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Sources of stem cells within the oral cavity – an overview of the literature

Źródła komórek macierzystych w obrębie jamy ustnej – przegląd piśmiennictwa

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Abstract

The aim of this article was to provide an overview of contemporary studies into various types of stem cells derived from oral cavity tissues applied in regenerative dentistry, with particular reference to their function which changes depending on the place of their origin. The growing number of clinical experiments, among which randomised studies conducted on numerous groups of patients are more and more frequent, makes it possible to expect certain therapeutic methods using stem cells of dental origin to be introduced to the standard repertoire of clinical applications in the near future.

Keywords: mesenchymal stem cells, induced pluripotent stem cells, dentistry, bone regeneration, tissue engineering.

Streszczenie

Celem niniejszej pracy był przegląd współczesnej wiedzy dotyczącej poszczególnych typów komórek macierzystych wywodzących się z tkanek jamy ustnej, mających zastosowanie w stomatologii regeneracyjnej, ze szczególnym uwzględnieniem funkcji, zmieniającej się w zależności od miejsca ich pochodzenia. Wzrastająca liczba doświadczeń klinicznych, wśród których coraz większy odsetek stanowią badania randomizowane prowadzone na licznych grupach pacjentów, pozwala przypuszczać, że w niedługim czasie wybrane metody terapii z użyciem komórek macierzystych pochodzenia zębowego mogą zostać wprowadzone do rutynowego repertuaru zastosowań klinicznych.

Słowa kluczowe: mezenchymalne komórki macierzyste, indukowane pluripotentne komórki macierzyste, stomatologia, regeneracja kości, inżynieria tkankowa.

Introduction

A stem cell is an unripe, primitive, non-specialised cell able to self-renew and to differentiate into more specialised descendant cells which build tissues and organs. The term "stem cell" was first used by a Russian histologist, Aleksander Maksimow, in 1908, in relation to hematopoietic stem cells [1]. Oral cavity tissues provide a rich source of stem cells and may constitute a valuable addition to tissue engineering therapy. The aim of this article was to review contemporary studies into individual types of stem cells being part of the stomatognathic system, which are applied in regenerative dentistry, with particular reference to their function which changes depending on the place of their origin.

Sources of stem cells

Stem cells are able to self-renew and proliferate. Depending on their type, they also show diverse abilities to differentiate. Two basic types of stem cells are distinguished, namely embryonic stem cells (ESC) and adult stem cells present in the tissues of a mature organism. Apart from these, induced pluripotent stem cells (iPSC), which are artificially obtained through genetic modification of somatic cells, can also be distinguished.

ESCs and iPSCs are both pluripotent cells, which means that they can transform into the cells of all three germ layers: endoderm, ectoderm and mesoderm. Adult stem cells are usually multipotent; they are able to differentiate in appropriate conditions within more than one cell line. The only totipotent stem cells are blastomeres, which are part of a developing zygote; they are able to create the whole organism, including the placenta [2, 3].

1. Adult stem cells (MSCs)

Adult stem cells constitute a varied biological and somatic source for further definitions, such as mesenchymal stem cells (MSCs), somatic stem cells or postnatal stem cells. Their presence has been determined in many tissues and organs of the human organism, such as bone marrow, retina and skin. The tissues of the stomatognathic system, including those of the oral cavity and teeth, may also be a source of stem cells. The discovery of

these dates back to the late 1960s, when Friedenstein observed cells creating colonies *in vitro* that resembled fibroblasts, and they were popularised under this name in the 1990s by Caplan.

Their presence in the tissues of the entire organism, compared with other types of stem cells, creates a real chance for their clinical use for therapeutic purposes. The application of adult stem cells is not as controversial as in the case of embryonic cells since the use of somatic cells does not require the destruction of embryos.

MSCs populate special tissue zones, the so-called stem cell niches. Somatic stem cells may remain inactive in the niches, not undergoing divisions or differentiation for a long time. The moment an organ is damaged or a physiological demand for cells appears in tissues the cells differentiate into such cells which then build into the given organ, leading to its regeneration or renewal.

Numerous studies have also confirmed their plasticity, i.e. the ability of adult stem cells deriving from one tissue to differentiate into adult cells of other tissues, not only those of mesodermal origin.

The mix of the adherent cells isolated from bone marrow is not homogeneous; therefore, it is difficult to determine a full list of molecular markers typical for adult stem cells only, as well as to define what these cells are, without controversy. In 2006 the International Society for Cellular Therapy (ISCT) suggested minimal criteria defining MSCs as mesenchymal stromal cells, regardless of the tissue which they were isolated from [4]. According to the criteria accepted by the ISCT, MSCs must display an ability to adhere to the surface of (plastic or glass) culture dishes, and be characterised by growth in *in vitro* cultures, conducted in standardised conditions. What is typical of MSCs is the presence of a set of specific CD (cluster of differentiation) proteins on their surface: CD73+, CD90+, and CD105+. MSC phenotype cells do not show expression of the following antigens: CD45-, CD34-, CD14– or CD11b, CD79a or CD19 and HLA-DR, and they are able to differentiate into bone, cartilaginous and adipose tissues.

1.1. Bone marrow-derived stem cells (BMSCs)

Mature bone marrow generates at least two different types of stem cells. The first one is called hematopoietic stem cells (HSCs). These differentiate into all possible kinds of blood cells in the organism. The second type – mesenchymal, multipotent stem cells – constitutes a small, heterogeneous population of stromal cells. Despite their inhomogeneity, they are able to differentiate into cells of connective tissue. The ability to build bones *in vivo* makes BMSCs an excellent source of stem cells to be applied in procedures of controlled bone regeneration [5].

1.1.1. BMSCs obtained from the wing of ilium

A characteristic feature of BMSCs collected from the wing of ilium is their great morphological variety and, hence, diverse proliferation potential. It is assumed that 5–20% of isolated cells show features of stemness, so have the ability to self-renew and differentiate into at least 3 cell lines. BMSCs give rise to osteoblasts, chondroblasts, adipocytes, and muscle and nerve cells of non-mesenchymal origin [6].

Bone marrow as a source of osteoblasts is an easily accessible material; the collection of this is an invasive procedure for the donor, but it does not generate high costs. In the case of its application in the course of reconstructive surgery performed on the same patient there is no risk of cross infection or rejection. Another advantage is the fact that this material is not subjected to processes of freezing, sterilisation, deproteinisation, etc., and contains living cells. This is why the time between its collection and application to the bone defect may be reduced to a minimum.

The procedure of controlled bone regeneration can be performed at any age, yet the donor cannot be more than 60 years old. Reports by many authors, however, imply that it is possible to lower the osteogenic potential of BMSCs isolated from the ilium, which may suggest that the donor's age is an important factor that may determine the clinical effectiveness and success of regenerative therapies. With age, both *in vivo* and *in vitro*, there appears a tendency towards MSC differentiation into adipose tissue, at the cost of osteogenesis. This phenomenon may provide an explanation for the defect of bone regeneration and mineralisation, as well as the conversion of part of the bone marrow into adipose tissue, occurring in elderly people. The defect of osteogenesis increasing with age manifests itself in lower expression of the genes specific to differentiation into osteoblasts, such as CBFA1, Runx2, Dlx5, together with simultaneous intensification of the activity of the genes typical of adipogenesis (PPAR-γ, aP2).

1.1.2. BMSCs obtained from flat bones of the facial skeleton

The ilium still remains the main source of stem cells. BMSCs may, however, be also obtained from the bones of the facial part of the skull, including the maxilla and the mandible. Isolate aspiration can be performed in ambulatory conditions, in the course of routine dentistry procedures such as

implantation, wisdom tooth extraction, cyst enucleation, etc. Stem cells may successfully be obtained from facial skeleton bones both from younger patients aged 6–53 years and elderly people (57–62 years old). It seems that the donor's age is a matter of secondary importance in the differentiation process of stem cells collected from the above mentioned location.

The maxilla and mandible bones and the ilium differ in their origin. During ontogeny, the maxilla and mandible originate from the cells of the cranial neural crest, whereas the ilium develops from the mesoderm. This different origin of the structures causes the BMSCs collected from the wing of ilium to differ in phenotype and function from the cells of the facial skeleton bones. The BMSCs from the ilium are characterised by a limited differentiating potential and reduced abilities to differentiate into osteoblasts, as well as a larger amount of the produced compact osseous tissue being richer in hematopoietic cells than the BMSCs collected from the facial skeleton bones.

Studies on animals have shown that stem cells taken from skull bone marrow make larger and more numerous new bone nodules, and the newly created bone is more mineralised [7]. The unfavourable phenomenon of adipose tissue creation, accompanying osteogenesis, is less intense. It appears, therefore, that skull bones may be a good source of stem cells intended for use in regenerative dentistry procedures; but the maximum amount of marrow collected from the above mentioned area cannot exceed 0.03–0.05 ml. In contrast to the 1000 ml of marrow able to be extracted, for instance, from the marrow of long bones, this amount may turn out to be insufficient. It is essential to determine a reliable and safe expansion protocol regarding the cells intended for clinical studies [8].

1.2. Stem cells from dental tissues

Two types of adult stem cells, derived from neuroectoderm, have been identified in the tissues of the dental organ so far, namely epithelial stem cells and mesenchymal stem cells [9]. The former were discovered in 1999 in a mouse incisor, in the structure called the cervical loop. As a result of asymmetrical divisions, the stem cells create ameloblasts – enamel producing cells. They may be used to analyse the role of stem cells in tooth development; there is no information about the presence of these cells in human organisms. Their presence may be typical of rodents only, because their incisors differ from human teeth in that they erupt during the whole ontogeny of the animal.

Unlike the epithelial structures of teeth, mesenchymal tissues display the ability to self renew and reconstruct lost structures. Thanks to the presence of mesenchymal stem cells in adult teeth it is possible to regenerate such tissues as cementum, dentine and periodontal ligament during the whole life of a human organism.

1.2.1. Dental pulp stem cells (DPSCs)

Among the abundant group of stem cells whose sources are tissues of the stomatognathic system, dental pulp stem cells (DPSCs) have been identified as the primary ones. DPSCs, located in the dental pulp, are a source of odontoblasts, or dentine producing cells. Their phenotype is similar to BMSCs, yet DPSCs have more growth and proliferation potential. For research purposes DPSCs are extracted from the dentine of impacted third molars, which start to develop at the age of approx. 6 years and erupt as the last teeth at the age of about 18 years. It is likely thereby that the stem cells isolated from the dentine of impacted wisdom teeth are at a very early stage of cell differentiation [10].

1.2.2. Stem cells from human exfoliated deciduous teeth (SHED)

The next cells to be isolated have been the stem cells from human exfoliated deciduous teeth (SHED). They are located, similarly to DPSCs, in the perivascular areas of the pulp, but show greater proliferation potential, which proves that SHED cells are at an early stage of differentiation. A feature specific to these cells is an intense expression of the genes related to the production of the extracellular matrix, e.g. the fibroblast growth factor (FGF), the transforming growth factor beta (TGF) as well as the ability to create osteoinductive conditions in vivo and recruit the host's osteoblasts to make new bone. Thanks to the properties of resorption of the roots of deciduous teeth, simultaneous bone tissue apposition may accompany this [11].

1.2.3. Periodontal ligament stem cells (PDLSCs)

The basic source of periodontal ligament stem cells (PDLSCs) is the periodontal ligaments. The effectiveness of isolating these cells from the surface of the roots of removed teeth has been confirmed. They show an ability to regenerate periodontium tissues, i.e. periodontal fibres, root cementum and alveolar ridge bones; these processes have been analysed through in vivo experiments on animal models. The properties of PDLSCs may depend on the place of their origin. Those located closer to the bone surface may be responsible for its regeneration, whereas the ones situated nearer the tooth root will be responsible for root cementum synthesis [12].

1.2.4. Stem cells found during tooth growth (SCAP and DFPCs)

Stem cells have also been identified in structures present only during tooth development. These are apical papilla and dental follicule [13, 14].

Two of the most accessible sources of stem cells are the pulp and apical papilla of the third molars. They start to develop at the age of about six years and erupt as the last teeth at the age of approx. eighteen years. The late formation of the wisdom tooth buds in relation to those of the other teeth suggests that the stem cells are at a very early stage of cellular differentiation [15, 16].

The stem cells of the apical papilla (SCAP) are located in the apical root area of teeth whose development has not been completed. SCAP are only present during the process of odontogenesis and are responsible for the creation of primary root dentine. After tooth development finishes, the root is fully formed and the apical foramen closes, so SCAP disappear. SCAP are characterised by great proliferation and mineralisation potential in comparison with DPSCs.

Dental follicule stem cells (DFPCs) demonstrate typical properties for stem cells of dental origin. They show the ability to proliferate and form the hard tissues of teeth. DFPCs are also able to secrete TGF β [17, 18].

1.3. Oral mucosa stem cells (GMSCs and OMSCs)

In 2009, Zhang et al. [19] were the first to characterise gingiva derived mesenchymal stem cells (GMSCs), which show clonogenicity, the ability to self renew and multipotent abilities to differentiate, similar to the properties typical of BMSCs. GMSCs proliferate more quickly, their morphological structure is stable for a long time, and they do not lose it in consecutive cultures (passaging). Marynka Kalmani et al. [20] demonstrated that within lamina propria there were cells resembling the multipotent neural crest stem cells, the so called oral mucosa stem cells (OMSCs). They are able to differentiate into cell lines originating from 3 germ layers. The fibroblast line cells from the oral mucosa show high effectiveness during iPS reprogramming. The multipotency of these cells, easy collection and isolation, presence in large quantities and fast expansion ex vivo are the features that distinguish them from other potential sources of stem cells intended for clinical use.

1.4. Periosteum-derived stem/progenitor cells (PSCs)

Stem/progenitor cells may also come from the periosteum (periosteum derived stem/progenitor cells – PSCs). The periosteum is a fibrous membrane covering the bone tissue. Its osteogenic abilities were noticed as early as 1932, and the capability of the periosteum to produce the mineralised extracellular matrix in in vitro conditions has been demonstrated [21].

Due to their strong bone forming properties, the periosteal cells are currently applied in the regeneration of facial skeleton bones. Clinical studies with the use of cultured periosteal cells have shown the great effectiveness of the application of these cells in techniques regenerating bone losses, which means that they make it possible to significantly reduce the time needed for implantation and healing of an implant inserted into the alveolar ridge bones. To summarise, the periosteum is a perfect source of stem/progenitor cells used to treat large bone losses.

1.5. Salivary gland stem cells (SGSCs)

Stem cells can significantly improve the quality of life of patients suffering from cancer developing within the head and neck, in whom radiotherapy has resulted in impaired secretion of saliva, leading, as a consequence, to xerostomia. Even though the existence of stem cells present in the salivary glands has been suggested in in vivo studies, so far cells able to undertake the endocrine function have not been successfully identified.

The salivary glands of patients irradiated with X rays within their head and neck irretrievably lose the ability to produce and secrete saliva due to the past cancer processes, which reduces the quality of their life considerably. To date, no effective therapy to restore the normal function of salivary glands has been developed. Autologous transplantation of adult salivary gland stem cells seems to be a promising therapeutic method. Unfortunately, a serious restriction for this method may be the short lifespan of these cells in in vitro cultures, and therefore the short time needed to perform the implantation procedure, which translates into an increased risk of cancerous metaplasia in these cells [22, 23].

1.6. Adipose-derived stem cells (ASCs)

Adipose tissue is a rich source of MSCs. The phenotype of adipose derived stem cells (ASCs) is similar to that of bone marrow derived stem cells, yet the former constitute a more homogeneous cell population. The presence of MSCs in bone marrow is less frequent than that of ASCs in the adipose cell population. No differences have been found in the dynamics of differentiation into osteo- and chondroblasts. In the experimental models used, the chondro- and osteogenic potential of

ASCs has been comparable to that of BMSCs; however, ASCs are exposed to less risk of partial inhibition of proliferation. For the donor it is easier and less invasive to obtain the adipose stem cells; this is done during surgical procedures of removal (lipectomy) or suction (liposuction) of the excess subcutaneous fat from such body areas as the chin, arms, abdomen, hips, buttocks and thighs. The obtained material used to be considered medical waste [24].

The application of ASCs in dentistry has been clinically confirmed. Pieri et al. [25] proved the high effectiveness of adipose stem cells, which were transplanted together with the bone substitute material Bio Oss in the course of intraosseous implantation, in the formation of new bone in vivo. The presence of the new bone was confirmed, particularly in its vertical dimension, in addition to integration of the inserted implant.

ASCs have been successfully applied in the experimental regeneration of periodontium and pulp tissues after previous pulpectomy.

2. Pluripotent stem cells

Pluripotency is the ability of a single cell to develop into any type of somatic cells. The process of pluripotent cell differentiation takes place in response to signals from the embryo environment or cell culture in vitro. Pluripotent cells include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Early embryonic stem cells, whose source is the embryo at an early development stage, from the phase of a zygote to the phase of a morula, should be excluded from the above classification. These cells are totipotent, i.e. able to build the whole organism, including extraembryonic tissues, as well as the placenta and amniotic sac [26].

2.1. Embryonic stem (ES) cells

Embryonic stem (ES) cells develop from undifferentiated cells of the embryoblast, a 5–6-day old blastocyst, at an early developmental stage of the embryo after fertilisation. The use of these cells for research or therapeutic purposes may mean the destruction of the embryo and this is the main moral and ethical obstacle to the further application of these cells for the aforementioned purposes [27].

2.2. Induced pluripotent stem cells (iPSCs)

In 2006, Takashi and Yamanaka performed the reprogramming of a diploid nucleus of an adult somatic cell (fibroblast) removed from mouse skin, which led to taking its development back to a cell equivalent to a pluripotent stem cell. The induction process of genes, whose activity is necessary to maintain pluripotency, took place through the transfection of somatic cells with virus derived vectors coding for four molecular markers: Oct3/4 and Sox2, which are pluripotency genes; Klf4, responsible for initiating the expression of the Nanog factor essential for ESCs; and the c Myc oncogene, whose activity ensures the intense divisions of transfected cells. A year after the experiment on mouse cells was conducted, trials with fibroblasts of human origin were successfully undertaken. The cells obtained by this method were induced pluripotent stem cells (iPSCs). iPSCs show an ability to differentiate into the cells of all three germ layers, are immunologically compatible with the recipient's organism, and using adult pluripotent somatic cells for research solves the conflicts and problems of a moral and ethical nature. A living organism constitutes an unlimited source of cells, which may be obtained from easily accessible areas, e.g. the oral mucosa. These cells are characterised by a great proliferation potential, which enables the obtaining of a sufficient number of cells for therapeutic use. The main drawback of these cells is their genomic instability and a potential ability to induce cancer processes in in vivo conditions, which is caused by the full integration of the virus derived vector genome with the reprogrammed cells genome. The risk connected with the application of iPSCs for therapeutic purposes is too high for the recipient's organism; therefore, for safety reasons, at the present state of the art, using them in human organisms in vivo is not recommended [28].

Conclusion

The oral cavity is a rich and, probably, unlimited source of stem cells. The easy access to its anatomical structures makes it possible to collect tissue samples for further tests in ambulatory conditions non invasively and without generating additional costs. These cells may often be obtained from material being "medical waste". It may be expected that in the near future therapies using stem cells will be part of standard, routine therapeutic solutions offered to patients by practising dentists.

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Conflict of interest statement

The authors declare that there is no conflict of interest in the authorship or publication of contribution.

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