Stem cells and their niches: importance in tissue engineering applied to dentistry

Células-tronco e seus nichos: importância na engenharia de tecidos aplicada à odontologia

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ABSTRACT

Niches are special microenvironments in tissue where stem cells are located. At these sites, which are a compound of stromal cells, extracellular matrix and soluble factors, complex molecular interactions that maintain the essential properties of stem cells occur, such as self-renewal and differentiation into multiple lineages, according to the organism's needs. Some adult stem cell niches have already been described, but the majority of them remain unclear, including the dental pulp stem cell niches. Dental pulp stem cells have been isolated from deciduous and permanent teeth and have the potential to self-renew and differentiate. However, little is known about the exact anatomic location of these cells, and the relationship between stem cells and surrounding cells in dental pulp. Understanding how stem cells behave in the niche is extremely important in order to extract these cells from their natural habitat, expand them in vitro and transplant the stem cells back to the patient, to repair and/or regenerate tissues and organs, with no risks to the individual's integrity. Likewise, the knowledge of stem cell biology is crucial to the development of stem cell therapies, based on tissue engineering applied to dentistry, seeking the regeneration of dental tissues damaged or lost by caries, trauma or genetic diseases.

***Indexing terms**: Dental pulp. Stem cells. Stem cell niche.*

RESUMO

Os nichos são microambientes especiais nos tecidos onde células-tronco de várias origens estão localizadas. Nestes sítios específicos, formados por vários tipos de células, matriz extracelular e fatores solúveis, complexas interações moleculares ocorrem para que a célula-tronco mantenha sua capacidade de autorrenovação e permaneça no seu estado indiferenciado ou se especialize em determinada linhagem celular, atendendo desta maneira as necessidades do organismo. Alguns nichos de células-tronco adultas já foram descritos, embora a maioria permaneça desconhecida, como o das células-tronco pulpares. As células-tronco pulpares, já foram isoladas tanto de dentes decíduos como de permanentes e apresentam as características essenciais de uma célula-tronco, como capacidade de autorrenovação e multi-diferenciação. Apesar disso, pouco se sabe a respeito da localização anatômica destas células na polpa, assim como as possíveis interações funcionais entre as células-tronco pulpares e as células do estroma circundante. O entendimento de como as células-tronco interagem com o microambiente onde estão inseridas é essencial para que se possa extrair as mesmas do seu habitat natural, cultivá-las in vitro e aplicá-las em diferentes sítios para que promovam o reparo e/ou regeneração de tecidos e órgãos, sem que isso represente um risco à integridade do organismo. Da mesma forma, o conhecimento de como estas células se comportam e respondem ao meio é fundamental para o desenvolvimento de terapias baseadas na utilização de células-tronco, que através da engenharia de tecidos aplicada à odontologia, visa à reestruturação de tecidos dentários danificados e/ou perdidos por cárie, trauma ou distúrbios genéticos.

Termos de Indexação: Polpa dentária. Células-tronco. Nicho de células-tronco.

INTRODUCTION

Therapies based on the application of stem cells have great potential in the prevention and treatment of several diseases, such as cancer, diabetes, cardiovascular disease, spinal cord injuries, neurological diseases such as Parkinson's and Alzheimer's, and in the regeneration of various tissues and organs. However, further studies are required to gain complete understanding of stem cell biology, which is fundamental for the development of successful cell-based therapies[1-3].

Stem cells are undifferentiated cells with an extraordinary capacity of self-renewal; that is, they have the ability to generate other stem cells and perpetuate themselves. Likewise, these cells give rise to progenitor cells committed to a particular cell lineage, and play a crucial role in tissue repair and homeostasis.

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themselves. Likewise, these cells give rise to progenitor cells committed to a particular cell lineage, and play a crucial role in tissue repair and homeostasis.

According to the origin of these cells, they can be classified into embryonic stem cells (ESC) and adult stem cells (ASC). ESCs are pluripotent cells derived from the inner cell mass of the embryo at the blastocyst stage, and are able give rise to all three embryonic germ layers - ectoderm, endoderm, and mesoderm. However, these cells can induce the development of teratomas[4-5]. In addition, legal and ethical issues make it difficult to use these cells in scientific studies. On the other hand, ASCs are present in virtually all tissues and organs of an organism at different stages of development, and are able to differentiate into one or more cellular types, but not into all, such as ESCs. ASCs are also classified in hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC), as shown in Figure 1[4,6-7].

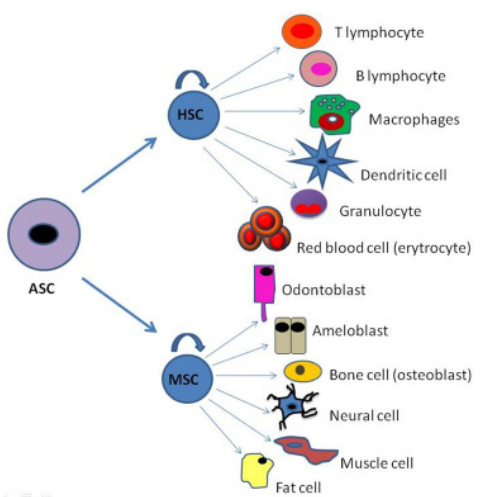

Figure 1. Schematic representation of self-renewal and multi-differentiation of hematopoietic and mesenchymal stem cells. ASC indicates adult stem cell; HSC, hematopoietic stem cell; MSC, mesenchymal stem cell.

MSCs are considered one of the most promising stem cell types, due to their availability in tissues, multi-differentiation capacity, lack of ethical problems and do not form teratomas[8]. Nevertheless, until now, there has been no specific marker or combination of markers that identify MSCs[9]. For this reason, the isolation of MSCs also depends on the biological characteristics, such as colony-forming capacity, fibroblast-like morphology (these cells are also known as colony-forming unit fibroblasts - CFU-Fs), plastic adherence, vigorous proliferative ability, self-renewal and multi-differentiation capacity[8-9]. Table 1 shows the surface markers frequently expressed by MSCs isolated from different tissues. Likewise, markers with little or no expression are listed[10-17].

Table 1. Surface antigens expressed by MSCs from various origins.

Expression	Surface antigen	References
Positive	STRO-1	10, 11, 12
	CD44	13, 14
	CD73	13, 14
	CD90	11, 12
	CD105	12, 14
	CD106	12, 15
	CD146	10, 12
	SSEA-1	16
	SSEA-4	17
Negative	CD31	12, 15
	CD34	14, 15
	CD45	14, 15
	CD80	11
	CD86	11
	HLA-DR	13

The key for the use of stem cell therapy in tissue and organ regeneration is the ability of SCs to differentiate into several cell types, depending on the stimulus received[18]. Stem cells present an enormous plasticity, being able to respond to the environment in which they are inserted, altering their original features and acquiring the characteristics of a given tissue, even if they had originated in a different site[6]. This ability of transdifferentiation has been evidenced in several studies[19-21], emphasizing that the niche or microenvironment where the stem cells reside exerts a great influence on them[22].

Stem cells: symmetric and asymmetric divisions

Most cells, including stem cells, can divide symmetrically, giving rise to two identical cells. However, stem cells also have the ability to undergo asymmetric divisions, in which two distinct daughter cells are generated. This process results in the generation of a stem cell daughter that remains in the niche and a progenitor daughter that leaves the niche and differentiates into a particular mature cell. Asymmetric division consists of a fundamental stem cell strategy to keep their self-renewal and differentiation capacity. An appropriate number of stem cells must be retained in the niche, and there must be a demand for specialized cells in the surrounding tissues, in order to maintain the organism homeostasis[6,22-23].

What are the stem cells niches?

Stem cells are located in special microenvironments called niches, which protect these cells from damage, and from inappropriate differentiation or apoptotic stimuli, and other stimuli that could challenge stem cell reserves and compromise tissue homeostasis[24]. The niches are composed not only of stem cells, but also a diversity of differentiated cells, extracellular matrix and soluble factors. Complex interactions among the components of the niche allow stem cells to preserve their unique intrinsic properties for long periods, including the maintenance of their undifferentiated state, their self-renewal ability and capacity to give rise to different cell types[22,25].

There is a constant cross-talk between stem cells and the surrounding niche cells that sometimes stimulates the differentiation of stem cells into progenitor cells, and sometimes protects them from many different stimuli. The primary function of the niche is to anchor stem cells and keep physical organization in a particular location in tissues. Adhesion molecules such as N-cadherins and integrins are essential for the maintenance of HSCs in the niche, for example. The microenvironment also exerts a regulatory function over stem cells, safeguarding excessive stem cell production that could lead to cancer[23-24].

Thus, a hallmark of a functional niche is to maintain the perfect balance between quiescence and activity of stem cells. This delicate equilibrium plays a key role during embryonic development, as well as in tissue regeneration, replenishing lost cells due to apoptosis or due to tissue damage[22-24]. This special and unique relationship between stem cells and their niche occurs through direct cell-to-cell contact and through the release of different soluble molecules, such as cytokines, chemokines and growth factors. The combination among the intrinsic genetic characteristics of stem cells and their microenvironment will drive their properties, as well as define the potential for the clinical application of these cells[26].

Structure of different stem cell niches

The stem cell niches vary in nature and location depending on the tissue type[23]. Exactly when and how these stem cell "sanctuaries" develop in tissues remains unclear[22]. What is known is that there is a considerable variation in structure and organization of these special microenvironments that shelter different types of stem cells[27].

In mammals, some adult stem cell niches have already been identified successfully. Epithelial stem cells reside in the bulge area of hair follicles, near the sebaceous glands. Upon activation, these cells give rise to daughter cells that are retained in the bulge and remain as stem cells, or to progenitor cells responsible for hair regeneration. These cells can also convert to epidermal progenitors and replenish lost or damaged epidermis[23,28]. On the other hand, the intestinal stem cell niche was identified near the crypt base of the small intestine. In this region, the intestinal stem cells are in close contact and interaction with MSCs[29].

Bone marrow hematopoietic stem cells (HSCs) are the best characterized stem cell population up until now[24]. HSCs are located proximal to the endosteal surface of trabecular bone in bone marrow, in direct contact with the osteoblasts. HSCs are attached to osteoblasts through a specific adhesive interaction between N-cadherin and b-catenin[30], although other adhesion molecules, such as integrins[22], are important in this process. In this location, MSCs appear to be an important component of the HSC niche[31]. HSCs were also identified in association with blood vessels in bone marrow, indicating that more than one niche may harbor stem cells in the same tissue[32].

In the nervous system, the neural stem cells (NSC) are located near the blood vessels in the subventricular zone of the lateral ventricle and in the subgranular zone of the hippocampus region[33]. The endothelial cells, which are essential components of the NSC niche, provide the adhesion of the stem cells in these sites and generate a variety of signals that control their self-renewal and lineage differentiation[34].

Stem cells in the dental pulp and the niche

Mesenchymal stem cells can be isolated from almost all tissues in the organism, including dental pulp. Although mesenchymal stem cells have already been isolated from deciduous and permanent teeth, there is a lack of information regarding the precise anatomical location of these cells[19,35-36]. This is mainly attributed to the rarity of stem cells in the pulp, as well as the absence of specific MSC markers that identify different developmental stages of these cells during odontogenesis, such as ectomesenchymal stem cells, cells from dental papilla, dental pulp stem cells, precursor cells from the pulp, pre-odontoblasts and mature odontoblasts[9-10].

In a traditional view of dental pulp, the cell rich zone situated close to the odontoblast layer shelters a population of stem/progenitors cells, serving as a reservoir for the replacement of odontoblasts damaged by carious processes[9]. However, Shi & Gronthos[10] demonstrated that the location of stem cells in dental pulp is restricted to the

perivascular region and to the perineurium of dental pulp fiber nerves, but is absent in the odontoblastic layer and in the surrounding fibrous tissue. Likewise, it has been demonstrated that the damage caused to the dental pulp tissue stimulated the migration of stem/progenitor cells located in perivascular areas in dental pulp towards the injury site[37].

According to Scadden[25], both endothelial cells, pericytes such as the smooth muscle cells surrounding blood vessels may constitute the MSC niche, and contribute to a perivascular location of these cells. Recent studies that associated the location of MSCs with blood vessels, have suggested a strong correlation between MSCs and pericytes[38]. Typical pericyte markers, such as CD146, have also been expressed in MSCs from several tissues, including dental pulp[10,39].

Location of MSCs at perivascular sites throughout the body would provide these cells with easy access to all tissues in the organism. In case of an injury, MSCs would be released by the rupture of blood vessels, migrate to the affected site and differentiate into the required cell type, promoting tissue repair[40]. In the affected area, MSCs would be capable of secreting immunomodulatory molecules, minimizing the extent of tissue damage and decreasing the inflammatory response, allowing tissue regeneration[8,14]. Similarly, the secretion of trophic factors by MSCs in the damaged area could inhibit apoptosis, stimulate angiogenesis, and stimulate the mitosis of tissue-intrinsic progenitors[41].

Importance of stem cells in dental pulp

Despite the technological advances in dentistry, to this date, no restorative material has been able to contemplate all the ideal physical, mechanical and biological properties to replace dental tissues[4]. Theoretically, biomaterials developed from autogenous tissues should be the best choice for clinical reconstruction of teeth lost or damaged by oral diseases, trauma or genetic disorders, in addition to the repair of craniofacial bone deffects[9,42-44]. Thus, tissue engineering applied to dentistry through the use of stem cell therapies, could contemplate this innovative and promising proposal in a masterful way.

MSCs obtained from the pulp of deciduous (SHEDs - stem cells from human exfoliated deciduous teeth)[36] and permanent teeth (DPSCs - postnatal human dental pulp stem cells)[35] may play a crucial role in the regeneration of the pulp-dentin complex, through their differentiation into functional odontoblasts. Different studies have shown that when these cells were transplanted into the subcutaneous space of immunocompromised mice, in association with biodegradable scaffolds and specific growth factors, areas of vascularized pulp tissue, surrounded by a layer of odontoblasts associated with dentin-like structures were observed[3,19,35-36,45]. According to Murray & Garcia-Godoy[43], dental tissues developed from stem cells derived from human dental pulp have the same chemical, physical and esthetic characteristics as a natural tooth.

An efficient vascular network is fundamental for the correct functioning of a regenerated or implanted tissue, promoting an adequate supply of oxygen and nutrients. Recent studies have demonstrated the the potential of SHEDs to differentiate into vascular endothelial cells, induced by the presence of VEGF (vascular endothelial growth factor), which is considered the most important growth factor related to angiogenesis and vaculogenesis[45-46]. These differentiated endothelial cells were able to form functional blood vessels, which are essential for the development of a "new tissue" in cases of pulp necrosis, for example. Likewise, dental pulp stem cells were capable of differentiating into osteoblasts, indicating that the use of stem cells may be a feasible therapy in cases of several bone loss due to periodontal disease, trauma or anodontia[47].

Mesenchymal stem cells isolated from dental pulp can be considered a promising alternative in the treatment of various conditions, such as muscular dystrophy, spinal cord injuries, autoimmune diseases, ischemic disorders, among others, in addition to the regeneration of orofacial structures, emphasizing the ability of DPSCs and SHEDs to specialize into different cell types[45,48-50]. The combination of characteristics such as self-renewal, high proliferation capacity, as well as the easy access to them and their availability, make the dental pulp an attractive source of MSCs for tissue regeneration, especially those cells extracted from deciduous teeth, which are usually disposed of after physiological exfoliation[3].

FINAL CONSIDERATIONS

The knowledge of how stem cells are inserted in their physiological microenvironment is crucial for the elucidation of the biology of these cells. In other words, understanding how niche cells and the extracellular matrix control the fate of stem cells is critical for the development

of therapies that apply stem cells in the prevention and treatment of several diseases, as well as in the regeneration of organs and tissues such as teeth and craniofacial structures.

Collaborators

All authors participated in the conception, data collection and composition of the article.

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