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Review

# Heterocellular molecular contacts in the mammalian stem cell niche

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ABSTRACT

Adult tissue homeostasis and repair relies on prompt and appropriate intervention by tissue-specific adult stem cells (SCs). SCs have the ability to self-renew; upon appropriate stimulation, they proliferate and give rise to specialized cells. An array of environmental signals is important for maintenance of the SC pool and SC survival, behavior, and fate. Within this special microenvironment, commonly known as the stem cell niche (SCN), SC behavior and fate are regulated by soluble molecules and direct molecular contacts via adhesion molecules providing connections to local supporting cells and the extracellular matrix. Besides the extensively discussed array of soluble molecules, the expression of adhesion molecules and molecular contacts is another fundamental mechanism regulating niche occupancy and SC mobilization upon activation. Some adhesion molecules are differentially expressed and have tissue-specific consequences, likely reflecting the structural differences in niche composition and design, especially the presence or absence of a stromal counterpart. However, the distribution and identity of intercellular molecular contacts for adhesion and adhesion-mediated signaling within stromal and non-stromal SCN have not been thoroughly studied. This review highlights common details or significant differences in cell-to-cell contacts within representative stromal and non-stromal niches that could unveil new standpoints for stem cell biology and therapy.

## 1. Introduction

Stem cells as a concept, particularly their behavior and potential use in cell-based therapies, has been constantly restructured in recent years by advances in cell imaging, monitoring, and handling. Many types of stem cells are formed at different time-points in different parts of the body. They are broadly divided into early pluripotent embryonic stem cells and more specialized, tissue-specific, adult stem cells. Adult stem cells are mainly responsible for insuring tissue homeostasis and tissue repair throughout adult life (Garcia-Prat et al., 2017).

Stemness in regards to adult cells is functionally defined as a capacity for self-renewal (as a result of infrequent, asymmetric cell divisions), proliferation, and differentiation into the cell types required for tissue maintenance (Wu and Izpisua Belmonte, 2016). Adult stem cells are typically found in a non-proliferative (quiescent, G0) state. Intrinsic mechanisms regulate this particular cell condition, but quiescent stem cells have the ability to respond to environmental cues by re-entering the cell cycle, ultimately giving rise to specialized cells of the tissue to which they belong (Cheung and Rando, 2013). Thus, the range of signals available to adult stem cells is highly relevant for their survival, conduct, and specific fate (Booth et al., 2008).

Maintaining stem cell quiescence (a means of avoiding genetic damage) requires special support for their distinct metabolic state and a means to control the stem cell pool by relaying information about the state of the tissue (Lander et al., 2012). All of these requirements imply the need for a special microenvironment, commonly known as the stem cell niche. This specific milieu comprises extracellular matrix and soluble endocrine, paracrine, or juxtacrine signaling molecules, neural inputs, and various interacting cell type(s) (Ferraro et al., 2010; Jones and Wagers, 2008; Scadden, 2006). Such cells may be stem cell progenies but are usually stromal or non-stromal cells that do not belong to the stem cell lineage. However, for some researchers and in some tissues, the concept of the stem cell niche is just a "widely accepted metaphor" (Lander et al., 2012).

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In addition to *in situ* identification of the adult stem cell, uncontestable demonstration of a niche requires to specifically pinpoint their distribution within the normal tissue and to demonstrate the repopulation of the niche by new stem cells after depletion. The flawless definition of such a special local microenvironment has been established in only a few cases, especially in invertebrates (Morrison et al., 2008).

In mammalian organisms, stem cell niches have been scouted and further analyzed in a variety of adult organs. A large amount of evidence has been built up to define various tissue-specific stem cell niches in terms of architecture, essential cellular and molecular components and interactions, and their influence on stem and progenitor cell biology (Ferraro et al., 2010; Nakanishi and Bhatia, 2017).

### 1.1. Niche design

There is considerable variation in the architecture of an adult stem cell niche, not only in terms of niche design. Depending on the ***distribution of the corresponding stem cells***, some niches harbor individual stem cells (e.g., skeletal muscle), others small clusters (e.g., the bulge of hair follicles, neural stem cell niche, or cardiac niche), or even surface spreading stem cells (e.g., basal layer of the interfollicular epithelium) (Pasut et al., 2013). Based on the ***interaction between stem cell niche elements*** (Morrison et al., 2008), two types of niche models can be defined, stromal cell niches and stroma-free niches.

In stromal cell niches, stromal cells direct niche morphogenesis and establish direct contacts with resident stem cells. Such niches do not depend on stem cell inhabitance and retain their morphology after stem cell depletion. The best characterized example of this category is the HSC niche (Crane et al., 2017; Szade et al., 2017). In contrast, one of the poorest characterized, somehow elusive niches, despite the potential impact on cell-based therapies, is the cardiac stem cell niche (Leri et al., 2014).

Stroma-free niches have no specialized interacting stromal cells, but may have direct contact with a region of the basement membrane. In such cases, the stem cell(s) interact(s) with cells that belong to the same lineage, which may be either terminally differentiated cells, as in the case of skeletal muscle (Bentzinger et al., 2013; Dumont et al., 2015), or their own progenies as in the case of brain (Conover and Todd, 2017) and epithelial niches. The best example of this category is represented by the epidermal stem cell niche (Gonzales and Fuchs, 2017).

### 1.2. Communication within the niche

Within the stem cell niche, stem cell behavior and fate are regulated either by soluble molecules or by direct molecular contacts. The influence and sources of soluble molecules have been extensively discussed and reviewed (Bentzinger et al., 2010; Lee et al., 2017). There are two types of specific direct molecular contacts: cell-to-cell and cell-to-matrix interaction. Both types of cell contacts are required to retain the stem cells in their niches and, consequently, are responsible for maintaining normal stem cell behavior (i.e., quiescence, retention, activation, proliferation, and mobilization) (Marthiens et al., 2010).

The expression of cell-to-matrix or cell-to-cell adhesion molecules is the fundamental mechanism regulating niche occupancy (Jin et al., 2008; Tanentzapf et al., 2007) and stem cell mobilization upon activation (Wilson et al., 2004). However, some of the regulatory mechanisms governing adhesion molecule expression have specific consequences depending on the tissue, likely reflecting the structural difference between stromal and non-stromal stem cell niches (Benitah et al., 2005; Marthiens et al., 2010; Wilson et al., 2004). Moreover, the altered dynamics of cell-to-cell interactions within a niche may be responsible for niche decline in aging or some diseases (Carlson and Conboy, 2007; Thorley et al., 2015).

Though the adhesion molecules within a niche perimeter have been discussed extensively and reviewed over the last decade (Chen et al., 2013; Ellis and Tanentzapf, 2010; Gattazzo et al., 2014; Xi, 2009), the distribution and identity of intercellular molecular contacts for adhesion and adhesion-mediated signaling within stromal and non-stromal stem cell niches have scarcely been approached.

The identities of most cells that populate the niche, including stem cells, remain elusive. In most cases, the accepted criteria for precise cellular identification have been determined by *in vitro* studies and require specific markers, some of which have a nuclear expression, making their exact *in situ* location unclear. In many cases, stem cell phenotypic heterogeneity could also lead to underestimating the tissue distribution and *in vivo* interactions. Even though mouse stem cells have been extensively characterized, the technical limitations of studying human biology *in vivo* limit the translational efforts (Rosen et al., 2014; Yu, 2011).

A careful dissection of the interactions between stem cells and their cellular companions within and outside the niche is important for the development of future therapies for both age-related and tissue-specific diseases. The aim of this review is to bring together relevant data on cell-to-cell interactions within representative niches that could highlight common elements or significant differences that may offer a new perspective for stem cell biology and manipulation.

## 2. Stromal niche

### 2.1. The adult hematopoietic stem cell (HSC) niche

In 1959, hematopoietic cells from bone marrow (BM) were the first stem cells successfully used in regenerative (cellular) therapy in humans (Thomas et al., 1959). HSC studies have led to advances in understanding histocompatibility mechanisms, identification of the main biological features of stem cells (quiescence, self-renewal, and differentiation) and their contribution to tissue homeostasis, as well as the establishment of the stem cell niche concept. In 1978, Schofield coined the term “stem cell niche”, defined as “the cellular environment that retains the stem cell” (Schofield, 1978); this assertion underscores the perceived importance of immediate stem cell vicinity in ensuring proper functioning of this cellular compartment.

#### 2.1.1. Niche architecture

The current view of human BM niches has been guided by recent studies in transgenic mice that used reporter genes to highlight various stromal cell populations or were subjected to conditional deletion of specific non-hematopoietic cell populations that express important regulatory signaling molecules (Crane et al., 2017). In the latter animal models, the effect of the ablation of specific cell types on overall hematopoiesis parameters can be estimated accurately. Previously, precise visualization of HSCs within their natural habitat was impaired by the very low numbers of long-term repopulating stem cells and several markers needing to be assessed simultaneously in order to identify them (Szade et al., 2017).

Adult mouse BM appears to have at least three distinct niches, recently reviewed by Crane et al. (2017), that are important in HSC maintenance and differentiation towards the various mature blood cell types: perisinusoidal, periarteriolar, and endosteal. Chronologically, the endosteal niche was the first compartment thought to harbor quiescent, long-time repopulating HSCs (Gong, 1978). However, recent data suggest that only a subset of early lymphoid progenitor cells depends on this particular microenvironment. Osteoblasts are the main cellular component of the endosteal niche, and it seems that their presence and CXCL12 production are not required for HSC maintenance (Ding and Morrison, 2013). The periarteriolar and perisinusoidal niches are both located around blood vessels and contain some common cell populations, including endothelial and stromal cells (pericytes and potentially other types). In addition to differences in physical location, the two niches also have stromal cell populations that differentially express leptin receptor (LEPR), neural/glial antigen 2 (NG2), and nestin (Crane