



Niches of Stem Cells

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Abstract

In niches, stem cells are associated with adhesion extracellular matrix molecules (ECM). This gives rise to cells that retain their 'stemness', control their self-renewal and their progeny production, by using asymmetric or symmetric divisions. The adhesion molecules include N-cadherin/ β -catenin, VCAM/integrin, and osteopontin/ β 1integrin. They create a microenvironment that favor cell division, and interactions leading to cell differentiation. Asymmetric division contributes to self-renewal (a single division) and produce daughter cells that conduct to terminal differentiation. C-Myc is involved in controlling the balance between stem cell maintenance and proliferation. Daughter cells are expressing low levels of c-Myc. They are retained in the niche in a quiescent state, whereas, high levels of c-Myc expression in the remaining daughter cells supports the proliferation of cells and the displacement of dividing transit cells and their replacement leading to terminal differentiation.

Keywords

Stem cells; Extracellular substrates; Asymmetric or symmetric division; Adhesion molecules; Cell terminal differentiation

Introduction

Schofield [1] developed the hypothesis of stem cell niche and proposed that stem cells reside within fixed niches contributing to the maintenance of definitive properties. Stem cells are multipotent and possess self-renewal abilities, regulated by extrinsic signals emanating from the surrounding niche. Cells and extracellular matrix are components in which stem cells are associated as undifferentiated cells. Niches give rise to stem cells, retain their 'stemness', and control their self-renewal and progeny production *in vivo* [1,2]. Stem cell niches are composed of molecules that nurture the stem cells them to maintain tissue homeostasis. An appropriate spatiotemporal dialog occurs between stem cells and the niche [3]. Stem cells are regulated by signals (ECM receptors such as integrins or tenascin C) and intrinsic programs including paracrine signals, and soluble ligands [fibroblast growth factor-2 (FGF2), bone morphogenetic protein-4 (BMP4), transforming growth factor β (TGF- β), heparan growth factors (HGF), sonic hedgehog (SHH), Wnt and biglycan]. They are producing firstly a set of transient amplifying cells, leading later to differentiated cells. Basement membrane are typically rich in laminins and type IV (non-fibrillar) collagen. Adhesion molecules such as cadherins, β -integrin chains representing an essential player in stem cell niche. Metalloproteinases induce the remodeling of ECM components and permit the release of factors which were in an insoluble state. The choice of a stem cell to undergo self-renewal is carried out by two cell division mechanisms that fulfill two different tissue requests:

- I. Asymmetric self-renewal, in which each stem cell divides into one stem and one differentiated cell, allowing to maintain a constant number of stem cells under physiological conditions. In the asymmetric cell division, the mitotic process leads to asymmetric segregation of components essential for the cell fate determination. Once cell division is completed, one daughter cell received RNAs, proteins and other molecules that maintain the undifferentiated program, whereas the other cell receives lineage commitment factors.
- II. In the symmetric cell division, the two daughter cells receive the same factors and the decision for differentiation is not linked to mitosis, rather it is a later event that can involve the newly formed cells. Symmetric self-renewal, in which each cell produces two daughter cells, is leading to an expansion of the stem cell pool. Several ECM molecules play regulatory functions for different types of stem cells, based on their molecular composition. The ECM is expressed, providing the most appropriate niche for stem cells.

Symmetric or asymmetric divisions are not mutually exclusive. A mixture of these two

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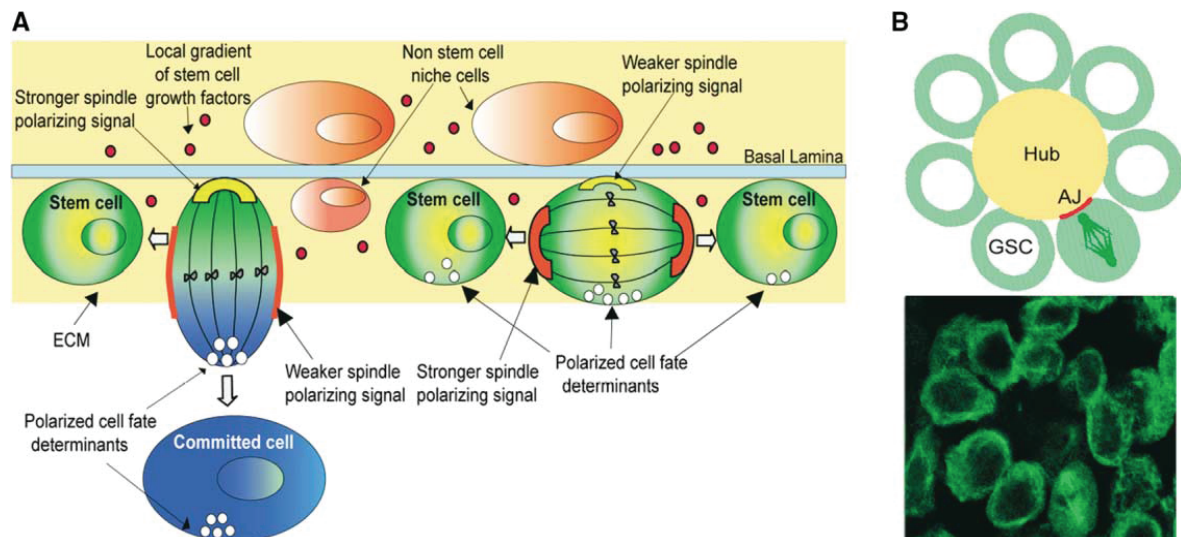


Figure 1: Potential Role of the Niche in orienting and defining the nature of stem cell divisions [16].

Schematic depicting the dual importance of cell polarity and spindle orientation in determining whether a stem cell division will be symmetric or asymmetric. Interactions between the basal lamina (basal surface) and neighboring stem cells (lateral surfaces) establish the polarity of the stem cells that in turn leads to the concentration of cell differentiation factors (white dots) at the apical surface. Two putative spindle-polarizing signals are depicted as aligned perpendicularly to one another. The spindle polarizing and cell fate determinants could be the Par complex (yellow) and adherens junctions (red).

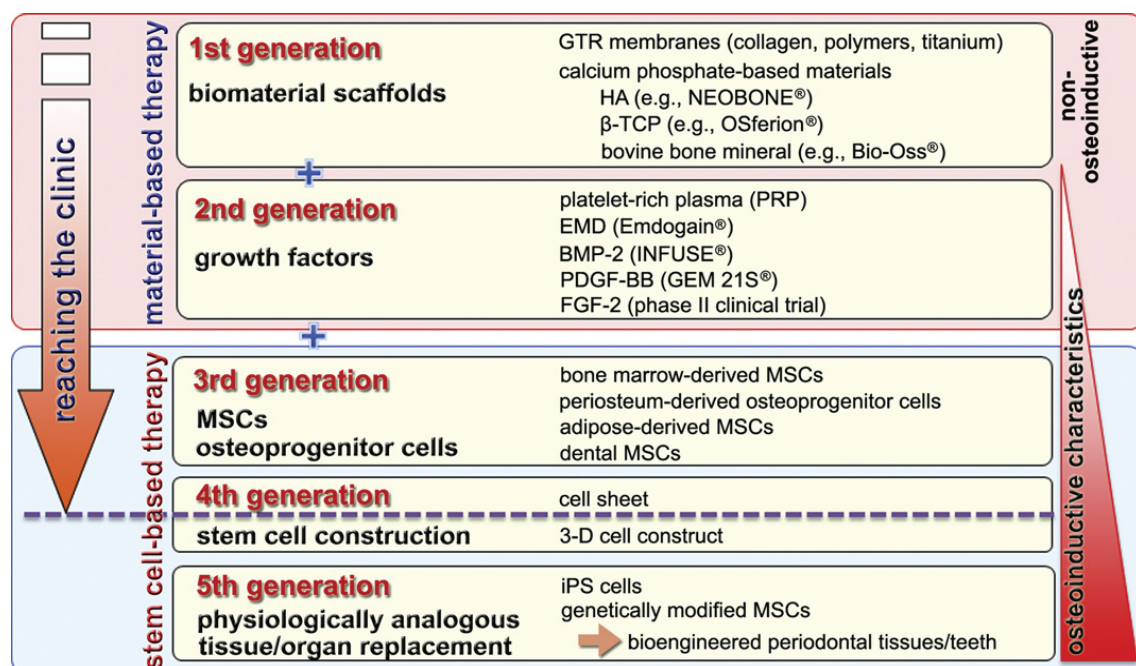


Figure 2: Regenerative periodontal/bonetherapies are categorized as material-based therapies (first generation biomaterial scaffold-based approach and second-generation growth-factor-based approach) and stem-cell-based therapies (third-generation MSC/osteoprogenitor cell-based approach, fourth-generation stem-cell construction-based approach, and fifth-generation physiologically analogous tissue/organ replacement approach) [17].

mechanisms can be used on subsequent divisions. During mid to late gestation, some mammalian progenitor cells are able to make a developmentally regulated transition from largely symmetric to predominantly asymmetric divisions. Similarly, adult stem cells dividing asymmetrically under steady-state conditions retain the capability to divide symmetrically to restore stem cell pools depleted. Recent studies demonstrated that in many stem cell niches, adhesion molecules to support cells and/or extracellular matrix determine the orientation of stem cell division plane, contributing to the control of

stem cell self renewing differentiation [4]. The daughter cell that remains bound to the niche adheres to the cell membrane and stays in the niche, where as the distal one differentiates. The daughter cell fate depends essentially on the extrinsic factors produced within the niche, rather than an asymmetric distribution of intrinsic determinants. Niches also share a requirement for a system to ensure that stem cells remain in the niche. An individual stem cell can give rise to two identical daughter cells or two non-identical daughter cells, one maintaining the stem-cell identity and the other becoming

a differentiated cell [5]. Extracellular matrix molecules are regulating primitive cells. Three examples worth comments in mammalian stem-cell systems.

- A. In the skin, β -1 integrins participate through presumed interaction with matrix glycoprotein ligands.
- B. In the nervous system, the absence of tenascin C alters neural stem-cell number and function. Tenascin C deletion affects primitive cell populations, raising the possibility that it participates in several stem-cell niches.
- C. The extracellular matrix protein osteopontin (OPN) contribute to HSCs regulation. OPN interacts with several receptors [6]. OPN is a negative regulatory element of the stem cell niche that limits the size of the stem cell pool [7]. The stem cell niche provides a regulatory environment including signals to maintain the stem cell pool, in which stem cells differentiate.

A growing body of data indicates that stem cell function is influenced by extrinsic signals derived from the microenvironment. The niches influence stem cells homeostasis, progression of disease and therapeutic strategies for tissue repair [8]. In adults, osteoblasts, responsible for osteogenesis, and hematopoietic cells are associated in the bone marrow, suggesting a reciprocal relationship between the two. A subset of osteoblasts functions as a key component of the osteoblastic niche controlling HSC numbers. HSCs interact not only with osteoblasts but also with other stromal cells, including endothelial cells [9]. In response to mitogens, c-Myc upregulation is required to release SCs from the stem cell niche. Similarly, c-Myc expression is repressed by antiproliferative signaling factors such as TGF- β . C-Myc expression represses N-cadherin and integrins. Upon stem cell division, daughter cells expressing low levels of c-Myc are retained in the niche in the quiescent state. In contrast, high levels of c-Myc expression in remaining daughter cells, along with downregulation of cell adhesion molecules, causes the daughter cells to leave the niche for proliferation and differentiation (Figure 1). SC is self-renewing cells that generate the differentiated cell types need to carry out specialized functions in the body. Asymmetric cell division allows stem cells to perpetuate themselves (self-renew). When SCs are expanding in number during development or after injury, they can also divide symmetrically [10]. The identification of perivascular cells as a native source of mesenchymal progenitor cells open the way to the development of novel regenerative therapies with improved efficacy using well-defined cell populations [11]. A highly regulative mechanism gives rise to daughter cells that have a probability of being either stem cells or committed progenitors. Between the stem cell and its terminally differentiated progeny there is an intermediate population of committed progenitors with limited proliferative capacity and restricted differentiation potential, sometimes known as transit amplifying cells.

- a) First, signals emanating from the niche regulate stem cell self-renewal, survival and maintenance.
- b) Second, the particular spatial relationship between stem cells and support cells can polarize stem cells within the niche to promote asymmetric stem cell divisions.
- c) Third, adhesion between stem cells and supporting stromal cells and/or the extracellular matrix anchors stem cells within the niche.

Niche turnover and iPSC

Stem cell niches are complex, interactive structures that integrate local and systemic signals for the positive and negative regulation of stem cell activities in a spatially and temporally defined manner. The initial formation depends on asymmetric division. The transcription factor Oct4 is essential for the After generation of cells submitted to direct reprogramming of somatic factors Oct3/4, Sox2, Klf4, c-Myc. They are called 'Induced Pluripotent Stem cells (iPS)'. NANOG and LIN28 Human induced pluripotent stem cells (iPSC) retain an epigenetic memory of their tissue of origin [12]. Mesenchymal

Stem Cells (BMMSCs) or Bone-derived stromal stem cells (BMSSCs) derived from dental tissues include:

- 1) Dental pulp SC (DCSCs)
- 2) SC from exfoliated deciduous teeth (SHED)
- 3) Periodontal ligament cells (PDLSCs)
- 4) Stem cells from apical papilla (SCAP), and
- 5) Dental follicle progenitor cells (DFPCs)

The stem cell's niche (SCN) is a unique microenvironment within tissues that regulate stem/progenitor cell proliferation, survival, migration, fate, and aging. Niche formation starts in early development and continues after the birth during childhood, providing cells for growth and self-renewal of the organism [13]. MSC may be derived from adipose tissue and from umbilical cord blood. Both endothelial cells and pericytes such as the smooth muscle cells surrounding blood vessels constitute the MSC niche, and contribute to a perivascular location of these cells [6]. DPSCs may reside in more than one anatomical site in the same tissue, since positive markers CD90, STRO-1 and ALDH1 were identified around blood vessels and also in the nerve fibres of the pulp. Perivascular niche of postnatal mesenchymal stem cells have been identified in dental pulp. They expressed as endothelial cells the von Willebrand factor, and CD146, as smooth muscle cells and pericytes, the α -smooth muscle actin, and CD146, and a pericyte associated antigen (3G5). It has previously been hypothesized that one possible niche for precursors of osteoblasts and odontoblasts may be the micro-vasculature networks of bone marrow and dental pulp, respectively [14]. ALDH1 was expressed by isolated dental pulp cells, which have mesenchymal stem cell characteristics. Thus, it was suggested that aldehyde dehydrogenase 1 (ALDH1) may be used as a DPSC marker [15]. Isolation of stem cells from human adult teeth has been reported, attracting researchers to this promising source. It has been shown that

- a) The explant culture of DP leading to collect a relatively pure cell population;
- b) SCs express pluripotent stem cell markers;
- c) Based on gene expression profile, different populations of SC can be isolated ;
- d) SCs are multipotent cells with high differentiation potential that are able to contribute to all embryonic germ lineage formation;
- e) *In vivo*, in animal models, SCs present tissue regeneration capacity in response to the cellular milieu;
- f) iPS cells can be easily obtained from SCs;
- g) SCs are more immature cells in comparison with DPSCs;

SCs are almost unlimited source of young stem cells with easy access [12,16,17] (Figure 2).

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