

Review

Extracellular matrix: A dynamic microenvironment for stem cell niche[☆]Francesca Gattazzo¹, Anna Urciuolo^{*,1}, Paolo Bonaldo^{*}

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ABSTRACT

Background: Extracellular matrix (ECM) is a dynamic and complex environment characterized by biophysical, mechanical and biochemical properties specific for each tissue and able to regulate cell behavior. Stem cells have a key role in the maintenance and regeneration of tissues and they are located in a specific microenvironment, defined as niche.

Scope of review: We overview the progresses that have been made in elucidating stem cell niches and discuss the mechanisms by which ECM affects stem cell behavior. We also summarize the current tools and experimental models for studying ECM–stem cell interactions.

Major conclusions: ECM represents an essential player in stem cell niche, since it can directly or indirectly modulate the maintenance, proliferation, self-renewal and differentiation of stem cells. Several ECM molecules play regulatory functions for different types of stem cells, and based on its molecular composition the ECM can be deposited and finely tuned for providing the most appropriate niche for stem cells in the various tissues. Engineered biomaterials able to mimic the *in vivo* characteristics of stem cell niche provide suitable *in vitro* tools for dissecting the different roles exerted by the ECM and its molecular components on stem cell behavior.

General significance: ECM is a key component of stem cell niches and is involved in various aspects of stem cell behavior, thus having a major impact on tissue homeostasis and regeneration under physiological and pathological conditions. This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

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1. Introduction

All cell types are in contact with the ECM, a complex and dynamic network of macromolecules with different physical and biochemical properties [1,2]. Although the ECM was once considered an inert supportive scaffold, the fundamental role of ECM in key aspects of cell biology became increasingly evident in last two decades. By either direct or indirect action, ECM regulates cell behavior and plays essential roles during development [3]. Indeed, the ECM is a dynamic and versatile compartment and by modulating the production, degradation, and remodeling of its components, it can support organ development, function and repairing [4,5]. On the basis of the relative amounts and organization of the different ECM components, this molecular scaffold

is peculiar for each tissue and reflects the specific functions required for the cells present in that tissue. Moreover, the structural, biochemical and functional diversity of ECM components confers well-defined physical, biochemical and biomechanical properties to the ECM. Physical properties such as rigidity, porosity, topography and insolubility are able to influence various anchorage-related biological functions, like cell division, tissue polarity and cell migration [6]. From a biochemical point of view, the ECM displays both direct and indirect signaling properties, since it can act directly by binding cell surface receptors or by non-canonical growth factor presentation [3]. A key concept in ECM biology regards how the biomechanical properties of the ECM can influence cell behavior. Indeed, ECM stiffness is an essential property by which cells sense the external forces and respond to the environment in an appropriate manner, a process known as mechanotransduction [7–13] (Fig. 1). Importantly, all these characteristics and properties are strongly interconnected and one can influence the others. This becomes even more evident when considering that cell–ECM connection is a reciprocal interaction in which cells continually remodel the ECM present in their microenvironment, and these dynamic modifications of the ECM direct cell behavior [3]. It is therefore not surprising that alterations in a specific ECM component or in a player of its regulation can have a remarkable impact on the biochemical, biomechanical and physical properties of the ECM, leading to disorganized network and ultimately failure of organ homeostasis and function.

Stem cells are defined by three essential features, as they are *i) undifferentiated cells* able to give rise both to *ii) differentiated daughter cells*

Abbreviations: ECM, extracellular matrix; CBCs, crypt base columnar cells; HFSCs, hair follicle stem cells; HSCs, hematopoietic stem cells; ISCs, intestinal stem cells; NSCs, neural stem cells; SGZ, subgranular zone; SVZ, subventricular zone

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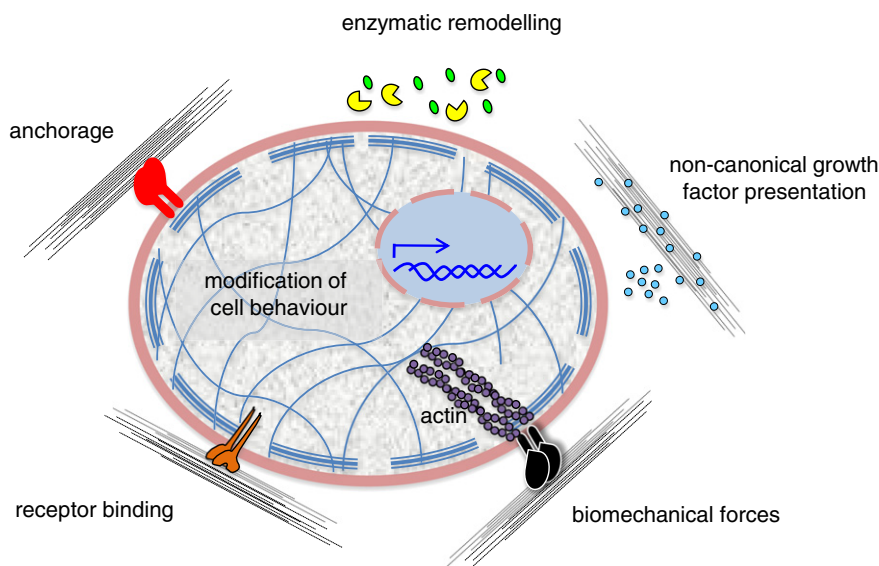


Fig. 1. Regulation of cell behavior by ECM. The effects exerted on cells by ECM can be differently mediated. The ECM can directly bind different types of cell surface receptors or co-receptors (red, orange, black), thus mediating cell anchorage and regulating several pathways involved in intracellular signaling and mechanotransduction. Moreover, the ECM can act by non-canonical growth factor (cyan) presentation and be remodeled by the action of enzymes (yellow pie), which can release functional fragments (green).

and *iii*) cells that retain their stemness by *self-renewal* [14]. Embryonic and adult stem cells have different capabilities to produce differentiated cells, a property known as *potency*. Cells present in the early embryo until the blastocyst stage are pluripotent, since they produce all differentiated cell types present in the body, whereas fetal and adult stem cells are able to produce multiple cell lineages (multipotent) or a single differentiated cell lineage (unipotent). In adult tissues, stem cells are usually in a quiescent state and in order to undergo self-renewal they have to enter the cell cycle, divide and generate a progeny of undifferentiated cells [15,16]. With this mechanism, the stem cell pool is maintained and the long-term homeostasis and regeneration of tissues can be preserved throughout the entire lifespan [17]. The choice of a stem cell to undergo self-renewal is carried out by two cell division mechanisms, which fulfill two different requests by the tissue [18]: *i*) *asymmetric* self-renewal, in which each stem cell divides into one stem and one differentiated cell, allows maintaining a constant number of stem cells, which is generally sufficient under physiological conditions; *ii*) *symmetric* self-renewal, in which each stem cell originates two daughter stem cells, leads to an expansion of the stem cell pool, a condition required after tissue injury or in diseased conditions causing loss of differentiated cells [19]. In the asymmetric cell division, the mitotic process leads to polarization and asymmetric segregation of components essential for the cell fate determination so that, once cell division is completed, one daughter cell has received RNAs, proteins and other molecules that maintain the undifferentiated program, whereas the other cell receives lineage commitment factors. In the symmetric cell division, the two daughter cells receive the same factors and the decision for commitment and differentiation is not linked to mitosis, rather it is a later event that can involve the newly formed cells [17]. Symmetric or asymmetric divisions are not mutually exclusive, and a mixture of these two 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 by injury or disease [19].

Stem cells reside in a dynamic, specialized microenvironment, denoted as '*niche*', which provides extracellular cues to allow stem cell survival

and identity. Moreover, the niche dynamically regulates stem cell behavior, maintaining a balance between quiescence, self-renewal and differentiation [20,21]. Despite their high potential to proliferate, the niche maintains stem cells in a quiescent and low metabolic state to prevent stem cell exhaustion [22]. Moreover, the niche is thought to protect stem cells from the accumulation of gene mutations that may lead to their malignant transformation into cancer cells [23]. Increasing evidence indicates that deregulation of the stem cell niche plays a key pathogenic role in a number of diseases associated with tissue degeneration, aging and tumorigenesis [24]. Both quiescent and active stem cell subpopulations coexist in several tissues, in separate yet adjoining locations [15,23]. In these niches, the precise regulation of the balance between symmetric and asymmetric divisions is critical for maintaining proper stem cell number and for fulfilling the needs for differentiated cells within the surrounding tissue [20]. The ability of a stem cell to seed in its niche represents one of the most important features of the niche itself, and the proper binding between stem cells and their niche is essential to maintain the stem cell pool for long-term self-renewal. Thus, the niche establishes a sort of crosstalk between the state and necessity of the tissue and the proper functioning of the stem cell pool [25,26]. Since its first definition originally proposed in 1978 for the hematopoietic microenvironment [27], the concept of the niche has increased in complexity (Fig. 2). Niches are highly specialized for each type of stem cell, with a defined anatomical localization, and they are composed by stem cells and by supportive stromal cells (which interact each other through cell surface receptors, gap junctions and soluble factors), together with the ECM in which they are located. Moreover, blood vessels carry systemic signals and provide a conduit for the recruitment of inflammatory and other circulating cells into the niche, whereas neural inputs transmit distant physiological cues to the stem cell microenvironment. The diverse and dynamic composition of the ECM provides controlled biochemical, physical, structural, and mechanical properties to the different niches. In addition, secreted or cell surface factors, signaling cascades and gradients, as well as physical factors, such as shear stress, oxygen tension and temperature, contribute to control stem cell behavior in a well-orchestrated manner [25,26]. Not only the niche components influence stem cell behavior, but also the interactions between stem cells and their niche are reciprocal, since stem cells are able to remodel the niche and secrete ECM components in response to the signals they receive from it [28–30].

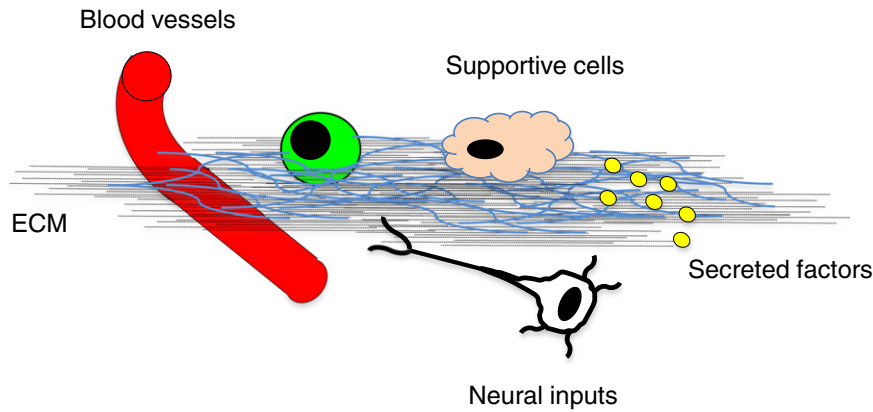


Fig. 2. Players in stem cell niche. The stem cell niche is a specialized and dynamic microenvironment in which a number of inputs regulate stem cell (green) behavior. These include signals departing from blood vessels, neural and supportive cells, as well as secreted factors and ECM components.

In this review, we will discuss the role of the niche in stem cell homeostasis, highlighting the functions of the ECM in determining niche properties. We focus on how ECM is able to mediate its effects on stem cells, starting from describing the players involved in ECM–stem cell interaction and the role of ECM in non-canonical growth factor presentation, and then examining the role of mechanotransduction and stiffness on cell fate determination. We also summarize the tools used for investigating ECM–stem cell interaction, discuss the properties of engineered niches, and conclude by recapitulating the current knowledge on specific stem cell niches.

2. Role of ECM in stem cell niche

As a constitutive part of the niche, ECM components are key players of the niche instructive power. These extracellular macromolecules, by their assembly and three-dimensional organization, supply a microenvironment in which the signals deriving from cell–ECM interaction, as well as soluble and ECM-bound factors, are integrated in a functional manner to permit the maintenance of stem cell homeostasis [31–34]. An *in vivo* evidence supporting the relevance of ECM in stem cell behavior is provided by the reduced ability of altered or aged niches in maintaining stem cell properties [30]. Experiments performed with decellularized tissues, in which the ECM is preserved, represent a further and direct demonstration of the primary role of ECM in the regulation of stem cell properties. These studies demonstrated that natural ECM scaffolds, derived from decellularized tissues, guide stem cell differentiation into the cell types residing in the tissue from which the ECM was derived [35]. On the basis of these properties, decellularized organs have been used in tissue engineering and for developing cell therapy approaches [36,37].

2.1. ECM–stem cell interaction

Interactions between ECM and stem cells can be directly mediated by a number of cell receptors, including integrins and other receptors. Despite the wide range of putative receptors involved in ECM–stem cell communication, only relatively few studies were focused on the role of non-integrin receptors, as for CD44, which was found to play an important role in the homing of hematopoietic stem cells (HSCs) during transplantation [38], and for Robo4, an axon guidance receptor which was shown to play a role in HSC adhesion to the niche during competitive repopulation assays [39]. On the other hand, an increasing number of studies demonstrated that integrins are key receptors involved in ECM–stem cell interactions and in the adhesion, anchorage and homing of stem cells. Integrins represent a large family of heterodimeric transmembrane receptors that connect the extracellular environment to the intracellular cytoskeleton, thus mediating cell migration, proliferation, survival and differentiation [40]. Different types of

integrins are involved in the direct binding to a number of ECM components or to other cell surface adhesion molecules and receptors [41–43]. Integrins can directly activate downstream signaling via focal adhesion kinase (FAK) and phosphoinositide 3-kinase (PI3K), thus regulating the self-renewal and proliferation of a large number of different stem cells [6, 40, 44]. Follicular stem cells of *Drosophila* ovary require integrin-mediated interaction for their anchorage to the niche and for their proper self-renewal and asymmetric cell division [45]. The $\alpha 6 \beta 1$ integrin, which binds the ECM protein laminin, is essential to home spermatogonial stem cells in the testicular niche [46], and is required for the adhesion of neural stem cells (NSCs) to their vascular niche [47]. The $\alpha 9$ integrin chain, which binds the ECM protein tenascin-C, plays a role in HSC proliferation [48] and in the NSC niche [49]. Moreover, the $\alpha 4$, $\alpha 6$, $\alpha 9$ and $\beta 1$ integrin chains play essential roles in homing HSCs to the bone marrow niche of irradiated recipient mice [50–53]. In addition, also $\alpha v \beta 3$ integrin regulates HSC homing and proliferation and its expression is mediated by the cytokine ligand thrombopoietin [54–56]. In the hair follicle, bulge stem cells produce the ECM protein nephronectin, which by interacting with the $\alpha 8 \beta 1$ integrin receptor present on the arrector pili muscle maintains the correct position and function of hair follicle stem cells (HFSCs) [57]. In the skeletal muscle, muscle stem cells (also known as satellite cells) interact on one side of their niche with the basal lamina through $\alpha 7 \beta 1$ integrin, and on the other side with myofiber plasma membrane through M-cadherin [58]. Furthermore, $\beta 1$ integrins were found to be essential in preserving the pool of different types of stem cells, by controlling the balance between symmetric and asymmetric divisions (like in skin and brain), as well as stem cell self-renewal and differentiation [59–62]. Since integrins can also regulate signaling pathways in response to growth factors and cytokines, such as IL-3 and TGF- β [40,63–66], and conversely signaling pathways can regulate integrin expression [43], the specific activities of these ECM receptors need to be set within each niche for a particular type of stem cell. Some examples of the interplay between integrins and other signaling molecules were demonstrated in NSCs and in mammary stem cells, where $\beta 1$ integrins were shown to regulate self-renewal and differentiation by controlling the activity of Notch and of EGF receptor [67,68]. Moreover, $\beta 1$ integrins were also found to be essential in regulating the proliferation of intestinal stem cells (ISCs), by mediating Hedgehog signaling [69].

2.2. Non-canonical growth factor presentation

Besides its ability to directly interact with stem cells, the ECM is also able to regulate stem cell activity by non-canonical growth factor presentation. Indeed, several ECM components are able to avidly bind growth factors, regulating their local availability and establishing a biochemical gradient [3]. On the one hand, the ECM can function as reservoir of growth factors, by making them insoluble, unavailable and not

bioactive. Examples of this action are represented by fibronectin, vitronectin, collagens and proteoglycans, which bind FGFs, HGFs, VEGFs, BMPs and TGF- β . On the other hand, proteins and proteoglycans of the ECM can function as distributors of growth factors following the action of enzymes, such as metalloproteinases, which induce the remodeling of ECM components and permit the release of factors that were otherwise in an insoluble state [3]. One example of the non-canonical growth factor presentation exerted by the ECM in the niche regards NSCs. Indeed, the ECM that composes the neural fractones was found to promote growth factor activity in the NSC niche by capturing FGF-2 from the milieu, thus favoring NSC function [70,71]. The same happens for the regulation of muscle satellite cells, where a number of secreted growth factors are bound to the proteoglycan components of the basal lamina or to the surface of satellite cells where they can be locally sequestered in an inactive zymogen form or presented in an active signaling state [18]. Thus, the action of ECM as 'dispenser on demand' of soluble biofactors well represents one of the most important features of the ECM, its dynamism.

3. Biophysical properties of the ECM: mechanotransduction, stiffness and cell fate determination

A growing body of evidence in ECM biology points at biophysical properties of the ECM as an important determinant of stem cell behavior. Indeed, every cell in its anatomical localization has to balance the external forces dictated by the mechanical properties of its environment, that results from the compression exerted by neighboring cells as well as the stiffness of the surrounding ECM. To do this, cells regulate their cytoskeleton tension, generating internal forces that are transmitted to the environment by adhesion sites [72]. The focal adhesion complexes, which include integrins, adaptors and signaling proteins, physically link the actomyosin cytoskeleton with the ECM. Together with cytoskeleton, nuclear matrix, nuclear envelope and chromatin, the focal adhesion complexes constitute a complex mechanosensing machinery that determines how cells react to forces generated from the ECM [13]. Therefore, mechanical forces are exerted on and from each single cell, and this interplay between cells and microenvironment generates an isometric tension within the cytoskeleton that allows the maintenance of cell shape and the dynamic response to the external forces, which in the end leads to the fine regulation of cell behavior [11,72,73]. The overall cellular response to mechanical stimuli is defined as mechanotransduction. Among a number of mechanotransduction pathways that were proposed (including Ras/MAPK, PI3K/Akt, RhoA/ROCK, Wnt/ β -catenin, and TGF- β pathways), the YAP/TAZ transcriptional factors recently emerged as downstream key mediators of the biological effects of ECM elasticity, cell geometry and cytoskeletal organization [72,74,75].

It is a matter of fact that stem cell behavior is dependent on tissue stiffness, which is in part regulated by ECM organization and composition [11,13], and that tissue elasticity is altered during aging, disease and injury [18,76]. The stiffness of the extracellular microenvironment, mainly expressed by the elastic modulus (or Young's modulus), is several orders of magnitude lower than that sensed by cells cultured onto a plastic dish or glass. Because of the difficulties in manipulating tissue stiffness *in vivo*, studies on the role of elasticity in regulating stem cell behavior were started together with the development of *in vitro* technologies able to mimic tissue elasticity (discussed in detail in the next paragraph). Notably, a recent study demonstrated that subtle *in vivo* modifications of muscle stiffness, by means of fibroblast-mediated collagen VI deposition, are able to affect muscle satellite cell self-renewal and maintenance [77]. Moreover, substrate elasticity was found to regulate muscle satellite cell self-renewal in culture [77,78]. A number of studies demonstrated that matrices characterized by a stiffness similar to that found in the brain drive cultured stem cells into the neurogenic lineage [79]. Notably, when human mesenchymal stem cells are cultured on ECMs characterized by stiffness values that mimic the elastic

moduli of brain, muscle or bone, they start expressing organ-specific transcription factors and undergo tissue-specific cell fate switches into neurons, myoblasts and osteoblasts, respectively [80]. Adult NSCs cultured on hydrogel containing fibronectin show a maximal neuronal differentiation potential when the stiffness of the biomaterials corresponds to that displayed by brain tissue, whereas stiffer gels promote their differentiation into glial cells [81]. The relevance of ECM and its biomechanical properties for *in vivo* NSC behavior was confirmed by the finding that there are stiffness gradients in the hippocampus. Moreover, in the presence of glial scars and brain tumors, as well as in aging, the mechanical properties change together with the behavior of neurons, NSCs and glioblastoma cells [76]. Human mesenchymal stem cells cultured on hydrogel characterized by an elastic modulus comparable to bone marrow increase their ability to self-renew and maintain multipotency, compared to mesenchymal stem cells grown on stiffer substrates [82]. The osteogenic differentiation of rat mesenchymal stem cells is strongly regulated by substrate stiffness and by the ECM macromolecules pre-adsorbed onto the biomaterials [83]. An additional example of cell behavior regulated by mechanical stiffness is cardiomyocyte commitment. These cells have been shown to correctly differentiate only on matrices that recapitulate the mechanical properties of developing cardiac microenvironment, while they are not able to develop spontaneous beating when grown on structures that mirror the property of a fibrotic scar [84]. Despite a large number of literature data pointing at substrate stiffness as an important feature in regulating stem cell fate, a recent work suggested that cells can sense ECM tethering, rather than the overall stiffness of the material on which they are located [85]. The ability of stem cells to respond to the stiffness of the collagen fibers themselves opens new insights about the role of ECM mechanical properties on the stem cell responses within tissues and niches.

4. Tools for investigating ECM–stem cell interaction and engineered stem cell niches

Ideally, the best way to investigate the function of specific ECM components in stem cell niches should be done by *in vivo* studies, and some recent works demonstrated the role of definite ECM components in regulating the *in vivo* activity of stem cells [77,86]. However, the complexity of the niche makes these studies quite challenging and difficult. Moreover, it should be considered that the lack or a defective function of one specific ECM component may not directly affect stem cell behavior, as on the one hand it may generate side effects acting indirectly on stem cells and on the other hand such effects could be masked by compensatory mechanisms. To overcome such difficulties, scientists have started developing *in vitro* engineered stem cell niches, with the aim to mimic the *in vivo* niche more closely than traditional cell culture methods. Currently, these tools are considered the best choice for investigating ECM–stem cell interactions *in vitro*, since they can not only deconstruct the effects of specific ECM molecules on the single-cell level but also reproduce the complexity of the niche environment. Those bioengineering tools include synthesizing novel biomaterials for stem cell culture, fabricating scaffolds in three dimensions with microscale or nanoscale topography, micropatterning ECM in two dimensions, and performing high-throughput ECM microarrays [32] (Fig. 3). Together with the contribution of sophisticated analysis methods and with modeling approach, these tools allow us to increase our knowledge on stem cell physiology [87]. As discussed above, one mechanism by which the ECM niche influences stem cell fate is through the realization of a bulk stiffness [88]. Hydrogels are a class of materials with high water content, similar to the ECM [89]. The stickiness of these polymers can be chemically tuned and used to reproduce the stiffness of healthy and pathological tissue and thus control differentiation and self-renewal of stem cells [77,78,80,81,90]. Importantly, in the *in vivo* conditions stem cells are subjected to gradients of stiffness depending on the ECM present in the niche, and such gradient can be recreated by hybrid

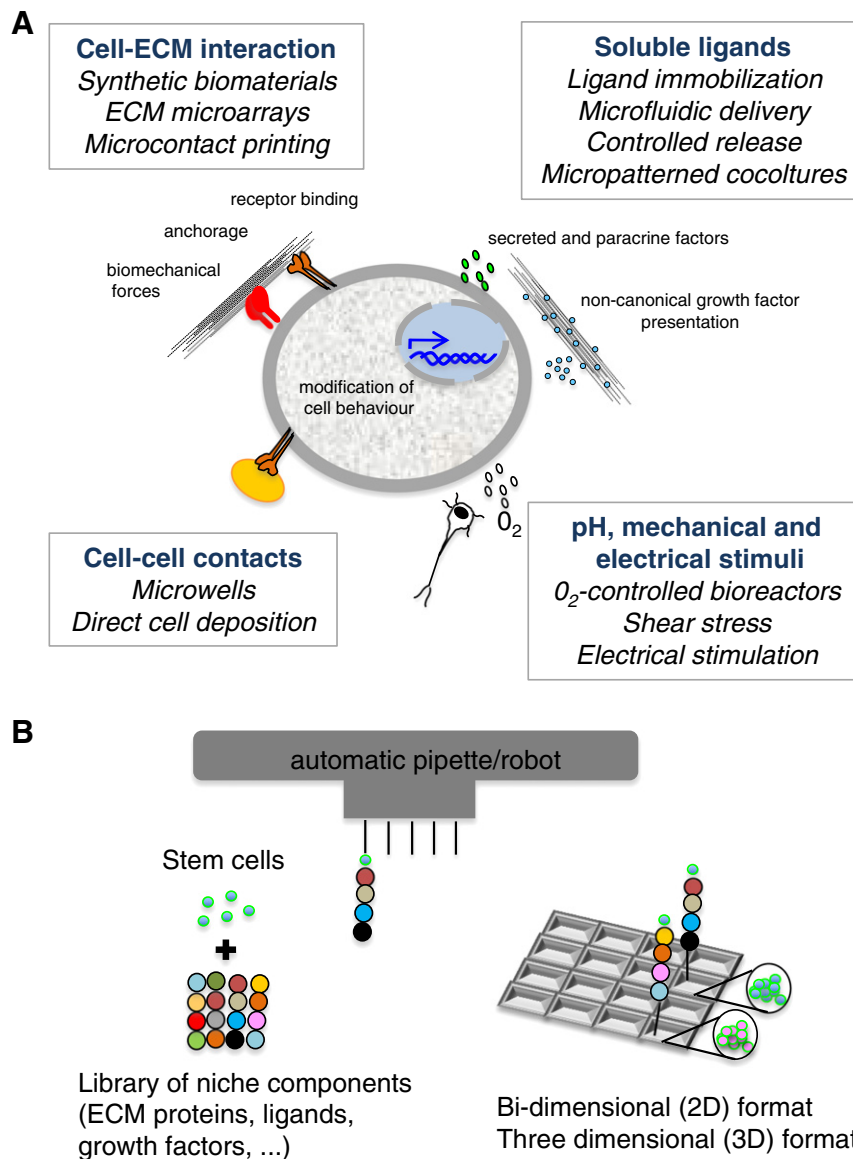


Fig. 3. Strategies for engineering stem cell niches. (A) Schematic representation of the engineering techniques used to reproduce the chemical, physical and mechanical microenvironment of stem cell niche. (B) Schematic diagram of high-throughput ECM microarrays. Hundreds of thousands of printed artificial ECM niches can be created in one single experiment by the use of automatic pipettes that mix together stem cells and different combinations of niche components.

hydrogels [91]. High-throughput ECM microarrays are used to screen the role of single ECM components, or a combination of them, in stem cell niche. This approach allows the screening of cell–ECM interactions with greater efficiency compared to conventional coating of a typical microplate covered by a biopolymer [32]. Automatic pipetting allows one to mix together chosen stem cells, ECM and soluble niche components in nanoliter volumes, and dispense the mixture onto a substrate, thus generating spots with a wide range of defined properties; up to one thousand printed artificial niches can be then analyzed in a single experiment [92]. Now such technologies can be also applied to three-dimensional (3D) formats [93]. Such high-throughput assays have begun to be used for analyzing the effects that ECM molecules and regulatory factors, or combination of them, exert on stem cell self-renewal and differentiation [94–96]. For example, PEG hydrogel substrates were functionalized with integrins and Notch ligands, and their effects evaluated on the clonogenic potential of NSCs, thus allowing a better understanding of the molecular signals that control NSC fate [97].

Another useful approach to understand the effect of ECM on stem cells is the use of micropatterned islands. Through this technique, it is

possible to pattern ECM onto glass coverslip with defined shape and dimension and make cells selectively adhere in that region and not onto unpatterned glass. Those micropatterned islands can accommodate single cells and are used to study how specific shapes control the fate of stem cells. Epidermal stem cells cultured on the smallest islands are more likely to differentiate than cells with greater freedom to spread, showing an effect of cell shape on the decision to differentiate [98]. Differently, niche shape can modulate the differentiation program of mesenchymal stem cells, where cell spreading favors osteogenesis and cell rounding promotes adipogenesis [99]. With the same approach, it is possible to generate libraries with thousands of different topographies (circles, triangles, rectangles) and investigate their effect on stem cell behavior. For example, topographical cues can instruct mesenchymal stem cell fate and direct their differentiation toward the osteoblast lineage [100]. Applications for micropatterned islands include also the study of asymmetric division, by controlling the position of the axis of the cell division [101]. In addition, the same patterning approach can be used to study cell–cell interaction at single level [102]. Mesenchymal stem cell differentiation toward the osteogenic or

adipogenic fate is dependent on cell–cell contacts, whereas isolated cells are less prone to differentiate [103]. To better recapitulate the niche and the exposure to growth factors, scientists have realized

microfluidic systems reproducing the spatio-temporal influence of secreted factors on cells [104]. Moreover, since in the tissues these soluble factors are often bound to ECM, biomimicking approaches are used to

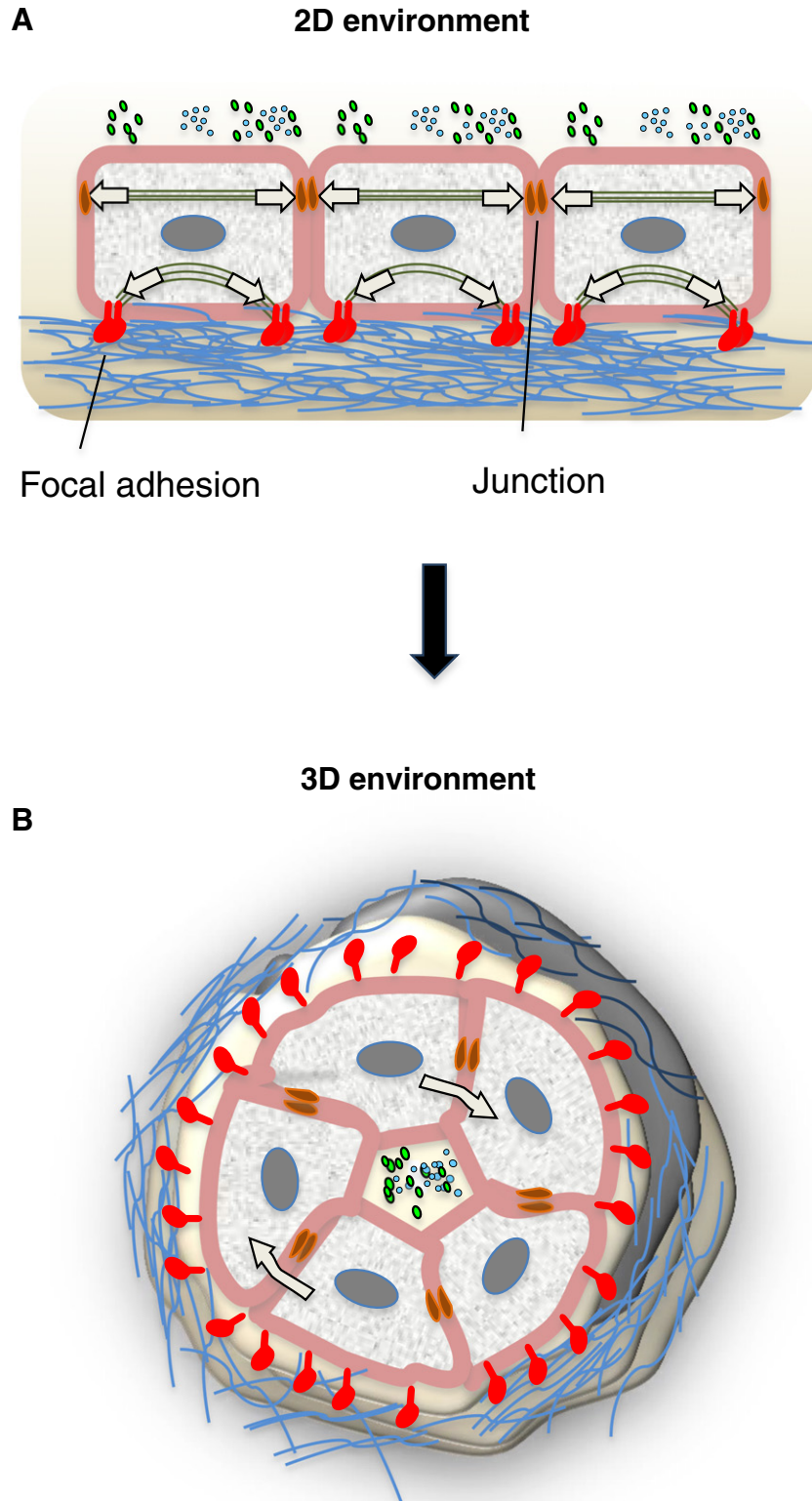


Fig. 4. 3D environment recapitulates *in vivo* niches. (A) Cells on a rigid planar surface organize focal adhesions and actin stress fibers at the basal surface of the cell and transfer contractile forces to their surface and to other cells. With their apical side, cells interface with secreted factors present in the medium, whereas with their basal side they interact with the ECM, which confers mechanical properties. (B) Inside a 3D microenvironment, the curvature and the softness of matrix materials limit the formation of actin stress fibers. Cells inside a 3D environment experience stress around the whole structure, both in planar and perpendicular directions to the cell basal surface. Secreted factors can be highly concentrated in the inner compartment. In addition, ECM displays a non-linear behavior and gradient of mechanical stiffness.

conjugate soluble factors to the surface of biomaterials and make them released by cell-mediated proteolysis or external physical stimulation [32].

Although bidimensional systems represent a helpful mean to analyze ECM–stem cell interplay *in vitro*, the great challenge is the recreation of 3D systems recapitulating the *in vivo* condition [105,106]. In fact, in a 3D environment cells naturally polarize with the basal compartment facing the gel, growth factors are highly concentrated compared to bidimensional systems, and cells sense the ECM rigidity and the transport of soluble components in a different way [107] (Fig. 4). With this aim, bioprinting approaches use the printing technology to deposit living cells alone or together with ECM components and soluble factors on a receiving solid or gel substrate. These technologies are able to create spatially defined gradients of immobilized biomolecules to control stem cell fate or can be patterned in a high-throughput manner to study stem cell behavior [108]. Alternatively, stem cells can directly be embedded inside hydrogels to recreate a 3D microenvironment [108,109]. Notably, for the study of ECM–stem cell interplay, “bioclick and bioclip reactions” into 3D culture systems can be used to covalently couple and selectively remove functional molecules from the ECM biomimetics, with a full spatial and temporal control, thus allowing to test how extracellular signals dynamically control cell behavior over time (the so-called four-dimensional biology) [110]. One representative example of the potentialities of stem cell niche engineering is the possibility to recreate *in vitro* 3D intestinal epithelial organoids, named “epithelial mini-guts”, from a single Lgr5-positive crypt base columnar cell (CBC) for periods greater than 1.5 years, with the use of ECM and specific growth factors [111]. This and other studies open the perspective to the four-dimensional stem cell biology, where manipulating stem cells through the fine-tuning of cellular interactions, pattern, shape, and size will allow to synthesize or de novo design mini-organs [112,113].

5. Composition and function of stem cell niches in different tissues

The complexity of the different niches rises from the necessity to protect the unique stem cell capabilities. Identifying and characterizing stem cell niches have been complicated by the fact that in most tissues stem cells are extremely rare and, in many cases, specific markers allowing the precise *in vivo* identification of a stem cell are lacking. Nonetheless, much progress has recently been made in identifying stem cell niches in several mammalian tissues, including the hematopoietic, epidermal, intestinal, muscular and neural stem cell compartments [24].

5.1. Hematopoietic stem cell niche

HSCs are multipotent progenitor cells that give rise to all types of mature blood cells [114], and are defined by their ability to self-renew and support long-term multi-lineage hematopoietic engraftment in lethally irradiated mice [115,116]. They reside along the endosteal surface of trabecular bone, in close proximity to both bone-forming osteoblasts and the endothelial cells that line blood vessels [117], and this anatomical localization represents their niche (Fig. 5A). The adult HSC niche consists of two anatomically distinctive cellular entities: *i*) the “endosteal niche”, populated by osteoblasts; and *ii*) the “vasculature niche”, located in the perivascular space. These two niches are proposed to be associated with the dormant and activated HSCs, respectively [118–120]. Despite being anatomically distinct, in the last year the concept of separated niches has been superseded. In fact, sophisticated three-dimensional imaging allowed revealing that there are intimate contacts between these two types of niche elements [121,122] and that HSCs can move among these niches quite readily and receive inputs from both of them simultaneously [123]. HSCs are anchored to the endosteal niche through tight cell–cell interactions, in particular thanks to N-cadherin. Overexpression of N-cadherin promotes quiescence and preserves HSC activity during serial bone marrow transplantation [124,125]. In this endosteal niche, osteoblasts have been shown to

influence HSC pool by regulating stem cell number [117,126], and to maintain HSC quiescence by releasing several signals, such as angiopoietin, thrombopoietin, and stromal cell-derived factor-1 [54,127], as well as HSC self-renewal via Notch activation [128]. On the other side, the vascular niche is located around small sinusoidal blood vessels associated with various stromal and neuronal elements, which regulate HSC differentiation and ultimately mobilization to the peripheral circulation [128,129]. Several studies demonstrated that a large number of cell types are active component of the HSC niche, including osteoclasts, stromal cells, bone marrow adipocytes, osteal macrophages (osteomacs), CXCL12-abundant reticular (CAR) cells, nestin-positive mesenchymal stem cells, sympathetic nerves including nestin-positive Schwann cells, and endothelial cells associated with leptin receptor-expressing perivascular stromal cells [129–133]. Moreover, it was recently found that also megakaryocytes can be considered as active components of the HSC niche [134,135]. HSC self-renewal and differentiation are regulated either through contact-dependent signals, such as VCAM-1 [136], or via soluble factors such as SCF [137]. Only recently several other factors, including calcium ions, oxygen tension and reactive oxygen species, were shown to be critical for proper HSC regulation and have been integrated into the concept of the bone marrow niche [123,138]. Despite the well-investigated cellular niche, the role of ECM components in the HSC niche has been poorly investigated. Collagen VI, collagen IV, fibronectin and tenascin-C represent some of the ECM proteins that are found in the bone marrow microenvironment [139–141]. In functional studies, collagen VI was shown to be a strong cytoadhesive substrate for various hematopoietic cell types, thus suggesting that this ECM component may play an important role within the bone marrow microenvironment [140]. In a recent work, it was demonstrated that tenascin-C is necessary for proper hematopoietic regeneration by promoting the *in vivo* and *in vitro* proliferation of hematopoietic stem and progenitor cells [48].

5.2. Hair follicle stem cell niche

HFSCs continually cycle to regenerate the hair follicle, but during wound healing they can also form the sebaceous glands and restore the epidermis [142,143]. Throughout hair formation, hair follicles undergo dynamic, synchronized cycles of growth (anagen), regression (catagen), and rest (telogen) [144,145]. During telogen, which can last for months, HFSCs are quiescent and reside within a specialized microenvironment called the bulge, surrounding the hair shaft produced in the previous cycle [146] (Fig. 5B). Throughout telogen, the underlying dermal papilla cells, a population of mesenchymal cells, act as a niche for regulating HFSC activation and are responsible for hair follicle formation and maintenance [142,147–149]. Importantly, the arrector pili muscle, a smooth muscle responsible for pulling the hair upright, is also a component of the hair follicle niche, connecting the bulge to the adjacent mesenchyme [57]. Several other non-epithelial cell types, including blood vessels, nerves, adipocytes and mesenchymal cells, participate to the control of HFSC activation and are active component of the dermal environment that surrounds the hair follicle [150–152]. Moreover, during the anagen phase, in the bulge HFSCs coordinately activate with melanocyte stem cells, needed for hair pigmentation [153,154]. At distinct stages of the hair cycle, HFSCs receive either inhibitory or activating signals from both the micro- and macro-environments to either remain quiescent or become proliferative [155]. Besides various cell types, also the ECM plays an important role in the HFSC niche. It was demonstrated that several genes encoding for ECM proteins, such as tenascin-C, collagen VI, collagen XVIII/endostatin, fibulin1 and SPARC, display higher expression levels in mouse bulge cells than in differentiated keratinocytes [20,156]. A seminal work showed that HFSCs in the bulge deposit nephronectin in the underlying basement membrane, thus regulating the adhesion to the bulge of mesenchymal cells expressing $\alpha 8\beta 1$ integrin. Interestingly, nephronectin null mice display fewer arrector pili muscles, and ablation of nephronectin or of $\alpha 8$ integrin

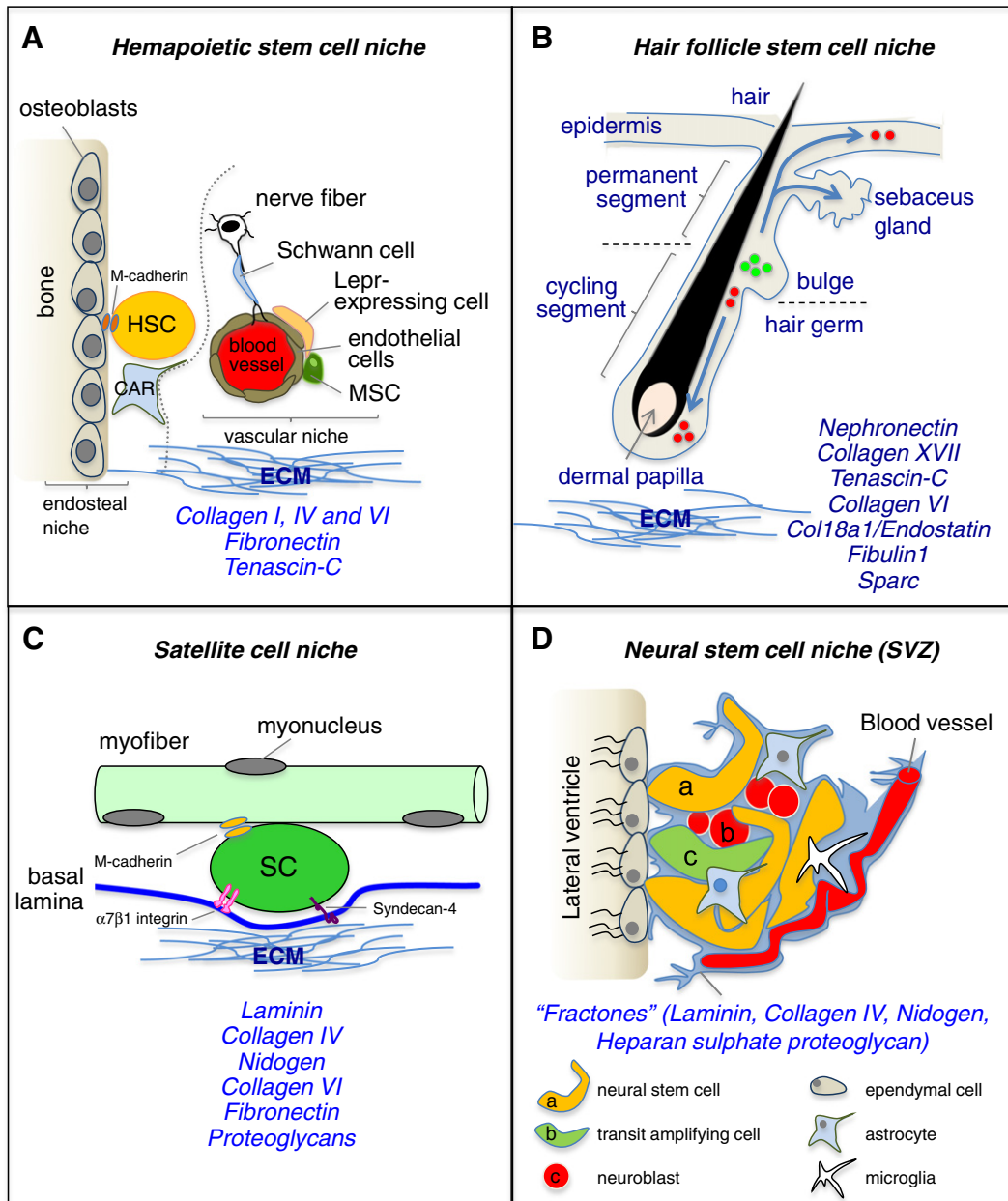


Fig. 5. Stem cell niches and their ECM. The diagrams show four different stem cell niches, together with their cellular and ECM components. ECM molecules playing major roles in the different niches are indicated. (A) HSC niche consists of two anatomically distinct (dotted line) cellular entities, the “endosteal niche”, populated mainly by osteoblasts, and the “vasculature niche”, located in the perivascular space. HSCs can move through those two niches and interact with ECM molecules. A variety of cells, including osteoblasts, Cxcl12-abundant reticular (CAR) cells, nestin-positive mesenchymal stem cells (MSC), Lepr-expressing perivascular cells, and endothelial cells, were shown to be active components of the niche. (B) Diagram of the hair follicle. Multipotent stem cells are located in the bulge, which lies in the outer root sheath just below the sebaceous gland, and contribute to the lineages of the hair follicle, sebaceous gland, and the epidermis (arrows). The ECM surrounds the dermal papilla, a cluster of specialized mesenchymal cells in the hair bulb. (C) In skeletal muscle, satellite cells reside in the niche between myofiber plasma membrane and basal lamina. The myofiber basal lamina is a network of ECM components, including collagen IV, laminin, collagen VI, fibronectin and proteoglycans, which facilitate satellite cell adhesion via binding to receptors such as $\alpha7\beta1$ integrin and syndecan-4. (D) In the adult brain, the SVZ niche is composed of three cell populations that lie immediately beneath a monolayer of ependymal cells lining the lateral ventricle and corresponding to the relatively quiescent NSCs (a), mitotically active transit amplifying cells (b), and neuroblasts (c). NSCs are intercalated into the ependymal layer and are also closely associated with the vasculature. NSCs within the SVZ are in contact with endothelial cells, microglia and astrocytes. NSCs are also in contact with fractones, structures rich in ECM molecules and continuous with the basal lamina of blood vessels.

affects the anchorage of arrector pili muscle to the bulge. These data led the authors to conclude that bulge stem cells create a smooth muscle cell niche via nephronectin expression, thus revealing a key functional role for a specific ECM component in HFSC niche [57]. HFSCs share their location with another skin stem cell population, the melanocyte stem cells, and it was shown that TGF- β signaling is one of the key niche factors regulating the maintenance of melanocyte stem cells [157]. In another study, it was shown that collagen XVII, a hemidesmosomal transmembrane collagen highly expressed by HFSCs, is required for the physical interaction between HFSCs and

melanocyte stem cell and maintains the self-renewal capacity of both stem cell populations. In agreement with this, *Col17a1* null mice display premature hair loss, with premature differentiation of HFSCs and melanocyte stem cells, thus demonstrating that this anchoring collagen is a critical component of the HFSC/melanocyte stem cell niche [153].

5.3. Intestinal crypt niche

The mammalian intestine is one of the tissues that renews most rapidly since its epithelium is constantly subjected to insults, such as

exposure to digestive enzymes and mechanical erosion. This renewal process requires a constant activation of stem cells located at the base of the crypts. The first identified ISCs were found to be located immediately above Paneth cells in the crypts, at an average position of four cells from the crypt base, and named label-retaining cells (LRC) or +4 cells [158]. Those cells are marked by the expression of *Bmi1* and are believed to generate distinct types of differentiated epithelial cells of the crypts and villi [159]. Lineage tracing studies allowed one to identify CBCs, a distinct population of ISCs interspersed between Paneth cells and marked by the expression of *Lgr5* [160]. These cells can self-renew continuously and produce transit-amplifying daughter cells that differentiate in all cell types of the small intestinal epithelium, such as enterocytes, goblet cells, enteroendocrine cells and Paneth cells [160,161]. Lineage tracing experiments have shown that ISCs, rather than dividing asymmetrically to generate daughter cells of different fates, divide symmetrically and adopt stem or transit-amplifying fates in a stochastic manner [162,163]. Nevertheless, the precise lineage and hierarchy of the two types of ISCs in the intestinal epithelium are still under debate [164–166]. Paneth cells are the main component of the ISC niche and release not only bactericidal products [167] but also EGF, TGF- α , Wnt3 and the Notch ligand *Dll4* [168]. The role of Paneth cells in ISC maintenance was confirmed by their *in vivo* genetic removal, resulting in the concomitant loss of CBCs [169]. The ISC niche comprises also other cell types such as enteric neurons, intraepithelial lymphocytes, smooth muscle cells of the muscularis mucosae, lymph and vascular endothelial cells, and a variety of bone-marrow derived stromal cells [170,171]. Among those cells, pericryptal myofibroblasts reside adjacent to ISCs and regulate their survival through Wnt signaling [170]. Intestinal homeostasis is tightly controlled by four well-characterized signaling pathways, namely Wnt, Notch, EGF and BMP [111]. In addition, the visceral musculature forms a regulatory niche for ISCs by producing several secreted factors that activate signaling pathway to promote maintenance and proliferation of ISCs [172]. The function of the niche in the intestinal crypt requires the presence of ECM molecules in the basement membrane and of humoral factors derived from mesenchymal stem cells and subepithelial myofibroblasts surrounding the epithelium and from epithelial cells proliferating within the crypt [173]. The importance of the basement membrane for ISCs was provided by *in vitro* experiments showing that, in the presence of appropriate ECM proteins, single *Lgr5*-positive cells are able to generate autonomously organoids similar to intestinal crypts [111,168]. ECM proteins and integrin receptors interact to keep ISCs within the niche, as the intestinal epithelium constantly undergoes physical compression and stretch enforced by the surrounding muscles [172]. Both positive and negative signals are finely tuned to regulate ISC behavior during tissue homeostasis and regeneration and protect them from dysfunction and disease [174,175].

5.4. Muscle satellite cell niche

In adult skeletal muscles, a population of muscle stem cells, also called satellite cells, is located on the surface of myofibers in close contact with the myofiber plasma membrane and beneath the basal lamina, and this well-defined anatomic localization represents their niche [176] (Fig. 5C). In physiological conditions, satellite cells are in quiescent state, but upon damage or following muscle exercise satellite cells become activated, thus leading to proliferation and terminal differentiation in order to regenerate the damaged myofibers. Satellite cells are able to fuse both with the existing damaged myofibers and with each other to form *de novo* myofibers. Once activated, a subset of satellite cells returns to the quiescent state in their original niche, thus providing the necessary replenishment for self-renewal [177]. Given their anatomical localization, satellite cells are exposed to an asymmetric distribution of niche components, with myofiber signals on their apical surface and basal lamina signals on their basal surface [58,178] (Fig. 5C). The myofiber basal lamina contains a network of ECM

components that include collagen IV, laminin, perlecan, nidogen, collagen VI, fibronectin and other proteoglycans and glycoproteins [179,180]. The location of satellite cells is often in the proximity of blood vessels, which release endocrine factors to regulate the homeostasis of myofibers and their associated myogenic progenitors [181]. Innervation also plays a critical role in muscle function, and in its absence myofibers become atrophic and the satellite cell pool decreases due to apoptosis and loss of proliferative capacity [182]. In addition, several other cell types, including fibroblasts, fibro-adipogenic progenitors, immune cells, endothelial cells and osteoblasts, contribute to the satellite cell niche via paracrine mechanisms [183–186]. Functional perturbations of skeletal muscle by chemical, electrical and mechanical stress also affect the muscle stem cell niche [187–190]. Interestingly, oxygen concentration was shown to modulate the function of satellite cells, by regulating their differentiation toward myogenic and adipogenic fates [191] or by controlling their quiescent state and self-renewal capability [192]. A number of other extrinsic factors are known to modulate satellite cells quiescence, activation, expansion, self-renewal and differentiation, including EGF, HGF, FGF, IGF, angiopoietin-1, nitric oxide, and members of the Wnt and TGF- β signaling molecules [18,193]. Similarly, myofibers generate numerous factors that, via secretion or presentation on the myofiber plasma membrane, influence satellite cell behavior, such as SDF-1, which binds the CXCR4 receptor present on satellite cells and activates a migratory response [194,195]. Additionally, satellite cells themselves express ligands that regulate their own cell fates through autocrine and juxtacrine signaling, such as Notch, the main regulator of their quiescence and self-renewal [196,197]. Satellite cells also express the Tie2 receptor, which interacts with the angiopoietin-1 ligand and contributes to the maintenance of quiescence [181].

The ECM plays a major role in skeletal muscles, not only by stabilizing myofiber during contraction and by transmitting forces along adjacent myofibers, but also by regulating myogenesis and muscle regeneration. Although the role of the ECM within muscle stem cell niche is still under investigation, recent studies have clearly demonstrated the influence of specific ECM components in regulating satellite cell activity and how their modifications alter the satellite cell function and the regenerative properties of skeletal muscle [77,86]. Reciprocally, also satellite cells transcribe in a regulated manner a number of genes coding for ECM proteins, such as versican, glypicans and fibrillin-2, based on the necessity to bind growth factors [198]. Satellite cells can dynamically remodel their niche based on their state of activation. For example, collagen VI, expressed not only by interstitial fibroblasts but also by quiescent satellite cells, represents a key component of muscle stem cell niche required for preserving satellite cell self-renewal and muscle regeneration, and its expression is down-regulated in activated satellite cells [77]. Conversely, activated satellite cells have a transient high-level expression of fibronectin, which in turn stimulates Wnt7a signaling through the Fzd7/Sdc4 co-receptor complex to induce the symmetric expansion of satellite cells [86]. At a more general level, increased ECM deposition and changes in ECM composition were shown to negatively affect satellite cell–myofiber interactions. Such global ECM changes may affect the muscle stem cell niche through multiple mechanisms, by changing the ability of the basal lamina to serve as a reservoir for ECM-bound growth factors, modifying satellite cell adhesion to the basal lamina, and altering the elastic properties of muscle tissue [18].

5.5. Neural stem cell niche

The brain contains two major locations for NSCs, corresponding to the subventricular zone (SVZ) of the lateral ventricles and to the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. NSCs in the SVZ generate neuroblasts that migrate to the olfactory bulb, where they generate interneurons, cells essential for the maintenance of the olfactory bulb. In contrast, neurons produced in the hippocampal SGZ integrate into the immediately adjacent granule cell layer,

where they are important for learning and memory. In addition, adult NSCs generate oligodendrocytes and astrocytes [199,200] (Fig. 5D). These two types of adult NSCs reside in different niches. In the SVZ, NSCs lie next to the ventricle, and possess processes that contact the cerebrospinal fluid and blood vessels. NSCs in the dentate radial gyrus are found deeper in the brain parenchyma, away from the walls of the ventricle and surrounded by neurons and other glial cells [201]. Both cell types have long processes that contact the vasculature. The intrinsic properties of NSCs present in the SGZ, such as self-renewal and multipotency, are still a matter of debate despite the fact that it was demonstrated that those cells can be isolated and cultured, generating self-renewing cells that can differentiate into neurons [202–205]. Several signaling molecules, such as Wnt, Notch, Shh and BMP, as well as growth and neurotrophic factors and neurotransmitters, were found to regulate hippocampal neurogenesis [206–210]. Other molecules implicated in axon guidance and synapse formation, such as Wnt7a, have been shown to regulate the early steps of neurogenesis, for example NSC self-renewal and the cell cycle progression of neural progenitors [211].

Independently from the niche they occupy, NSCs are closely associated with the vasculature and with basal lamina components. They reside adjacent to a variety of neighboring cells, including their own neuronal progeny, resident mature astrocytes and microglia, and endothelial and smooth muscle cells of blood vessels [200, 212, 213]. Among those, the perivascular niche has a key influence on progenitor cells, regulating their mobilization and differentiation [214]. Astrocytes were also found to regulate NSC self-renewal and differentiation [215,216]. Adding further complexity, the presence or absence of mature neurons can influence NSC fate through a feedback loop [200]. Additional factors, such as oxygen tension, regulate NSC activities; for example, mild hypoxia strongly enhances both self-renewal and neurogenic abilities [217]. Moreover, different physiological stimuli, such as learning, exposure to environmental enrichment, running and stress, can affect the rate of proliferation, differentiation, and survival of newborn neurons in the hippocampus [209]. Besides these different cells and factors, the ECM is also an important component of the neurogenic microenvironment. Both SVZ and SGZ niches express various ECM molecules, such as tenascin-C, netrins, laminin and various proteoglycans [49, 70, 218, 219]. In the SVZ, NSCs are in association with projections of the vascular basement membrane, referred to as fractones and composed mainly of laminin, collagen IV, nidogen and proteoglycans [70]. Those ECM molecules modulate NSC maintenance and differentiation, and influence the migration of their progeny [220]. One example is represented by heparan and chondroitin sulfate proteoglycans, which regulate the proliferation and neurogenic differentiation of NSCs, mainly by presenting growth factors, such as EGF and FGF, to NSC receptors [221,222]. Some ECM molecules, such as netrin-1, Slit-1 and Slit-2, are involved in providing the direction for migration of neurogenic precursors [223]. Another ECM protein, reelin, plays a key role in controlling the migration of neurogenic precursors to the target olfactory bulb [224], and this process is abolished in *reeler* mutant mice, where the protein is missing [225]. It was also shown that decreased reelin expression in the adult brain leads to defective brain plasticity, suggesting that reelin deficiency may be implicated in some brain disorders [226]. Other studies demonstrated that the tenascin family of ECM protein plays key roles in NSC niche. Tenascin-C is highly expressed in the SVZ, and tenascin-C deficient mice have altered numbers of NSCs due to defective response to FGF2 and BMP4, thus suggesting a role for this ECM molecule in the regulation of growth factor signaling in NSC niche [227]. Tenascin-R is expressed in the olfactory bulb, where it promotes the detachment and radial migration of neurogenic precursors. Interestingly, grafting of cells expressing tenascin-R into non-neurogenic regions redirects neurogenic precursors toward these regions, indicating that tenascin-R mediates the recruitment of neurogenic precursors in the adult forebrain [228].

6. Conclusions

In recent years, progressions in our knowledge of cell biology demonstrated that the study of cell behavior cannot exclude signals deriving from the environment in which cells are located. The key role of ECM in regulating cell behavior now represents a well-established fact and this concept is especially critical for stem cells, which are defined by a unique and specialized niche in which ECM represents one essential player. The instructive cue of ECM on stem cells is a result of a number of different characteristics of the extracellular environment, starting from its biophysical and biomechanical properties up to its biochemical activity. All these aspects are dynamically orchestrated *in vivo* in order to retain stem cell identity, guide cell fate determination and maintain stem cell pool. Further *in vivo* studies, together with the application of *in vitro* engineered niches, will allow us to increase our understanding about which specific components and characteristics of the ECM play a role in the behavior of stem cells in the different tissues. These studies will likely open promising new scenarios, as the more accurate mimicking of some essential features of *in vivo* niches using *in vitro* systems can not only improve the knowledge of stem cell biology, but also develop new application for cell-based therapies in humans [229]. The possibility to synthesize well-defined extracellular environments as scaffolds for implanting stem cells in the body represents a fascinating and promising venue for allowing the proper maintenance and activity of stem cells in a broad range of degenerating diseases [230,231].

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