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Discarded and Inflammed Oral Stem Cells Shows Considerable Stemness Inspite of Lesser Yeild - A Systematic Review

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Abstract: Adult mesenchymal stem cells (MSC's) have a promising treatment in regenerative medicine from bone marrow transplant to current treatment of superceneterian cells in aging and progeria. There remains lot of regenerative aspect which are still in clinical trials in dentistry. Inspite of easy availability, remarkable capacity and efficient colony forming units of known oral stem cells there is limitation in using them in vivo, this remains an important aspect to use it clinically. The current review emphasizes on the quantification and characterization of inflamed stem cells from dental pulp and gingiva (I-DPSC's and I-GMSC's) which are commonly discarded tissue in dental treatment and the ability of these inflamed cells which are thought to maintain stemness over limited expansion in vitro and its capacity to display considerable phenotype and functional heterogeneity in par with healthy oral tissue as like with umblical tissue cells (UCB-MSCs) and adipose tissue (AT-MSCs) over bone marrow stem cells (BM-MSC's).

Keywords: BM-MSC's, I-DPSC's, I-GMSC's, UCB-MSC's, AT-MSC's

1. Introduction

Stem cell biology has become an important field for the understanding of tissue regeneration and implementation of regenerative medicine. An essential charecterstic of stem cell is it must be capable of asymmetrical cell division producing exact cell multipotent replica and an additional progeny to perform more specialized function and needs to prospectively be isolated purified to homogenity and well characterized before in vivo testing [1].

Stem cells can be described as undifferentiated cells that are characterized by three fundamental abilities: proliferation, self-renewal, and differentiation towards multiple cell lineage. Adult stem cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis [2].

Currently stem cell based therapies has significant growth in treatment of blindness, and in chronic medical conditions like diabetes, cardiomyopathy and most important unique property of stem cells to migrate towards cancer cells which makes them excellent vectors for targeting cancer cells both in metastatic and primary stages which are under study [3].

Since the discovery and characterization of multipotent mesenchymal stem cells (MSCs) from bone marrow, adipose tissue and umbilical cord cells, MSC-like populations from bone marrow is considered as stem cells that can be easily expanded. However the ability of stem cells derived from adipose tissue and umbilical cord cells could be cultured longest with high proliferative ability and could be a better alternative to bone marrow stem cells because of their marked stemness. But still BMSC'S are considered as 'gold standard' criteria in regenerative medicine [3-5].

In regenerative dentistry, dental-tissue-derived MSC-like populations are among many other stem cells residing in specialized tissues that have been isolated and characterized.

The first type of dental stem cell was isolated from the human pulp tissue and termed 'post-natal dental pulp stem cells' (DPSCs) in the year 2000. Subsequently more types of dental-MSC-like populations were isolated and characterized: stem cells from exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), Gingival stem cells (GSC's) and stem cells from apical papilla (SCAP). And recently a dental-tissue-derived progenitor cell population, referred to as 'dental follicle precursor cells' (DFPCs). These oral stem cells mentioned above guarantee a autologous donor match are easy accessible with no ethical concerns being adult stem cells. Amongst these DFPCs and SCAP and SHED represents promising and accessible source, from which induced pluripotent stem cells (IPSC's) can be obtained and can be future use in regenerative procedure. [5-7].

This article reviews to understand

1) The correlation of the potency of cord stem cells and adipose tissue stem cells to the multipotentiality of the better known BM-MSC's.
2) To compare the similarities and differences between the bone marrow stem cells and dental pulp stem cells.
3) To review studies on MSC's from healthy and inflammed oral stem cells in vitro and in vivo.

Though lots of studies have been done on inflamed oral stem cells which is generally discarded pulp during root canal treatment and from gingiva in flap surgeries, operculotomies and enlarged gingival conditions. These MSC's shows considerable heterogeneity and maintain stemness over normal healthy oral stem cells like umblical cord tissue and adipose tissue though they yield less.

2. BMSC's VS UB-MSC's and AT-MSC MSC

Bone marrow, adipose tissue and umblical cord derived mesenchymal tissues are morphologically and immunophenotypically similar but not identical. Comparative studies depicts that isolation rates of MSC's are highest in bone marrow and adipose tissue, inspite that umblical cord derived tissues MSC's have lowest proliferation but still it has capacity to culture longest. The below tabular chart depicts comparative studies studies done by (Sussane kern et al and katia merschi et al, and Li Hu, JingquiongHu et al) [8, 3, 9]. [Table 1].

Along with the above studies, other studies on comparison shows that cord blood MSC's are slower to establish in culture though they lack expression of phenotype of multiple lineages still they lack bone antigen expression and neural antigen expression in few in vitro cultures. MSC's though decreased at each passage, cryopreservation has no effect on the morphology and the proliferation and differentiation capacity (approximately 90% viability of cells were obtained on in vitro cultures after thawing. This proves that even long storage has its future applications owing to their stemness, and because of its immunosuppressant and immunomodulatory effects through inhibition of lymphocyte it have more proliferation over BMSC [10, 11].

3. Similarities and Compartive Analysis BMSC's and DPSC's

Oral tissue stem cells are specialized, restricted or committed cells with ecto- mesenchymal origin and do not undergo continuous remodeling unless respond to injury. In characterizing the multi-differential potential of both the DPSCs and BMSC'S they are capable of differentiating into 3 lineages (osteoblast/odontoblast, adipogenic and neurogenic) when grown in defined conditions in vitro. Though osteogenesis and dentinogenesis are controlled by different mechanism the bone and dentine are similar in matrix protein composition but their organ structure is totally different [5].

According to studies in vitro DPSC's compared to BMSC's are highly clonogenic with known stem cell markers. Although they share similar immuno-phenotype functional studies showed that DPSC's produced only sporadic but densely calcified nodules and do not form adipocytes where as BMSC's calcifies throughout and form clusters of adipocytes. DPSC's have ability to form bony tissue and pulpal tissue when mediated by their carriers but BMSC's are not capable of producing pulp like tissue [12].

Three aspects are considered when quantifying and charecterizing the cells from cultures after a certain passages when confluence is reached to identify the number of cells formed, colony forming efficiency (CFE) population doubling (PD) and in vitro culture. Suggesting dental pulp stems cells forms smaller colonies and are more lineage restricted though the proliferation capacity (PD's) was similar to BM. [13]

Studies done on BMSC's and DPSC's show that though the population doubling and colony forming efficiency is more in BMSC's and inspite of low cell harvest the DPSC's are capable of producing reparative dentine either in tubular or amorphous matrix which is a pre requisite in regenerative dentistry. [Table 2].

4. Inflammed Oral Stem Cells VS Non Inflammed

MSC's like population within inflamed tissue are functionally equivalent to healthy tissue. Inflammatory environment causes autocrine cell production (positive feedback loop). MSC's proliferate faster as it mediates cytokiene dependent chaperons and stress response proteins which causes changes in ECM and the resident local cells (chondrocytes, endothelial cells, fibroblast, osteoblast) are secreted by MMP production meanwhile TIMP's inhibits MMP's activity and reduce ECM degradation [14-16].

Though MSC's derived from inflamed hyperplastic tissue display a stable phenotype and maintain normal karyotype, they are not tumerogenic. Proinflammatory cytokienes (TNF-α, Interleukins) have been shown to suppress the multipotent differentiation capacity of single derived

mesenchymal stem cells. Proinflammatory cytokienes (TNF -Alpha and interleukins) are upregulated and they act on local stem cells. Inflammatory environment has lesser proliferative capacity but decreased differentiation ability. There is greater expression of STRO-1, CD90, CD105, CD146 in inflamed environment and also higher expression levels of several embryonic stem cell genes OCT4, Nanong which suggest highly robust stemness [17, 18].

Studies done to date shows that irrespective of proliferation and quantification differences, the source of MSC's obtained from inflamed origin has intact stem cell properties as the inflammatory background controls the fate of MSC's through several regulatory mechanism involving remodelling of the cytoskeleton and stress response process [14]. [Table 3].

Table 1. *Comparative studies on proliferation and charecterization in vitro cultures amongst BMSC'S vs UB-MSC'S and AT-MSC.*

CELL TYPE	ISOLATION CAPACITY of MSCs	COLONYFORMING UNITS (POPULATION DOUBLING)	INVITRO MULTIPOTENCY	STUDIEDBY
BM-MSCs AT-MSCs UCB-MSCs	Highest (100%) Highest (100%) Moderate (63%)	Lesser proliferation capacity with shorter culture period Moderate proliferation capacity with longer culture period High proliferation capacity with longest culture period	Adipogenic, osteoblastic and chondrogenic tissues were formed Adipogenic, osteoblastic and chondrogenic tissues were formed *NO ADIPOSE TISSUE WAS FORMED*, there was osteogenic and chondrogenic differentiation	Sussane kern et al
BM-MSCs UCB-MSCs	(100%) Lesser rate of isolation	Reached confluence and grew exponentially Number of viable cells decreased with each passage	Osteoblastic, chondrogenic and adipogenic tissues differentiation was seen *HEAMATOPEOTIC TISSUE WAS FORMED*	Mareschi et al
AD-MSCs UCB-MSCs	100%(24 hrs 100%(72 hrs	Faster growth Moderarte growth	ALL TISSUES GREW EFFICIENTLY Osteoblastic, chondrogenic and adipogenic tissues differentiation was seen.	Li Hu, JingquiongHu

Table 2. *Similaraties and comparative studies among BMSC'S and DPSC'S.*

Type of stem cells	CFE (COLONY FORMING EFFICIENCY	PD's (Population doublings)	In vitro	Studied by
BMSC's DPSC's	Less Higher	Lesser proliferating cells than DPSCs Number of proliferating cells were higher	Extensive sheets of calcified tissue was formed and adipocytes were formed. Lesser mineralized structures were seen with NO ADIPOCYTES	Gronthos 2000
BMSC's vs DPSC's	BM clones were expanded by 50% and dp were expanded by 10% THE COLONY FORMING EFFICIENCY WAS 12 TIMES GREATER FOR DSPSCs than BMSC'S	Population doublings were 1.5 slower for DPSCs DPSCs achieved 40 pds at 114-245 days BMSCs achieved 40 pds in 96-180 days	BMSSC readily formed osteoblast, chondroblast and adipocyte, but the efficiency of DPSCS were scattered.	Jodie Harrington 2014

Table 3. *In vitro studies done in healthy vs inflammed oral stem cells.*

Cell type	Isolation of MSC's or CFU	In vitro Multipotency and stemness	Studied by
Normal vs Inflamed stem cells	Higher proliferation rate in inflamed cells	Lesser amount of bone formation in inflamed environment	Luara tomsello 2017
Healthy vs inflammed	No difference in proliferation rates	There was formation of osteogenic and adipogenic differentiation NO CHONDROGENIC DIFFERENTIATION WAS SSEN	Shahue Ge Krzysztf 2012
Healthy vs inflammed	No difference in proliferation rates	There was decreased formation of mineralized nodules	Hao yang, Li gao 2013
Healthy vs inflammed stem cells	Lesser Proliferation of cells were seen in inflamed stem cells		Dominick J AlongiTakayoshi Yamaza 2010

5. Conclusion

This review emphasizes that though there sufficient studies done on inflamed gingival and pulpal stem cells it seems that they have different immunomodulatory properties and capacity to generate sufficient amount of tissue in vitro (the capacity to differentiate in vitro still remains an aspect which needs further investigation).

The reason could be in inflammatory environment (cytokines) provides positive feedback and create more cells via paracrine effect, in that case the population doubling rates may be higher or it may happen that direct exposure of cytokienes can cause cell senescence which may cause decreased proliferative rates. Till date DPSC's are limited to form reparative dentine, regeneration is still a promising strategy.

Regeneration of oral tissues and its ability to expand in vitro and to be applicable in vivo is target of stem cell research. Inflammed stem cells could be employed as further studies as they show high levels of stemness. Irrespective of their proliferation rates the marked stemness in inflammatory

environment cells may in future can be used like UCB-MSC's which has though decreased at each passage, its cryopreservation has no effect on the morphology and the proliferation and differentiation capacity (approximately 90% viability of cells were obtained on in vitro cultures after thawing. This proves that even long storage has its future applications owing to their stemness.

6. Future Perspective and Research Gap

1. Obtaining a cytotype capable of forming complete tissue is of importance in vivo, before setting up clinical trials.
2. Inflammed MSC's retains the property of stemness inspite of low harvest and efficient colony forming units which could yield better regeneration capacity. Studies are required to see these changes lasts for a period and may reverse after period of time and yield sufficient tissue matrix.
3. Further studies can be done to analyze whether inflamed gingival and pulp tissue can be used over normal dental stem cells similarly like umbilical cord stem cells and adipose tissues are being used over BMSC'S as the differential capacity is more efficient.

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