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Stem Cells – Prospects in Dentistry

Key words: stem cells, tooth ontogeny, regeneration, literature search, dental pulp stem cells

Summary Stem cell biology, an emerging field of research, provides promising methods in vitro as well as in vivo in animal models which make speculation about a future application in human dentistry reasonable.
The objective of this study was to review the literature of stem cell research concerning fields relevant for dentistry. In dentistry, different stem cells are discussed. Adult dental ectomesenchymal stem cells seem promising for future therapy. Human stem cells have been isolated from the dental pulp, exfoliated deciduous teeth, the periodontal ligament, the dental follicle and the dental papilla. Stem cell markers such as STRO-1 were used for the characterization and isolation of stem cells. Adult dental stem cells can differentiate into many dental components, such as dentin, periodontal ligament, cement and dental pulp tissue, but not into enamel.

Abbreviations:

ABCs	apical bud cell	MSCs	mesenchymal stem cells
BMP	bone morphogenetic protein	PDLSCs	periodontal ligament stem cells
DFSCs	dental follicle stem cells	SCAPs	stem cells of the (dental) apical papilla
DPSCs	dental pulp stem cells		
FDPMCs	follicle dermal papilla mesenchymal cells	SHEDs	stem cells of human exfoliated deciduous teeth
FGF	fibroblast growth factor	TGF	transforming growth factor

Introduction

Dental exfoliation in humans is a genetically regulated event during childhood. If the permanent teeth are damaged or lost, they do not regenerate. At present, teeth can only be replaced with conventional prostheses, i. e., removable prostheses, fixed dental prostheses, or implants, with prior bone augmentation if necessary. However, progress in stem cell biology and tissue engineering may present new options for replacing heavily damaged or lost teeth, or even individual tooth structures. The promise of such treatment possibilities puts stem cells in the focus of dental research.

Stem cells are cells which divide to produce one stem cell and one cell capable of differentiation. In addition to this asymmetrical division, stem cells can also divide symmetrically into further stem cells or into differentiated cells, as necessity demands.

The distinction is made between embryonic and adult stem cells. Embryonic stem cells are pluripotent, that is, they can differentiate into all types of somatic cells and theoretically divide an unlimited number of times (Morsczeck et al. 2007). Using immunosurgery, they can be harvested from early blastocyst stages (i. e., at about the 4th day of embryonic development). During this procedure, the blastocyst's trophoblasts are destroyed by an antibody-activated complement reaction. The embryoblast cells – the part of the blastocyst that is of interest for stem cell research – are maintained and, thanks to their ability to self-regenerate (which is typical of stem cells), can be multiplied. Their pluripotency remains intact. Through variations in growth factors, they can be specifically differentiated

(Cowan et al. 2004, Terskikh et al. 2006, Moore & Persaud 2007). Ethically, the use of human embryonic cells is a highly contentious matter, because harvesting them requires the destruction of human embryos early in development.

Information on human embryonic dental stem cells is not yet available in dentistry. Up to now, only isolated studies on animal embryonic stem cells have been conducted (Honda M. J. et al. 2008, Kang et al. 2008, Zhu et al. 2008, Ikeda et al. 2009).

Tissue samples from various "parent" tissues can serve as the source for harvesting adult stem cells. Adult stem cells can only proliferate a limited number of times. They are distinguished according to their developmental potential. There are uni- and bipotent progenitor cells, which can usually only be differentiated into mature cells of their parent tissue, and multipotent adult stem cells, which can also differentiate into tissues that are not identical to the parent tissue (Morsczeck et al. 2007).

Adult stem cells are theoretically present in every type of tissue. Organs that are particularly suited for yielding adult stem cells include the bone marrow (Pittenger et al. 1999), the umbilical cord, and umbilical cord blood (Noll 2003). In order to minimize the lesion inflicted by taking the tissue sample and limit the weakening of the organ or organism, the concentration of stem cells in the obtained tissue sample should be as large as possible (d'Aquino et al. 2008).

With stem cell therapy, scientists hope to make it possible to cure such severe conditions as Parkinson's disease, paraplegia, leukemia, and brain tumors, among others.

Some initial success with dental tissue indicates that stem cell research may be of therapeutic use in dentistry as well, for instance, to regenerate individual tissue types, such as bone (de Mendonca Costa et al. 2008, Graziano et al. 2008, Sauerbier et al. 2009, Zheng et al. 2009), periodontal tissue (Shi et al. 2005, Silverio et al. 2008, Xu L. et al. 2009a), or someday even entire teeth (Sonoyama et al. 2006, Ikeda et al. 2009).

Currently, clinical application is hindered by unpredictable timepoints of tooth eruption, the morphology and color of the generated tooth, and the as yet impossible regeneration of human dental enamel.

Fundamentally, two means of regenerating teeth are described. The first is conventional *tissue engineering,* in which the application of cells in a carrier material in vitro under the influence of a stimulus leads to tissue regeneration. The second is the much more innovative process of tooth regeneration using dental epithelium and mesenchymal cells in vivo after direct implantation, representing a kind of *tissue engineering* in the broader sense (Wang & Wang 2008), based on knowledge of general embryogenesis and physiological tooth development during childhood.

No systematic literature review exists yet on the topic of "implementation of stem cell biology in tooth development". Thus, the following questions underlie the present systematic literature review: In the future, how can natural teeth be generated for use in humans? Which cells of a stem cell nature are suitable for regeneration?

The purpose of this systematic literature review is to present an overview of the current status of stem cell biology research in the field of dentistry and identify which methods now being developed have the potential to be used in humans in the future. These questions will be answered based largely on in vitro studies and in vivo animal experiments.

Materials and Methods

The literature was acquired in a systematic search of the titles on stem cells and dental cell therapy listed in the databank PubMed. Additional sources (secondary literature) became available through references in the literature thus found. Table I lists the search words with which the databank search was initiated. First, the articles were judged based on their titles, then on the abstracts, and finally on the entire text. Articles which contained no information on dental stem cells were excluded, as were doctoral theses, case reports, and expert opinions. The search period was 1999 to 2009. Current sources in the English and German languages were taken into consideration.

Results

From a total of 1,837 hits in the databank search, 1,633 were excluded based on the title and another 47 were excluded based on the abstract. Different search words sometimes led to the same publications. With the results of the widened literature search (including secondary literature), this systematic literature review included 126 studies.

Taking the listed literature into consideration, Figure 1 illustrates the basics of embryogenesis and odontogenesis. Up to now, the literature has not contained a systematic scheme which elucidates these sequences as a whole.

In the following, the processes of embryogenesis and odontogenesis are briefly summarized.

In the human embryo, deciduous and permanent teeth develop as a result of sequential and reciprocal interactions of the ectodermal epithelium of the oral vestibule and the mesenchyme in the cranial area, which formed from neural crest cells (Pispa & Thesleff 2003, Bloch-Zupan 2007). Dental enamel originates from epithelial cells, while all other structures are formed from mesenchymal cells (Moore & Persaud 2007, Hacking & Khademhosseini 2009). In about the 5th embryonic week, odontogenesis is induced from the oral epithelium; the underlying mesenchyme of the tooth papilla is responsible for

Tab.I Search words and number of hits in databank search

Search word 1	Search word 2	Number found	Number excluded (based on title)	Number excluded (based on abstracts)
dental stem cell	in vitro	869	784	24
dental stem cell	in vivo	359	278	13
DPSC		42	23	5
SHED	stem cell	545	535	3
PDLSC		12	6	0
DFSC		4	4	0
SCAP	stem cell	6	3	2

Tab. II Overview of contents of the relevant primary literature (PubMed)

Cell type(s)	Author, year	Title	Study design	Factor(s)/ influence	Target cells
DPSCs	Arthur et al. 2008	Adult Human Dental Pulp Stem Cells Differentiate Towards Functionally Active Neurons Under Appropppriate Environmental Cues	In vivo and in vitro study	Neurally inductive conditions	Neurons
	Batouli et al. 2003	Comparison of Stem-cell-mediated Osteogenesis and Dentinogenesis	In vivo study	Transplantation (mouse)	Odontoblasts
	Braut et al. 2003	Analysis of the odontogenetic and osteogenetic potentials of dental pulp in vivo using a Col1a1-2.3-GFP transgene	In vivo study	Transplantation (renal capsule)	Osteoblasts and odontoblast-like cells
	Cheng et al. 2008	Postnatal stem/progenitor cells derived from the dental pulp of adult chimpanzee	In vitro study	Appropriate cell cultures	Osteogenic, adipogene, chondrogene differentiation
	d'Aquino et al. 2007	Human postnatal dental pulp cells co-differentiate into osteoblasts and endotheliocytes: a pivotal synergy leading to adult tissue formation	In vivo and in vitro study	Cell culture and transplantation	Osteoblasts, endothelocytes
	de Mendonca Costa et al. 2008	Reconstruction of large cranial defects in nonimmunosuppressed experimental design with human dental pulp stem cells	In vivo study	Application in bone lesion	Bone regeneration
	El-Backly et al. 2008	Regeneration of dentine/pulp-like tissue using a dental pulp stem cell/poly(lactic-co-glycolic) acid scaffold construct in New Zealand white rabbits	In vivo study	Subcutaneous transplantation (rabbit)	Dentin- and pulpa-like tissue
	Graziano et al. 2008	Human CD34+ stem cells produce bone nodules in vivo	In vivo study	Absorbable scaffold, transplantation (rat)	Bone nodules
	Gronthos et al. 2002	Stem Cell Properties of Human Dental Pulp Stem Cells	In vivo study	Transplantation subcutaneous (mouse)	Ectopic dentin with pulpal tissue
	Gronthos et al. 2000	Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo	In vivo and in vitro study	Cell culture and transplantation	Osteoblast progenitors
	He et al. 2009	Effects of Notch ligand Delta 1 on the proliferation of human dental pulp stem cells in vitro	In vitro study	Delta 1	Odontoblasts
	He et al. 2008	Effects of FGF2 and TGFbeta(1) on the differentation of human dental pulp stem cells in vitro	In vitro study	a) FGF2 b) FGF2+TGFbeta(1); TGFbeta(1)	Dentin and pulp tissue, adipocytes, neuron-like cells
	Huang et al. 2006	Formation of odontoblast-like cells from cultured human dental pulp cells on dentin in vitro	In vitro study	Application on dentin surface	Odontoblasts
	Iohara et al. 2004	Dentin regeneration by dental pulp stem cell therapy with recombinant human bone morphogenetic protein 2	In vivo and in vitro study	BMP-2	Odontoblasts
	Kerkis et al. 2006	Isolation and characterization of a population of immature dental pulp stem cells expressing OCT-4 and other embryonic stem cell markers	In vitro study	Cell culture	Smooth and skeletal muscles, neurons, cartilage and bone
	Kumabe et al. 2006	Human dental pulp cell culture and cell transplantation with an alginate scaffold	In vitro study	Alginate scaffold (+beta-glycerophosphate)	Odontoblast-like cells, calcification
	Laino et al. 2006	In vitro bone production using stem cells derived from human dental pulp	In vitro study	Cell culture	Osteoblasts
	Laino et al. 2005	A new population of human adult dental pulp stem cells: a useful source of living autologous fibrous bone tissue (LAB)	In vivo and in vitro study	a) Culture b) Transplantation (mouse)	a) Osteoblast progenitor cells, osteoblasts b) Lamellar bone with osteocytes
	Liu et al. 2007	Multilineage potential of pulp stem cells from human young permanent teeth in vitro	In vitro study	Culture medium	Osteogenic, adipogenic and neurogenic differentiation
	Lu et al. 2008	A study of osteogenic induction of dental pulp stem cells from deciduous teeth in vitro	In vitro study	Cell culture	Osteoblasts
	Mina & Braut, 2004	New insight into progenitor/stem cells in dental pulp using Col1a1-GFP transgenes	In vivo study	Transplantation in renal capsules (mouse model)	Odontoblast-like, osteoblast-like cells
	Nakashima et al. 2004	Stimulation of reparative dentin formation by ex vivo gene therapy using dental pulp stem cells electrotransfected with growth/differentiation factor 11 (Gdf11)	In vitro and in vivo study	Gdf11	Odontoblasts
	Nakashima et al. 2002	Induction of dental pulp stem cell differentiation into odontoblasts by electroporation-mediated gene delivery of growth/differentiation factor 11 (Gdf11)	In vitro study	Gdf11	Osteoblasts

Tab. II (continuation) Overview of contents of the relevant primary literature (PubMed)

Cell type(s)	Author, year	Title	Study design	Factor(s)/ influence	Target cells
DPSCs	Otaki et al. 2007	Mesenchymal progenitor cells in adult human dental pulp and their ability to form bone when transplanted into immunocompromised mice	In vivo study	Subcutaneous transplantation (mouse)	Bone
	Papaccio et al. 2006	Long-term cryopreservation of dental pulp stem cells (SBP-DPSCs) and their differentiated osteoblasts: a cell source for tissue repair	In vivo and in vitro study	Cell culture and transplantation	Osteoblasts
	Pierdomenico et al. 2005	Multipotent Mesenchymal Stem Cells with Immunosuppressive Activity Can Be Easily Isolated from Dental Pulp	In vitro study	Cell culture	Osteogenic and adipogenic differentiation
	Prescott et al. 2008	In vivo generation of dental pulp-like tissue by using dental pulp stem cells, a collagen scaffold, and dentin matrix protein 1 after subcutaneous transplantation in mice	In vivo study	Simulated furcation perforation, Kollagen-gerüst, DMP1, mouse model (subcutaneous implantation)	Signs of tissue regeneration
	Takeda et al. 2008	Characterization of dental pulp stem cells of human tooth germs	In vivo study	Transplantation sub-cutaneous (mouse)	Odontoblasts, osteoblasts
	Yang et al. 2009	The performance of dental pulp stem cells on nanofibrous PCL/gelatin/nHA scaffolds	In vivo and in vitro study	PCL/gelatine/nHA scaffold	Hard tissue formation, odontoblast-like cells
	Yang et al. 2008b	Hard Tissue Formation of STRO-1-Selected Rat Dental Pulp Stem Cells In Vivo	In vivo study	Subcutaneous transplantation (mouse)	Hard tissue formation
	Yang et al. 2008a	Non-Viral Bone Morphogenetic Protein 2 Transfection of rat Dental Pulp Stem Cells Using Calcium Phosphate Nanoparticles as Carriers	In vitro study	BMP-2	Odontogenic differentiation
	Yang et al. 2007	The odontogenic potential of STRO-1 sorted rat dental pulp stem cells in vitro	In vitro study	Cell culture	Odontoblasts
	Yu et al. 2006	Differentiation of dental pulp stem cells into regular-shaped dentin-pulp complex induced by tooth germ cell conditioned medium	In vivo and in vitro study	TGC-CM	Odontoblasts, dentin-pulpal complex (in vivo), mineralization buds (in vitro)
	Yu et al. 2007	Odontogenetic capability: bone marrow stromal stem cells versus dental pulp stem cells	In vivo and in vitro study	ABC-Micro environ-ment, renal capsules of rats	DPCSs: higher osteogenic potency
	Yu et al. 2009	Dynamic hydrostatic pressure promotes differentiation of human dental pulp stem cells	In vivo and in vitro study	Subcutaneous transplantation (mouse)	Odontogenic differentiation
	Zhang et al. 2008b	In vivo evaluation of human dental pulp stem cells differentiated towards multiple lineages	In vitro study	Subcutaneous transplantation (mouse)	Odontoblasts, myoblasts, adipoblasts
	Zhang et al. 2008a	Hard tissue formation in a porous HA/TCP ceramic scaffold loaded with stromal cells derived from dental pulp and bone marrow	In vivo and in vitro study	Osteogenic medium in vitro, subcutaneous transplantation (mouse) in vivo	Osteoblasts
	Zhang et al. 2005	Differentiation ability of rat postnatal dental pulp cells in vitro	In vitro study	3D-scaffold	Odontoblast-like cells, mineralization buds with dentin-like components
DPSCs and ABCs	Sumita et al. 2009	The location and characteristics of two populations of dental pulp cells affect tooth development	In vivo study	Transplantation (omentum of immune-deficient rats)	Dentin and cementum or enamel and dentin
	Yu et al. 2008	Epithelial-mesenchymal Cell Ratios Can Determine the Crown Morphogenesis of Dental Pulp Stem Cells	In vivo and in vitro study	ABCs and DPSCs in vitro, in vivo transplantation (rat)	Odontoblast and ameloblast line of descent
DPSCs and SHEDs	Koyama et al. 2009	Evaluation of pluripotency in human dental pulp cells	In vitro study	Cell culture	Osteoblasts, chondrocytes, adipocytes
SHEDs	Cordeiro et al. 2008	Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth	In vivo study	Transplantation of tooth section (mouse)	Odontoblast- and endothelial-like cells
	Miura et al. 2003	SHED: Stem cells from human exfoliated deciduous teeth	In vivo study	Cell culture and transplantation	Odontoblasts, neurons, adipocytes
	Seo et al. 2008	SHED repair critical-size calvarial defects in mice	In vivo study	Transplantation in calvarial defects (mouse)	Bone regeneration
	Xu et al. 2009	Isolation and identification of stem cells derived from human exfoliated deciduous teeth	In vitro study	Cell culture	Adipogenic and osteogenic differentiation
	Zheng et al. 2009	Stem cells from deciduous tooth repair mandibular defect in swine	In vivo study	Transplantation in de-fect of mandible (pig)	Bone regeneration

Tab. II (continuation) Overview of contents of the relevant primary literature (PubMed)

Cell type(s)	Author, year	Title	Study design	Factor(s)/ influence	Target cells
SHEDs and DFCs	Morsczeck et al. 2009b	Comparison of human dental follicle cells (DFCs) and stem cells from human exfoliated deciduous teeth (SHED) after neural differentiation in vitro	In vitro study	Cell culture	Neural differentiation
PDLSCs	Chang et al. 2009	Isolation and identification of dog periodontal ligament stem cells	In vitro study	Cell culture	Osteoblasts, cementoblasts
	Fujii et al. 2008	Investigating a clonal human periodontal ligament progenitor/stem cell line in vitro and in vivo	In vivo and in vitro study	a) Culture b) Transplantation (mouse)	a) Osteoblasts, adipocytes b) Cementum-/bone-like structures
	Gay et al. 2007	Isolation and characterization of multipotent human periodontal ligament stem cells	In vitro study	Osteogenic, chondrogenic or adipogenic conditions	Osteoblasts, chondrocytes, adipocytes
	Liu et al. 2008	Periodontal ligament stem cell-mediated treatment for periodontitis in miniature swine	In vivo study	Transplantation (miniature pigs)	Periodontal tissue
	Ma et al. 2008	The biological effect of dentin noncollagenous proteins (DNCPs) on the human periodontal ligament stem cells (HPDLSCs) in vitro and in vivo	In vitro and in vivo study	DNCPs	Cementogenic differentiation
	Seo et al. 2004	Investigation of multipotent postnatal stem cells from human periodontal ligament	In vitro and in vivo study	Cell culture and transplantation	PDL, cementocytes, adipocytes, collagen-forrming cells
	Singhatanadgit et al. 2009	Isolation and characterisation of stem cell clones from adult human ligament	In vitro study	Cell culture	Osteogenesis
	Trubiani et al. 2007	The performance of human periodontal ligament mesenchymal stem cells on xenogenic biomaterials	In vitro study	Cell culture	Odontoblasts
	Yang et al. 2009	Tissue Engineering of Cementum/Periodontal-Ligament Complex Using a Novel Three-Dimensional Pellet Cultivation System for Human Periodontal Ligament Stem Cells	In vivo study	Transplantation (mouse)	Cementum, periodontal ligament
SCAPs and PDLSCs	Sonoyama et al. 2006	Mesenchymal Stem Cell-Mediated Functional Tooth Regeneration in Swine	In vivo study	Miniature pig model	Root-periodontal complex (to hold a ceramic crown)
DFSC	Kémoun et al. 2007	Human dental follicle cells acquire cementoblast features under stimulation by BMP-2/-7 and enamel matrix derivates (EMD) in vitro	In vitro study	BMP, EMD	Cementoblasts, periodontal ligament cells, osteoblasts
	Morsczeck et al. 2009a	Gene expression profiles of dental follicle cells before and after osteogenic differentiation in vitro	In vitro study	Cell culture	Osteogenic differentiation
	Morsczeck et al. 2006	Gene expression of runx2, Osterix, c-fox, DLX-3, DLX-5, and MSX-2 in dental follicle cells during osteogenetic differentation in vitro	In vitro study	Dexamethasone and insulin	Cementoblast-like or osteoblast-like cells
	Morsczeck 2005	In vitro differentation of human dental follicle cells with dexamethasone and insulin	In vitro study	Dexamethasone and insulin	Cells which express OCN, BMP-2 and nestin (osteoblast-like and cementoblast-like)
	Völlner et al. 2009	A two-step strategy for neuronal differentiation in vitro of human dental follicle cells	In vitro study	Cell culture	Neural differentiation
	Wu et al. 2008b	Dentin non-collagenous proteins (dNCPs) can stimulate dental follicle cells to differentiate into cementoblast lineages	In vivo study	dNCPs	Cementum
	Yokoi et al. 2007	Establishment of immortalized dental follicle cells for generating periodontal ligament in vivo	In vivo study	Transplantation (mouse)	PDL progenitor cells
SCAP	Ikeda et al. 2006	Osteogenic differentiation of human dental papilla mesenchymal cells	In vitro study	Cultivation	Osteoblasts
	Kikuchi et al. 2004	Odontoblasts induced from mesenchymal cells of murine dental papillae in three-dimensional cell culture	In vitro study	ECM	Odontoblasts
	Park et al. 2009	In vitro osteogenic differentiation of cultured human dental papilla-derived cells	In vitro study	Cell culture	Osteogenic differentiation
	Tetè et al. 2008	Changes in matrix extracellular phosphoglyco-protein expression before and during in vitro osteogenic differentiation of human dental papilla mesenchymal cells	In vitro study	Culture in osteogenic medium	Osteoblasts

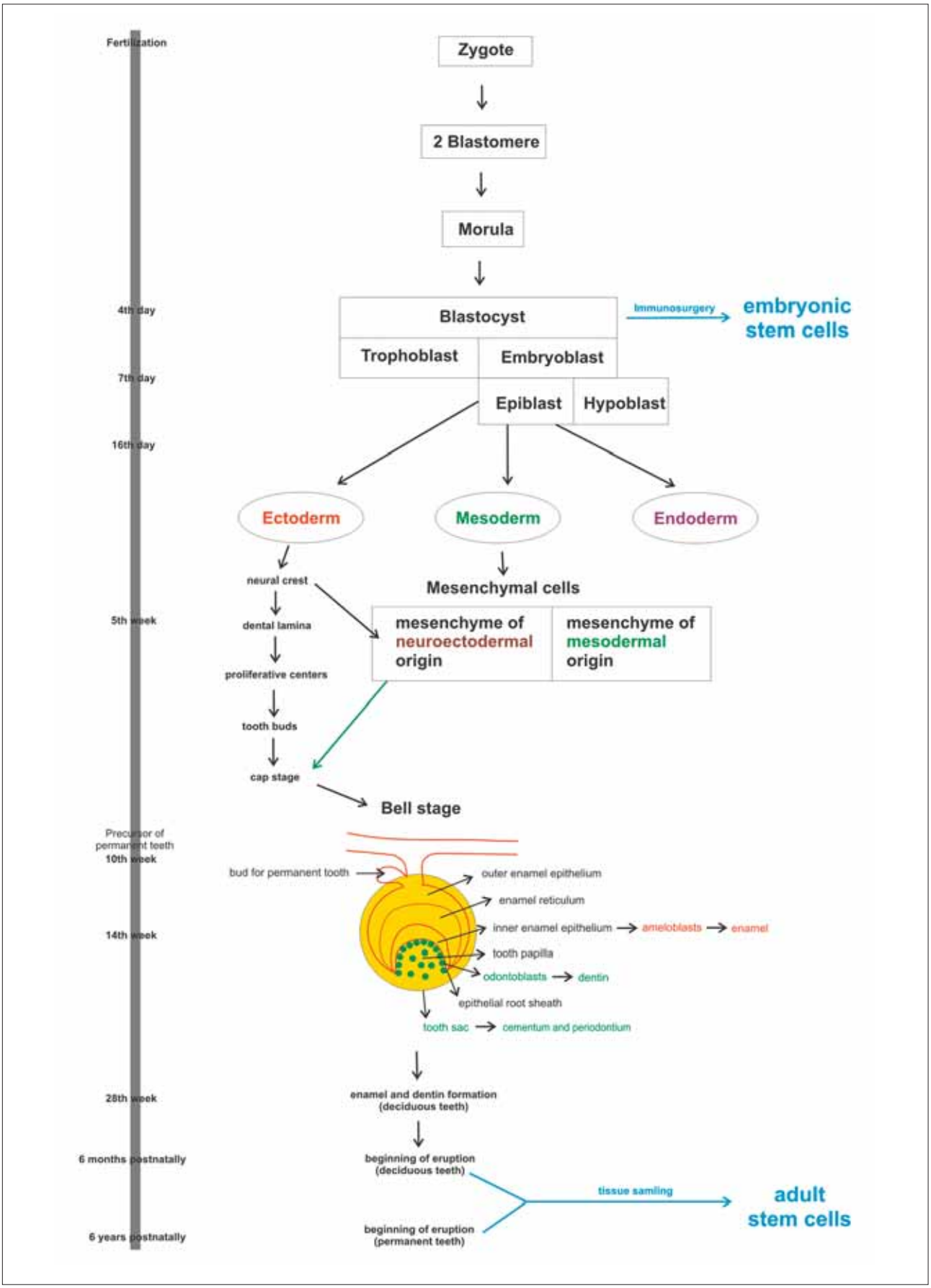

Fig. 1 Embryogenesis and odontogenesis

the regulation and differentiation of these cells as well as the control of crown and root formation (Schröder 2000, Bluteau et al. 2008). Over 200 regulatory genes are involved in odontogenesis. Cells communicate via signal molecules and growth factors. Predominantly, growth factors from the four eminent families *fibroblast growth factor* (FGF), *Hedgehog, wingless* (WNT) and *transforming growth factor-β* (TGF-β), to which the *bone morphogenic proteins* (BMPs) also belong, are important in the regulation of odontogenesis (Pispa & Thesleff 2003, Bloch-Zupan 2007, Koch 2007).

The maxillary and mandibular dental laminae of oral cavity ectoderm each form ten proliferation centers, out of which the tooth buds seem to shift into the underlying mesenchyme by means of the simultaneous growth of all jaw sections surrounding the oral cavity (Schröder 2000, Moore & Persaud 2007). The bud structures, or enamel organs, first assume the shape of a cap and then that of a bell. The external enamel epithelium is the outermost cell layer of these structures, and is connected to the dental lamina. The inner layer adjacent to the papilla is called the internal enamel epithelium, and the ameloblasts differentiate from its cells. The mesenchymal cells which are partially enveloped by the bell-shaped enamel organ later form the dental papilla. The mesenchymal cells adjacent to the enamel epithelium differentiate into odontoblasts. In the bell stage, the internal and external enamel epithelium unite to form the cervical loop, which, after crown formation is complete, grows down as the epithelial (Hertwig's) root sheath and controls root formation. The mesenchyme surrounding the epithelial root sheath condenses into the so-called tooth sac, from which the cementum and periodontium arise (Moore & Persaud 2007).

In humans, odontogenesis begins in about the 10th embryonic week (Koch 2007).

Wisdom teeth develop postnatally; their enamel organ has formed by about the 72nd month of life (Schröder 2000). This means that up to that point, undifferentiated dental embryonic tissue exists in the jaw. The development of the third molars is the only organogenesis which takes place completely after birth.

The basis for the regeneration of teeth or individual dental tissues is the acquisition of suitable stem cells and a suitable environment in which these cells can differentiate into the target tissues.

The combination of cells, suitable biomaterials, and biochemical factors are important in tissue engineering to improve or replace biological functions. Isolated cells can be cultivated using tissue engineering in vitro prior to in vivo transplantation.

Different carrier materials, such as collagen sponges (Zhang et al. 2006b, Zhang et al. 2008a, Gebhardt et al. 2009), HA/TCP (hydroxyapatite tricalcium phosphate) (Gronthos et al. 2000, Gronthos et al. 2002, Miura et al. 2003, Sonoyama et al. 2006, Zhang et al. 2008b), calcium phosphate (Takeda et al. 2008, Gebhardt et al. 2009), fibrin polymer ceramic (Schantz et al. 2005), alginate (Kumabe et al. 2006) or polymers (Duailibi et al. 2004, Gebhardt et al. 2009), PCL gelatin scaffolds (Yang X et al. 2009a), the use of growth factors such as fibroblast growth factors (Batouli et al. 2003) and some of the transforming growth factor β family, e. g. bone morphogenic proteins (Gronthos et al. 2002, Iohara et al. 2004, Durand et al. 2007, He H et al. 2008, Yang X et al. 2008a, Yang X et al. 2008b), are being examined for their ability to enable and ease transplantation and differentiation.

Both in vivo and in vitro, the environment must provide suitable physiological parameters to allow the cultivation of the cells.

A great challenge is the search for a source of human mesenchymal and epithelial stem cells which possess odontogenic potential, to enable the regeneration of a functional tooth. The known human dental stem cells are dental pulp stem cells (DPSCs), stem cells of human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PDLSCs), dental follicle stem cells (DFSCs), and stem cells of the dental apical papilla (SCAPs). Examples of a suitable environment are organic in vitro cultures, subcutaneous transplants or renal capsules in experimental animals. The not yet fully developed tooth progenitors could then be transplanted into their physiological anatomical region and continue to develop there.

Isolated cells from animal tooth buds have already been cultivated and differentiated in certain biomaterials, then reimplanted in the alveoli of immunosuppressed animals. In 2009, a functional tooth with all its components, particularly including an enamel crown, was regenerated in an experimental animal for the first time (Ikeda et al. 2009).

Analogous to the animal model, the future goal is to regenerate human autologous functional teeth.

Dental epithelial stem cells

The embryonic oral epithelium induces odontogenesis (Ohazama et al. 2004). The dental enamel is formed from ameloblasts, which arise from epithelial stem cells (Fig. 1). They are the only cells of ectodermal origin which play a role in odontogenesis. They are lost after tooth eruption, thus leaving no adult human ectodermal stem cells available for cell therapy. Consequently, no information exists yet on dental adult epithelial stem cells in humans.

In animal experiments, epithelial stem cells have been obtained from third molars of newborn or juvenile, still developing animals. The cells were enzymatically dissociated from epithelia and associated in vitro with mesenchymal stem cells of the same tooth to regenerate teeth (Young et al. 2002, Honda M J et al. 2005, Honda M J et al. 2007b).

As opposed to human teeth, the incisors of rodents grow throughout the animal's life. A source of epithelial stem cells, the apical bud cells (ABCs), in the apical epithelium is responsible for continuous enamel production (Harada et al. 1999, Harada et al. 2002, Morotomi et al. 2005, Lin et al. 2009). The homeostatic microenvironment in this region provides stem cells with a space in which they can develop. In rats, it was shown that ABCs with DPSCs develop molar-like structures; the most natural crown shape resulted when the two cell types were at a ratio of 1:1 (Yu J et al. 2006, Yu J et al. 2008).

Dental mesenchymal stem cells

With the exception of ameloblast progenitor cells, all stem cells involved in odontogenesis originate in mesenchyme (Fig. 1).

Up to the third week of development, the mesenchyme of the oral and facial region originates almost exclusively from the paraxial mesoderm. In the fourth week, neural crest cells of the ectoderm migrate into the hyoid arches, so that ultimately, most of the mesenchyme is of neuroectodermal origin. These cells are said to have an ectomesenchymal origin (Moore & Persaud 2007).

The various mesenchymal stem cell populations are usually found in prevascular niches of their corresponding tissue. Mesenchymal stem cells can differentiate into nerve, muscle, vascular, fat, cartilage or bone cells.

The differentiation potential of the various dental mesenchymal stem cells is described in the following. The references are listed in Table III.

Tab. III Thematic overview of the literature

Stem cells	Target tissue/target cells	Literature
DPSCs	Odontoblasts	Batouli et al. 2003, Braut et al. 2003, Iohara et al. 2004, Mina & Braut 2004, Nakashima et al. 2004, Zhang et al. 2005, Huang et al. 2006, Kumabe et al. 2006, Yu J. et al. 2006, Yang X. et al. 2007, Takeda et al. 2008, Yang X. et al. 2008b, Yu J. et al. 2008, Zhang et al. 2008a, Zhang et al. 2008b, He F. et al. 2009, Yang X. et al. 2009, Yu V. et al. 2009, Nakashima et al. 2002, Sumita et al. 2009
	Dentin & pulp tissue	Gronthos et al. 2002, Yu J. et al. 2006, El-Backly et al. 2008, He H. et al. 2008
	Osteoblasts	Gronthos et al. 2000, Gronthos et al. 2002, Braut et al. 2003, Mina & Braut 2004, Laino et al. 2005, Pierdomenico et al. 2005, Kerkis et al. 2006, Laino et al. 2006, Papaccio et al. 2006, Yu J. et al. 2006, d'Aquino et al. 2007, Jo et al. 2007, Liu H. S. et al. 2007, Otaki et al. 2007, Yu J. et al. 2007, Cheng et al. 2008, de Mendonca Costa et al. 2008, Graziano et al. 2008, Lu et al. 2008, Takeda et al. 2008, Yu J. et al. 2008, Koyama et al. 2009
	Chondrocytes	Kerkis et al. 2006, Cheng et al. 2008, Koyama et al. 2009
	Adipocytes	Pierdomenico et al. 2005, Jo et al. 2007, Liu H. S. et al. 2007, Cheng et al. 2008, He H. et al. 2008, Zhang et al. 2008a, Koyama et al. 2009
	Endothelocytes	d'Aquino et al. 2007
	Neurons	Gronthos et al. 2002, Kerkis et al. 2006, d'Aquino et al. 2007, Liu H. S. et al. 2007, Arthur et al. 2008, He H. et al. 2008
	Musculature	Kerkis et al. 2006, Zhang et al. 2008a
SHEDs	Odontoblasts	Miura et al. 2003, Cordeiro et al. 2008
	Osteoblasts	Seo et al. 2008, Singhatanadgit et al. 2009, Xu N. et al. 2009, Zheng et al. 2009, Koyama et al. 2009
	Neurons	Miura et al. 2003, Morsczeck et al. 2009b
	Adipocytes	Miura et al. 2003, Xu N. et al. 2009, Koyama et al. 2009
	Endothelocytes	Cordeiro et al. 2008
PDLSCs	Odontoblasts	Trubiani et al. 2007
	Periodontal tissue	Seo et al. 2004, Sonoyama et al. 2006, Liu Y. et al. 2008, Yang Z. et al. 2009
	Osteoblasts	Gay et al. 2007, Fujii et al. 2008, Chang et al. 2009, Singhatanadgit et al. 2009
	Cementoblasts	Seo et al. 2004, Ma et al. 2008, Chang et al. 2009, Yang Z. et al. 2009
	Chondrocytes	Gay et al. 2007
	Adipocytes	Seo et al. 2004, Gay et al. 2007, Fujii et al. 2008
DFSCs	PDL progenitor cells	Yokoi et al. 2007
	Osteoblasts	Morsczeck et al. 2005, Morsczeck 2006, Morsczeck et al. 2009a
	Cementoblasts	Morsczeck et al. 2005, Morsczeck 2006, Kemoun et al. 2007, Wu J. et al. 2008b
	Neuroblasts	Völllner et al. 2009, Morsczeck et al. 2009b
SCAPs	Odontoblasts	Kikuchi et al. 2004, Sonoyama et al. 2006
	Osteoblasts	Ikeda et al. 2006, Tete et al. 2008, Park et al. 2009

Dental pulp stem cells

Dental pulp stem cells (DPSCs) can be isolated from the dental pulp. Depending on specific signals from their environment, DPSCs can either regenerate new stem cells or undergo a differentiation process. In the dental pulp, there are different progenitor cell subpopulations, which differ in terms of self-renewal ability, proliferation rate, and differentiation potential (Gronthos et al. 2002, Honda M et al. 2007a, Sumita et al. 2009). Dental pulp can be acquired from third molars or pulpectomized teeth left in situ (d'Aquino et al. 2008). Even after temporary storage in liquid nitrogen, the DPSCs do not lose their multipotent ability to differentiate (Papaccio et al. 2006, Zhang et al. 2006a, Woods et al. 2009).

In vitro, DPSCs can differentiate to odontoblasts, osteoblasts, endothelocytes, smooth muscle cells, adipocytes, chondrocytes, and neurons.

The developmental ability of DPSCs in vitro is limited. In vivo, more complex tissues can arise. For instance, DPSCs differentiate in vitro to osteoblast progenitor cells and mature into osteoblasts which produce LAB (living autologous fibrous bone tissue) (Laino et al. 2005), while DPSCs in vivo can form calcified bone tissue with Haversian canals and osteocytes (Laino et al. 2005, Kumabe et al. 2006, Yang X et al. 2008a, Yu V et al. 2009), and dentin/pulp-like tissue complexes (Gronthos et al. 2000, El-Backly et al. 2008).

In animal experiments in vivo, various differentiation directions – i. e., odontogenic, myogenic, adipogenic, and osteogenic differentiation – were found. In addition, DPSCs influence angiogenesis (d'Aquino et al. 2007).

Dentistry has long exploited the life-long regeneration potential of adult stem cells in human dental pulp which give rise to tertiary dentin, therapeutically employed for direct and indirect pulp capping after caries excavation near the pulp. The application of calcium hydroxide or calcium phosphate, among other substances, can induce pulpal progenitor cells to differentiate into odontoblasts. In the future, DPSCs could also be used to treat perforated furcations (Prescott et al. 2008).

Stem cells from human exfoliated deciduous teeth (SHEDs)

Human exfoliated deciduous teeth are a relatively easily accessible source of adult stem cells. SHEDs can be isolated from the coronal pulp of exfoliated deciduous teeth. It is assumed that in addition to their role in the eruption of permanent teeth, they also influence the osteogenesis associated with the same (Miura et al. 2003).

In vitro, they can differentiate odontogenically, osteogenically, adipogenically, chondrogenically, or neurally, depending on different conditions.

In vivo, these multipotent stem cells have the potential to differentiate into neurons, adipocytes, odontoblasts, and osteoinductive and endothelioid cells.

Periodontal ligament stem cells (PDLSCs)

The periodontal ligament, which connects the alveolar bone to the root cementum and suspends the tooth in its alveolus, contains stem cells which have the potential to form periodontal structures such as cementum and ligament. It can be harvested from the roots of extracted teeth.

In vitro, PDLSCs differentiate into osteoblasts, cementoblasts, and adipocytes.

In vivo, after transplantation into mice, structures resembling bone, cementum, cartilage, and PDL have been found. In a study using pigs, PDLSCs were implemented to treat periodontal lesions (Liu Y et al. 2008). Combined with SCAPs from impacted third molars, PDLSCs on a hydroxyapatite-tricalcium scaffold were transplanted into the alveoli of juvenile miniature pigs. A root and a periodontal complex were formed that were able to support a ceramic crown, thus fulfilling the function of a natural tooth (Sonoyama et al. 2006).

Dental follicle stem cells (DFSCs)

The dental follicle surrounds the developing tooth. It plays a major role in the genesis of cementum, periodontal ligament, and alveolar bone. DFSCs can be isolated from the follicles of impacted third molars (Yalvac et al. 2009).

DFSCs cultivated in vitro exhibit characteristics of cementoblasts and osteoblasts, and can differentiate neurally.

In vivo, tissue similar to dental cementum and differentiation into PDL progenitor cells have been observed.

Stem cells from the dental apical papilla (SCAPs)

SCAPs are stem cells from the apical part of the papilla, a precursor tissue of the dental pulp. Impacted third molars serve as a suitable source.

In vitro, SCAPs can differentiate osteogenically, odontogenically, and adipogenically.

In vivo, SCAPs have been found to differentiate into odontonblasts and osteoblasts.

Non-dental stem cells

Dental tissue can also be regenerated from non-dental adult multipotent stem cells (Modino & Sharpe 2005, Yen & Sharpe 2008). Embryonic oral epithelium can stimulate an odontogenic response in mesenchyme which does not have a dental origin (Ohazama et al. 2004). It would be desirable to have an extraoral, easily accessible source of stem cells, in order to make odontogenesis possible in a minimally invasive manner.

Human bone marrow is not only a source of adult hematopoetic stem cells. From bone marrow, multipotent mesenchymal stem cells can also be obtained and cultivated. These bone marrow derived mesenchymal stem cells (BMSCs) can replicate themselves and, in experiments, be differentiated into osteoblasts (Batouli et al. 2003, Pierdomenico et al. 2005, Schantz et al. 2005), chondrocytes (Pierdomenico et al. 2005), myoblasts, adipocytes (Pierdomenico et al. 2005), and neuron-like cells (Pittenger et al. 1999, Sonoyama et al. 2005), among others.

Embryonic oral epithelium induces BMSCs to express odontogenic genes. The in vivo development of tooth-like structures with bone has been observed (Ohazama et al. 2004).

In humans, BMSCs are already being used therapeutically in bone augmentation by sinus lifts (Shayesteh et al. 2008, Sauerbier et al. 2009). They are minimally invasively harvested from the iliac crest and inserted into the maxillary sinus on a carrier. In this way, it is possible to do without the surgical removal of autologous bone prior to conventional implant procedures.

Stem cells can also be isolated from the bone marrow of the mandible. These MBMSCs (mandibular bone marrow stem cells) possess a high osteogenic potency (Jo et al. 2007). However, there are far fewer stem cells here than in the iliac crest marrow.

Mesenchymal cells can be isolated from odontomas and differentiated into dental hard tissue, such as dentin (Song et al. 2009).

From umbilical cord blood (Noll 2003), cartilage (Archer 2007), the cornea (Du 2007), mammary glands (Labarge 2007), and adipose tissue (Scafford 2007) stem cells can be obtained. Medical research has been done on multipotent neural stem cells from areas such as the hippocampus and subventricular zone to examine possible uses in neurological therapy (Winkler 2003). Renal stem cells have the potential to generate functional, human renal tubule structures in the future (Minuth 2003).

In dentistry, hair follicles have been studied as an easily accessible source of mesenchymal stem cells. FDPMCs (follicle dermal papilla mesenchymal cells) from mouse tactile hairs have been isolated and differentiated to odontoblast-like cells in vitro (Wu G et al. 2008a). Adipose-derived stem cells regenerate in vivo after transplantation into rat periodontal tissue (Tobita et al. 2008).

Dermal multipotent cells have been differentiated to odontoblasts in embryonic tooth-bud medium (Huo et al. 2009).

Dental stem cell markers

Stem cell markers help identify, characterize, and isolate stem cells. Some examples are described below as an overview.

STRO-1, a trypsin-resistant cell-surface antigen, is a commonly used dental stem cell marker for all dental MSCs. It is expressed, for example, from bone marrow mesenchymal cells (Zhang et al. 2005, Zhang et al. 2006a, Gay et al. 2007, Morsczeck et al. 2007, Yang X et al. 2007, Xu J et al. 2008, Yang X et al. 2008a). STRO-1 is one of the early surface markers of mesenchymal stem cells. Its expression diminishes gradually during cultivation of the stem cells (Sonoyama W 2007).

Another stem cell marker, Stro-4, binds to heat shock protein–90 beta of multipotent MSCs and is also suited to identifying stem cells (Gronthos et al. 2009).

Markers for differentiated cells can also be used to characterize stem cells. For instance, the osteoblast marker osteocalcin is also a stem cell marker of DPSCs (Gronthos et al. 2000).

In addition to mesenchymal stem cell markers, immature dental pulp stem cells also express markers of embryonic stem cells, such as Oct-4, Nanog, SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81 (Kerkis et al. 2006).

The neural marker nestin on dental stem cells indicates that dental mesenchymal stem cells originate in progenitor cells of

the neural crest, which can also differentiate into neural tissue (Mao 2008).

Discussion

Literature search methods

Given the search strategy employed (Datenbank PubMed) and the expanded search of secondary literature, it is safe to assume that the systematic literature review is based on a reliable selection of publications. Due to limited resources, a search of other databanks (e.g., Excerpta Medica Data BASE) or in other languages was not conducted. Nevertheless, the relevant literature was covered with the search strategy that was used.

Discussion of results

Research on the cytological and molecular processes of odontogenesis and tooth regeneration forms the foundation for the future use of these mechanisms for guided, controlled odontogenesis. The vision of natural dental restorations generated from stem cells, or the stem-cell-based autologous regeneration of tissues is what makes stem cell research interesting for dentistry.

To date, embryonic stem cells have hardly been examined in dentistry. In contrast to them, adult stem cells pose no ethical conflicts. They, too, have the potential to differentiate into dental structures.

Epithelial stem cells, such as apical bud cells (Harada et al. 1999, Harada et al. 2002, Morotomi et al. 2005, Lin et al. 2009) have already been examined in vivo and in vitro. These epithelial stem cells can be extracted from adult rodents (Harada et al. 1999, Harada et al. 2002, Morotomi et al. 2005, Lin et al. 2009). However, their clinical implementation in humans is problematic due to the immunological reaction provoked by animal donor cells, which increases the risk of rejection.

It has not yet been possible to find a source of human adult ectodermal stem cells to regenerate enamel post-eruptively. A promising approach to tooth regeneration in animal experiments may be to obtain epithelial stem cells from third molars of newborn or juvenile animals (Young et al. 2002, Honda M J et al. 2005, Honda M J et al. 2007b, Ikeda et al. 2009). Analogously in children, it must be theoretically possible to isolate dental ectodermal stem cells from the tooth buds of the third molars. At this time, the wisdom tooth buds are not yet radiographically visible because mineralization has not yet occurred. The attempt to operatively obtain stem cells from children would not, however, be ethically defensible.

Therefore, for the future as well, the question remains unanswered as to the source of adult epithelial stem cells for enamel regeneration. An alternative could be conventional crowns supported by a rudimentary tooth generated from stem cells.

Various adult mesenchymal stem cells, such as dental pulp stem cells, stem cells from human exfoliated deciduous teeth, periodontal ligament stem cells, dental follicle stem cells, and stem cells from the dental apical papilla, have already been examined in vivo and in vitro for their potential to generate tooth components. The relevant references are listed in Table III.

Dental mesenchymal stem cells can be substituted by stem cells of other origins (Ohazama et al. 2004, Modino & Sharpe 2005, Yen & Sharpe 2008). An application of non-dental stem cells as in bone augmentation (Shayesteh et al. 2008, Sauerbier et al. 2009) seems promising.

For tissue engineering with different stem cells, various carrier materials for differentiation and transplantation are being examined. The stem cell's environment, its niche, controls its behavior and thus represents the basis for its potential manipulation. Particularly polymer and collagen scaffolding materials are suited to in vitro cultures of DPSCs and PDLSCs (Gebhardt et al. 2009).

The various adult dental stem cells can be used to regenerate various dental tissues. To regenerate dentin or pulp tissue, DPSCs, SHEDs and SCAPs are appropriate. The periodontium and cementum can be generated from PDLSCs or DFSCs.

The different stem cells exhibit different potencies in tissue regeneration. Compared with DPSCs, SHEDs have a higher proliferation rate (Miura et al. 2003). The potential of SCAPs to regenerate dentin is greater than that of DPSCs (Sonoyama et al. 2006). Further, mesenchymal stem cells of the dental papilla were shown to be more potent osteoblast progenitor cells than were DPSCs (Tete et al. 2008). DFSCs can induce osteogenesis and dentin formations, but not – as opposed to DPSCs – a dentin-pulp complex (Miura et al. 2003, Bluteau et al. 2008).

Even within a stem cell type, there are differences. DPSCs from pulp horns differentiate with ABCs to dentin and cementum. DPSCs from the apical pulp are less mature than those from the pulp horns, and differentiate with ABCs to dentin and enamel (Honda M et al. 2007a, Sumita et al. 2009).

The adult stem cells have different sources. To harvest SCAPs and DFSCs, impacted third molars are necessary. An easily accessible source of SHEDs are exfoliated deciduous teeth. Only a few patients who request the replacement of teeth still have impacted wisdom teeth. Even fewer possess deciduous teeth from which SHEDs can be isolated. In contrast, the development of a treatment concept to regenerate teeth using DPSCs and PDLSCs could be implemented in every patient. However, these cells seem to have a lower dentogenic potential than the stem cells from teeth which are still in the process of maturing. For instance, if human DPSCs are extracted from the tooth buds at an early stage of development, they exhibit an even higher proliferation rate in osteogenic and odontogenic differentiation (Takeda et al. 2008).

Stem cell markers are of great interest for obtaining adult stem cells. They should identify stem cells in tissue, to subsequently be able to isolate them. Different markers have already been examined, showing that Stro-1 may be a suitable stem cell marker for mesenchymal stem cells (Zhang et al. 2005, Zhang et al. 2006a, Gay et al. 2007, Morsczeck et al. 2007, Yang X et al. 2007, Xu J et al. 2008, Yang X et al. 2008a).

Controlled odontogenesis in animal experiments has succeeded a number of times. Using SCAPs and PDL stem cells, tooth roots have been generated which were functional after conventional crowning (Sonoyama et al. 2006). In animal experiments with murine embryonic epithelial and mesenchymal stem cells, it is also possible to generate functional, innervated teeth with dentin, pulp, alveolar bone, blood vessels, periodontal ligament, and enamel (Ikeda et al. 2009). In the future, this procedure could be applicable in humans.

In the future, it could be possible to minimally invasively isolate suitable stem cells, profile and differentiate them in vitro, combine and differentially develop them into a tooth, in vivo in humans.

For dentistry, stem cell biology and tissue engineering are of great interest. Various in vivo and in vitro studies provide hope of future application in humans. However, a great deal of research must be done before it is possible to cultivate entire teeth as natural, autologous tooth replacements.

Résumé

Dans le domaine de recherche relativement jeune de la biologie des cellules souches, des méthodes prometteuses in vitro et in vivo ont été appliquées dans le modèle animal; celles-ci font paraître réaliste une future application chez l'homme dans le domaine de la médicine dentaire. Le but de ce travail était de mettre à jour systématiquement la littérature de la recherche des cellules souches dans les domaines importants de la médecine dentaire. Dans le cadre de la dentisterie, on discute l'utilisation de différentes cellules souches. En ce qui concerne une future application chez l'homme, les cellules souches dentales ectomésenchymales adultes semblent particulièrement prometteuses. On a pu examiner des cellules souches humaines de la pulpe dentaire, des dents de lait exfoliées, du ligament parodontal, du follicule dentaire et de la papille dentaire. Pour la caractérisation et l'isolation des cellules souches, on se sert en règle générale de différents marqueurs de cellules souches, comme STRO-1. Les cellules souches dentaires adultes ont le potentiel de se diviser en tous les composants d'une dent, comme la dentine, le parodonte, le cément et le tissu de la pulpe, mais pas en émail de la dent.

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