Minireview

Revisiting the role of lysophosphatidic acid in stem cell biology

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Impact statement

The evolving concepts of SSC provide insights into the highly dynamic nature of stem cell plasticity, a phenomenon that is often observed in CSC as well. LPA has been documented to play a prominent role in regulating stem cell biology in multiple levels; ESC, SSC and CSC. In particular, several recent studies have shown that targeting the LPA signaling axis could have new therapeutic applications in the area of dentistry as well as gastrointestinal and neurodegenerative diseases. Despite this, pharmacological agents targeting the autotaxin (ATX)-LPA receptor (LPAR) signaling axis for use in regenerative medicine and cancer has not been explored fully.

Abstract

Stem cells possess unique biological characteristics such as the ability to self-renew and to undergo multilineage differentiation into specialized cells. Whereas embryonic stem cells (ESC) can differentiate into all cell types of the body, somatic stem cells (SSC) are a population of stem cells located in distinct niches throughout the body that differentiate into the specific cell types of the tissue in which they reside in. SSC function mainly to restore cells as part of normal tissue homeostasis or to replenish cells that are damaged due to injury. Cancer stem-like cells (CSC) are said to be analogous to SSC in this manner where tumor growth and progression as well as metastasis are fueled by a small population of CSC that reside within the corresponding tumor. Moreover, emerging evidence indicates that CSC are inherently resistant to chemo- and radiotherapy that are often the cause of cancer relapse. Hence, major research efforts have been directed at identifying CSC populations in different cancer types and understanding their biology. Many factors are thought to regulate and maintain cell stemness, including bioactive lysophospholipids such as lysophosphatidic acid (LPA). In this review, we discuss some of the newly discovered functions of LPA not only in the regulation of CSC but also normal SSC, the similarities in these regulatory functions, and how these discoveries can pave way to the development of novel therapies in cancer and regenerative medicine.

Keywords: Cancer stem cells, therapy resistance, chemoresistance, metastasis, lysophosphatidic acid, autotaxin, mesenchymal stem cells, somatic stem cells, intestinal stem cells, stem cell therapy

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Introduction

Lysophosphatidic acid (LPA) is a bioactive lipid mediator that regulates many cellular functions such as cell proliferation, survival, differentiation, migration and invasion. There are several pathways that lead to the generation of LPA: (1) hydrolysis of lysophosphatidylcholine (LPC) by autotaxin (ATX), which produces the bulk of circulating LPA in biological fluids, and (2) actions by the enzymes glycerol-3-phosphate acyltransferase, phospholipase A, and acylglycerol kinase, which are responsible for the intracellular production of LPA.[1,2] LPA exerts many of its biological functions via six extracellular G protein-coupled receptors (termed LPAR1-6), and the intracellular nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ).[2] The physiological levels of LPA in the plasma ranges from 0.1 to 1 μM. In serum, concentrations above 10 μM have been reported as well.[3,4] Dysregulation of LPA signaling leads to many pathological disorders ranging from neuroinflammatory and cardiovascular diseases to fibrosis, bone disorders, obesity, and cancer.[5] In many instances, LPA levels are found to be elevated in these pathological conditions.[6–9]

Regulation of embryonic stem cells by LPA

Early efforts in generating ATX knockout mice revealed the importance of LPA signaling in embryonic development.

In particular, deletion of ATX (encoded by the gene *Enpp2*) in mice led to death at embryonic days E9.5 to E10.5 as a result of severe abnormalities in the vascular and neural systems.[10,11] Paradoxically, overexpression of ATX at the embryonic stage can also result in severe vascular defects that leads to embryonic death, suggesting that the expression of ATX and hence LPA signaling, must be tightly regulated during embryonic development to ensure proper vascular development.[12] Consistent with these findings, mice lacking lipid phosphatase 3 (LPP3), the enzyme that catalyzes LPA degradation, also suffer the same fate of vascular abnormality and embryonic lethality.[13] Based on the critical role of LPA signaling in embryonic development, it is not surprising to find that mouse embryonic stem cells (ESC) express almost all LPA receptors—LPAR1-3[14] and 5,[15] whereas human ESC and induced pluripotent stem cells (iPSC) express LPAR1-6.[16–21] LPA via activation of LPAR initiate a variety of downstream signaling pathways such as phospholipase C (PLC), extracellular signal regulated kinase (ERK), c-jun N-terminal kinase (JNK), p38, and signal transducer and activator of transcription 3 (STAT3) to regulate ESC proliferation, survival, self-renewal, and pluripotency.[14,22,23] More recently, LPA has been shown to modulate the Hippo signaling pathway by activating downstream transcription cofactors Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) to induce naïve pluripotency in human ESC and iPSC.[24,25] Both YAP and TAZ are gaining recognition as essential drivers of stemness not only in ESC, but also in somatic stem cells (SSC) and cancer stem-like cells (CSC).[26] As the role of LPA on the regulation of ESC has been covered extensively in Lidgerwood et al.,[27] we focus herein on other aspects of LPA regulation—stemness of SSC and CSC.

Regulation of somatic stem cells by LPA

Our understanding of stem cell biology is constantly evolving, especially in the case of SSC, also known as adult stem cells. Traditionally, our view of SSC biology is based solely on the hematopoietic stem cell (HSC) system, which suggests that stem cell population is rare, largely quiescent and long-lived in nature. HSC undergo asymmetric division giving rise to one daughter stem cell and a progenitor stem cell. Dividing progenitor stem cells then proceed through a unidirectional and well-structured hierarchical differentiation pathway which concludes once terminally differentiated cell types of the blood are formed.[28] However, the discovery of SSC in organs such as the intestinal tract,[29] esophagus[30] and testis[31] have unveiled mechanisms that differ from the HSC system. For example, the pool of SSC in certain niches can be abundant, short-lived and rapidly proliferating. In the following section, we discuss how LPA signaling regulates different pools of SSC in various tissues and highlight its therapeutic applicability in these areas.

Hematopoietic stem cells

HSC pass through a series of proliferation and differentiation processes to give rise to all cellular components of blood. It is highly regulated by numerous factors present in hematopoietic organs such as the bone marrow and spleen. Interestingly, high concentrations of LPA, ATX, and lipid phosphate phosphatases have been identified in the microvessels of human bone marrow, where they are known to promote early stages of myeloid differentiation. Moreover, gene profiling results showed that hematopoietic progenitors express LPAR1-6 at various levels in a manner that is dependent on the stage of differentiation.[32] In particular, LPA-LPAR4 axis has been shown to indirectly regulate early stages of HSC differentiation by affecting stromal cell activity in the bone marrow.[33] With regard to HSC mobility, LPA has been reported to increase HSC proliferation and rate of migration across the stromal cell layer.[34] So far, many evidence suggested that LPA regulates HSC commitment toward myeloid lineage.[27,35] For example, LPAR1 has been reported to promote myeloid differentiation in $CD34^+$ HSC,[32] leukemia cells,[36] and erythroid-megakaryocytic progenitors.[37] In both human and mouse, activation of the LPA-PPARγ signaling axis promoted the differentiation of monocyte into macrophage.[38] Furthermore, LPAR2 and LPAR3 are differentially expressed at various stages of hematopoiesis and play key roles in deciding the fate of the myeloid-erythroid-megakaryocytic lineage.[39,40] Finally, studies using LPAR agonist in a murine anemia model demonstrated the potential therapeutic utility of targeting the LPA-LPAR signaling axis for the treatment of blood disease.[39,41] These findings clearly highlight the critical roles of the LPA-LPAR signaling axis during early and late stages of hematopoiesis through precise regulation of HSC niches.

Neural stem cells

Neural stem cells (NSC) are present not only in the embryonic stage but also in adult brain and function in the renewal of neurons throughout life. Recent advances in imaging mass spectrometry showed variations in lipid composition in the human subventricular zone of the brain where NSC and neural stem progenitor cells (NSPC) reside and participate in the regulation of adult neurogenesis.[42] For instance, LPA is a potent neuromodulator that regulates either positively or negatively various aspects of neurogenesis ranging from NSPC proliferation,[43–45] migration[46] to differentiation.[45–47] The reported contradictory effects that LPA has on NSPC could be attributed to differences in species, cell-origins, and/or concentrations of LPA used that could impact the overall fate of NSPC. NSPC derived from human PSC are found to express LPAR1-5,[45,47] whereas LPAR1-4 are differentially expressed in murine NSPC in a manner that is dependent on the developmental stage.[46,48,49] LPA has been reported to induced dysregulation of LPA-LPAR signaling not only led to neurodevelopmental defects such as fetal hydrocephalus[50] but can also affect adult hippocampal neurogenesis, a process that plays a critical role in establishing and maintaining memories. This is particularly important in the context of addiction in which the generation of new hippocampal neurons from NSPC could help reverse the long-term cognitive defects induced by cocaine. Interestingly, a recent study demonstrated that repeated intracerebroventricular

infusion of LPA improved contextual memory in cocaine-treated wild type mice, but not in LPAR1 knockout mice.[51] These findings highlight the critical role that LPA-LPAR1 signaling axis play in adult hippocampal neurogenesis and hippocampal-dependent memory functions and could potentially serve as a novel therapy to treat cognitive defects associated with cocaine addiction.

Mesenchymal stem cells

Mesenchymal stem cells (MSC) are present in the bone marrow, adipose tissue, lungs, teeth, Wharton's jelly, and umbilical cord blood. Undeniably, these multipotent stem cells have gained clinical interest for use in regenerative medicine due to their ability to differentiate into multilineage cell types (e.g. chrondocytes, osteoblasts, adipocytes, and myocytes). Moreover, in the bone marrow, MSC secrete soluble factors that supports HSC maintenance and differentiation into mature blood cells.[52] Human MSC derived from various sources (bone marrow, adipose, and blood cord) express LPAR1-6 receptors at varying degrees,[53–55] whereas bone marrow-derived murine MSC express LPAR1, 4, and 6.[33,56] LPAR display differential, sometimes opposing functions in MSC biology. For instance, in skeletal bone activation of LPAR1 has been shown to promote MSC differentiation into osteoblasts, whereas LPAR4 was found to be inhibitory.[57] Likewise, differentiation of MSC into myofibroblasts in the lungs was also mediated via LPAR1.[58] In terms of migration, LPA via activation of LPAR1 induced the recruitment of bone marrow-derived MSC into the synovial fluid of patients with rheumatoid arthritis[59] and promoted the migration of lung-resident MSC to the site of inflammation in response to lung injury.[60] In addition, LPA protected MSC against apoptosis induced by serum deprivation, hypoxia, and lipopolysaccharide by activating prosurvival pathways such as ERK 1/2 and AKT.[55,56] Taken together, these findings highlight a profound role of LPA in the proliferation, survival, migration, and differentiation of MSC.

Periodontal ligament stem cells

Periodontal ligament stem cells (PDLSC) are multipotent SSC that reside in the perivascular space of the periodontium. Similar to MSC, PDLSC have the ability to differentiate into multilineage specialized cells ranging from periodontal ligament, alveolar bone and cementum to adipocytes, neurons, and blood vessels.[61,62] Because of the multipotent nature of PDLSC and the ease of obtaining these cells (less invasive dental procedure compared to isolation of MSC from bone marrow), they are considered to be an excellent source of MSC for use in a wide range of regenerative therapy not limited to dental applications. However, one major drawback of PDLSC is the low yield of stem cells, requiring substantial *in vitro* expansion that may result in the loss of stem cell properties.[63] In this regard, LPA has recently been shown to promote the proliferation PDLSC in culture, suggesting that LPA could potentially be used as a mitogenic growth factor in the expansion of PDLSC.[64] In fact, LPA is present in normal human saliva and its levels can increase up to 10-fold in patients with moderate to severe periodontitis.[65] LPA appears to modulate periodontal inflammation and wound healing by regulating the expression of pro- and anti-inflammatory genes in gingival fibroblasts.[66] Using *Porphyromonas gingivalis*-derived lipopolysaccharide to mimic periodontitis *in vitro*, Kim *et al*.,[64] demonstrated that blocking LPAR1 with the LPAR1 antagonist AM095 decreased the expression of proinflammatory cytokines and promoted the survival and osteogenic differentiation of PDLSC, suggesting that therapeutic targeting of LPAR1 could be explored for the treatment of periodontitis. An intriguing observation from this study is that treatment of PDLSC with the LPAR2 antagonist AMGEN35 significantly reduced the viability of PDLSC in culture,[67] which indicate that the proliferative effects of LPA in PDLSC reported earlier in Kim et al.[64] could potentially be mediated via LPAR2. Other studies have shown that LPA promoted the adhesion and migration of dental pulp cells to the site of injury, thus facilitating dental pulp repair. This process appears to be mediated via the Rho/Rho-associated kinase pathway.[68] LPA has also been reported to protect dental pulp cells from ischemia-induced apoptosis; clearly establishing a regulatory role of LPA in oral tissues.[69]

Intestinal stem cells

The intestinal epithelium is known to continuously renew itself every four to five days via a specific pool of SSC located at the base of the crypt that express Leu-rich repeat containing G protein-coupled receptor 5 (Lgr5). Unlike the quiescent nature of HSC, Lgr5+ intestinal stem cells (ISC) are highly proliferative and, functioning like a conveyor belt, differentiate into epithelial cells as they move towards the tip of the villi where they undergo apoptosis and shed off into the lumen.[29] Lgr5+ ISC are known to be highly sensitive to radiation and are rapidly depleted following exposure to ionizing radiation.[70] We have recently showed that LPA via activation of LPAR2 protects Lgr5+ ISC from radiation-induced apoptosis, allowing for the survival and subsequent expansion of enteroids.[71] Previously, we reported that radiation or chemotherapy increase the expression of both ATX, the lysophospholipase that generates LPA, and LPAR2,[72] which could reflect a feed forward protective mechanism initiated by cells in an attempt to survive genotoxic insults. We found this mechanism to also exist in Lgr5+ ISC. Moreover, treatment with a non-lipid agonist of the LPAR2, termed Radioprotectin-1 alone led to an increase in LPAR2 expression as well.[71] In fact, Radioprotectin-1 when given at 24 h after exposure to sub-lethal dose of ionizing radiation decreased mortality in mice by 51% compared to vehicle treated mice.[71] The unique anti-apoptotic actions of LPAR2 is attributed to its C-terminal region, which contains LIM- and PDZ-binding domains that interacts with several key players such as Siva-1, TRIP6 and NHERF2. These interactions enhance prosurvival signaling pathways including ERK1/2 and AKT, and contribute to the arrest of apoptotic progression following genotoxic injury.[73] Moreover, activation of LPAR2 promotes DNA damage repair by accelerating the resolution of DNA double strand breaks.[72,74]

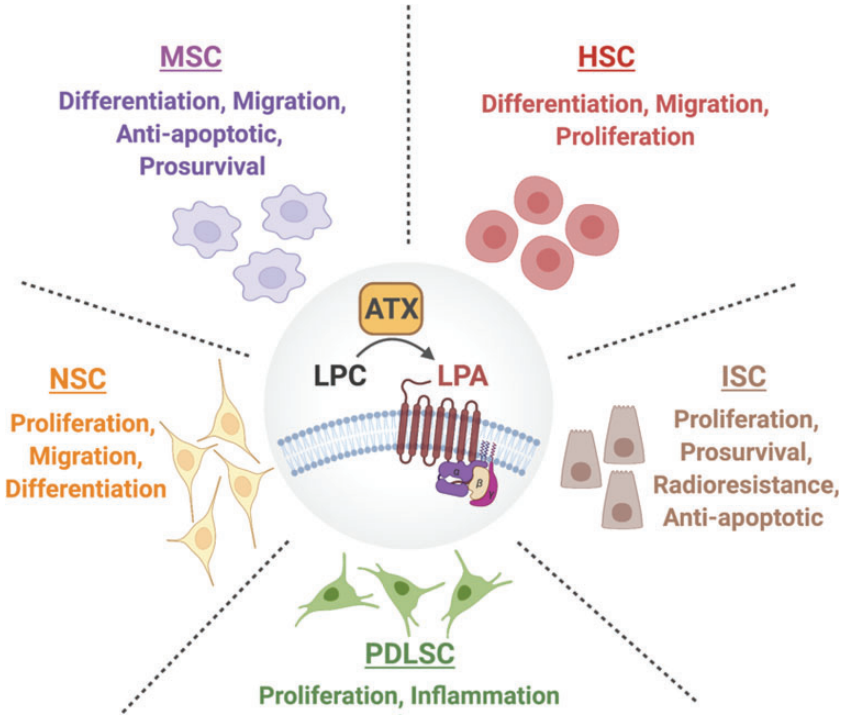

Figure 1. Regulation of SSC pools by the ATX-LPA-LPAR signaling axis. The ATX-LPA-LPAR signaling pathway regulates the proliferation, migration, differentiation, and prosurvival of various SSC pools within the body. ATX: autotaxin; LPC: lysophosphatidylcholine; LPA: lysophosphatidic acid; HSC: hematopoietic stem cell; MSC: mesenchymal stem cells; NSC: neural stem cells; ISC: intestinal stem cells; PDLSC: periodontal ligament stem cells. (A color version of this figure is available in the online journal.)

Thus, targeting LPAR2 could potentially be a novel strategy to mitigate the negative effects of radiation by promoting DNA damage repair and survival of the gastrointestinal epithelium. The differential roles of LPA-LPAR signaling axis in SSC biology are summarized in Figure 1.

Potential roles of LPA on cancer stem-like cells

Only a handful of studies reported a role of LPA in the regulation of CSC. Seo *et al*. demonstrated that the ATX-LPA-LPAR1 signaling axis is involved in the maintenance of ovarian CSC stemness. Specifically, treatment of ovarian CSC with LPA augmented CSC characteristics such as inducing the expression of stemness-related genes (e.g. OCT4, SOX2, and ALDH1), enhancing sphere-forming abilities, promoting resistance to chemotherapeutics, and increasing the tumor-initiating potential in mice. All these observations were abrogated when LPAR1 was silenced either via pharmacological or genetic interference.[75] In another study, Fan *et al*., demonstrated that activation of the nuclear receptor PPARγ by LPA led to the increase in the expression of ZIP4, an oncogene responsible for the maintenance of stemness in ovarian CSC.[76] In therapy-resistant breast CSC, ATX was found to be the second most upregulated gene, while lipid phosphate phosphatase 2 (LPP2) the enzyme that degrades LPA, is the most down-regulated gene when compared to chemosensitive cancer cells, suggesting that the levels of LPA may be critical in promoting therapeutic resistance.[77] In fact, we have recently showed that radiation or chemotherapeutics increase the expression of ATX and LPAR2 in murine breast CSC; similar to what we have seen in the Lgr5+ ISC. Moreover, treatment of murine breast CSC with either ATX inhibitor or LPAR2 antagonist reduced the number of CSC spheres formed compared to vehicle treated control.[78] Collectively, these studies points to a key regulatory role of the ATX-LPA signaling axis in the self-renewal, therapeutic resistance, and maintenance of CSC.

CSC are also key to the seeding of metastasis. In this context, we showed that downregulation of ATX by shRNA reduces the number of B16-F10 melanoma metastasis to the lungs.[79] Seeding of pulmonary melanoma metastasis by CSC is also affected by LPAR expressed in the lung stroma. We found that the number of B16-F10 cells detected 24 h after intravenous inoculation is significantly reduced in LPAR1 and LPAR5 knockout mice.[79] Inhibition of stromal ATX using pharmacological blockade of this enzyme reduced the number of B16-F10 lung metastases in mice.[79,80] Taken together, the ATX-LPAR axis appears to play a profound role in the metastatic process by affecting the tumor cell—microenvironment interaction.

The plasticity nature of SSC and CSC

A pool of intestinal stem cells known as the +4 stem cells (designated based on their location within the crypt) constitute a reserve pool of stem cells that are largely quiescent and give rise to the highly proliferative Lgr5+ ISC periodically or after injury-induced cell loss. However, recent studies uncovered that these reserve +4 stem cells are, in fact, precursor cells that are committed to terminally

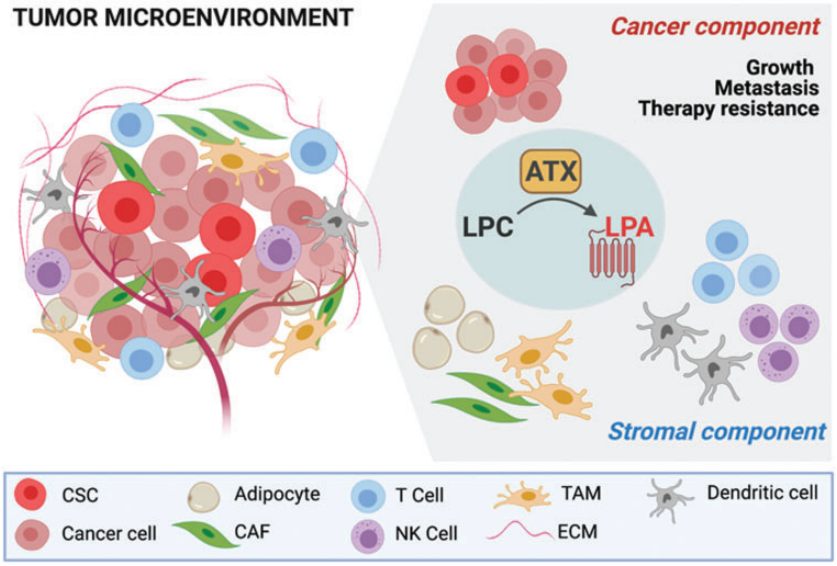

Figure 2. Regulation of CSC, non-CSC and different stromal cells within the TME by the ATX-LPA-LPAR signaling axis. The ATX-LPA-LPAR signaling pathway is commonly upregulated in cancer cells, CSC, and in response to chemo- and radiotherapy. This signaling pathway is also dysregulated in adipocytes, CAF, TAM, and T cells, which functions to further drive malignancy in cancer. CAF: cancer-associated fibroblasts; NK: natural killer cells; TAM: tumor-associated macrophages; ECM: extracellular matrix; ATX: autotaxin; LPC: lysophosphatidylcholine; LPA: lysophosphatidic acid. (A color version of this figure is available in the online journal.)

differentiate into secretory cells of the Paneth and enteroendocrine lineage. Yet, sudden loss of Lgr5+ ISC following intestinal injury can cause +4 precursor cells to reacquire a multipotent Lgr5+ stem cell phenotype and repopulate the Lgr5+ ISC pool.[81,82] Such plasticity goes against the unidirectional hierarchical differentiation system seen in HSC. In fact, similar observations were reported in other organs such as the lungs where differentiated airway epithelial cells can reacquire a multipotent stem cell phenotype following the ablation of basal stem cell pool.[83]

This phenomenon appears to play out in cancer as well. For example, de Sousa e Melo et al. have elegantly demonstrated that CSC hierarchies may be much more plastic and dynamic than previously appreciated. By crossing a mouse that models the human colon cancer with one that expresses diphtheria toxin receptor fused to GFP under the endogenous regulation of Lgr5, the authors were able to selectively track and ablate Lgr5+ CSC upon treatment with diphtheria toxin. Intriguingly, selective ablation of Lgr5+ CSC resulted only in the restriction of primary tumor growth and not complete tumor regression. A surprising observation was that tumor growth was maintained by Lgr5-cells, working continuously to repopulate the loss of Lgr5+ CSC pool. This led to rapid regrowth of tumors in mice upon withdrawal of diphtheria toxin treatment.[84] Similarly, Shimokawa *et al.* demonstrated that following depletion of Lgr5+ CSC pool, differentiated colorectal cancer cells (i.e. non-CSC pool) can revert to a CSC phenotype upon residing in the emptied niche previously occupied by Lgr5+ CSC.[85]

In a separate study, Gunjal *et al.* sorted cells from the human ovarian A2780 cancer cell line into four distinct groups based on the surface expression of stem cell markers; (1) $CD24^{-}CD44^{-}$, (2) $CD24^{+}CD44^{-}$, (3) $CD24^{-}CD44^{+}$, and (4) $CD24^{+}CD44^{+}$. Single cell representing each phenotype were then cultured under limiting dilution conditions. Surprisingly, all single cell gave rise to clones that expressed surface markers comparable to that of the parental cell line. More importantly, all four phenotypes could be detected in the expanded clones arising from group 1 (i.e. single cell that lack both $CD24^{-}CD44^{-}$ stem cell surface markers at the time of isolation).[86] Taken together, these studies lead to the proposition of a secondary CSC concept known as the stochastic model in which stemness within a tumor is not hardwired but rather fluctuates in response to cell expansion, competition for space, injury or in response to cues from local niches. In no way does the stochastic model of CSC meant to disregard the existence of "true" CSC or cells with intrinsic stem-like traits, but rather highlight the dynamic nature of stem cell plasticity that could emerge in a context dependent manner influenced not only by intrinsic properties but also by extrinsic factors in the tumor microenvironment (TME)—much like in the regeneration of the intestinal epithelium following injury. In this context, the ATX-LPA-LPAR signaling axis has been shown to regulate not only the functions of CSC and cancer cells, but also various stromal cells within the TME such as fibroblasts, adipocytes, and immune cells (Figure 2).[78,87] Dysregulation of the ATX-LPA-LPAR signaling pathway in each component of the TME spurs tumor progression, metastasis, therapy resistance and immune evasion. For example, breast cancer cells have been reported to reprogram adjacent adipocytes to increase ATX expression and further promote cancer progression.[88] In ovarian cancer, tumor cell-derived LPA can induce aerobic glycolysis in normal fibroblasts, a metabolic event which mediates the priming from normal fibroblasts to activated cancer-associated fibroblasts.[89] Furthermore, the ATX-LPA-LPAR5 signaling axis has been demonstrated to play a prominent role in mediating cancer immune evasion by inhibiting the cytotoxic effector

function of CD8 T cells as discussed extensively in Lee et al.[87] Thus, a comprehensive understanding on the role of the ATX-LPA-LPAR signaling axis in regulating the TME, stem cell niche, and CSC; how one component influences and shapes the plasticity of another and vice versa, is of paramount importance.

Conclusions

There remains much to learn about the biological nature of stem cells, particularly in the context of stem cell plasticity where loss of SSC in a niche can result in the rapid replacement by differentiated daughter cells that reacquire stem-like traits. In a way, cancer can be viewed as defective or misappropriated tissue regeneration. The sobering observation that stemness is not hardwired but highly plastic further complicates the identification and eradication of CSC. Despite significant progress being made in the molecular analysis of markers that could help identify distinct CSC populations, the more pressing and important questions on the biology underlying CSC and the contributions of non-CSC and the TME to the growth and progression of cancer remain to be addressed.

Authors' contributions

GT, KHL, IHJ, and SCL wrote the manuscript.

Authors' note

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