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CURRENT STATE OF STEM CELLS IN RESTORING ORAL HEALTH: CLASSIFICATION, ROUTES OF DELIVERY AND HOMING

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ABSTRACT

Regenerative medicine, the newest and most developing field focuses on the functional regeneration of cells or organs for patients with persistent illnesses or serious injuries. Transplantation of stem cells has become a promising approach in regenerative medicine as a Cell-based treatment for diseases compared to traditional medications because of their pleiotropic therapeutic capacity, which includes the prevention of inflammation or apoptosis, cell recruitment, promotion of angiogenesis, and differentiation. A stem cell line is a collection of cells that can multiply in vitro or outside the body for a long time. There are different stem cell types according to their differentiation potential: oligopotent, totipotent, pluripotent, multipotent, and unipotent. The tissues from which these cells are derived include stem cells originating from embryos or adult individuals. How stem cells are administered should be carefully considered since they can either compromise safety and cause major adverse events or alter the localization and engraftment of the cells, reducing therapeutic efficacy. In this review, we have discussed and summarized several types of stem cells, their various administration techniques, the homing mechanism of stem cells, and some studies that utilized stem cells in regenerative dentistry.

KEYWORD: Mesenchymal Stem cells; Types; Routes of delivery, Homing; Oral Tissues Repair.

INTRODUCTION

Regenerative medicine is a new and auspicious therapeutic approach whose ultimate objective is to return tissues and organs to their original functioning (Sajib et al., 2024).The application of stem cells (SCs) developed the field of regenerative medicine, which aims to increase longevity and health by repairing damage caused by aging, trauma, infection, or inflammation in both human and veterinary medicine (Markoski, 2016; von Schwarz, 2024). Some SC treatments are currently used in clinical settings, while several others have demonstrated remarkable success in the lab. Numerous clinical trials are also testing newer stem cell types (Sajib et al., 2024).

The study of SCs began in the 1960s when Friedenstein and associates isolated, cultivated, and differentiated bone marrow-derived cells

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from guinea pigs into osteogenic cell lineage (Friedenstein et al., 1974; Friedenstein et al., 1966). Due to the intense interest in SCs over the last 20 years, our knowledge of their properties and potential therapeutic uses has significantly advanced (Zakrzewski et al., 2019).

SCs are a special kind of cell that can self-renew and specialize into distinct cell lineages. Since they are the source from which particular cell types within differentiated tissues and organs are formed, they play a crucial role as mediators in the development of newborns and the healing, processes following damage or disease (Poliwoda et al., 2022). While SCs' main function in adults is regenerative and restorative, in neonates they serve to differentiate and proliferate into a wide range of cell types and lineages necessary for ongoing development (Dekoninck & Blanpain, 2019).

SCs were thought to be limited to differentiating into adult cells of the same organ. There is now sufficient evidence that SCs can develop into ectoderm, mesoderm, and endoderm, among other cell types. Different tissues, including bone marrow, liver, heart, kidney, and others, have varying quantities of SCs (Fathi & Farahzadi, 2016; Rajabzadeh et al., 2019).

The ability of transplanted SCs to survive, proliferate, and differentiate within the affected tissue is essential in achieving effective tissue reconstruction. Additionally, integration with the host's circulatory system is vital to guaranteeing an adequate flow of nutrients and signaling molecules that support the successful repair of diseased or damaged tissue (Kharbikar et al., 2022).

Asymmetrical stem cell division produces a daughter SC and an extra progenitor cell. SCs are, therefore, capable of both regeneration and self-renewal. Their specification potential determines their capacity for differentiation. Furthermore, SCs can divide symmetrically, producing two identical daughter cells, preserving the SCs' identity (Arnaud Martino et al., 2023; Yan et al., 2023).

The two types of SCs used in cell-based therapy are (1) autologous, referred to as self-to-self therapy, which uses the patient's cells, and (2) allogeneic, which uses cells from a healthy donor (Srijaya et al., 2014). Based on their origin, SCs can be divided into 2 main groups: embryonic and somatic (tissue-derived) (Ntege et al., 2020). Moreover, multipotent, oligopotent, unipotent, pluripotent, and totipotent are the five main categories into which SCs can be separated based on their level of potency or differentiation (El Barky et al., 2017; Łos et al., 2019).

Classification of stem cells according to their potency

Potency is the term used to describe SCs' capacity to differentiate into various cell types (Poliwoda et al., 2022). SCs can be classified into totipotent, pluripotent, multipotent, oligopotent, and unipotent cell types depending on their potency (Fig. 1A) (Sajib et al., 2024).

Totipotent stem cells

The greatest differentiation potential is exhibited by totipotent stem cells, which enable the production of both embryonic and extra-embryonic tissues. A zygote, created when a sperm fertilizes an egg, is an example of a totipotent cell. These cells can potentially grow into a placenta or any of the three germ layers (Hu et al., 2023).

Pluripotent Stem Cells (PSCs)

PSCs can differentiate into cells of all germ layers, but they are unable to develop extraembryonic structures like the placenta. These cells include Embryonic stem cells (ESCs) and cells that have been separated from the germ layers of mesoderm, endoderm, and ectoderm that are arranged during the early stages of ESC development (Liu et al., 2020; Rajabzadeh et al., 2019).

Multipotent Stem Cells

Cells that have undergone differentiation from a single germ are multipotent and present in

most bodily tissues (Shah & Khan, 2021). They can specialize in distinct cells of particular cell lineages, but their range of differentiation is more limited than that of PSCs (Zakrzewski et al., 2019). Haematopoietic stem cells and mesenchymal stem cells (MSCs) are two types of multipotent stem cells. The most popular type of multipotent cell is the MSC, which can be found in bone marrow, adipose tissue, bone, Wharton's jelly, umbilical cord blood, and peripheral blood (Shah & Khan, 2021; Zakrzewski et al., 2019). Any blood cell can be produced by hematopoietic stem cells, including lymphoid and myeloid cells (Vanickova et al., 2023).

Oligopotent Stem Cells

Adult multipotent hematopoietic stem cells can differentiate into both myeloid and lymphoid cells; these progenitors are regarded as oligopotent as they can differentiate into a limited number of cell types, such as lymphoid or myeloid stem cells, are regarded to be oligopotent (El Barky et al., 2017). All blood cells can be produced by myeloid SCs, except for lymphoid cells, which are produced by lymphoid SCs (Lee & Hong, 2020)

Unipotent Stem Cells

Unipotent SCs have a limited capacity for differentiation and the unique ability to divide repeatedly. This latter characteristic makes them a viable option for regeneration-based treatment. They can transform into a single kind of cell as muscular SCs, which aid in the process of muscle regeneration (Charitos et al., 2021; Zakrzewski et al., 2019).

Classification of stem cells according to their origin

The two main cell types in the origin-based classification are tissue-derived (somatic) stem cells and embryonic stem cells (ESCs). The tissue-derived stem cells are divided into two categories: adult stem cells extracted from different tissues and fetal stem cells extracted from fetus tissues. More recently, two more tissue-derived stem cell subtypes have been identified: induced tissue-specific stem cells (iTSCs) and induced pluripotent stem cells (iPSCs) (Fig. 1A) (Cerneckis et al., 2024; Miyagi-Shiohira et al., 2018; Ntege et al., 2020).

Embryonic stem cells (ESCs)

The pluripotent cells known as ESCs can develop into any mature cell type in 3 germ lines. The main source of ESCs is the inner cell mass of a human blastocyst that is 5–6 days old (Thomson, 1998). The ESCs develop into multipotent stem cells after differentiating into a particular germ layer. ESC lines can be created by transferring undifferentiated ESCs from the inner cell mass into a dish for growth under particular conditions (Bongso, 2006). ESCs have unique qualities, including self-renewal, pluripotency, and genetic stability, that make them attractive options for cell-based therapy (Yoon et al., 2014). ESCs have enormous potential in regenerative medicine, providing novel approaches to the treatment of diseases that were thought to be incurable (Park et al., 2024).

Nevertheless, while employing ESCs in treatment, researchers face several obstacles, such as the rejection of cell engraftment due to incoherence between the recipient and donor cells, ethical problems such as embryo loss during sampling, and the development of teratomas following transplantation (Arjmand et al., 2016; Arjmand et al., 2019; Ben-David & Benvenisty, 2011).

Tissue derived stem cells

Fetal stem cells (FSCs)

Multipotent FSCs have few ethical limitations (Götherström, 2016). The most extensively researched FSCs types are fetal MSCs and fetal hematopoietic cells (HSCs), but also include neural crest cells (Barzegar et al., 2019).

Fetal MSCs can be extracted from extra fetal (perinatal) tissues, including the placenta,

amniotic fluid, Wharton jelly, umbilical cord blood, decidua basalis, and decidua parietalis, as well as from fetal tissues like blood and bone marrow. (Abbaspanah et al., 2018; Alatyyat et al., 2020; Loukogeorgakis & De Coppi, 2017; Song et al., 2022; Stefańska et al., 2020).

Depending on their gestational age and the tissue from which they originated, the FSCs' phenotypic characteristics and features, as well as their cell expression markers, vary widely (Shah & Khan, 2021). Compared to adult stem cells, fetal MSCs have been reported to have lower immunity, more multipotency, and superior internal migration and implantation capacity (O'Donoghue & Fisk, 2004).

Adult stem cells (ASCs)

ASCs are a rare population of undifferentiated cells found in a specialized structure known as a niche within a developed tissue or organism. They are sometimes referred to as resident SCs. The regional microenvironments that control SC development and proliferation are preserved by these niches (Gurusamy et al., 2018). The ASCs can develop into a small number of mature cell types and are capable of self-renewal. The preservation of tissue homeostasis is the primary function of ASCs. Normally kept in a quiescent condition, these ASCs can be stimulated to multiply and develop into the necessary cell type in response to tissue damage or cell loss (Fuchs & Blau, 2020; Mannino et al., 2022).

In terms of clinical uses, adult stem cells are somewhat superior to iPSCs and embryonic stem cells. During autologous implantation, there are no ethical or immunological rejection issues.

Adult stem cells can be either unipotent or multipotent (Barzegar et al., 2019). The three subtypes of multipotent ASC are mesenchymal stem cells (MSC), neural stem cells (NSC), and hematopoietic stem cells (HSC) another ASCs known as epidermal stem cells (ESCs) are unipotent, meaning they can differentiate into only one type of cell, such as keratinocytes (Crane et al., 2017; Dulak et al., 2015; Liu et al., 2016).

Hematopoietic stem cells (HSCs)

Multipotent primordial cells known as HSCs could differentiate into both myeloid and lymphoid blood cell types. Numerous organs, including bone marrow (BM), umbilical cord blood (UCB), and peripheral blood (PB), contain HSCs (Lee & Hong, 2020). HSCs are essential for hematopoiesis, which keeps the blood system in balance throughout an organism's life (Tajer et al., 2019).

Neural stem cells (NSCs)

There are two categories of NSCs the 1st one called endogenous NSCs are found in the olfactory bulb, subventricular zone, and hippocampal regions. They secrete factors for synaptic plasticity, release proangiogenic complexes, control inflammation, and create neurotrophic factors (Lakshman et al., 2018; Zhou et al., 2019). And the other called exogenous NSCs can divide and differentiate into neurons, astrocytes, and oligodendrocytes. These include ESCs, iPSCs, bone marrow and adipose-derived MSCs, embryonic NSCs, and SCs from the infant and adult nervous systems (Hou et al., 2017; Hu et al., 2019).

Mesenchymal stem cells (MSCs)

In the latter half of the 1960s, MSCs were initially identified as bone marrow (BM)-derived fibroblast-like cells with the capacity to undergo significant differentiation and self-renewing (Friedenstein et al., 1966). Later, Caplan et al. discovered that fibroblast-like cells derived from BM also have osteogenic and chondrogenic properties in 1991, they gave these cells the name "MSCs" (Caplan, 1991; Goshima et al., 1991).

They are multipotent cells that have the capacity to undergo differentiation into mesenchymal cell types such as osteoblasts, adipocytes, and

chondrocytes. In recent decades, MSCs have become increasingly popular in clinical settings due to their lack of ethical concerns and teratoma-forming potential when compared to ESCs and IPSCs (Heris et al., 2022; Samsonraj et al., 2017). MSCs are special cells since they can migrate to wounded areas and are simple to isolate. In addition, they show paracrine immunomodulatory properties and antibacterial, anti-inflammatory, and anti-apoptotic features. They can stimulate endogenous SCs and neo-angiogenesis (Maacha et al., 2020; Yang et al., 2023).

Minimum standards for identifying MSCs were released in 2006 by the International Society for Cellular Therapy's (ISCT) Mesenchymal and Tissue Stem Cell Committee including the capacity to differentiate into osteoblasts, adipocytes, and chondrocytes, is one of the three traits that set MSCs apart. Second, MSCs stick to plastic in a tissue culture flask while preserving a typical culture environment. The third feature is the existence of particular surface markers, as determined by flow cytometry, such as CD105, CD73, and CD90 (Dominici et al., 2006).

The most popular MSCs for regenerative applications are still those derived from bone marrow (BM-MSCs) and adipose tissue (AT-MSCs). Dental tissue-derived stem cells (DT-MSCs) have become more attractive cell sources for bone and dental tissue reconstruction in recent years due to their ease of use and easy access (V. J. Costela-Ruiz et al., 2022; Ivanovski et al., 2024).

Bone marrow mesenchymal stem cells (BM-MSCs)

BM's main job is to send signals that promote hematopoiesis, or the formation of blood cells, as well as the resident SCs' quiescence and capacity for self-renewal. The two main types of SCs found in the BM are stromal, which support hematopoietic development and differentiate into various cell types, and hemopoietic, which produce blood cells (Lucas, 2017).

The BM's medullary stroma contains BM-MSCs. Traditionally, they are obtained either directly for plastic adherence in vitro or via gradient cell separation. Flow cytometric techniques, like fluorescence or magnetic separation of cells, are further isolation techniques (V. J. Costela-Ruiz et al., 2022; Gronthos et al., 2003; Miltenyi et al., 1990) .

Because of their obvious benefits, BM-MSCs are most commonly used in regenerative medicine. They are ethically free because they can be autologously transplanted and are relatively easy to obtain from a rich resource. They are also easily amplified in vitro because of their high genetic stability, rapid rate of proliferation, ease of culturing and separation, and, last but not least, their low immunogenicity and ability to undergo differentiation in multiple directions (Re et al., 2023). Unfortunately, Human BM aspirates comprise only 0.001–0.01% of the total stromal cell population, and their characteristics are highly dependent on the donor's age, sex, and pathological conditions the harvesting process is extremely invasive, painful, and necessitates hospitalization and general anesthesia (V. J. Costela-Ruiz et al., 2022; Siegel et al., 2013).

Adipose tissue mesenchymal stem cells (AT-MSCs).

AT-MSCs appear to be the most beneficial for tissue engineering and cell treatments. It has been claimed that 500 times more stem cells may be extracted from adipose tissue than from equivalent amounts of BM because of the abundance of AT-MSCs in adipose tissue compared to other different tissues in the human body (Bacakova et al., 2018; Mizuno, 2013; Ong & Sugii, 2013). AT-MSCs can be separated from the stromal vascular fraction (SVF) and are found in the perivascular niches of white adipose tissue. Following liposuction collection of the SVF cells, the lipoaspirate is cleaned, digested, and centrifuged before being transferred to plates and cultured to obtain AT-MSCs (Andia et al., 2019; Barba et al., 2017).

AT-MSCs are easier to harvest in greater quantities than BM-MSCs, and because of their subcutaneous location, they cause less discomfort and harm to the donor site (Varghese et al., 2017). Additionally, it has been noted that AT-MSCs have a greater propensity for proliferation than BM-MSCs as well as reaching senescence later than BMMSCs (Barba et al., 2013; Ding et al., 2013; Kokai et al., 2014). Additionally, compared to other MSC populations, AT-MSCs exhibit a greater autocrine synthesis of some growth factors and immunomodulators (Hsiao et al., 2012).

Dental-derived mesenchymal stem cells (DMSCs)

Since the first isolation of a clonogenic population of dental mesenchymal stem cells (DP-MSCs) from the pulp of human third molars in 2000, MSCs have been gained from other dental tissues (Gronthos et al., 2000). DMSCs are made up of any MSCs extracted from various oral apparatus locations. There are eight main types of MSC generated from tooth dental pulp stem cells (DP-MSCs), MSCs from the pulp of exfoliated deciduous teeth (SHEDs), apical papilla (AP-MSCs), periodontal ligament (PL-MSCs), dental follicle precursor (DFP-MSCs), gingival mesenchymal stem cells (G-MSCs), alveolar bone-derived mesenchymal stem cells (AB-MSCs), and tooth germ progenitor cells (TP-MSCs) (Victor J. Costela-Ruiz et al., 2022).They have the same neurogenic potential as neural crest-derived stem cells (NCSCs) and share general characteristics with other MSCs because of their embryonic origin (Liu et al., 2015). DMSCs exhibit the capacity to attach to plates and create colonies under specific cultural conditions. Their strong ability to proliferate and differentiate into several lineages, including adipogenic, chondrogenic, and osteogenic lineages (Aydin & Şahin, 2019). They are therefore excellent candidates for applications involving tissue regeneration. DMSCs also possess immunomodulatory qualities that allow them to control and preserve the periodontal microbiome's homeostasis through immune response (Andrukhov et al., 2019; Wen et al., 2024).

Induced pluripotent stem cells (iPSCs)

Mature cells can be genetically reprogrammed to develop iPSCs, which are SCs with embryonic features. Using iPSC technology, terminally differentiated cells can operate similarly to ESCs after they are stimulated to become pluripotent again. Their cultivation and applications hold great promise for regenerative medicine both now and in the future (Cerneckis et al., 2024; Ramakrishna et al., 2020). Three separate research teams (Loh et al., 2009; Takahashi & Yamanaka, 2006; Yu et al., 2007) Reported successfully genetically reprogramming somatic cells to become stem-like cells between 2006 and 2009. Because their application does not present significant ethical concerns, like ESCs, iPSCs have recently become more and more popular (Fan et al., 2017). Furthermore, it is thought that iPSCs and ESCs have the same differentiation patterns and the expression of particular genes and proteins. Moreover, iPSCs are highly advantageous in a variety of cell-based treatments since they are known to help identify the earliest disease-causing events in cells (Ramakrishna et al., 2020).

These iPSC cells could be differentiated utilizing the proper mechanisms to produce the cells needed for the treatments. Unlike transplanted cells of donor SCs, this approach avoids the necessity for lifelong histocompatibility immunosuppression, which is what makes it desirable (Wiegand & Banerjee, 2019).

The viability of SCs in the body, including immunological rejection, has been a source of recent uncertainty and controversy surrounding SC therapy. To overcome this, scientists have created autologous iPSCs in the hope that the body's immune system won't recognize them. But goals have not been fulfilled by reality. The oncogenic characteristics of iPSCs also prevent them from being used in more

therapeutic settings (Liu et al., 2017). This could be partly because different stimulating agents with oncogenic capacity are used for generating iPSCs (Kaji et al., 2009). Even though some research has employed the development of benign teratomas as a standard for confirming the pluripotency of SCs this is never appropriate for use in clinical applications (McDonald et al., 2020). Furthermore, some individuals' cells might not be reprogrammable. The cost of creating iPSCs for every patient is also high, and there are issues with repeatability and quality control (Han et al., 2024).

Consequently, because of unresolved problems with using iPSCs for clinical treatments, especially their tendency to form tumors and their restricted capacity to produce pure differentiated cells in vitro, Tissue-specific stem cells were successfully produced by Noguchi Hirofumi and associates. They came up with the term "induced tissue-tissue specific stem cells" (iTSCs) (Noguchi et al., 2015). They are partially reprogrammed cells that fall somewhere between somatic cells and iPSCs so called intermediate cells. They are derived from the de-differentiation process of differentiated somatic cells (like fibroblasts) into PSCs (like iPSCs and ESCs) (Saitoh et al., 2021). They were produced from the liver and pancreas of mice by temporarily overexpressing the reprogramming factors utilizing the transcription factors hepatocyte nuclear factor 4 alpha (HNF4a) and pancreatic and duodenal homeobox factor-1 (Pdx1). In their study they highlighted the better differentiation ability, lack of teratoma development, and relative significance of iTSCs to clinical application of stem cells (Noguchi et al., 2015).

Routes of stem cell delivery

Preclinical models have investigated a variety of SC delivery methods to attain the best possible homing and implantation in the afflicted organ. Numerous investigations have demonstrated that the delivery method significantly affects the biodistribution and mode of action of SCs, and consequently, the clinical result (Bonaventura et al., 2021; Golpanian et al., 2016; Kanelidis et al., 2017; Kean et al., 2013).

The administration of SCs can be broadly classified into two categories: systemic and local delivery (Mousaei Ghasroldasht et al., 2022). To improve engraftment, SCs can be incorporated in cell carrier substances for local delivery, extending the time viable cells remain in the tissue (Antunes et al., 2014; O'Cearbhaill et al., 2014). Scaffold-based SC treatment, for example, can significantly improve tissue shape and function by delivering therapeutic biomolecules at damaged locations in a regulated manner (Gu et al., 2021). Despite being the most common method in both recipients and research models, the systemic route has disadvantages, including the possibility of injected cells being trapped in the lungs as a first-pass organ in the case of intravenous injection. As a result, the beneficial impacts are lessened, and the SCs' access to the desired organs is decreased, as well as reduced blood flow and microembolism formation in intra-arterial injection (Cui et al., 2015; Petrus-Reurer et al., 2021). Nevertheless, certain varieties of stem cells, such as MSCs, can exert therapeutic effects on the target organ from a distance by secreting paracrine factors and extracellular vesicles (Naldini, 2019; Ratajczak & Suszynska, 2016).

Local delivery of SCs

Local SC delivery includes different methods such as 1- local injection into organs: Injections administered intramuscular, intradermal, translesional, intranasal, and intrathecal; 2- Topical delivery involves applying a cell suspension by spray, drops and hydrogel; 3- Externally generated frameworks such as bioscaffolds, fibrin, and nanofibers have been thoroughly studied as adjuvants for local SC treatment (Fig. 1B) (Barmada et al., 2023; Caplan et al., 2019; Gotoh et al., 2024; Jenkins & Little, 2019; Lopes et al., 2021; Mahmoud et al., 2024; Qazi et al., 2017).

Systemic delivery of SCs

The two primary methods of administering systemic SCs are intravenous and intra-arterial infusion. Systemic cell administration is suitable for treating systemic illnesses or vast areas of pathology that are not responsive to local treatment because it improves interaction with the patient's immune response and healing signaling pathways (Caplan et al., 2019; Mousaei Ghasroldasht et al., 2022). When opposed to intravenous treatment, intra-arterial infusion allows for cell distribution to the place of interest with less cell loss (Watanabe & Yavagal, 2016). Concerns about the intra-arterial approach are raised by the production of thrombi and emboli, particularly in intra-coronary and intra-carotid administration. By regulating the infusion rate, cell quantity, and size, these issues can be avoided (Caplan et al., 2019; Janowski et al., 2013). On the other hand, the intravenous injection method reduces the stem cells' ability to reach the target organ because they are initially trapped in the lungs and may be removed by the host immune system (Fig. 1B) (de Witte et al., 2018; Eggenhofer et al., 2012; Fischer et al., 2009).

Mesenchymal stem cell homing

One major benefit of MSC-based therapies is their ability to home injured tissues selectively, which includes both non-systemic and systemic homing as shown by earlier reviews (Nitzsche et al., 2017). Non-systemic homing involves local transplantation of MSCs at targeted tissue, followed by chemokine gradient guidance to the injury site. MSCs must go through many steps to leave the circulation and travel to the site of damage after being injected or endogenously recruited into the circulatory system. This process is known as systemic homing. Five steps comprise the process of systemic homing: tethering and rolling, activation through cytokines, arrest of cells by integrins, transmigration, and migration (Ullah et al., 2019; Wu et al., 2020).

When MSCs are given therapeutically, they initially enter the circulation. The homing starts when MSCs slow down, and come into touch with the endothelium wall, as MSCs expressed CD44 that attach to the endothelial cells' selectins, and begin rolling along the vascular wall (Labusca et al., 2018; Sackstein et al., 2008). Second, G-protein-coupled chemokine receptors as stromal cell-derived factor-1 (SDF-1) 1 bind ligands expressed by MSCs including CXCR4 or CXCR7, activating integrin receptors as VLA-4 (Ullah et al., 2019). After integrin activation, MSCs rest on the endothelium membrane because integrins such as MSC-expressed VLA-4 attach to endothelial cells' VCAM-1 (Rüster et al., 2006). Early activation raises the binding capacity of integrins necessary for cell arresting; as a result, the VLA-4/VCAM-1 interaction enables MSCs to attach to endothelial cells securely (Ullah et al., 2019). After that, transmigration occurs as MSCs migrate across the layer of endothelial cells and basement membrane. This is made by producing matrix metalloproteinases (MMPs), which break down the endothelial basement membrane (Chamberlain et al., 2011; Guan et al., 2018). On the other hand, MSC's removal and disruption of endothelial cells' tight connections may also promote their transmigration (Schmidt et al., 2006). It has also been documented that MSCs can enter the endothelia through plasmic podia (Chamberlain et al., 2011; Steingen et al., 2008). Eventually, MSCs go to the area of injury under the guidance of different signals that the injured tissue releases, including chemokines and growth factors (Ullah et al., 2019; Zachar et al., 2016). MSCs can alter the injured tissue circumstances once they reach the desired side, promoting preservation and regeneration (Joyce et al., 2010).

Studies showed stem cells' role in restoring oral health

In dental and maxillofacial recovery, treatment with stem cells has emerged as a viable substitute since it can enhance physiological and functional criteria (Yang et al., 2017).

Periodontium

In vivo, PL-MSCs, DFP-MSCs, and AT-MSCs (adipose tissue – mesenchymal stem cells). all demonstrated the capacity to develop into cementoblasts, restore the periodontium to create cementum-like tissue and produce PDL fibers and periodontal vessels (Lemaitre et al., 2017; Zhu & Liang, 2015). Balaban et al demonstrated that in rats having periodontitis, the local G-MSC treatment with hydrogel helped to create healthy alveolar bone and periodontal ligament. Gingiva is a readily available tissue, making it an attractive candidate for therapeutic applications using autologous cell-based therapies (Balaban et al., 2024). Furthermore, Prasetyo et al showed that the apical periodontal region in diabetic rats treated with umbilical cord MSCs (UCMSCs) for apical periodontitis had significantly reduced inflammation and promoted vascularization (Prasetyo et al., 2024) .

Temporomandibular joint

Ogasawara et al found that in mice with temporomandibular joint osteoarthritis (TMJ OA) caused by mechanical stress, injection of stem cells from human shed baby teeth in a conditioned medium, aided in the healing and restoration process (Ogasawara et al., 2020). In addition Pan et al demonstrated that UCMSC transplantation ameliorates joint pathology, lowers inflammatory markers, and decreases chondrocyte death, offering OA patients a possible treatment alternative (Pan et al., 2023) also, Zaki et al used BM-MSCs to treat TMJ OA in rabbits, and the results showed that BM-MSCs can be utilized safely and effectively to treat degenerative abnormalities in the TMJ (Zaki et al., 2017).

Tooth regeneration

Dental pulp-like tissue is created when allogeneic MSCs are transplanted into permanent immature apex teeth having periodontitis and pulp death. MSC implants represent a promising treatment option in pediatric dentistry's regenerative endodontics (Gomez-Sosa et al., 2024). This is not only in immature teeth but also in a mature necrotic tooth, the case study demonstrates how allogeneic transplantation of MSC caused periodontal bone growth, remodeling of the apex, and dental pulp restoration (Gomez-Sosa et al., 2022).

Oral mucosa

By promoting neovascularization and efficient wound contraction, MSCs administered intralesional hasten the healing of oral mucositis caused by chemotherapy and radiation (Guan et al., 2023; Jung et al., 2020), it also proved that oral ulcer treatment with local implantation of BM-MSCs showed improvements in the number of blood vessels, thickness, collagen fiber organization, inflammatory cell population, rate of migrating of epithelial cells (Rashed et al., 2019). Wicaksono et al studied the topical application of gel consisting of the secretome from AT-MSC and found that the major inflammatory pathway declined during the initial stages of oral ulcer healing (Wicaksono et al., 2024)

The histological alterations in the tongue were reversed and the proliferation of cells was restored by the local injection of BM-MSCs in the case of hypothyroidism, diabetes, and radiation adverse effects (Aboushady et al., 2012; El-Sherif et al., 2021; Mahmoud et al., 2024), while in the case of systemic injection in (Mohsen et al., 2019; Radwan et al., 2024).

Salivary glands

In experimental vivo studies, MSC therapy significantly improved Salivary gland tissue regeneration and function by promoting regeneration through paracrine factors, restoring normal glucose levels, and differentiating into new cell populations in different conditions as in the case of post-radiation and chemotherapy damage, ovariectomy, and diabetes (Al-Serwi et al., 2021; Carlander et al., 2024; El-Badawy et al., 2024; Elbehairy et al., 2024; Zayed et al., 2024).

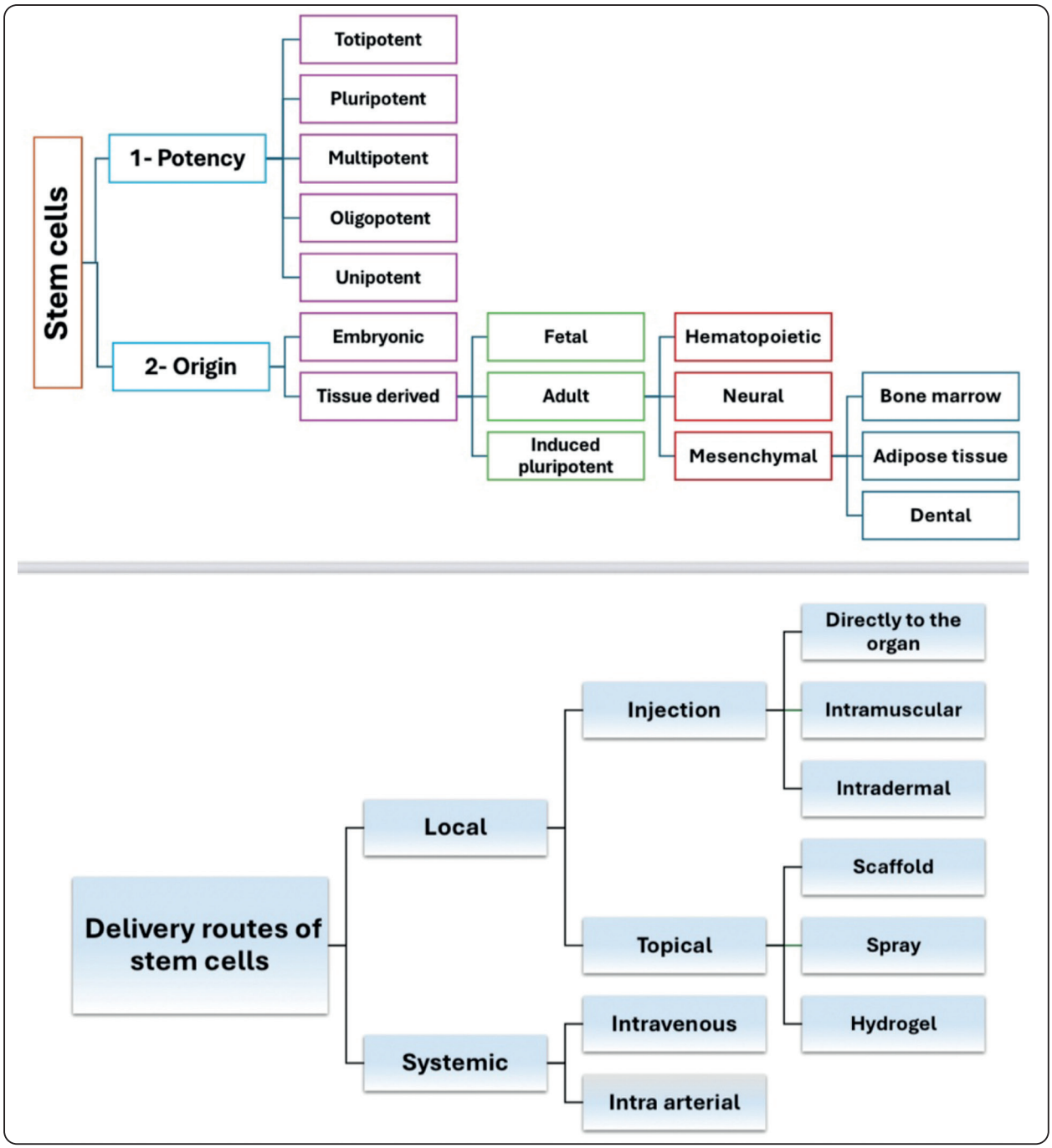

Fig. (1) A: Shows stem cell classification according to their potency and origin, (B): Shows different delivery routes of stem cells.

Jaw & maxillary sinus

A promising method for improving new bone formation and regeneration scores in the healing of critical-size fractures in rabbit lower jaw was the combination of exosomes produced from DP-MSCs with xenografts (Gönen et al., 2025). Another investigation put AT-MSCs on commercial surgical gel foam as a cell carrier and demonstrated considerable bone growth in extra-large bony defects (Mesgarzadeh et al., 2021). Zhou et al used BM-MSC implantation during the elevation of the maxillary sinus floor and found a marked increase in BM-MSCs differentiation into osteoblasts and an improvement in the production of new bone (Zhang et al., 2013; Zhou et al., 2016).

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