Commentary
Volume 15:4, 2021

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862 Open Access

Adipose-Derived Stem Cells: A New Player in Radiation Fibrosis Therapy

Ejaz A* and Rubin JP

Department of Plastic Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Radiation therapy (RT) is an important component of modern cancer management. RT inherent more benefits as compared to both chemotherapy and surgical intervention due to its cost effectiveness, targeted effects and organ saving properties. Despite the advancement in the field of radiation delivery, radiation induced side effects; mainly to the skin is the limiting factor in delivering high intensity therapeutic doses.

Keywords: *Radiation therapy • Fibrosis • Cellular damage • Immunogenicity*

Introduction

Radiation therapy (RT) side effects to the skin range from acute effects like skin rashes, erythema and mucositis to chronic side effects like fibrosis, resulting in diminished life quality. Skin of the head, neck and trunk is more sensitive to radiation thus making head, neck and breast cancer patient more susceptible to fibrosis development due to heavy treatment dose. Fibrosis can be compared to an uncontrolled wound healing reaction characterized by excessive deposition of extracellular matrix at the radiation injury site and can occur within 6 months to 2 years' timeframe post therapy.

Radiation induced fibrosis is a complex process governed by both cellular and molecular mechanisms. Radiation damage epithelial, endothelial and resident progenitor cells thus limiting the regeneration process. Cellular damage triggers an acute inflammation reaction resulting in influx of inflammatory cells to the damage site. These inflammatory cells secrete a plethora of cytokines and inflammatory signals which drive the proliferation and differentiation of fibroblasts to myofibroblasts. In normal wound healing scenario myofibroblast secrete extracellular matrix and undergo apoptosis upon healing. However, in case of radiation injury perpetual cytokine cycles keep myofibroblasts functional, resulting in excessive deposition of extracellular matrix and development of fibrosis. Transforming growth factor β1 (TGF β1) plays a key role in fibrogenesis via promoting differentiation of fibroblasts to myofibroblasts and regulating the fibrotic gene expression through the Smad signaling pathway.

Discussion

Currently, very few therapeutic options are available having moderate clinical success. Adipose tissue-based therapies have clinically shown promising results in treating radiation induced fibrosis. Autologous adipose tissue is harvested as lipo-aspirates using hollow bore cannula and injected into the fibrosed tissue planes. Evidence suggests adipose-derived stem cells (ASCs) are major beneficial contributor in lipo-aspirate mediated fibrosis mitigation. ASCs reside within the perivascular region of adipose tissue and are immune-phenotypically defined as CD34+CD90+CD29+CD45-CD31- cells of mesenchymal origin. Although, having distinct phenotype, ASCs share several functional characteristics common to bone marrow derived mesenchymal stem cells. However, sample abundance, relative ease of harvest, ability to culture and amplify, and higher stem cell yield designate ASCs as cells of choice for therapeutical applications. Additionally, lower immunogenicity of ASCs made them a possible candidate for allogeneic applications.

ASCs secrete plenty of growth factors and cytokines which perform the regenerative function attributed to these cells. ASCs contribute pro-angiogenic, anti-oxidant, immunomodulatory, and anti-inflammatory role in the mitigation of radiation fibrosis. ASCs secrete hepatocyte growth factor as a possible mechanism of mitigation upon exposure to fibrotic environment which directly block TGF β1-expression in radiation damaged cells and recruit bone marrow cells to irradiated site for performing regenerative actions [1,2].

Conclusion and Future Prospects

Future prospects towards developing and optimizing ASCs based therapies for mitigation of radiation fibrosis include in-depth investigation of the molecular mechanisms and possible factors secreted by ASCs upon exposure to irradiated environment. Investigations for optimizing the cell dose and time of delivery will increase the clinical adaptation of ASCs based therapies. Finally, exploration of allogeneic use of ASCs will be a vital step towards developing an off-the-shelf therapy approach for mitigation of radiation fibrosis.

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***Address for Correspondence:** Dr. Asim Ejaz, Department of Plastic Surgery, University of Pittsburgh Medical Center, 3550 Terrace Street, 6B Scaife Hall, Pittsburgh, PA 15261, USA, E-mail: ejaza@upmc.edu*

Received 07 September, 2020; **Accepted** 23 May 2021; **Published** 31 May 2021

How to cite this article: Ejaz, Asim and Rubin JP. "Adipose-Derived Stem Cells: A New Player in Radiation Fibrosis Therapy." J Mol Genet Med 15(2021): 492.