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Stem Cell Therapy in Oral Mucosal Lesions: A Future Vision

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Abstract: ***Dentistry is a consistently changing field that has witnessed a lot of progression in the previous century, like advances in stem cell therapies have opened new vistas for therapy of oral mucosal lesions. stem cells are defined as unique cells which have the capacity to develop rapidly and can possibly form into particular cell types in the body. Due to these, Tooth banking has become an emerging concept in developed nations around the world as dental stem cells retain the property of differentiation into neurogenic, adipogenic and odontogenic components and are used in the reconstruction of orofacial structures with the advantage of having an added opportunity of storing a tooth even if one opportunity is missed, unlike umbilical cord stem cells. In this review, we summarize current knowledge regarding stem cells as immune-modulatory agents, anti-inflammatory agents, immuno-reconstitution and regenerative properties in various oral mucosal lesions. Also, the future role of stem cell therapy in treatment of oral mucosal lesions.***

Keywords: stem cell, stem cell therapy, ulcerative lesions, oral submucous fibrosis, oral lichen planus, squamous cell carcinoma, pemphigus vulgaris

1. Introduction

Stem cell research not only offers extraordinary doors for growing new treatments for incapacitating infections but also provides another approach to investigate the fundamentals of science.[1]

Stem cells have an fascinating history that follows from mid of 1800 to the date, and it remains the most disputable subject of exploration even today. The word stem cell was first used by Ernest Haeckel in 1868. Wilson coined the term stem cell. They were first derived from mouse stem cells in 1981 since then much research is going on in regenerative medicine.[2] In 2006 Shinya Yamanaka, discovered induced pluripotent stem cells (iPS) for which he was awarded Nobel Prize in 2012.[3]

The stem cells from dental pulp have new viewpoints in the regeneration of dentin, tissue of periodonium and bone-joint tissue of the craniofacial region, yet addition in the treatment of neuro-trauma, autoimmune diseases, myocardial infarction, muscular dystrophy and connective tissue damage. As Present day therapeutic modalities for oral mucosal lesions like ulcerative sores, pre-malignancies and malignancies, predominantly comprise of steroids and cancer prevention agents and surgical procedure/ chemo/ radiotherapy, the advances in stem cell therapies have opened new vistas for therapy of the same.[4,5]
"We present the following article in accordance with the narrative review reporting checklist"

Classification of Stem Cells

They are classified according to their origin and potency.[6] (figure.1)

Stem Cell Therapy in Dentistry

The expanded knowledge on the reparative events within dental tissues has come up with the proposal of alternative methods for the treatment of dental pathologies.[7] The hypothesis of tooth regeneration was initially shown by a stomatologist G. L. Feldman (1932) with the evidence of regeneration of dental pulp under certain ideal biological conditions. Significant discovery in dentistry was accomplished in year 2000 by Gronthos *et al.*, Who identified and isolated odontogenic progenitor population in adult dental pulp. These cells were referred to as dental pulp stem cells (DPSCs)[2] (figure.2)[7]. Ongoing advances in stem cell-based therapies in dentistry offer an abiding solution by means of biological repair or replacement of damaged teeth.[7]

Goals of stem cell therapy in dentistry

Goals of regenerative dentistry include[8]

- Continuation of root formation
- Regeneration of pulpal tissues
- Reconstruction of periodontium
- Aiding in transplantation and replantation
- Root bio-engineering and engineering of pulp-dentin complex
- Regeneration of craniofacial bones, the temporomandibular joint, ligaments, skeletal muscles, tendons, skin, subcutaneous soft tissue and salivary glands.

Collection and Banking of Dental Stem Cells[9]

Tooth banking is an emerging trend principally in developed nations around the world. To prepare stem cells matched for the patient requiring treatment is critical to the achievement of cell therapy. (Figure: 3 Schematic portrayal of dental stem cell banking process)

In the event that tooth banking framework is creating and exhibited to be protected and effective, dental experts would have great opportunities to make their patients aware of the capability of new therapeutic sources and encourage them to store their dental stem cells for future clinical uses.

One bit of leeway of stem cells from teeth is that there is one more chance of putting away a tooth regardless of whether one open door is missed, not normal for umbilical cord blood stem cells, which is a once in a blue moon opportunity at each birth.

Stem Cell Therapy in Oral Mucosal Lesions

Among oral mucosal lesions, stem cell research is as of now centered around the treatment of certain lesions only. These oral mucosal lesions are:[4]

- **Ulcerative lesions:** Like oral ulcers and wounds, oral mucositis, pemphigus vulgaris
- **Premalignant disorders:** Oral submucous fibrosis (OSMF), oral lichen planus (OLP)
- **Malignant lesions:** Like oral carcinomas.

Ulcerative Lesions:

Oral ulcers and wound healing

In oral wounds, mesenchymal stem cells (MSCs) exhibit expanded re-epithelialisation, cellularity, intracellular matrix formation and neo-angiogenesis, hastens wound healing.[10] Hence, MSC therapy can be a promising therapeutic treatment for oral ulcers and wounds[4] [Figure 4].

Oral mucositis

Oral mucositis is one of the most debilitating results which happen with chemo or radiotherapy. Management of mucositis is completely symptomatic up 'til now. As of now MSCs have been investigated in its administration by excellence of their immunomodulatory, anti-inflammatory functions and also for regenerative properties. Their therapeutic efficacy can additionally be expanded by transgenic approach or preconditioning them with specific elements like pro-inflammatory cytokines.[11]

Pemphigus vulgaris

Pemphigus vulgaris is a potentially life-threatening illness, fundamentally affects the older indivuduals characterised by development of intraepithelial bullae and mucosal ulceration. The effective treatment of pemphigus vulgaris is long-term use of corticosteroids that itself has detrimental systemic complications.[12]

The properties of stem cells like immunomodulation and anti-inflammation can be used in the treatment this condition. Vanikar et al.(2007) performed allogenic hematopoietic stem cell transplant (HSCT) with non-myeloablative low-intensity conditioning in nine patients of Pemphigus vulgaris and found that the existing skin lesions started to regress within 24 h of stem cell therapy.[13]

Stem cell therapy in pemphigus not only has shown promises in treatment as well as achieves a move towards non-steroidal approach in autoimmune diseases. However, the use of stem cell therapy for oral pemphigus is yet to be found out and needs clinical preliminaries.[13]

Premalignant disorders:

Oral lichen planus

Oral lichen planus is a chronic mucocutaneous disease with unknown etiopathogenesis. Different components like stress, genetics, systemic diseases, drugs, dental restorative materials and viruses are known to cause the disease either by an antigen-specific mechanisms like activating cytotoxic T-cells or by a nonspecific mechanisms like mast cell degranulation and matrix metalloproteinase enactment, which cause the seperation of the basement membrane and triggers apoptosis of basal cells of epithelium.[14,15]

As Conventional treatment results are not satisfactory, a new therapy employing T-cell immune modulation using MSCs have been proposed to treat OLP. As MSCs possess immunosuppressive properties it can be used in T cell-mediated autoimmune disease like OLP. Making use of multiple pathways, MSCs suppress the function of a broad range of immune cells, including T-cells and B-cells[16] [Figure 5].

Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is a chronic, insidious disease associated with both significant morbidity and an increased risk of malignancy. Various agents like Areca nut, gutkha, spices are known to cause damage to oral mucosa by increasing cytokine production and release of reactive oxygen species; which in turn results in increased synthesis of collagen, decreased collagen breakdown, compromised vascularity and increased tissue oxidative stress, resulting in clinical features of OSMF.[17]

Various treatments have been tried to intervene the disease process at different stages but have shown limited success and Stem cell-based therapy is arising as a promising new approach.

Stem cell therapy is primarily aimed at neo-angiogenesis by releasing cytokines and growth factors (paracrine effect).

- This may bring about increased free radical scavenging by antioxidants (either naturally occurring or extraneous)
- Neo-angiogenesis may also encourage the removal of senescent cells from the lesions by providing more number of scavenging defense cells and inversion of hypoxia in the diseased tissue.

Stem cell therapy act on resident tissue stem cells to convert them into new fibroblasts, which help in the removal of disintegrated biochemically and morphologically altered collagen fibers[18,19] [Figure 6].

Clinical trials using stem cells for treatment of OSMF was done only by Sankaranarayanan et al., he demonstrated the effectiveness of stem cell treatment in OSMF patients by injecting derived stem cell concentrate into labial and buccal mucosa and tongue under local anesthesia. They noticed reduced blanching, improved flexibility of mucosa, decreased burning sensation, significant increased mouth opening and the outcomes were discovered to be supported in the follow up period from a half year to 5 years.[18,19]

Malignant lesions

Oral carcinomas

Surgery and external beam radiation has been the backbone of therapy for head and neck squamous cell carcinomas. Notwithstanding the new improvement in treatment modalities, the cancer recurrence and treatment failures continue to happen in a significant percentage of patients.[20,21]

Studies in a wide assortment of malignancies have exhibited that a particular sub population of tumor cells, termed cancer stem cells (CSCs), contain the capacity to go through self renewal and differentiation and thus can start tumorigenesis and support ongoing tumor growth. [20,21]

Stem cells here play a double role in carcinogenesis and in the advancement of conceivable new malignancy treatment alternatives in future.[20] Apart from their utilization in the immune-reconstitution, the stem cells have been accounted to contribute in the tissue regeneration as they have phenomenal ability to regenerate and differentiate. The MSCs have been utilized in the cell based bone reconstruction following chemotherapy and surgery in malignancies like osteosarcoma and Ewing sarcoma.[22]

Another significant part of their utilization in cancer therapy is the utilization as delivery vehicles.[22] Systematic delivery of drug or gene therapy has promising future however is right now restricted by different factors, for example, immune detection, nonspecific accumulation in normal tissues and poor permeation.[23]

Stem cells can act as cell based carriers that may focus on the ideal site. The new idea of utilization of stem cells as delivery vehicles comes from the way the tumors convey chemo attractants such as VEGF to enlist MSC to frame the supporting stroma of the tumor. However, further work is needed to comprehend the role of stem cells in cancer therapies, with the possible objective of eliminating the residual disease and reduce the rate of recurrence[24] [Figure 7].

2. Future Perspectives of Stem Cell Therapy

It is essential to understand that most new treatments of any kind (e.g., bone marrow transplantation to treat blood illnesses or monoclonal antibodies against malignancy), by and large, take 30 years or more to turn out to be clinically helpful at routine practice. Stem cell therapy in its new structure is, in this regard is still very young. Another inquiry could be: what we should not expect of stem cells in treatment in the coming decade? This sort of inquiry is in every case generally hard to hypothesize on, in light of the fact that scientific research frequently surprises us, however it merits referencing a couple of challenging diseases where desires for stem cell therapy are lower: Alzheimer's disease, multiple sclerosis in adults, atherosclerotic heart disease, and stroke.

Reasons incorporate difficulties of cell delivery to the appropriate location in the body, inability to produce the necessary cell types, and the nature of the tissue destroyed. Beyond direct cell therapy, we do have the exciting prospect of using stem cells (both from diseased and healthy individuals) for drug discovery: in the event that we can display sickness in a culture dish in the research facility might have the option to find novel medications, as necessary in combination, to hinder the rate at which a disease develops or ameliorate the symptoms. This would eventually becomes tremendous advantage to patients, especially those with chronic progressive disease, since it may extend the period in which they live in relatively good health, hinder improvement of their most debilitating symptoms, or even reverse them after their onset[4]

3. Conclusion

Remedies in the medical and dental field have consistently come about because of human curiosity to know the nature and copy it. The ability to treat currently incurable diseases has become a reality with the advancement of stem cell therapy. Stem cell research and therapies are promising new strategies for the treatment of different ailments and are picking up worldwide interest. With a better understanding of the stem cell biology, along with appropriate legal public policies and moral rules, safe and reliable therapies can be offered later on.

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Conflicts of Interest: none

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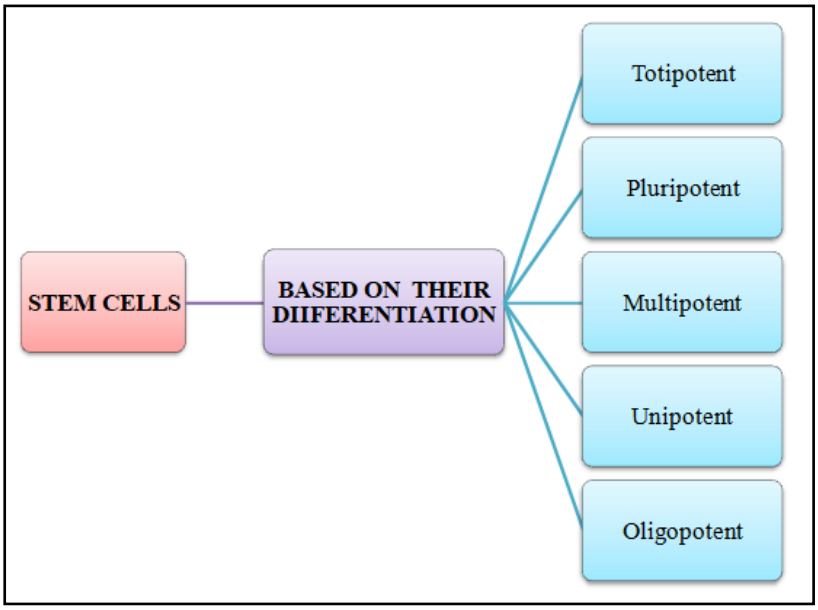

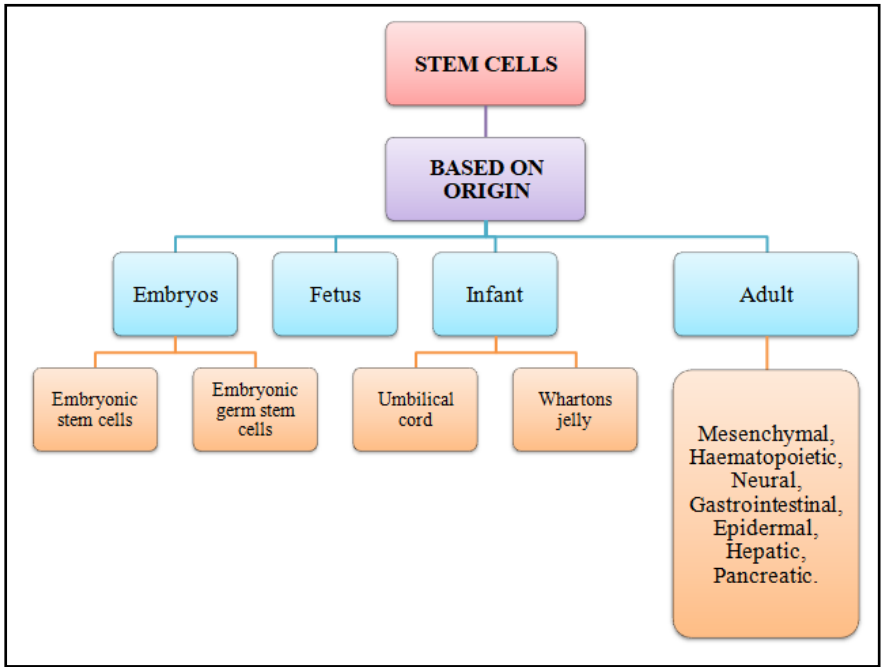

Figure 1: Types of stem cells

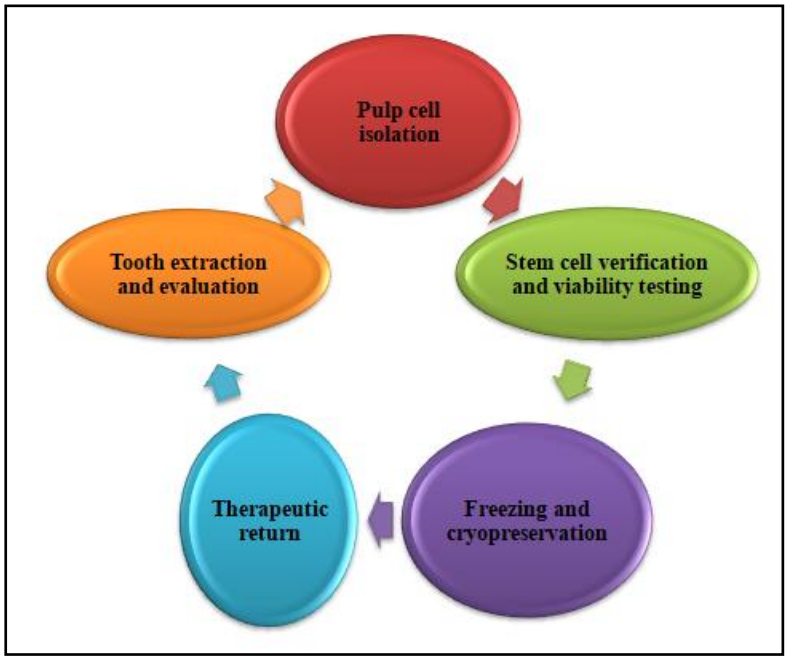

Figure 2 Schematic portrayal of dental stem cell banking process. Teeth lost by shedding, avulsion or extraction are preserved in transport medium, to tooth banking office. Dental pulp is taken out and stem cells are separated, tested for various parameters including viability then frozen. Frozen stem cells are at last put away under liquid nitrogen until needed by the donor. Around then, they can be defrosted and developed to a therapeutically appropriate number of cells before return to the donor.

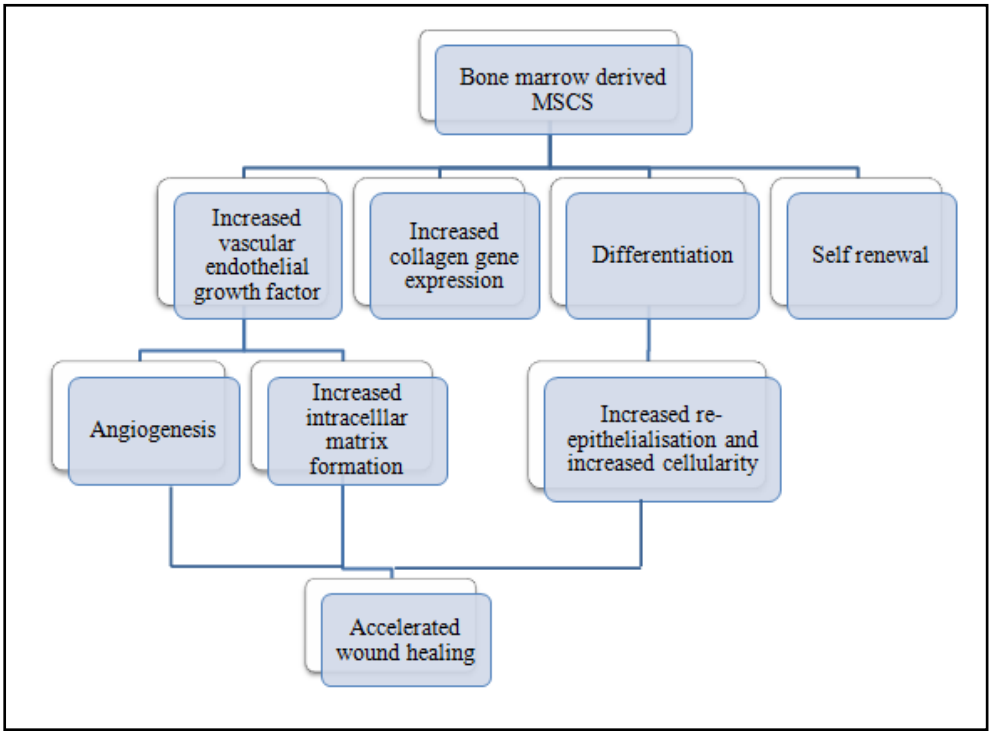

Figure 3: Role of mesenchymal stem cells in wound healing

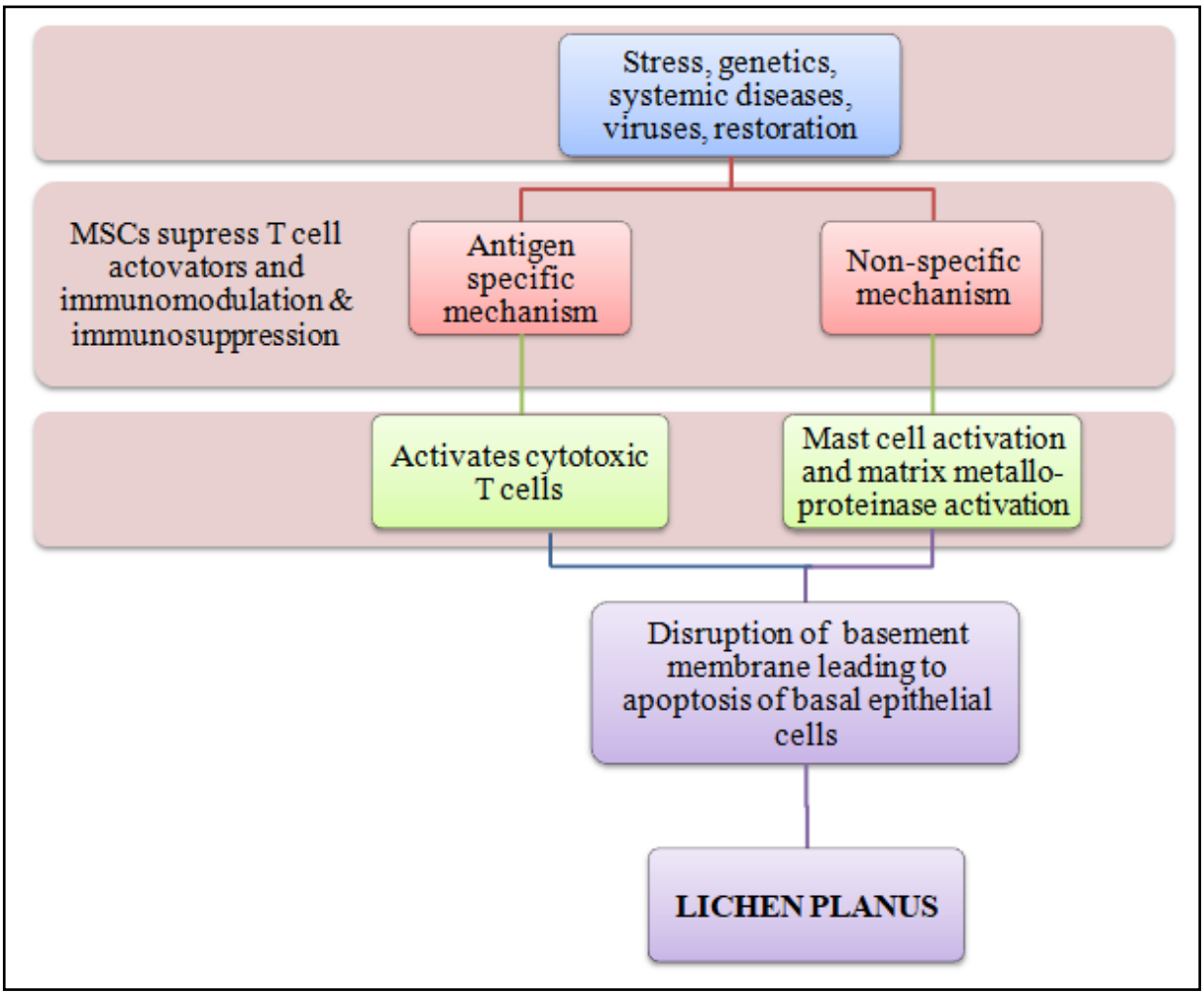

Figure 4: Action of stem cells in modulation of immune response in oral lichen planus

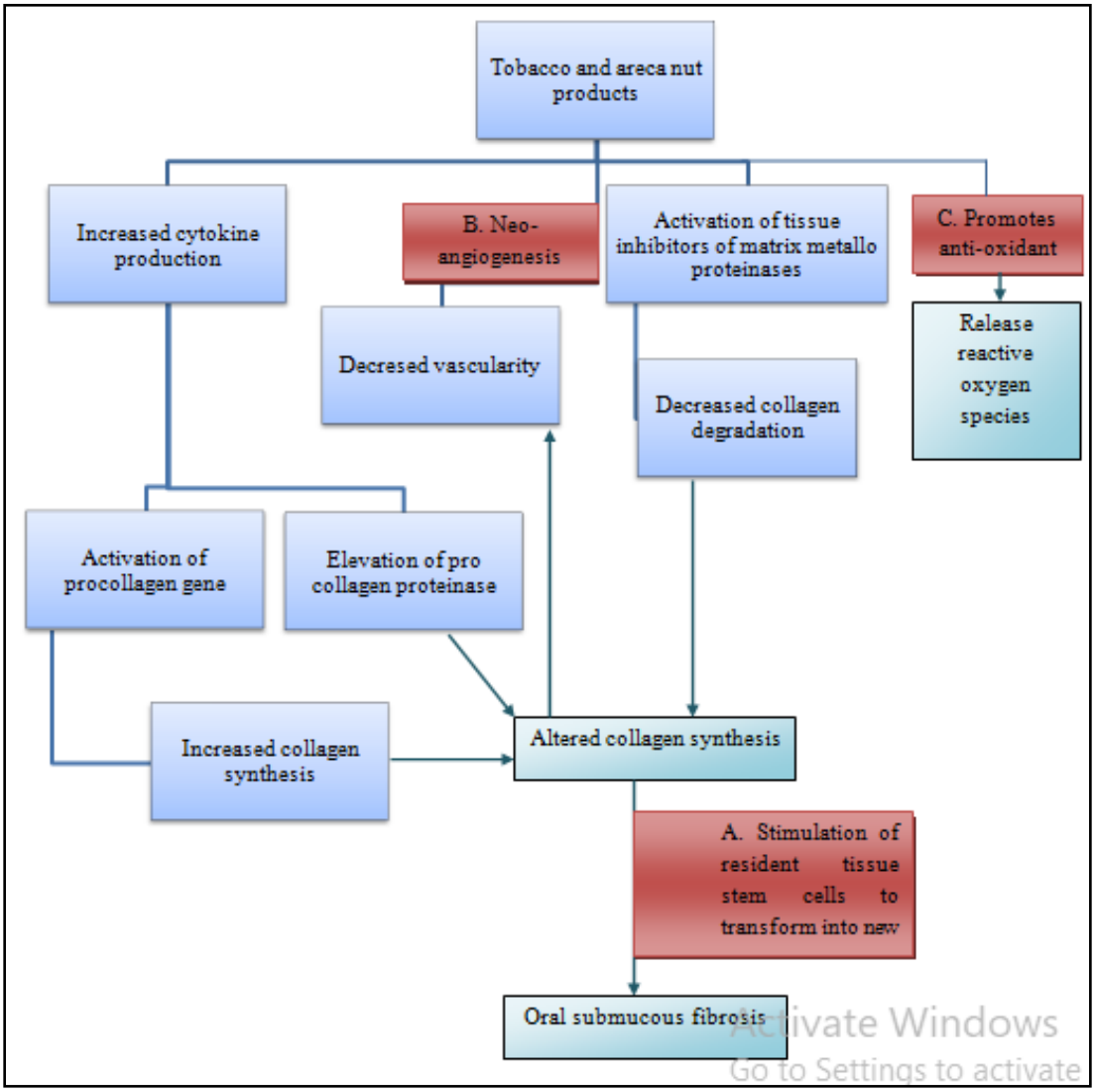

Figure 5: Role of stem cell therapy in oral submucous fibrosis at various levels. (a) Removal of pathologically altered collagen and stimulation of healthy collagen. (b) Promoting neoangiogenesis. (c) Promoting antioxidant action

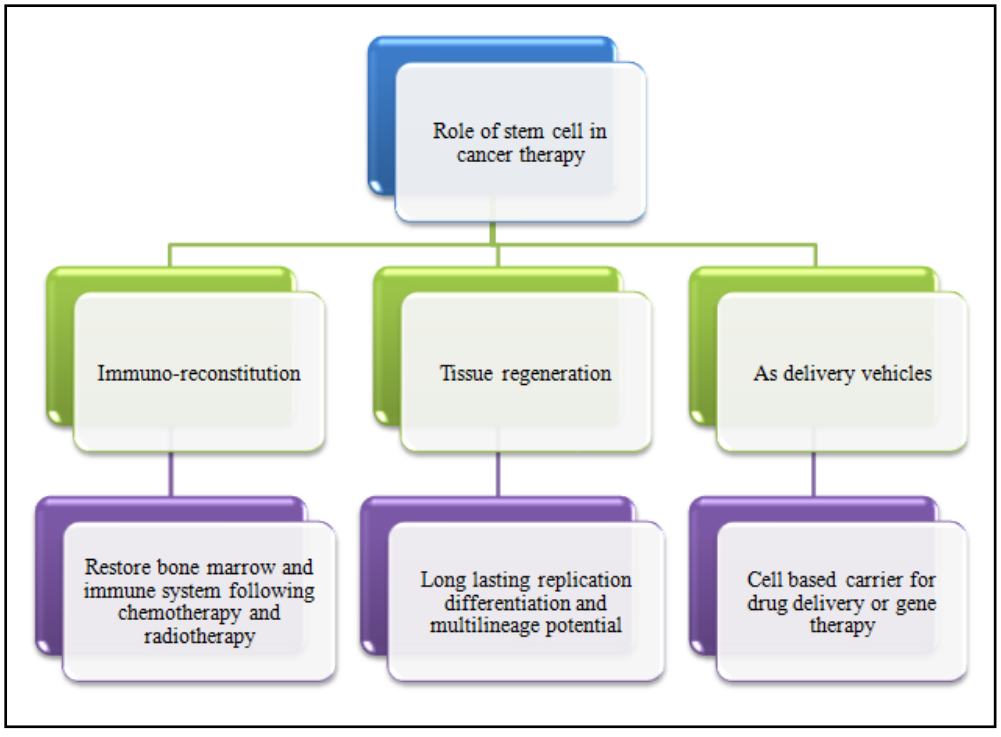

Figure 6: Role of stem cells in cancer therapy

Abbreviations:
ips - induced pluripotent stem cells
DPSCs - dental pulp stem cells
OSMF - Oral submucous fibrosis
OLP - oral lichen planus
MSCs - mesenchymal stem cells
HSCT - hematopoietic stem cell transplant
CSCs - cancer stem cells
VEGF - vascular endothelial growth factor

Author contributions

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(II) Administrative support: none
(III) Provision of study materials or patients: Varshitha thanmai Janumpally, Vaishnavi reddy Poreddy.
(IV) Collection and assembly of data: Vishwadha Chintha, Tejaswi Katne, Vaishnavi reddy Poreddy.
(V) Data analysis and interpretation: Vishwadha Chintha, Ramlal Gantala, Varshitha thanmai Janumpally, Tejaswi Katne
(VI) Manuscript writing: Vishwadha Chintha, Ramlal Gantala, Tejaswi Katne
(VII) Final approval of manuscript: All authors