

Current Understanding of the Pathways Involved in Adult Stem and Progenitor Cell Migration for Tissue Homeostasis and Repair

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Abstract With the advancements in the field of adult stem and progenitor cells grows the recognition that the motility of primitive cells is a pivotal aspect of their functionality. There is accumulating evidence that the recruitment of tissue-resident and circulating cells is critical for organ homeostasis and effective injury responses, whereas the pathobiology of degenerative diseases, neoplasm and aging, might be rooted in the altered ability of immature cells to migrate. Furthermore, understanding the biological machinery determining the translocation patterns of tissue progenitors is of great relevance for the emerging methodologies for cell-based therapies and regenerative medicine. The present article provides an overview of studies addressing the physiological significance and diverse modes of stem and progenitor cell trafficking in adult mammalian organs, discusses the major micro-environmental cues regulating cell migration, and describes the implementation of live imaging approaches for the exploration of stem cell movement in tissues and the factors dictating the motility of endogenous and transplanted cells with regenerative potential.

Keywords Adult stem cells · Progenitor cells · Cell migration · Cell motility · Live imaging

Introduction

Orchestrated movement of cells is fundamental for the organ development, postnatal growth and adequate performance at the different stages of adulthood. For many years, the complex pathways regulating cell migration in the physiology of adult organism and with various pathologies are subject matters of intense investigations [1–4], <https://www.cellmigration.org/science/>. Yet, the journey to uncover the mechanisms controlling the directional translocation of tissue-specific stem and progenitor cells and the importance of immature cell trafficking for organ homeostasis and repair is at the exciting beginning.

It is postulated that in order to preserve organ integrity, the adult tissue-specific primitive stem cells or their undifferentiated progeny [5] migrate to the sites of tissue repair, compensating for the “wear and tear” or supporting the wound healing [4, 6–9]. Consequently, along with the potency to generate cells of diverse lineages and capacity for self-renewal, cell motility is a vital property of stem and progenitor cells, which evidently changes with pathologies and aging. Hence, the knowledge of the pathways that guide the immature cell trafficking is essential for elucidating the origins and evolution of diseases in stem-cell regulated organs. Moreover, the targeted movement of transplanted cells from the sites of administration to the foci of injury is key for the success of cell-based regenerative treatments [10–12].

The research into the mechanisms of adult stem cell migration has evolved in the course of the past decade as a result of cumulative efforts to better understand the intricate nature of stem cell behavior and augment its function in therapeutic purposes. This review, dedicated to mammalian stem and progenitor cells, describes documented examples and biological relevance of the immature cell movement in adult organs, examines the implications of the alterations in stem cell

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motility, and summarizes the recognized features of the primitive cell environment that govern the migratory responses. Additionally, the use of live imaging is discussed as a compelling tool for the studies of stem cell migratory activity *in vitro* and *in vivo*.

Biological Significance of the Stem and Progenitor Cell Movement in Adult Tissues

The most studied manifestation of the adult mammalian stem cell migration is the trafficking of hematopoietic stem and progenitor cells between the bone marrow, blood circulation and peripheral organs (for comprehensive reviews on the hematopoietic stem cell trafficking, see [7, 13–20]). In adults, the primitive hematopoietic cells reside in specialized bone marrow niches (the concept of bone marrow niches was recently reviewed in [8, 21–24]). It is established that the immature cells of the hematopoietic system constantly emigrate from and return to the bone marrow [25–27]. For instance, the circadian rhythm creates cycles of the hematopoietic progenitor cell mobilization to the blood, with maximal cell release during the resting period [28–30], which presumably occurs in the absence of injury in purpose of homeostatic surveillance of peripheral tissues by stem cells. Furthermore, plethora of stresses, such as inflammation or damage to distant organs, significantly increases the numbers of circulating progenitors [18, 31, 32]. These emergency responses by undifferentiated hematopoietic cells have been observed after trauma and hemorrhagic shock [33], wounding of the liver [34, 35], stroke [36], and myocardial infarction [37, 38]. Remarkably, even following infusion into the bloodstream, the transplanted hematopoietic stem and progenitors exhibit tropism towards the host bone marrow and are capable of engrafting into the supporting niches. The astonishing migratory ability of immature hematopoietic cells is widely employed in everyday clinical practices for the bone marrow transplantation in patients with hematological malignancies, as well as novel therapies for regenerative medicine [39–42].

Another well-known process of the stem cell movement in adult organs involves stem cell emigration from the storage niches as a step in their differentiation program. For example, the intestinal epithelial stem cells are situated at or near the bottom of crypts formed by the convolution of the epithelial sheet, where stem cells proliferate and give rise to progenitor cells. While moving to ascend the crypt axis, the stem cell progeny divide and further mature, acquiring terminally differentiated phenotype (recently reviewed in [5, 43–46]). Multiple studies have demonstrated that proper communication of the primitive intestinal cells with their microenvironment is essential for the prevention of unrestrained growth and development of neoplasms [47–50]. In this regard, it was found that the abnormalities in signal transduction pathways

involved in the immature cell migration contribute to tumorigenesis at all stages of intestinal cancer [51].

The different populations of primitive cell types in the skin also leave their specialized niches located in the hair follicles, basal layer of interfollicular epidermis, and other skin compartments, in order to differentiate and participate in the tissue maintenance cycles and wound re-epithelization (for recent reviews on the skin stem cells, see [52–58]). Specifically, it is described that in the basal layer of the epidermis, the progenitor cells, or their transient-amplifying progeny, detach from the underlying basement membrane and migrate towards the skin outmost layer. Their movement is accompanied by progressive maturation. Unlike the epidermis, which regenerates continuously, the hair follicles undergo cycles of growth, degeneration and rest. The position of primitive cells in the bulge of the hair follicle and hair germ region is strictly controlled, and shifts in their placement relative to other cells affect the lineage commitment and self-renewal potential. Importantly, after skin wounding, cells from both the hair follicles and interfollicular epidermis migrate to the site of tissue damage [59–63]. Of interest, there is evidence that the activity of telomerase promotes the egress of stem cells from hair follicles in response to chemical injury, whereas telomerase deficiency interferes with the stem cell recruitment, and might constitute a mechanism for prevention of skin cancers in old tissues [64]. Also the melanocyte stem cells, which are normally present in the hair follicle, exit from the bulge when the skin is wounded or exposed to UV-radiation, partaking in the re-pigmentation and renewal of the epidermis. It is suggested that in these conditions the stem cell emigration is not compensated by proliferation, which might lead to melanocyte stem cell depletion and deficient injury repair [65].

The immature cells of the skeletal muscle are likewise required to migrate for tissue maintenance and regeneration. The dedicated muscle stem cells, often referred as satellite cells, are maintained in a quiescent state in the supporting niches, localized between the sarcolemma of myofibers and surrounding basal lamina. Growth-promoting stimuli or muscle injury induce satellite cell activation, egress from the niches, commitment to differentiation and movement towards the target site, where the myogenic progenitors align in preparation for the cell-cell fusion into muscle fibers (diverse aspects of the satellite cell biology are reviewed in [5, 66–73]). Sub-optimal migration of the immature myogenic cells and lack of proper alignment prior to fusion hinder the organ's ability to correctly repair the damage [74], and are speculated to contribute to the etiology of muscular dystrophy [75] and aging [76].

Further, the immature neurogenic cells in the central nervous system also have to leave their birthplace in order to differentiate, reach the target locations, and appropriately integrate into the neural network. In the adult brain, a category of neural stem cells is reported to occupy the neurogenic

niches concentrated in the subventricular zone adjacent to the lateral ventricles, and the subgranular zone within the hippocampal dentate gyrus (detailed reviews of the adult neural stem cells and their niches are provided in [6, 7, 77–80]). In the subventricular zone, activated neural stem cells give rise to transiently amplifying progenitors, which, in turn, become neuroblasts. Neuroblasts collectively migrate rostrally into olfactory bulb, where they change the type of movement to radial and then terminally differentiate. The primitive cells in subgranular zone also produce progenitors that generate neuroblasts, which disperse into the granule cell layer and complete the differentiation there. Conceivably, the aberrant translocation of primitive cells is associated with neuropathology [78, 79, 81, 82]. For example, the traumatic brain injury alters the movement of adult-born neurons in the hippocampus [83], while progressive reduction in the neuroblast migration with aging limits the maturation and lineage-commitment of newly-generated neurons, and might be causative of the senescence-related neurological impairments [84]. Additionally, there are documentations that when transplanted at a locus distant from a brain lesion, cells with the properties of neural progenitors migrate to the injured area [85–87]; and methodologies are considered for cell-replacement therapies with neurogenic cells to ameliorate neurodegenerative diseases and stroke (the challenges and future directions in this field are discussed in [87–90]).

Thus, the motility of stem and progenitor cells in adult organs is crucial for the preservation of tissue health and functionality, and, potentially, for the success of cell-based regenerative approaches.

Molecular Mechanisms Involved in Stem and Progenitor Cell Trafficking

The movement of cells in tissues is a combinatorial outcome of multiple signaling inputs from the cell close surroundings and the remote sites. The stem cell niches, that is functional units of the stem cell maintenance and activation, are proposed to dictate the responses of the primitive cells to the changing needs of the organ [9], greatly impacting the stem cell decision to migrate. The niche constituents, although varied by the stem cell class, are believed to generally include the mature cells of the same lineage, the undifferentiated stem cell progeny and even heterologous stem cells, as well as endothelial cells of the vasculature, mesenchymal cells that are characteristic to a given tissue type, and neural and inflammatory cells. The non-cellular materials, such as extracellular matrix proteins, are also integral to the stem cell niche (for up-to-date reviews on the stem cell niches, see [21–24, 56, 91–97]). In the stem-cell regulated organs, tissue injury evokes multifarious short- and long-range feedbacks to the niches, deploying programs for stem cell activation and mobilization. Some of

the major molecular systems mediating these processes are discussed below.

Signaling by Secreted Mediators

Commonly, changes in the cell migratory behavior occur in response to variations in local concentration of secreted agents, such as cytokines and bioactive lipids.

Chemotactic Cytokines and Growth Factors

Chemotaxis is directional movement of cells according to concentration gradient of soluble chemical factors. Chemotaxis is arguably one of the most explored mechanisms governing cell translocation, indispensable for any biological phenomenon relying on cell migration [2, 3, 98–100], and for the stem and progenitor cell trafficking. Over the years, a multitude of growth factor and cytokines was described as motility-inducing agents for the different categories of primitive cells, guiding their migration and recruitment to the site of tissue repair. For example, the chemotaxis towards the cytokine CXCL12 (a.k.a., SDF-1) is a major pathway regulating immature hematopoietic cell circulation to and from the bone marrow (recently reviewed in [16, 19, 101, 102]). CXCR4 and CXCR7 are two identified receptors for CXCL12, although the expression and function of CXCR7 in normal hematopoietic cells is less studied. Since the initial report on the necessity of CXCL12/CXCR4 system for the hematopoietic stem cell migration and bone marrow engraftment in adults [103], hundreds investigations addressed the various biological processes modulating CXCL12/CXCR4 axis in health and disease, as well as its translational applications for the mobilization of primitive hematopoietic cells and bone marrow transplantation procedures. Moreover, it is now understood that CXCL12/CXCR4-mediated signaling plays a central role in hematopoietic progenitor cell migration to the organs other than the bone marrow, such as the injured liver [35]; or the recruitment of other stem cell types, as shown for endothelial [104] and neural [105] precursors.

Of interest, in primitive hematopoietic cells, the cytokine stem cell factor (SCF) has a synergistic effect with CXCL12 [35]. SCF also stimulates dental pulp progenitor migration, and is suggested to act as a homing factor for immature cells in the course of dental pulp regeneration [106]. Another well-documented stem cell chemoattractant is hepatocyte growth factor, HGF (known as scatter factor), which binds and activates c-Met receptor. HGF/c-Met pathway induces migration of hematopoietic progenitors and facilitates stress-induced mobilization from the bone marrow [35, 107, 108]. HGF/c-Met promotes chemotaxis of satellite cells as well [109–113], which is required for myoblast directional motility and myocyte fusion during adult skeletal muscle restoration [113].

Although substantial knowledge has been already accumulated on the necessity of cytokines and growth factors for the regulation of stem cell migration, with the progress of the research into the trafficking of immature cells, new pathways driving adult stem cell translocation are coming into focus.

Bioactive Lipids

In addition to soluble proteins, the diverse groups of bioactive lipids constitute an important mechanism for the cell communication with the surroundings. As exemplified by sphingosine 1-phosphate (S1P) and lysophosphatidic acid (LPA), the signaling evoked by bioactive lipids via respective receptors is crucial for multiple aspects of cell behavior (for recent reviews, see [114–119]). Intriguingly, it was demonstrated that the expression of the LPA receptor by itself serves as a specific functional marker of hippocampal precursor cells in the adult brain [120]. The migratory responses of stem and progenitor cells are likewise dictated by these molecules (reviewed in [38, 118, 121, 122]). It is demonstrated that S1P acts as a chemoattractant for primitive hematopoietic cells, affecting their mobilization and homing to the bone marrow and the circulation to other organs [26, 123–126]. There is also indication that S1P and LPA stimulate the motility of skeletal muscle satellite cells [127, 128], which might improve progenitor recruitment to the site of damage. S1P is involved in the migration between blood and bone of osteoclast precursors, thus fine-tuning their localization to the bone surface and balancing bone remodeling [129, 130]. Further, the activation of a neural-specific subtype of S1P receptors antagonizes the motility of immature oligodendrocytes [131], while treatments that inhibit S1P signaling potentiate the migration of endogenous neural progenitors in the brain [132] and transplanted neural progenitors in the spinal cord [133].

As it is the case with virtually any stimulus received by the cell, the intracellular signaling cascades evoked by bioactive lipids frequently converge with other pathways governing stem cell trafficking, for example, CXCL12-induced chemotaxis [121, 133]. Such a complex and multifaceted regulation of the tissue progenitor cell motility likely enables coordinated and measured reactions to the environmental changes. Moreover, as discussed in the following sections, physical contacts with the neighboring cells and extracellular components are critical as well for the optimal stem cell movement and recruitment to the site of injury repair.

Juxtacrine Signaling

Along with the secreted factors, the stem cell migratory behavior within and outside the niches is determined by direct binding to the various surrounding cell types and the properties of the extracellular milieu. Several classes of adhesion

molecules mediate these interactions and are considered fundamental for the control of stem and progenitor migration.

Eph and Ephrins

Widely implicated in determining cell positioning is a large and versatile family of receptor tyrosine kinases called Eph (the name is derived from the erythropoietin-producing human hepatocellular carcinoma cell line, from which the first member was isolated), and their membrane-tethered ligands, ephrins. Ephrin/Eph axis directs processes requiring immediate changes in cell morphology, adhesion and motility (for recent comprehensive reviews on the ephrin and Eph signaling and function, see [134–145]). This cell contact-dependent communication is bi-directional, namely, the message is transduced into the Eph receptor-expressing cells (“forward signaling”) as well as the ephrin ligand-presenting cells (“reverse signaling”). Since multiple members of the ligand and receptor families are often co-expressed on the same cell, the ephrin/Eph axis is subjected to an additional level of regulation by “cis”-binding, which may antagonize the effect induced by the associations in “trans” to a partner on an opposing membrane. Extensive cross-talk with other signaling pathways and a kinase-independent activity of Eph receptors further contribute to the diversity of the possible downstream cascades.

It is increasingly recognized that ephrin/Eph axis plays a vital role in the biology and migratory behavior of adult stem and progenitor cells. In the hematopoietic system, the activation of ephrin A5 potentiates immature hematopoietic cell adhesion in the bone marrow niche, and can be manipulated to diminish their retention and enhance mobilization to the blood [146]. Moreover, binding to EphB4 on the bone marrow stroma modulates ephrin B2 expression in the primitive hematopoietic cells, impacting the stem cell ability to translocate beneath the stromal layer and colonize the niches [147–149]. Likewise, in the adult dental tissue, EphB and ephrin B proteins are involved in the interactions of the primitive cells with the microenvironment: ephrin B1 and ephrin B3 expression on the pulp cells restricts the progenitor attachment and migration in the niche in homeostatic conditions [150] and after tooth injury [151].

Diverse ephrin/Eph-mediated pathways are extensively described in the development of the nervous system, and there are numerous findings corroborating their direct involvement in adult neurogenesis, and the control of migratory behavior of the immature cells in the brain: it is documented that EphB receptors and ephrin B1-3 ligands are expressed in the sub-ventricular zone, potentiating the proliferation and migration of neuroblasts [152]; and in the dentate gyrus, where the EphB2 forward signaling is necessary for the migration of the sub-ventricular zone progenitors [153]. Also in the hippocampus, the proliferation, polarity and positioning of immature cells

are altered in animals lacking the EphB1 receptor or ephrin B3 ligand [154]. In contrast, ephrin A2 and EphA7 knockouts are characterized by amplified progenitor cell proliferation and neuron formation with no obvious migratory defects [155]. Furthermore, an intriguing study by Parrinello and colleagues shows that after transection of the sciatic nerve, EphB forward signaling, by inducing progenitor cell separation from surrounding cells, directs peripheral nerve regeneration [156]. Specifically, the immature Schwann cells that migrate into the wound present EphB2, which is activated by ephrin B on fibroblasts; this causes augmentation of the N-cadherin-mediated homotypic adhesion between the moving cells and the formation of Schwann cell cords that support the regrowth of neurons.

In the skeletal muscle, ephrins and Ephs were previously suggested to guide the migrating myoblasts from the storing niches to the site of injury [111, 112, 157]. Indeed, a recent study by Gu et al. provides *in vivo* evidence that the immature muscle cells, moving towards the end of extending myofibers, bind ephrin A5, which is abundantly presented on the adjacent interstitial cells [158]. Although the specific Eph receptors controlling the behavior of satellite cells and their progeny remains to be determined, ephrin A5 is essential for the activation of the directional translocation of myoblasts and neonatal muscle growth [158].

Ephrin A proteins are also important in the adult heart: undifferentiated cells in the myocardial parenchyma preferentially express EphA2 [159, 160], whereas ephrin A1, one of the EphA2 ligands, is highly represented in cardiomyocytes [159–161]. EphA2 stimulation by ephrin A1 promotes cell motility in the infarcted tissue [159, 160], and there are reports indicating that the ephrin A1/EphA2 signaling is beneficial for cardiac recovery after ischemic injury [159, 161–163]. Intriguingly, with cellular aging, EphA2 is subjected to post-translational modifications, which hinder its kinase activity, interfering with the cell chemotaxis towards HGF *in vitro* and the ephrin A1-induced motility of transplanted cells in the infarcted myocardium [160]. Ephrin A1 protein level is also somewhat reduced in the old heart tissue [160]. Hence, it is tempting to speculate the existence of an interrelationship between the age-associated decline in the ephrin A1 and EphA2 functionality and the weakened performance of the senescent heart. In the same way, the aging progenitor cells of the tendon display a downregulation of the ephrin B1, EphA4, EphB2 and EphB4, accompanied by diminished ability to migrate, which can be ameliorated by enhancing EphA4 and EphB2 reverse signaling [164].

Of note, the complementary expression pattern of the Eph receptors in the primitive cells and the ephrin ligands in the differentiated progeny of those cells, is widely described in epithelial tissues, in which EphB receptors and B type ephrins are essential for the correct cell positioning [62, 165–170]. For instance, the highest level of EphB2 and EphB3 is detected in

the immature cells residing in the intestinal crypt, whereas dividing and differentiating cells that move upward the crypt gradually lose EphBs and acquire ephrins B, e.g., ephrin B1 and ephrin B2. Consequently, there is a counter-gradient of EphB and ephrin B proteins along the crypt axis, with the most Eph receptors in stem and progenitor cells at the crypt base, and the ephrin ligands in the mature cells, situated at the crypt boundary with the villus. It is assumed that the EphB receptors generate repulsive cues, which prevent an untimely migration of precursors into the ephrin-enriched zone of the more differentiated cells. Interfering with the EphB forward signaling alters the location of cells in the crypt and reduces their proliferation. Interestingly, there are indications that the Eph mitogenic activity in stem cells, controlled by Abl/cyclin D1 pathway, is distinct from the receptor downstream signaling via PI3 kinase, which is involved in cell positioning [166, 168, 171]. In a similar manner, in the course of branching morphogenesis, ephrin A1/EphA axis concomitantly evokes two independent pathways correspondingly triggering cell proliferation and inhibiting the formation of HGF-induced cellular protrusions [172]. It is important to point out that the activity of ephrin/Eph family is known to frequently modulate other processes required for progenitor cell translocation, especially, the primitive cell responses to chemotactic stimuli by cytokines and growth factors [111, 112, 159, 172–174].

In conclusion, owing to an extraordinary ability of facilitating direct communication between heterogeneous cell types, the capacity of simultaneously eliciting responses in the ligand and receptor bearing cells, and great versatility of the downstream signaling modes, the ephrin/Eph axis is central for the patterning of stem and progenitor cell translocation in adult tissues.

Other Modules of Direct Cell-to-Cell Communication

One can envisage that in the stem cell microenvironment, additional mechanisms mediating the cell-to-cell binding impact the propensity of immature cells to migrate. For example, the cadherins constitute a large family of intercellular adhesion molecules that regulate multiple biological processes, including determination of the cell polarity and collective cell migration (the cadherin family is extensively reviewed elsewhere [175–179]). Recent studies indicate that cadherin-containing adherens junctions enable the attachment of primitive cells to other cellular constituents of the niche, as well as homotypic adhesion between the stem cells themselves, which helps to preserve their quiescence [180–183]. Thus, inhibition of cadherin-mediated binding might be required to antagonize stem cell dormancy and promote emigration from the niches. In support, there are findings that N-cadherin protein on neural progenitor cells is cleaved in response to tissue injury, leading to cell activation [182, 184], egress from the sub-ventricular zone, and translocation into demyelinated lesions [184].

Also gap junctional proteins, connexins, are described in the context of stem cell interactions with the neighboring tissue cells (reviewed in [185–187]). Interestingly, whereas connexin 43 deficiency in osteoblasts and osteogenic progenitors in the bone marrow niches does not impair the steady state hematopoiesis, it disrupts the trans-stromal migration of immature hematopoietic cells, which consequently impedes their mobilization and homing [188]. However, these alterations might not result from the changes in connexin-mediated cell-to-cell adhesion, but rather be triggered by the elevated level of CXCL12 in the connexin 43-knockout cells [188]. Indeed, it was shown that CXCL12 secretion by bone marrow stroma is cell contact-dependent and involves gap junctions built by connexin 43 and connexin 45 [189].

Additional group of the cell-cell adhesion receptors participating in the trafficking of primitive cells includes P- and E-selectins, which are required for the initial tethering of circulating hematopoietic progenitors to the endothelium of bone marrow vasculature, thus constituting the first critical step in the homing process (reviewed in [20, 190, 191]). Recently, selectins have been credited with a significant function in the hematopoietic stem cell communications with the bone marrow niche [192, 193]. Whether selectins are involved in the migration of adult progenitors of non-hematopoietic origins remains to be established.

The adhesion molecules of the integrin family are essential mediators of both cell-to-cell and cell-to-substrate binding. Integrins are discussed in details below in the section on the extracellular matrix. Importantly, integrins are key players in the hematopoietic stem and progenitor cell migration. Several integrin subtypes, e.g., $\alpha 4\beta 1$, have been implicated in the hematopoietic cell attachment to the endothelium and subsequent trans-endothelial migration during homing to the bone marrow [20, 190, 191] and, possibly, in the course of hematopoietic and endothelial progenitor cell recruitment to ischemic tissues [194].

The CD44 antigen is another major receptor performing multiple tasks for the interaction of cells with microenvironment. Of special interest is a distinct selectin-binding glycoform of CD44, termed HCELL (for Hematopoietic Cell E-selectin/L-selectin Ligand), which is uniquely expressed on the immature human hematopoietic population. HCELL facilitates hematopoietic stem cell adhesion to the endothelium and bone marrow homing (reviewed in [195, 196]). Notably, a novel technology has been developed to transform CD44 into the HCELL glycoprotein in other progenitor types that lack native HCELL expression. This approach has the potential of improving cell binding to activated endothelial cells and, as a result, the targeting of intravascularly administered progenitors to the sites of injury and inflammation [197, 198].

It is plausible that the diverse modalities of cell-to-cell communication have evolved to address the complex and dynamic processes of stem cell activation and translocation in

response to the changes in immediate tissue environment. In a similar manner, physical interactions with the non-cellular tissue components are pivotal for the immature cell trafficking.

Extracellular Matrix and Mechanical Cues

The term extracellular matrix (ECM) broadly refers to the non-cellular constituents of the tissue milieu, in which the cells are embedded. ECM consists from the network of fibrous proteins, sugar moieties, immobilized cytokines and growth factors, and other molecules secreted by the cells. The composition and structural properties of the ECM are highly specific to each organ and substantially vary in the presence of pathologies and with aging [199–204]. In addition to providing scaffolding, ECM fulfils instructive roles by transducing biochemical and biomechanical signals to the cells and being a substrate for cell adhesion and migration [6, 202, 205–208].

It is demonstrated that the contacts of immature cells with the ECM in niches determine the stem cell behavior: the molecular complexity of the ECM, its microscale topography, degree of elasticity, and amplitude and frequency of static and dynamic deformations, are all influencing the stem cell choices of quiescence versus proliferation, self-renewal versus differentiation, and death versus survival (for the discussion on these topics, see the following recent reviews [199, 205, 206, 208–213]).

How the ECM conveys information to the cells? The binding of cells to the ECM primarily occurs via integrins. Integrins are heterodimer transmembrane proteins composed of α subunit and β subunit, each has multiple variants. The combinations of subunits confer specificity to the cell recognition of the diverse ECM proteins, such as fibronectin, laminin or collagen, and the specific epitopes within the protein sequence. Intracellularly, integrins are associated with the cytoskeleton and a panel of signaling molecules. Integrins mediate inside-out and outside-in communication between the cell and the physical neighbors and, therefore, are vital for the processes of cell migration, differentiation, and tissue morphogenesis and maintenance in the adult (for comprehensive reviews on integrin structure and function, see [214–220]).

As expected, integrin-mediated adhesion to the ECM impacts stem and progenitor cell motility. For example, integrin $\alpha v\beta 1$ is postulated to control translocation of oligodendrocyte precursors in the central nervous system, whereas downregulation of this receptor is associated with the cell maturation and changes in the migratory phenotype [221]. Likewise, epithelial progenitor cells in the hair follicles require $\beta 1$ integrin signaling for the adhesion and migration of their progeny, and, of note, the various sub-classes of immature endothelial cells exhibit disparate responses to the changes in the $\beta 1$ activity [222]. In the populations of primitive hematopoietic cells, the adhesion to fibronectin via integrin $\alpha 4\beta 1$ is functionally linked to the cytokine-induced chemotaxis [223].

Intriguingly, whereas cytokines activate the movement of resting progenitors, the cell migration speed is modified by the fibronectin concentration [224]. The immature hematopoietic cells also exhibit variations in the integrin $\alpha\beta 1$ -mediated adhesion and movement when presented with distinct isoforms of laminin [225]. Interestingly, it was noticed that the contribution of different integrin α chains to the substrate binding by hematopoietic progenitors is donor-dependent [226].

Further, mechanosensing is an important function of the integrins (reviewed in [208, 214, 218, 220, 227–229]). There are accumulating confirmations, mainly from the studied on developmental morphogenesis, that mechanical forces, applied by the microenvironment to the primitive cells, control their activity [202, 205–207, 230]. The progenitors in the adult tissues are equally subjected to the changes in shear stresses, tension, or periodical stretches, which, as mentioned above, significantly impact cell fate decisions [199, 205, 206, 208–213]. Surprisingly, considerably less data are available on the role of biomechanical cues in the adult tissue stem and progenitor cell translocation. Yet, there are indications that immature hematopoietic cells attach and migrate better on stiffer substrates [231, 232], which might be relevant for the homing and engraftment in the bone marrow. Similarly, the migration of osteoblast precursors is highly dependent on the matrix stiffness [233]. Along with the ECM rigidity, the technological advances in bioengineering approaches brought to light the significance of surface nanotopography for the regulation of cell binding and locomotion [210]. It was shown that primitive hematopoietic cells change the tendency to adhere to fibronectin- or osteopontin-derived peptides according to the nanometer scale variations in the spacing of these elements [226]. Cell's perception of the nanoscale substrate distribution and structure, e.g., existence of pillars and grooves, is also known to dictate the alignment and polarization of immature neural cells [234], which might enhance their differentiations [234–236]. Moreover, dissimilar motility responses are observed when undifferentiated neural stem cells and astrocyte progeny, and the stem cell-derived neurons, are concomitantly exposed to laminin-coated micropatterned surfaces, allowing *in vitro* separation of newborn astrocytes and neurons [237].

It must be indicated that mechanosensory functions are not limited to integrin-mediated adhesions to the ECM. Forces are transmitted via cadherins in the adherens junctions and other types of cell-to-cell attachments [238–240]. Hence, the disruption of the intercellular connections after tissue injury or in pathological states might cause aberrations in the migratory pattern of progenitor cells.

Moreover, there are receptors outside the integrin family that are required for the cell contacts with the ECM and control of primitive cell translocation. For example, the different isoforms of the CD44 protein are critically implicated in the adhesion to bone marrow matrix and the lodgment of normal

and malignant hematopoietic progenitors to specialized endosteal niches, which are rich in the ECM protein, hyaluronic acid (reviewed in [15, 19, 241]). In the hematopoietic stem cell niche, CD44 and CXCL12/CXCR4 pathways cross-react: interference with the CD44 activity impairs CXCL12-induced chemotaxis, whereas treatment with CXCL12 potentiates CD44-mediated ECM binding and niche engraftment of immature hematopoietic cells [242]. In the course of hematopoietic progenitor cell mobilization, CD44 is cleaved by matrix metalloproteinases, facilitating cell egress from the bone marrow [243].

Curiously, the CD34 molecule, a primary marker of the primitive hematopoietic cells in humans, is also an adhesion receptor. The function of the CD34 protein in early hematopoietic progenitors is insufficiently known: on the one hand, ectopically expressed human CD34 increases murine hematopoietic cell interactions with the human bone marrow stroma [244], on the other hand, there are studies pointing to the anti-adhesive and pro-migratory roles of CD34 [245]. CD34 is also highly present in endothelial and skeletal muscle progenitors, and the CD34 knockout impairs satellite cell proliferation and motility [246].

A striking confirmation of the essential and multiplex involvement of the ECM in the contact-dependent guidance of progenitor cells for tissue repair was recently provided by live imaging of the satellite cell translocation in injured skeletal muscles [74]. This study revealed that following myofiber death and degradation, the remaining ECM structures, coined by authors the “ghost fibers”, direct the muscle regenerative response by orienting the migration and subsequent division of activated myogenic progenitors along the longitudinal axis of the fiber ECM. Alterations in the positioning of these ECM arrangements disturb the migratory path and division plane of satellite cells, causing disorganization of the newly - formed myofibers. Interestingly, the satellite cells from an uninjured fiber are not mobilized from their location to the affected area, suggesting that the myofiber ECM acts as autonomous architectural unit necessary for proportionate regeneration of the tissue.

To summarize, based on the extensive research, spanning the matrix features from nanoscale to whole-organ level, it is apparent that the diverse modes of immature cell interactions with the substrate evoke multitude of biochemical and mechanical signals, operating in tandem to coordinate the motile behavior of stem and progenitor cells. Furthermore, cellular behavior is highly context-specific: the propensity of stem cells to migrate is regulated by copious mechanisms and is dictated by the tissue composition, disease state and age. Importantly, the processes of cell movement are dynamic by nature. Thus, as discussed in the next section, imaging approaches for the visualization of live cells in their microenvironment are among most powerful tools employed today for the studies of immature cell trafficking in different organs.

Live Imaging for the Investigations of Stem and Progenitor Cell Motility

There are diverse biological imaging platforms enabling observations of isolated cells, as well as visualization of endogenous or transplanted cells *in vivo*. These methodologies range from monitoring single-cell behavior in an artificial environment to the longitudinal analysis of the distribution of cells in live organisms. The resolution of each approach depends on the type of label (for instance, fluorescence, bioluminescence, nuclear, or magnetic), the corresponding imaging modality (namely, light imaging, positron emission tomography, or magnetic resonance imaging), as well as the nature of examined samples (e.g., *in vitro* cell analysis versus studies of cells in organs). The technological details and relative advantages of the currently employed procedures for the stem cell imaging are extensively discussed in the literature [11, 247–252]. The present paper focuses on the light imaging using fluorescence microscopy, since it is one of the better established and commonly used methods for the identification of stem cells *in situ* and exploration of their motility.

The migration of stem and progenitor cells is frequently examined by observing the behavior of isolated cells *in vitro*. Many of the findings on the juxtacrine and paracrine signaling in the stem cell translocation, as described in the above sections, were obtained by this methodology. For example, the live imaging of cells from a skeletal myoblast line has revealed that fibronectin promotes integrin- and cadherin-mediated cell-to-cell alignment and collective movement, which facilitates ensuing myoblast fusion [253]. Also, by microscopic observations of primary muscle progenitors, it was established that *Wnt7a/Fzd7* axis increases cell polarity and directional migration, and has a beneficial effect on the myogenic cell engraftment after transplantation [254]. Similarly, by monitoring live cell motility in collagen gel cultures, HGF was identified as a major chemoattractant for satellite cells [112]. In the same study, the live imaging of the endogenous cells in the explanted whole myofibers emphasized the intricacy of the mechanisms regulating stem cell migratory behavior, impacted by a host of environmental inputs [112]. Thus, while *in vitro* imaging is particularly instrumental for establishing specific chemoattractants for the immature cells, or pinpointing the fine characteristics of the substrate that influence cell migration, the extreme complexity of the stem cell native environment is only partially reflected in these setups. Consequently, intravital imaging, that is live imaging of cells in the animal organs [248, 255–257], is invaluable for elucidating the pathways orchestrating stem cell migratory responses in the conditions that are close to physiological.

A pioneering work implementing intravital imaging for the studies of stem cell trafficking was performed by Mazo and colleagues, who developed a methodology for the live observations of transfused, fluorescent dye-labeled hematopoietic progenitor cells in the bone marrow of the mouse calvarium

[258]. Using this approach, they demonstrated for the first time that the unique expression pattern of P-/E-selectins and the vascular cell adhesion molecule-1 on the bone marrow microvasculature enables adhesion of circulating hematopoietic progenitors and facilitates their homing. The intravital microscopy of the mouse calvarium for the studies of homing and retention of transplanted hematopoietic stem and progenitors was subsequently applied by other groups, who introduced new platforms of monitoring primitive cell behavior after engraftment in the bone marrow niches with differentially labeled stromal cell populations, modified dyes for the stem cell tracking, and advanced technologies for image acquisition and quantitative analysis [259–263]. These methodologies hold promise to accelerate the research into the molecular mechanisms governing hematopoietic stem cell trafficking after transplantation. Indeed, in a recent work by Itkin et al., the observations of mouse bone marrow by live imaging led to the documentation of distinct vascular compartments, i.e., high-permeability sinusoids, functioning as dedicated sites for immature hematopoietic cell transmigration [264]. The activation of cell motility occurs in these locations due to exposure to the peripheral blood plasma, which, on the other hand, antagonizes bone marrow stem cell quiescence and hampers self-renewing and long-term repopulating potentials. These findings bring forth new considerations of manipulating vascular integrity and adjusting the degree of plasma penetration via blood-bone marrow barrier for the clinical mobilization and transplantation protocols.

The migration of skeletal muscle satellite cells was also addressed by intravital imaging. In confirmation of the *in vitro* studies, it was documented by live observations that exogenous HGF induces cell migration in the rat soleus muscle [110], where the cells are prompted to move by the tissue damage [265]. However, in these works no specific markers of the myogenic progenitors were utilized. A more recent study by Webster et al. introduced intravital imaging in a transgenic mouse with the progeny of muscle stem cells tagged by the expression of a fluorescent protein: in this model, the live imaging of muscle progenitor migration was crucial for the identification of the specific ECM structures remained after the myofiber death that guide the directional translocation of activated myogenic cells for adequate tissue repair [74].

In the adult brain, intravital imaging was recently used to study the trafficking of newly-born neurons: by infecting the endogenous cells with fluorescent protein-expressing lentivirus, and introducing fluorescent calcium indicators, the functional incorporation of migrated cells in the olfactory bulb was evaluated [266]. This work suggests that in addition to intrinsic spontaneous activity of neuronal circuits, extrinsic sensory-driven signals propel the integration of immature stem cell progeny within the adult nervous system.

A critical insight on the stem cell behavior during hair follicle regeneration originated from a series of intravital imaging studies performed by the group of Greco and collaborators [56, 255, 267–270]. To visualize the hair follicle constituents, several fluorescent reporters were combined in a transgenic mouse model in order to differentially label epithelial and mesenchymal populations, and repeated observations of the ear skin were conducted. By this approach, it was demonstrated that the migration, as well as commitment, proliferation, death and clearance of primitive and maturing cells, are spatially restricted events within the sub-compartments of hair follicle epithelium, and these processes are determined by the cell proximity to mesenchymal dermal papilla niche.

Despite the implicit importance of monitoring stem cell behavior in the natural environment of a live organism, the number of published studies implementing intravital imaging of adult organs in rodents is relatively limited, as this type of investigations presents extreme technical challenges. Some of the confounding factors include the need in advanced and elaborated equipment, as well as an expertise in image acquisition and quantitative analysis. Further, the imaging has to be performed in anesthetized animals for the extent of hours, while the imaged tissue is exposed for the optical observations. This entails development of complex surgery protocols and imaging set-ups aiming at maintaining organ function, minimizing tissue injury and attenuating its deterioration, diminishing light-induced damage to the imaged cells and their environment, and avoiding motion artifacts. Moreover, transgenic animals or other modalities for the specific expression of fluorescent protein/s in population/s of interest are required, whereas for many types of stem cells, a single marker is insufficient for faithfully discrimination of primitive cells from other cell cohorts. Additionally, in some tissues, the location of stem cells is uncertain, or their sites are inaccessible to the light due to the organ size (for example, sub-ventricular zone in the brain or the marrow of long bones).

Consequently, alternative approaches for exploring stem cell motility in tissues using *ex vivo* organotypic cultures have been used. For instance, by imaging of brain slices, the characteristics of the sub-ventricular zone neuroblast movement were examined by several groups [271–274], showing that contrary to the expectations, the neuroblast migratory chains remain stable and immotile for relatively long periods of time. Interestingly, in these settings, it was found that physiological electrical signals promote the chain migration of neuroblasts by augmenting purinergic receptors and enhancing cell adhesion [275]. Additionally, imaging of the excised perfused hearts has been utilized to demonstrate the involvement of the ephrin A1/EphA2 pathway in the control of cardiac progenitor cell movement after transplantation into the acutely infarcted myocardial parenchyma [159, 160]. Likewise, live observations of the isolated myofibers were instrumental in uncovering the role of various cytokines,

ECM components and adhesion molecules in directing satellite cell translocation [112, 246].

Therefore, by combining different methodologies for the live imaging *in vitro*, *in vivo* and *ex vivo*, one can achieve a better comprehension of the complex mechanisms defining the stem cell trafficking in the course of tissue homeostasis and after injury.

Concluding Remarks

The rapidly expanding field of adult stem cells prompted investigations into the molecular underpinnings of the migratory behavior of immature cells, leading to considerable advancements in elucidating the elements in tissue microenvironment that impact the stem cell trafficking. Among the key factors are secreted mediators, direct contacts of primitive cells with their neighbors, and biochemical and physical characteristics of the extra-cellular matrix, all acting in concert to optimally coordinate the stem cell movement. While these regulatory pathways are not unique to stem cells, it is argued that the intricate responses of the immature cells address in a specific manner the needs of organ maintenance and repair, and could be exploited for regenerative approaches of modulating the translocation of endogenous or transplanted progenitors. Moreover, there is evidence that the abnormalities in the migratory ability of stem cells are causative of pathological changes in tissues, which occur with age and diseases. Future research in this area, facilitated by the implementation of innovative live imaging platforms and other new technological tools for the studies of immature cell biology and function, will improve our understanding of the multifaceted processes governing cell recruitment to the site of injury and hold great promises for the success of cell-based regenerative therapeutics.

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Compliance with Ethical Standards

Conflicts of Interest The author indicates no potential conflicts of interest.

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