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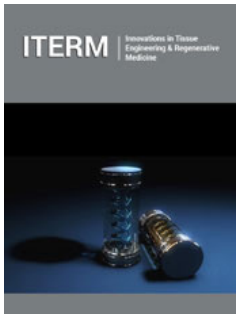
Mini Review

New Regenerative Medicine in Postoperative Functional Recovery, Empowered by Adipose-Derived Stomal Cells



Rie Hayashi[1,2], Norikatsu Miyoshi[1,2]* and Shiki Fujino[1,2,3]

[1]Osaka International Cancer Institute, Department of Innovative Oncology Research and Regenerative Medicine, Japan

[2]Department of Gastroenterological Surgery, Graduate School of Medicine, Japan

[3]Central Clinical School, Monash University, Australia

***Corresponding author:** Norikatsu Miyoshi, Osaka International Cancer Institute, Department of Innovative Oncology Research and Regenerative Medicine, Japan and Department of Gastroenterological Surgery, Graduate School of Medicine, Japan

Submission: May 17, 2023
Published: May 26, 2023
Volume 2 - Issue 1

How to cite this article: Rie Hayashi, Norikatsu Miyoshi* and Shiki Fujino. New Regenerative Medicine in Postoperative Functional Recovery, Empowered by Adipose-Derived Stomal Cells. Innovations Tissue Eng Regen Med. 2(1). ITERM.000526.2023.

Abstract

In gastroenterological fields, curative surgical resection leads good survival; however, defective function may be caused as the postoperative complications, resulting in poor quality of life. Regarding the cases of tumor or disease located at the lower rectum, although surgical resection is commonly performed, it also carries increased risks of function loss. Defecation disorders after rectal surgery are termed Low Anterior Resection Syndrome (LARS), and the major (severe) LARS is serious postoperative complication, and some predictive models were reported previously. However, there are still few reports on effective treatments for LARS which can be performed after the operation. The interdisciplinary field of regenerative medicine offers strategies that can potentially restore injured tissues and organs. Adipose-Derived Stromal Cells (ASCs) are an abundant and accessible source of adult stem cells. We believe that stromal material/ASC-based therapies are a promising strategy for the regeneration of tissues and function restoration after severe injury due to surgery. This mini-review provides an overview of the utility of the ASCs-based therapies, and we discuss future prospects by the regenerative medicine-based therapies.

Keywords: Regenerative medicine; Postoperative functional recovery; Adipose; Stomal cells; Postoperative complications; Gastroenterological fields; Function restoration; Rectal surgery

Introduction

Colorectal cancer is one of the most common cancers in the world [1]. In cases of tumor or disease located at the lower rectum, surgical resection is commonly performed for curative treatment. But, surgery for lower rectum frequently causes defecation disorders, with a reported incidence of 37-71% [2-4]. Defecation disorders after rectal cancer surgery are termed Low Anterior Resection Syndrome (LARS). The LARS is serious complication that significantly reduces quality of life, and some predictive model of LARS occurrence were reported. Although various predictive models have been constructed, there are still few reports on effective treatments for LARS. Thus, it remains to be solved for the postoperative concerns, and it is necessary for efficacious treatment strategies to restore the functions and improve the defecation disorders. The field of regenerative medicine has been rapidly evolving and now offers multiple strategies to compensate for or fully restore the lost/impaired function and/or structure. In particular, Adipose-Derived Stromal Cells (ASCs) are promising therapeutic agents for tissue regeneration owing to their stem cell potency [5]. And, the ASCs has been reported as a new treatment for several diseases and is attracting attention. We consider that the ASCs-based therapies are a promising strategy for the regeneration of tissues and function restoration after severe injury due to surgery. In this mini-review, we describe defecation disorders after rectal resection and summarize the application and potential of ASCs as a novel treatment for several diseases. We also discuss future prospects by the ASCs-based therapies.

Defecation Disorders after Rectal Resection and Predictive Models

In cases of tumor or other serious diseases located at the lower rectum and close to the anal canal, tumor surgical resection is commonly performed. Recently, total mesorectal excision and Intersphincteric Resection (ISR) have become widespread in treating rectal cancer [6,7]. This technique has reduced the local recurrence, but results in negatively impacted anorectal function [8,9]. Surgery for rectal cancer, particularly low rectal cancer, frequently causes defecation disorders, with a reported incidence of 37-71% [2-4]. The spectrum of symptoms associated with postoperative defecation disorders and the associated bowel-related quality of life impairment has been termed Low Anterior Resection Syndrome (LARS). The LARS score is an index used to assess the severity of LARS [10], and the LARS score can accurately measure the severity of postoperative defecation disorders and it has been proven to correlate well with quality of life measures. The LARS is one of the serious postoperative complications, and some predictive models were reported. For example, a European group created a nomogram of a predictive model of LARS occurrence after rectal cancer surgery [11]. The key variables identified from both cohorts were age, gender, tumor height from the anal verge, use of defunctioning ileostomy, preoperative radiotherapy and a TME compared with a partial, mesorectal excision. And, we also reported the predictive model of the LARS [12]. We found that sex, age, and tumor location were independent predictors of major LARS in Japanese patients that underwent rectal cancer surgery. Thus, although several prediction models of LARS have been reported, there are still few reports on effective treatments for LARS.

ASCs as a Potential Treatment for Defecation Disorders

The field of regenerative medicine has been rapidly evolving and now offers multiple strategies to compensate for or fully restore the lost/impaired function and/or structure. Cell transplantation for organ and tissue regeneration involves the use of stem cells [13]. Regenerative medicine based on autologous Mesenchymal Stem Cells (MSCs) is a promising frontier for the regeneration of tissues and function restoration after severe injury due to surgery. MSCs can be retrieved from multiple tissues and adipose tissue is considered their largest source [14]. ASCs are considered ideal for application in regenerative therapies, since they show multilineage differentiation ability. ASCs also provide a less invasive therapeutic approach, as they are easily accessible and have expansion potential, and their plasticity allows these cells to differentiate into multiple lineages. Several reports have described the utility of the ASCs as novel treatments for some diseases. For example, Osteoarthritis (OA), breast reconstruction in breast cancer patients, and Rheumatoid Arthritis (RA) were reported [15-17].

An Italian group injected autologous concentrated adipose tissue into the knee, and reported the treatment resulted safe, and patients improved in terms of pain reduction and function [15]. We also reported the regeneration of the femoral muscles by ASCs [18]. We transplanted cells isolated from human stromal tissues, including a 6%-7% ASC population, into heat-damaged femoral muscles of non-obese diabetic immunodeficient mice. The movement of the limbs was observed to determine the functional recovery three months after transplantation. In the control group, only 20% were able to walk, while in the ASC-treatment group, all mice were able to walk with all limbs. Furthermore, all mice in the ASC-treatment group were able to stand on both back paws; the opposite trend was observed in the control group, in which none of the mice were able to stand on both back paws. Our results suggested that ASCs could be an effective regenerative medicine leading to restore the functions of damaged tissues and organs by surgery, leading to the function recovery of the defecation disorders.

Possibility of Improving the Efficacy of ASC Treatment by Activating Anti-Aging Genes

The possibility that treatment with ASCs may be effective for postoperative defecation disorders has been discussed, but some factors that promotes regeneration may be necessary. The role of the mitochondria in organ function is critical with increased mitochondrial apoptosis with accelerated aging [19]. The role of anti-aging genes in organ disease has become of central interest to maintain mitochondria functions. Since anti-aging genes are involved in cell proliferation, they may have applications in regenerative medicine. For example, Sirtuin1 (Sirt1), which is one of the anti-aging genes, is involved in telomerase reverse transcriptase and genomic DNA repair with its involvement in telomere maintenance that maintains chromosome stability and cell proliferation. Sirt1 is essential for neurogenesis and calorie restriction activates Sirt1 with effects on longevity by modulation of phosphoinositide 3 kinase pathways and age associated cardiovascular changes. There is a reports of applying Sirt 1 to ASC treatment [20]. It was reported, that resveratrol activates the Sirt1, which inhibits NF-κB signaling by deacetylating the p65 subunit of NF-κB complex and thus protects the cells against apoptosis [21]. The ASCs treated with resveratrol, herein called SIRT+, in alginate hydrogel were applied to 5 years old warm breed mare was clinically evaluated due to the left hind lameness due to subchondral bone cyst. After therapy, complete bone remodeling occurred and the horse came back to training. This case report suggested that SIRT1+ cells exhibit antiaging and anti-oxidative properties might enhance multipotency of ASCs. The combination of anti-aging gene activation and ACS treatment may provide further regenerative benefits.

Future Prospects by the ASCs-Based Therapies

ASCs are useful for tissue regeneration and we believed that ASCs can be applied to postoperative functional recovery, defecation disorders. We created an anal sphincter injury mouse model by means of a balloon catheter and reported the utility of the mouse model and the efficacy of electrical stimulation as a treatment modality using this model [22]. To induce anal sphincter injury, a balloon catheter (outer diameter: 10mm) was used. The balloon dilation time was set at 2 min and was performed twice. Now, our plan to administer ASCs to the rectum of this mouse

model is undergoing to evaluate the regeneration of the damaged anal sphincter, and next future of human trials.

Conclusion

ASCs can be an effective treatment to improve the postoperative complication which is anal sphincter disorders after rectal resection, resulting in better quality of life. And it may be required to use activators that rapidly stimulate regeneration. Further benefits can be provided by the combination of anti-aging gene activation and ACSs. It is necessary to examine safety and efficacy in a mouse model and demonstrate them through application to humans in the future.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5): E359-386.
2. Nakahara S, Itoh H, Mibu R, Ikeda S, Oohata Y, et al. (1988) Clinical and manometric evaluation of anorectal function following low anterior resection with low anastomotic line using an EEA stapler for rectal cancer. Dis Colon Rectum 31(10): 762-766.
3. Oya M, Komatsu J, Takase Y, Nakamura T, Ishikawa H (2002) Comparison of defecatory function after colonic J-pouch anastomosis and straight anastomosis for stapled low anterior resection: Results of a prospective randomized trial. Surg Today 32(2): 104-110.
4. Duijvendijk P, Slors JF, Taat CW, Tets WF, Tienhoven G, et al. (2002) Prospective evaluation of anorectal function after total mesorectal excision for rectal carcinoma with or without preoperative radiotherapy. Am J Gastroenterol 97(9): 2282-2289.
5. Zamperone A, Pietronave S, Merlin S, Colangelo D, Ranaldo G, et al. (2013) Isolation and characterization of a spontaneously immortalized multipotent mesenchymal cell line derived from mouse subcutaneous adipose tissue. Stem Cells Dev 22(21): 2873-2884.
6. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S (2009) Standardized surgery for colonic cancer: Complete mesocolic excision and central ligation-technical notes and outcome. Colorectal Dis 11(4): 354-364.
7. Dimitriou N, Griniatsos J (2015) Complete mesocolic excision: Techniques and outcomes. World J Gastrointest Oncol 7(12): 383-388.
8. Yamada K, Ogata S, Saiki Y, Fukunaga M, Tsuji Y, et al. (2007) Functional results of intersphincteric resection for low rectal cancer. Br J Surg 94(10): 1272-1277.
9. Ito M, Saito N, Sugito M, Kobayashi A, Nishizawa Y, et al. (2009) Analysis of clinical factors associated with anal function after intersphincteric resection for very low rectal cancer. Dis Colon Rectum 52(1): 64-70.
10. Emmertsen KJ, Laurberg S (2012) Low anterior resection syndrome score: Development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg 255(5): 922-928.
11. Battersby NJ, Bouliotis G, Emmertsen KJ, Juul T, Glynne-Jones R, et al. (2018) Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: The POLARS score. Gut 67(4):688-696.
12. Paku M, Miyoshi N, Fujino S, Hata T, Ogino T, et al. (2022) Development and evaluation of a Japanese prediction model for low anterior resection syndrome after rectal cancer surgery. BMC Gastroenterology 22(1): 239.
13. Jain A, Bansal R (2015) Applications of regenerative medicine in organ transplantation. J Pharm Bioallied Sci 7(3): 188-194.
14. Zuk PA, Zhu M, Ashjian P, Ugarte DA, Huang JI, et al. (2002) Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell 13(12): 4279-4295.
15. Ilalia R, Dimas CB, Mara C, Aurora B, Luca M, et al. (2019) Concentrated adipose tissue infusion for the treatment of knee osteoarthritis: clinical and histological observations. International Orthopaedics 43(1): 15-23.
16. Ejaz A, Yang SK, Venkatesh PK, Chinnapaka S, Kokai EL, et al. (2022) The impact of human lipoaspirate and adipose tissue-derived stem cells contact culture on breast cancer cells: Implications in breast reconstruction. Int J Mol Sci 21(23): 9171.
17. Seo P, Park S, Han S, Kim A, Lee E, et al. (2022) Long-term treatment of allogeneic adipose-derived stem cells in a dog with rheumatoid arthritis. J Vet Sci 23(4): e61.
18. Miyoshi N, Fujino S, Takahashi Y, Yasui M, Ohue M, et al. (2020) Implantation of human adiposederived stromal cells for the functional recovery of a murine heatdamaged muscle model. Surgery Today 50(12): 1699-1706.
19. Martins JI (2016) Anti-aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations. Advances in Aging Research 5(1): 9-26.
20. Golonka P, Garbowska KK, Marycz K (2020) $SIRT_1^+$ Adipose Derived Mesenchymal Stromal Stem Cells (ASCs) suspended in alginate hydrogel for the treatment of subchondral bone cyst in medial femoral condyle in the horse. Clinical report. Stem Cell Reviews and Reports 16(6): 1328-1334.
21. Bhullar KS, Hubbard BP (2015) Lifespan and healthspan extension by resveratrol. Biochimica Biophysica Acta 1852(6): 1209-1218.
22. Yukimoto R, Miyoshi N, Fujino S, Mori R, Ogino T, et al. (2022) Usefulness of an anal sphincter injury mouse model by means of a balloon catheter and a new method of evaluating anal sphincter function. Ann Gastroenterol Surg 6(2): 282-287.