs. Correcting genetic defects (e.g. in combination with gene therapy) and thereby stimulating regeneration.

1.3 Extracellular Vesicles and Exosomes

To reduce the risks associated with cell therapy (e.g., cell migration, oncogenesis, immunogenicity), cell-secreted exosomes and extracellular vesicles (EVs) are being used as delivery vehicles for regenerative effects. They can act as carriers for cytokines, miRNAs, and growth factors, and can influence the macroenvironment.

EV applications in surgery: Stimulation of tissue proliferation and angiogenesis by local injection of EVs into wounds and defects.

Alleviation of organ reperfusion injury—e.g., reduction of cell apoptosis during reperfusion. Improvement of graft adaptation in transplantation operations.

2. Biomaterials and scaffolds

2.1 Types of scaffolds and requirements

Regenerative strategies use scaffolds made of biomaterials (short-term or long-term degradable), hydrogels, nanofibrillar matrices, hydroxyl apatite, bioceramics, polymer composites (PLGA, PCL, etc.) and natural matrices (collagen, gelatin, alginate).

The following requirements are important for scaffolds:

Biocompatibility and non-toxicity

Microporous structure (pore size, interconnectivity)

Degradation kinetics (appropriate degradation rate)

Mechanical stability and symmetric (gradient) structure

Promoting vascularization

Functional modifications on the surface (adhesive ligands, growth factor-absorbing cubes)

In general surgery, scaffolds can be used for the following:

Filling tissue defects - e.g., abdominal wall, diaphragm defect, muscular spaces

Reconstruction of organ segments - e.g., intestinal segment, liver lobule microsegment

Supporting cells and angiogenesis within flaps and grafts - grafts filled with biomaterials can create a unique regenerative environment

Local delivery of growth factors through the scaffold - using modifications that bind growth factors (VEGF, FGF, TGF-β, PDGF, etc.) to the scaffold to integrate.

2.2 Scaffold modifications and “smart” materials

In recent years, biomaterials have been enriched with “intelligent” properties — stimuli-responsive (pH-responsive, thermosensitive, electroactive) materials, scaffolds modified with nanoparticles, scaffolds combined with controlled release of growth factors and bioprinting.

Examples: Surface modification with nanotechnological modifications, acceleration of MSC differentiation by nanofibrillar structure and graphene incorporation (e.g., graphene substrate can stimulate cell osteogenesis)

Creation of microchannel networks within the scaffold (sunset-like angiogenic channel structures) — for example, the LBMS laboratory is working with such an approach. Local, dosed delivery of growth factors (microcapsules, liposomes, nanoparticles) Control of cell fate using stimuli-responsive materials (e.g., electrical signal, ultrasound, magnetic nanoparticles)

2.3 3D-bioprinting and organotypic structures

3D-bioprinting is a technology for layer-by-layer printing of biomaterial “bioink” and cells, which allows the creation of complex tissue and organ structures. This method can be used in general surgery as follows:

➢ Printing intestinal segments, vascular structures, liver lobules, pancreatic tissues, etc.

Tissue creation according to patient-specific anatomical cuts

3D-bioink with incorporation of cells and growth factors

Creating wound-specific “patches” or defect closures

For example, there are developments on creating suitable “patches” for covering diabetic foot ulcers using a 3D-bioprinter.

However, there are also problems associated with 3D-bioprinting: nutrition and creation of a safe vascular network during volumetric tissue growth; development of a suitable bioink for the printer; control of cell activity and degradation rate.

3. Growth factors, signals and genetic modification

3.1 Growth factors and bioactive molecules

Signaling molecules such as VEGF (vascular endothelial growth factor), FGF (fibroblast growth factor), TGF-β (transforming growth factor), PDGF (platelet-derived growth factor), IGF (insulin-like growth factor) are used to stimulate regeneration. They can be bound to scaffolds, encapsulated in microcapsules or delivered as local injections.

Example: VEGF and FGF integrated scaffolds are used to stimulate angiogenesis. When this strategy is combined with microchannel structures, a faster vascular network can be formed in tissues.

3.2 Gene therapy and gene knockdown

Gene therapy can deliver genes that promote regeneration (e.g., VEGF gene, angiogenesis-related genes) to cells or tissues. This approach allows for the expression of growth factors in cells and tissues that are either constant or inducible.

Possibilities for gene therapy in surgery:

➢ Delivery of genes contained in Os or vectors to the wound site

➢ Genetic modification of MSCs or other cells and subsequent implantation

Suppression of pro-inflammatory genes in the wound with RNA interference approaches

However, gene therapy requires caution due to safety issues (risk of oncogenesis, immune responses, vector control).

4. Wave therapies and physical stimuli

Physical stimuli — ultrasound (low-intensity pulsed ultrasound, LIPUS), electrotherapy, laser therapy, magnetic fields — can be used to optimize regenerative approaches.

Example: LIPUS stimulation, when combined with MSC transplantation, is known to improve articular cartilage cell differentiation and reduce inflammation.

In surgery, these stimulatory approaches can be used as follows:

✓ Promote cellular integration

✓ Accelerate angiogenesis

✓ Induce cellular activity in the early stages

However, it is necessary to determine the optimal parameters of physical stimuli and ensure that they are not harmful.

5. Clinical and translational applications

5.1 Regenerative methods in animal models

A number of animal experiments have tested RT methods in general surgery. For example:

➢ MSC solution for intestinal wall defects

Hepatocyte transplantation and scaffold integration in a liver resection model

Biomaterial approaches to diaphragm defects

Cell and biomaterial approaches to purulent wounds and wound problems

A number of problems — cell migration, cell integration with scaffolds, lack of vascularization, immunological responses — have been identified in these experiments.

5.2 Early clinical experiences

Clinical studies on the application of RT in general surgery are still limited, but there are some examples:

➢ MSC application and regeneration in post-radiation wounds (e.g. mesenchymal cell application)

Integration with cell-antibody biomaterials in reconstructive surgery

Combination of biomaterials and cell flaps in the repair of abdominal wall defects

For example, good results have been reported with a combination of MSCs, fetal bovine dermis and porcine urinary bladder xenografts in radiation-damaged areas of the anus.

5.3 Limitations and risk factors

Immunological response and cell immunogenicity — immune reactions may occur with cells or modified scaffolds.

Cell migration and lack of control — the problem of controlling cell recruitment and distribution to the target site.

Oncogenesis and differentiation control — cell therapy is associated with oncological risk.

Vascularization and nutrient problems — the lack of a vascular network in large tissues creates a problem of oxygenation of cells.

Scale and production — expansion, storage and delivery of cells and scaffolds under GMP conditions is complex and expensive.

Regulatory and ethical issues — regulatory, ethical issues and approval processes in the fields of gene therapy, cell therapy and bioprinting.

6. New opportunities and perspectives

The integration of RT elements into general surgery opens up the following perspectives:

1. Personalized approach: creation of individual regenerative implants based on MSCs or iPSCs derived from the patient's own cells.

2. Bioink and 4D-bioprinting: more flexible implants using time-dependent structures, deformable scaffolds.

3. Hybrid strategies: achieving a synergistic effect through the addition of cell therapy + gene therapy + biomaterial.

4. Advanced vascularization strategies: prefabricated angiogenic microchannel scaffolds or channels written with endothelial cells.

5. Robot-assisted regenerative surgery: robotically assisted cell implantation and biomaterial placement with precision.

6. Artificial intelligence and controlled cell models: predicting cell fate and controlling it in real time — through AI tools.

7. Clinical translation and multicenter studies: conducting clinical trials of RT approaches for safety and efficacy and promoting their widespread use.

Analysis and results

The analyzed literature shows that the use of regenerative medicine elements in general surgery, although still in its infancy, has promising potential. In animal models, tissue repair, angiogenesis, and cell integration have been observed through cell therapy and scaffold combinations. However, clinical trials are limited and many questions remain. The following are some of the key findings: MSCs have shown promising results in many trials, but optimal dosage, contours, cell source, and implantation methods remain to be determined. Scaffolds and biomaterials are the "skeleton" of regenerative approaches, and their structure, modification, and degradation play a critical role. 3D bioprinting holds great promise, but the challenges of nutrition and vascularization in generating large-scale tissue are significant barriers. Exovascular vesicle and EV approaches may be safer than cell therapy, but their regenerative effects require further investigation. RT strategies combined with gene therapy and genetic modification have high potential, but safety and control risks must be considered. Physical stimuli (e.g., ultrasound) can support regenerative processes, but optimization of parameters is required. Ethical, regulatory, manufacturing, and financial aspects remain significant constraints in integrating RT. The results show that elements of regenerative medicine can open up new paradigms in general surgery, but this path requires a lot of research, clinical trials, and technological development.

Conclusion

The application of regenerative medicine elements (cell therapy, biomaterials, 3D bioprinting, growth factors, physical stimuli, and gene therapy) in general surgery holds great promise. These approaches offer the potential to accelerate postoperative recovery, improve tissue integrity, reduce immunogenicity, and improve surgical outcomes.

However, there are currently limited clinical trials, safety, control, vascularization, cell integration, and regulatory constraints in this area. Future work will focus on:

▪ Large-scale clinical trials and translational studies

▪ Identification of optimal cell, biomaterial, and module strategies

▪ Development of methods to support vascular networks and neural integration

▪ Real-time control through AI and controlled cell models

▪ Addressing regulatory, ethical, and economic issues

Finally, regenerative medicine in general surgery is a promising area that could change the paradigm of future surgery.

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