Life Sciences 231 (2019) 116520

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Cancer stem cell (a)symmetry & plasticity: Tumorigenesis and therapy relevance

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ARTICLE INFO

Keywords:
Cancer stem cell (CSC)
Niche
Plasticity
Asymmetric division (AD)
Symmetric division (SD)
Dedifferentiation
Tumor microenvironment (TME)
Resistance
Stemness
Quiescence
Epithelial-mesenchymal transition (EMT)
Numb

ABSTRACT

Cancer stem cells (CSCs) are self-renewal population localized within cancer niches and play critical roles in tumor initiation, recurrence and metastasis. Despite extensive research, challenges about identity of CSCs and combating them in cancer therapy still remain steady. Cellular plasticity is a cardinal feature of tumor microenvironment (TME) tremendously influencing tumor aggressive behavior. Plasticity and CSC a (symmetry) are interconnecting processes essential for shaping a cancer through nurturing a wide number of cells with tumor promoting capacities. The plastic nature of TME cellularity infers that destemming just CSCs is not sufficient in respect with therapy, especially for high-grade cancers—instead, deploying mechanisms to retard tumor type-dependent TME-CSC interplay is a suggested strategy for making a durable remission of cancer. This requires extending our understanding about CSC divisional profiling and plasticity in order to find critical drivers in cancer progression.

1. Introduction

Cellular origin of cancer and the nature of cells responsible for maintenance and progression of tumor are still unsolved challenges in regard with cancer therapy [1]. It is predictive that cancer is originated from a single cell that expands upon cancer progression [2]. Cancer stem cells (CSCs) (also called cancer-initiating or tumor-propagating cells) are small population of self-renewing cells that have potential to initiate cancer [3,4] and to cause tumor recurrence (relapse) [2,3,5]. Common therapeutic approaches like radio- and chemotherapy can exert a counter-effect by potentiating CSC self-renewal and tumor relapse [1]. It has been proposed that only complete eradication of these cells will eliminate the chance of tumor recurrence [6]. This strategy is not always effective, especially for high-grade tumors, due in part to the existence of, intrinsic or extrinsic, cellular plasticity [7]. There is an intense reciprocal interplay between cancer cells with their nearby stroma required for maintaining CSC properties [8]. It is obvious that tumor microenvironment (TME) is distinct in primary tumors than metastatic cancers [9]. In fact, this TME adds variability and complexity to the evolutionary processes of tumorigenesis [2] through promoting adaptation and heterogeneity of CSCs, the two important drivers of therapy resistance [10] in which a cell type can take a variety of phenotypical state switching in this milieu [11]. This perspective aims to unravel important values of CSC divisional profiling (i.e. symmetric division [SD] and asymmetric division [AD]) along with cellular plasticity in tumorigenesis and therapy. CSC plasticity is one of the major obstacles in cancer targeted therapies. Information provided in this review acknowledge the importance of dampening cross-talking between CSCs and their nearby TME as a promising strategy for reducing the chance of cancer recurrence. CSCs can transition between multiple types of phenotypes (stem/non-stem) and conditions (quiescence/proliferation) enable them to easily evade from therapy. CSCs in close association with other cells within the TME could acquire such capability, so in regard with plasticity it is reasonable to assert that not essentially CSCs but all cells within the TME have the capacity to initiate a tumor. Therefore, combating this high cellular turnover requires extending our understanding about CSC divisional profiling and plasticity in order to specifically address critical drivers in cancer progression.

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https://doi.org/10.1016/j.lfs.2019.05.076
Received 11 May 2019; Received in revised form 22 May 2019; Accepted 28 May 2019
Available online 31 May 2019
0024-3205/

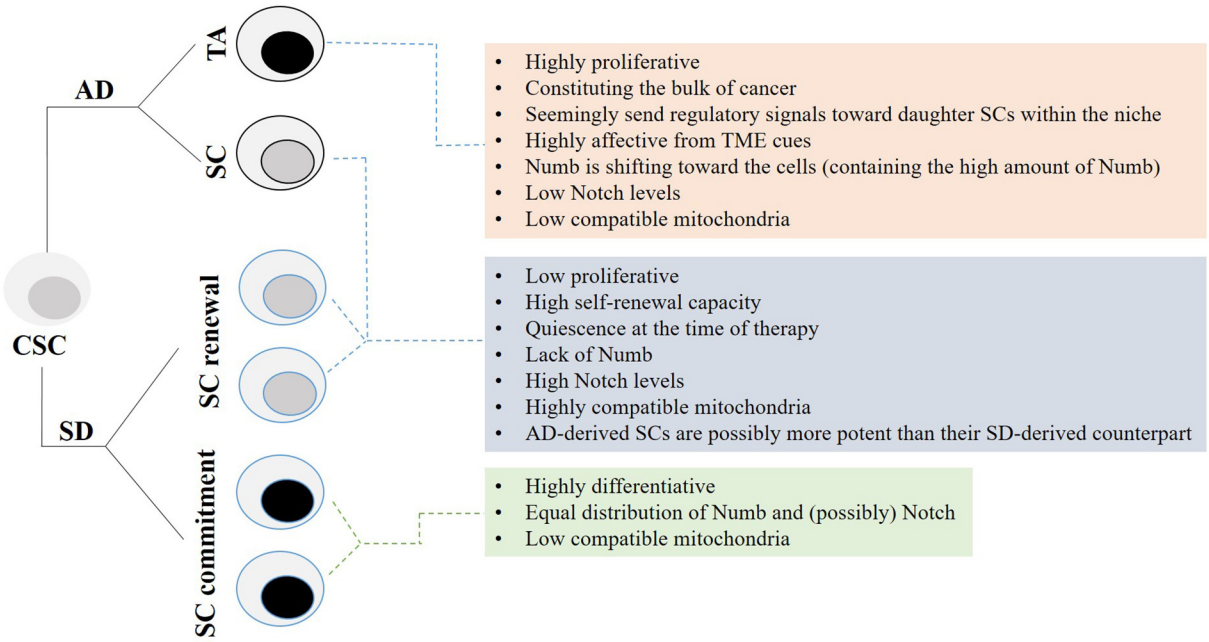

Fig. 1. Differential characteristics of cells derived from cancer stem cell (CSC) asymmetric (AD) and symmetric (SD) divisions. The cells undergo AD and SD divisions depending on the type and grade of cancer. The two cells derived from SD are either stem cell (SC)-renewal or SC-committed, while upon AD, one of the cells is transient amplifying (TA) and the other one is SC. TA cells are highly proliferative constituting most of the cancer bulk. TME, tumor microenvironment.

1.1. CSCs and divisions

CSCs reside in distinct areas within the TME called SC niches. These niches preserve CSC self-renewal [6] in which cells within the niche all exhibit SC features and have more aggressive behavior [12,13]. Cells outside the niche through receiving signals from TME can undergo differentiation into cancer cells [12] and/or dedifferentiation toward attaining a CSC-like phenotype enriching the niche of SCs [6]. CSCs undergo AD to form a SC and a progenitor or committed cell (so called transient amplifying [TA]), while the two daughter cells derived from SD are either SCs (symmetric renewal) or committed (symmetric commitment) [14]. Characteristics of cells derived from AD and SD is shown in the Fig. 1. The heterogeneity of tumor is so determined by AD [5], and this heterogeneous nature is related to cancer robustness and influences patient survival and the efficacy of therapy [6,15]. In fact, the AD is for maintaining the equilibrium between cellular proliferation and death [16]. Cell fate determinants and external cues are responsible for these two different divisional features of CSCs [5]. The TA cells proliferate actively before commitment to differentiation [5,12] constituting a bulk of cancer [13]. TA cells also have the capacity to dedifferentiate into CSC-like cells depending on their genotype and signals receiving from the TME, so the cells are able to re-enter the CSC pool [6]. The general consensus may be on that the committed cells propagate within a tumor and guide retaining of cancer progressive features.

Daughter SCs are less proliferative and exhibit self-renewal activity. Quiescence or dormancy of the SCs in niches [17] along with cellular plasticity and heterogeneity within a tumor [3,6,18] are leading causes of CSC resistance to therapy. When called upon, CSCs escape regulation and retain their aberrant proliferative capacity in order to initiate and promote cancer progression [6,12]. Both SD and AD occur in one cancer [12,19,20], but they are not in balance, as what is seen for normal precursor cells within a tissue. Oncogenic cues (extrinsic and intrinsic) [14] in different types [12] of cancers with diverse grading [21] along with the space available within the niches [12] determine the dominancy of one division over another. For instance, in papilloma [22] AD dominates over SD, while an opposing divisional fate occurs in colon [4] and breast [5] cancers. Regulation over CSC niches is also different in melanoma, glioblastoma and (in particular) hematopoietic cancers than other common malignancies [6].

1.2. CSC divisional profiling in tumorigenesis

CSCs although have the ability to hijack normal SC niches [6], competition occurs for niche spaces, inferring different potency of SCs localized in these specialized areas in which mutant faster proliferative SCs are more prone to fill the niches [23]. Previous concepts infer that the pool of long-lived SCs is maintained more with SD (rather than AD) [5]. P53 is a fate determinant tumor suppressor known to suppress stemness [5,24] and to restrict plasticity [25]. Cicalese et al. reported that p53 reactivation and loss promote AD and SD, respectively, in breast CSCs. The authors characterized SD as a promoter of cancer growth, while AD is identified as a suppressor of cancer [5]. Similarly, Sugiarto et al. showed in glioma that a decreased rate of AD is related to an increase in the tumor-initiating potential [26]. Converse to these results, there is a work on prostate cancer by Qin et al. who identified diverse activities for PSA^- and PSA^+ cancer cells. They noticed that PSA^- cells undergo AD exhibiting higher propagating and resistance activity, compared to the PSA^+ cells that undergo SD [27]. In line to this study, Ali et al. reported over 90% reduction of cancer size after decrease of AD in lung adenocarcinoma [19].

Numb is another cell fate determinant that in cells undergoing AD accumulates exclusively in TA cells [28,29], while distribution of this protein is uniform in the SD-derived committed cells [29]. Numb acts as an inhibitor of CSC self-renewal through suppressing Notch expression [20]. Notch along with other stemness markers like CD133 are expressed mainly by daughter SCs (not committed cells) [19], so they provide effective tools for evaluation of AD. Wu et al. recently published opposing results to that reported by Cicalese et al. They found that in mammary CSCs, epithelial-mesenchymal transition (EMT) is a process by which stemness is maintained through directing the cells toward the AD [29]. Stem progeny populations derived from AD receive highly compatible reactive oxygen species (ROS) scavenging mitochondria [29]. This virtue enables them to keep ROS at low levels making them highly compatible to evade from oxidative targeted therapies [30]. Numb is segregated from AD-derived SC and directed toward the TA committed cell, thus sustaining self-renewal of SC pool.

By contrast, uniform distribution of Numb and mitochondria in cells derived from SD promotes a symmetric committed fate, and thereby exhausting SC pool and promoting cellular differentiation [29]. These results indicate that although rapid expansion of CSC pool occurs by symmetric renewal during cancer recurrence (reported by Li et al) [16], a converse outcome may occur when the cells undergo symmetric committed division. However, this is not occurring in a cell undergoing AD, implying that CSCs taking AD are possibly more active and tumorigenic than the cells undergoing SD. The study performed by Wu et al. tightly support the notion that AD is not essentially a suppressor, but instead a potent promoter of cancer possibly stronger than SD. However, there is no report comparing the potency of SCs derived from AD to that derived from SD. Supporting this, there is a report by Pece et al. demonstrated that poorly differentiated G3 (unlike well-differentiated G1) breast cancers are enriched in PKH^{Pos} (PKH is a fluorescence dye labeling quiescence SCs, not committed cells) CSCs expressing normal mammary SC markers, and due to the higher tendency of the normal SCs toward the AD [21] and that this propensity is possibly much akin to the CSCs, it seems plausible to claim that daughter SCs derived from AD are well-qualified to retain stem-like features at high-stage cancer, while in cells derived from SD this capacity is weakened.

In hematopoietic cancers, cellular polarity is abolished due to Numb deregulation, thereby acquiring more tendency toward SD [26]. In leukemia, shifting from slow growing to aggressive blast crisis stage occur by transitioning Numb expression from high to low levels, so augmentation of Numb expression using activators can repress symmetric renewal of hematopoietic cancers, and thereby regulating disease progression [28]. It is interesting to note that TA cells although receiving the high content of Numb contributed to the more differentiated state, the cells are also highly proliferative [6] before taking a differentiation state. In addition, breast CSCs with enhanced NP1/Numb signaling is reported by Tominaga et al. to have increased SC-renewal capacity [31], which is in contrast with what mentioned above about Numb action. It seems that mechanisms controlling over Numb distribution and function are varying possibly depend on the stage of cancer and the cross-talking between SC niche with the surrounding TME, so TA cells taking proliferation, differentiation, or dedifferentiation states in response to cancer demands. Generally, cellular differentiation in normal conditions is associated with restricted epigenetic plasticity; however, the differentiated cells have unique susceptibility to the oncogenic signals [25], possibly for potentiating their transformation and retaining their plastic nature. TA cells, for instance, although are committed to differentiate into cancer cells forming the cancer bulk, the cells also replenish tumor-propagating pool in response to the activation of inherent or extrinsic plasticity signals acting in promotion of their dedifferentiation. As shown in the Fig. 2, refilling of CSC niche is well-maintained by AD due to the capability of both TA cells and cancer cells derived from them to dedifferentiate into CSC-like cells. This capacity is also inferable to the committed cells derived from SD. Every cells within the TME have the competency to initiate cancer upon exposure to a proper environment, and regarding SD-derived committed cells, the cells, similar to the TA cells, are able to differentiate into cancer cells that in turn can reverted back to the CSC-like phenotype. An unsolved question here is which type of the cells are more potent in cancer promotion? AD-derived TA or SD-committed cells? As discussed, unique plastic tendency of TA cells into attaining a diversity of phenotypes with high competency might tend us to take a more depth thinking and put this as a proposal for further investigations.

1.3. Plasticity in tumorigenesis

Cancers upon progression share many features with embryonic mesenchyme including cellular plasticity [32]. Cellular plasticity is a characteristic of TME refers to reversible transitioning between a variety of cellular states including SC/non-SC (i.e. de/trans differentiation) [6,8,33–35], AD/SD, quiescence/proliferation, EMT/MET, and drug sensitivity/resistance [36]. Dedifferentiation (also called redifferentiation or retrodifferentiation) occurs within the same lineage, while transdifferentiation occurs between different cell lineages [8]. Aberrant activation of plasticity is contributed to the initiation, maintenance and progression (dissemination) of cancer [8], forcing CSC aggressive behavior.

Cellular plasticity expands cancer heterogeneity [37] and is a reason for uncertain origin [18], phenotype and function [38] of CSCs deducing that the newly formed CSCs may inherit markers that are different from one type of cancer to another or even in a specific cancer [1,6], thereby allowing steady cellular adaptions to the various TME conditions [39]. Identification of these cells is thus difficult when considering marker expression profile, demanding functional assays to trace the cells [1]. Thus, plasticity complicates eradication of cancer because of extending frequency and diversity of cells aiming to target [6,35], and that the newly formed CSCs acquire dynamic epigenetic alterations [3], enhancing the tendency for dissemination and therapy resistance [34].

Plasticity enables CSCs to transit between proliferative and quiescent phenotypic states, which is for cancer initiation, growth and invasive purposes [40]. Highly invasive CSCs can remain in a quiescent state for several years before initiating their growth [11], causing cancer relapse years after therapy [3]. Quiescence cells have intact basement membrane [11], while a permissive bm (marked by integrity loss) is a trigger for retaining the invasive feature of the cells. This permissive bm is formed by the function of cancer-associated fibroblasts (CAFs) in making a physical force (through production of a stiffened ECM) over the basement membrane [41]. The architecture of cancer vasculature takes an additive role in which a sprouting neovasculature promotes cancer proliferative state while a stable vasculature mediates cancer quiescence [15].

Plasticity is induced by inherited (or intrinsic) and acquired (or extrinsic) factors. Intrinsic factors take action via forced expression of transcription factors, such as drug transporter genes [2] or EMT markers [39]. Extrinsic factors are cues from the TME [35,42], in particular signals from CAFs [43]. Existence of extrinsic plasticity is suggestive that hierarchy is not essentially referred to CSCs (an irreversible cell state in which a cell that left stemness fate cannot revert back to the state again), instead every cells within a cancer (not necessarily CSCs) have a chance to initiate cancer (a reversible cell state) [6,35,37,42]. Although the cell-type origin of CSC-like cells is important for determining cancer aggressiveness, the more crucial role is taken by the type of mutation [2] or simply the potency of signals in making alterations in morphology and function of the desired cell(s). CSCs are orchestrated spatiotemporally [7]. Interactions between extrinsic and intrinsic cues could cause interconversions from low to high tumorigenic states, and vice versa [34]. For example, TME signals such as transforming growth factor (TGF)-β promote chromatin configuration in non-CSCs to activate genes like ZEB1 (one of the key EMT regulators essential for maintaining stemness plasticity [39]) in the cells for switching them toward CSCs [34]. TGF-β^{high} promotes EMT to invade (disseminate) toward the distant sites (early metastasis) [9,11,44], while TGF-β^{low} induces mesenchymal-epithelial transition (MET) to maintain self-renewal in the sites of invasion (late metastasis) [9,11]. Monocytic myeloid-derived suppressor cells (mMDSCs) are reported to promote EMT for dissemination and metastasis, while granulocytic (g) MDSCs are contributed to MET for cellular colonization and proliferation in the metastatic sites [45]. In addition, perivascular cells can switch their phenotype toward attaining pluripotent SC-like cells by exhibiting increased expression of *Klf4*, a plasticity mediator, induced by TME signals. These transformed cells modulate the metastatic TME for supporting SC-like phenotypes in cancer cells. Toward this metastatic niche, mobilization of hematopoietic SCs occurs, promoting the chance of metastasis upon cancer development [46]. Moreover, the impact of TME signals on MITF, a transcription factor, causes different cellular states in melanoma switching between proliferative ($MITF^{high}$)

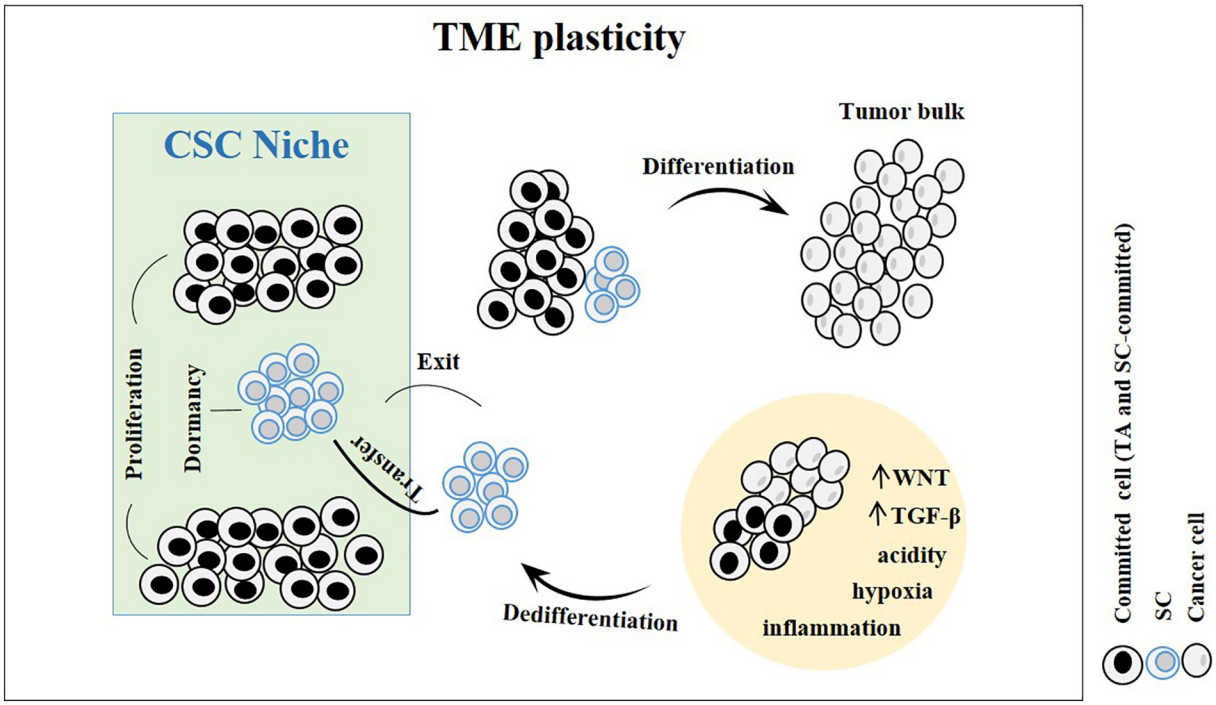

Fig. 2. Control over cancer stem cell (CSC) division. CSCs reside within distinct regions in the tumor microenvironment (TME) called stem cell (SC) niches. SCs within the niches sustain their self-renewal potential and are kept in quiescence (dormant) state, which is for evading from therapy. SCs are controlled by intrinsic (i.e. transcriptional regulators) and extrinsic (i.e. cues from TME) factors. Cells exit from CSC niches under the control of the TME acquire plasticity through which daughter SCs and committed cells differentiate into cancer cells, the cells in turn dedifferentiate toward attaining a CSC-like phenotype. These SCs can replenish stem niches or may take aggressive behavior. Existence of TME plasticity necessitate the acquisition of an adjuvant therapy by targeting TME cues along with controlling CSC intrinsic regulators. This is for enhancing the efficacy of therapy and reducing the chance of cancer relapse after surgical resection of cancer, so targeting just CSCs (even their complete eradication) is a transient therapy followed by cancer recurrence due to the plasticity of TME cellularity.

and invasive ($MITF^{low}$) states [42]. TME also regulates differential states of breast CSCs transitioning between more proliferative epithelial-like and more quiescent invasive mesenchymal-like phenotypes [1,47].

Plasticity of CSCs is controlled by different conditions within the TME as follows: (1) An inflammatory TME can activate CSCs in the niche and expand their number through promoting dedifferentiation of cells outside the SC niche [3,8,37,48]. This inflammation may result from an injury induced by therapeutic approaches to the cancer tissue, altering cancer cell antigenic landscape (for mediating phenotypic plasticity), and thereby promoting therapy resistance [3]. NF-κB is a main mediator of inflammation that induces Wnt signaling [48]. Activation of Wnt promotes dedifferentiation [48–50]. In addition, positive regulatory circuits between NF-κB and interleukin (IL)-6 favorites cancer cell/CSC transformation [51]. (2) Hypoxia is another TME condition associated with therapy resistance [13,47]. Tang et al. reported that CAFs in the hypoxic TME induce activation of GLI2 in CSCs for enhancing their stemness and enforcing their intrinsic resistance to chemotherapy [52]. Upregulation of EZH2 is possibly occurs in a hypoxic TME, which is for expanding the number of CSCs [53]. (3) TME acidity is another plasticity inducer, promoting dedifferentiation of non-CSCs [54]. (4) Metabolic plasticity is another key condition within the TME. CSCs from various cancer types have different metabolic demands. For example, pancreatic CSCs rely mostly on OXPHOS, while breast CSCs use glycolysis to meet their metabolic demands [55]. Thus, TME can be reprogrammed metabolically to suppress the CSCs functionality, and thereby reducing the number of the cells [56].

Plasticity is a bidirectional event occurring between CSCs and their surrounding stroma [15,37,54]. For instance, CSCs maintain TME in a hypoxic condition that is for sustaining stemness, quiescence and resistance of the cells [10], and reinforcing their genetic instability [37]. In addition, breast cancer cells release of Hedgehog (HH) stimulates CAFs to produce fibroblast growth factor5 (FGF5) and fibrillary collagen that are contributed to promotion of cancer cell/CSC switching [57]. Interaction between FGF5 with FGFR expressed in CSCs reprograms the cells toward attaining a CAF-like phenotype to construct SC niches [58,59] and to promote metastasis [59]. Moreover, CSCs secrete IL-4 [60] and IL-6 [61,62] to induce M2 polarity, and release TGF-β [63] and interferon-β [64] to stimulate the M2 cells for secretion of IL-37 and interferon stimulated gene 15 (ISG15), respectively, both of which potentiate CSC self-renewal and invasiveness. Thus, CSCs acquire intricate cross-interactions with their nearby stroma for propagating a stemness phenotype, facilitating escaping mechanisms and aggravating responses upon cancer progression.

2. Therapy relevance

The dynamic and reversible plasticity of TME enriches cancers with cells that are morphologically and functionally similar to CSC-like cells. CSCs are resilience switching from one type of division to another through continuous exposure to the TME plastic nature. The plastic bed imposes a burden in clinic indicating that approaches for targeting CSCs must not be restricted to just eradication of these cells by methods like immunotherapy, instead a more broaden strategy is necessary to dampen CSC-TME cross-talking. Although dependent on the type and grade of cancer, CSC targeting as a single therapy is possibly effective only for low-grade cancers. CSCs are genetically instable [2] and easily adaptive to conditions within the TME including inflammation [8], acidosis, metabolic alterations (glucose restriction) and hypoxia [10], and that sufficient number of the CSC-like cells will be provided via TME plasticity to acquire growth and invasive features in high-grade cancers, so the role of CSC niche is seemingly shadow when cancers evolve an aggressive behavior due to exhibiting high cellular turnover within the TME. In these cancers, daughter cells derived from CSCs via

AD and/or SD would leave the niche to make intricate cross-connections with signals from TME, which is for intense growing and therapy resistance. This is a predictable reason for enrichment of cancers with CSCs following chemotherapy [36,57], which is due to the more resistant nature of CSCs than their nearby differentiated cancer cells [65]. This depicts higher aggressive behavior of CSC-richen cancers than that enriched with mature cells [2]. In fact, this is the ecology of the environment that determines the fate of cancer, and it is clear that the TME cellularity and interactions have huge diversities among one type of cancer to another and even in a same lesion [11], and that plasticity related heterogeneity could cause diverse responses to therapy [15]. Therefore, abolishing plasticity and related signal transduction within the TME in situ for individual cancers would pave the way for enhancing the efficacy of CSC-targeted therapies. This is for retarding cellular switching potency and restricting the number of cells aiming to target, and thereby improving the outcomes so saving the time and cost of therapy. Gathering more knowledge about TME plasticity and related signaling specifically in cancers is cardinal to accurately predict the sequences of events occurring in that type of cancer, and thus augmenting the efficacy of therapy. This would also be helpful to identify the type of CSC division dominate in a tumor so as to specify the strategies specifically on that type. Complexity of signal transduction is a characteristic of TME and due to the impossibility of targeting all of the tumor-promoting signals for patients, a particular focus must be on identification of the critical drivers of plasticity aiming to achieve desirable and durable outcomes and lessening the chance of cancer relapse after surgical resection. In triple-negative breast cancer, for instance, EGF and insulin-like growth factor-1 (IGF-1) are identified as plasticity modulators and their targeting is shown to prevent disease progression [66]. TME can be reverted back from a cancer-promoter toward cancer-suppressor, as the one in normal tissue or organ [11]. GATA3 activation in breast cancer, for instance, is reported to alter TME from an EMT, stemness and inflammatory state to a more differentiated, low metastatic luminal cell architecture [67]. The role of TME interactions can also be considered for targeting signals contributed to self-renewal capacity of CSCs including Notch, HH and Wnt in combinational therapies [65]. Taken all into consideration, it is fair to say that this is the plasticity that takes superior roles in determining the fate of cells within a cancer, with a special focus on CSCs and their divisional dominancy.

3. Conclusion

Information gathered in this review provide compelling evidence for highlighting CSC a(symmetry) and plasticity influenced from TME factors in promoting cancer aggressive behavior, resistance and recurrence. Controversy about the extent of tumorigenic nature of either AD or SD divisional features still remains, but from what is understood in papers published so far, it is fair to infer that AD as a more potent promoter of cancer than SD, so it could be a focus in cancer therapy. Plasticity could recall oncogenic signals, multiplying cellular interconnections and bearing heterogeneity to the cancer cellularity, so understanding more about plasticity drivers would be a promising strategy in combatting cancer resistance and relapse. TME is different from one type of tumor to another or even in the same lesion, so future directions must be on designing therapeutic approaches specific for TME, considering the type and grade of cancer.

Acknowledgement

We are thankful of Sachin Khiste, working at Department of Medicine, Harvard Medical School, Boston, MA 02115, USA, for editing the manuscript.

Declaration of Competing Interest

No conflict of interest to declare.

References

[1] M.D. Brooks, M.L. Burness, M.S. Wicha, Therapeutic implications of cellular heterogeneity and plasticity in breast cancer, Cell Stem Cell 17 (2015) 260–271.
[2] S. Badve, H. Nakshatri, Breast-cancer stem cells—beyond semantics, Lancet Oncol. 13 (2012) (e43-e8).
[3] M. Hölzel, A. Bovier, T. Tüting, Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? Nat. Rev. Cancer 13 (2013) 365.
[4] C.A. O'Brien, A. Kreso, P. Ryan, K.G. Hermans, L. Gibson, Y. Wang, et al., ID1 and ID3 regulate the self-renewal capacity of human colon cancer-initiating cells through p21, Cancer Cell 21 (2012) 777–792.
[5] A. Cicalese, G. Bonizzi, C.E. Pasi, M. Faretta, S. Ronzoni, B. Giulini, et al., The tumor suppressor p53 regulates polarity of self-renewing divisions in mammary stem cells, Cell 138 (2009) 1083–1095.
[6] V. Plaks, N. Kong, Z. Werb, The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? Cell Stem Cell 16 (2015) 225–238.
[7] K.J. Lenos, D.M. Miedema, S.C. Lodestijn, L.E. Nijman, T. van den Bosch, X.R. Ros, et al., Stem cell functionality is microenvironmentally defined during tumour expansion and therapy response in colon cancer, Nat. Cell Biol. 20 (2018) 1193.
[8] J. Varga, F.R. Greten, Cell plasticity in epithelial homeostasis and tumorigenesis, Nat. Cell Biol. 19 (2017) 1133.
[9] C.-C. Lee, J.-C. Lin, W.-L. Hwang, Y.-J. Kuo, H.-K. Chen, S.-K. Tai, et al., Macrophage-secreted interleukin-35 regulates cancer cell plasticity to facilitate metastatic colonization, Nat. Commun. 9 (2018) 3763.
[10] B.C. Prager, Q. Xie, S. Bao, J.N. Rich, Cancer stem cells: the architects of the tumor ecosystem, Cell Stem Cell 24 (2019) 41–53.
[11] A. Brock, S. Krause, D.E. Ingber, Control of cancer formation by intrinsic genetic noise and microenvironmental cues, Nat. Rev. Cancer 15 (2015) 499.
[12] E. Batlle, H. Clevers, Cancer stem cells revisited, Nat. Med. 23 (2017) 1124.
[13] N.K. Lytle, A.G. Barber, T. Reya, Stem cell fate in cancer growth, progression and therapy resistance, Nat. Rev. Cancer 1 (2018).
[14] M. Wu, H.Y. Kwon, F. Rattis, J. Blum, C. Zhao, R. Ashkenazi, et al., Imaging hematopoietic precursor division in real time, Cell Stem Cell 1 (2007) 541–554.
[15] S. Koren, M. Bentires-Alj, Breast tumor heterogeneity: source of fitness, hurdle for therapy, Mol. Cell 60 (2015) 537–546.
[16] L. Li, J.-C. Li, H. Yang, X. Zhang, L.-L. Liu, Y. Li, et al., Expansion of cancer stem cell pool initiates lung cancer recurrence before angiogenesis, Proc. Natl. Acad. Sci. 115 (2018) (E8948-E57).
[17] J.E. Visvader, G.J. Lindeman, Cancer stem cells in solid tumours: accumulating evidence and unresolved questions, Nat. Rev. Cancer 8 (2008) 755.
[18] X. Wang, Y.-S. Jung, S. Jun, S. Lee, W. Wang, A. Schneider, et al., PAF-Wnt signaling-induced cell plasticity is required for maintenance of breast cancer cell stemness, Nat. Commun. 7 (2016) 10633.
[19] S.A. Ali, V. Justilien, L. Jamieson, N.R. Murray, A.P. Fields, Protein kinase Cι drives a NOTCH3-dependent stem-like phenotype in mutant KRAS lung adenocarcinoma, Cancer Cell 29 (2016) 367–378.
[20] P. Bu, L. Wang, K.-Y. Chen, T. Srinivasan, P.K.L. Murthy, K.-L. Tung, et al., A miR-34a-Numb feedforward loop triggered by inflammation regulates asymmetric stem cell division in intestine and colon cancer, Cell Stem Cell 18 (2016) 189–202.
[21] S. Pece, D. Tosoni, S. Confalonieri, G. Mazzarol, M. Vecchi, S. Ronzoni, et al., Biological and molecular heterogeneity of breast cancers correlates with their cancer stem cell content, Cell 140 (2010) 62–73.
[22] G. Driessens, B. Beck, A. Caauwe, B.D. Simons, C. Blanpain, Defining the mode of tumour growth by clonal analysis, Nature 488 (2012) 527.
[23] A. Reilein, D. Melamed, S. Tavaré, D. Kalderon, Division-independent differentiation mandates proliferative competition among stem cells, Proc. Natl. Acad. Sci. 201718646 (2018).
[24] C.-J. Chang, C.-H. Chao, W. Xia, J.-Y. Yang, Y. Xiong, C.-W. Li, et al., p53 regulates epithelial–mesenchymal transition and stem cell properties through modulating miRNAs, Nat. Cell Biol. 13 (2011) 317.
[25] A. Puisieux, R.M. Pommier, A.-P. Morel, F. Lavial, Cellular pliancy and the multistep process of tumorigenesis, Cancer Cell 33 (2018) 164–172.
[26] S. Sugiarto, A.I. Persson, E.G. Munoz, M. Waldhuber, C. Lamagna, N. Andor, et al., Asymmetry-defective oligodendrocyte progenitors are glioma precursors, Cancer Cell 20 (2011) 328–340.
[27] J. Qin, X. Liu, B. Laffin, X. Chen, G. Choy, C.R. Jeter, et al., The PSA−/lo prostate cancer cell population harbors self-renewing long-term tumor-propagating cells that resist castration, Cell Stem Cell 10 (2012) 556–569.
[28] T. Ito, H.Y. Kwon, B. Zimdahl, K.L. Congdon, J. Blum, W.E. Lento, et al., Regulation of myeloid leukaemia by the cell-fate determinant Musashi, Nature 466 (2010) 765.
[29] M.-J. Wu, Y.-S. Chen, M.R. Kim, C.-C. Chang, S. Gampala, Y. Zhang, et al., Epithelial-mesenchymal transition directs stem cell polarity via regulation of mitofusin, Cell Metab. 29 (2018) 993–1002.
[30] V. Sosa, T. Moliné, R. Somoza, R. Paciucci, H. Kondoh, M.E. LLeonart, Oxidative stress and cancer: an overview, Ageing Res. Rev. 12 (2013) 376–390.
[31] K. Tominaga, H. Minato, T. Murayama, A. Sasahara, T. Nishimura, E. Kiyokawa, et al., Semaphorin signaling via MICAL3 induces symmetric cell division to expand breast cancer stem-like cells, Proc. Natl. Acad. Sci. 116 (2019) 625–630.
[32] T. Yamashita, J. Ji, A. Budhu, M. Forgues, W. Yang, H.Y. Wang, et al., EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/

progenitor cell features, Gastroenterology 136 (2009) 1012–1024 (e4).
[33] C.L. Chaffer, I. Brueckmann, C. Scheel, A.J. Kaestli, P.A. Wiggins, L.O. Rodrigues, et al., Normal and neoplastic nonstem cells can spontaneously convert to a stem-like state, Proc. Natl. Acad. Sci. 108 (2011) 7950–7955.
[34] C.L. Chaffer, N.D. Marjanovic, T. Lee, G. Bell, C.G. Kleer, F. Reinhardt, et al., Poised chromatin at the ZEB1 promoter enables breast cancer cell plasticity and enhances tumorigenicity, Cell 154 (2013) 61–74.
[35] P.B. Gupta, I. Pastushenko, A. Skibinski, C. Blanpain, C. Kuperwasser, Phenotypic plasticity: driver of cancer initiation, progression, and therapy resistance, Cell Stem Cell 24 (2018) 65–78.
[36] A. Zeuner, M. Todaro, G. Stassi, R. De Maria, Colorectal cancer stem cells: from the crypt to the clinic, Cell Stem Cell 15 (2014) 692–705.
[37] F. Cabillic, A. Corlu, Regulation of transdifferentiation and retrodifferentiation by inflammatory cytokines in hepatocellular carcinoma, Gastroenterology 151 (2016) 607–615.
[38] M. Latil, D. Nassar, B. Beck, S. Boumahdi, L. Wang, A. Brisebarre, et al., Cell-type-specific chromatin states differentially prime squamous cell carcinoma tumor-initiating cells for epithelial to mesenchymal transition, Cell Stem Cell 20 (2017) 191–204 (e5).
[39] A.M. Krebs, J. Mitschke, M.L. Losada, O. Schmalhofer, M. Boerries, H. Busch, et al., The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer, Nat. Cell Biol. 19 (2017) 518.
[40] M. Luo, L. Shang, M.D. Brooks, E. Jiagge, Y. Zhu, J.M. Buschhaus, et al., Targeting breast cancer stem cell state equilibrium through modulation of redox signaling, Cell Metab. 28 (2018) 69–86 (e6).
[41] G. Itoh, S. Chida, K. Yanagihara, M. Yashiro, N. Aiba, M. Tanaka, Cancer-associated fibroblasts induce cancer cell apoptosis that regulates invasion mode of tumours, Oncogene 36 (2017) 4434.
[42] I.S. Kim, S. Heilmann, E.R. Kansler, Y. Zhang, M. Zimmer, K. Ratnakumar, et al., Microenvironment-derived factors driving metastatic plasticity in melanoma, Nat. Commun. 8 (2017) 14343.
[43] W.-J. Chen, C.-C. Ho, Y.-L. Chang, H.-Y. Chen, C.-A. Lin, T.-Y. Ling, et al., Cancer-associated fibroblasts regulate the plasticity of lung cancer stemness via paracrine signalling, Nat. Commun. 5 (2014) 3472.
[44] J.N. Zhou, Q. Zeng, H.Y. Wang, B. Zhang, S.T. Li, X. Nan, et al., MicroRNA-125b attenuates epithelial-mesenchymal transitions and targets stem-like liver cancer cells through small mothers against decapentaplegic 2 and 4, Hepatology 62 (2015) 801–815.
[45] M. Ouzounova, E. Lee, R. Piranlioglu, A. El Andaloussi, R. Kolhe, M.F. Demirci, et al., Monocytic and granulocytic myeloid derived suppressor cells differentially regulate spatiotemporal tumour plasticity during metastatic cascade, Nat. Commun. 8 (2017) 14979.
[46] M. Murgai, W. Ju, M. Eason, J. Kline, D.W. Beury, S. Kaczanowska, et al., KLF4-dependent perivascular cell plasticity mediates pre-metastatic niche formation and metastasis, Nat. Med. 23 (2017) 1176.
[47] M.P. O'Connell, K. Marchbank, M.R. Webster, A.A. Valiga, A. Kaur, A. Vultur, et al., Hypoxia induces phenotypic plasticity and therapy resistance in melanoma via the tyrosine kinase receptors ROR1 and ROR2, Cancer Discov. 3 (2013) 1378–1393.
[48] S. Schwitalla, A.A. Fingerle, P. Cammareri, T. Nebelsiek, S.I. Göktuna, P.K. Ziegler, et al., Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties, Cell 152 (2013) 25–38.
[49] P.M. Comoglio, L. Trusolino, C. Boccaccio, Known and novel roles of the MET oncogene in cancer: a coherent approach to targeted therapy, Nat. Rev. Cancer 1 (2018).
[50] J.P. Medema, L. Vermeulen, Microenvironmental regulation of stem cells in intestinal homeostasis and cancer, Nature 474 (2011) 318.
[51] D. Iliopoulos, H.A. Hirsch, K. Struhl, An epigenetic switch involving NF-κB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation, Cell 139 (2009) 693–706.
[52] Y.-A. Tang, Chen Y-f, Y. Bao, S. Mahara, S.M.J. Yatim, G. Oguz, et al., Hypoxic tumor microenvironment activates GLI2 via HIF-1α and TGF-β2 to promote chemoresistance in colorectal cancer, Proc. Natl. Acad. Sci. 201801348 (2018).
[53] C.-J. Chang, J.-Y. Yang, W. Xia, C.-T. Chen, X. Xie, C.-H. Chao, et al., EZH2 promotes expansion of breast tumor initiating cells through activation of RAF1-β-catenin signaling, Cancer Cell 19 (2011) 86–100.
[54] J.D. Lathia, J.M. Heddleston, M. Venere, J.N. Rich, Deadly teamwork: neural cancer stem cells and the tumor microenvironment, Cell Stem Cell 8 (2011) 482–485.
[55] P. Sancho, E. Burgos-Ramos, A. Tavera, T.B. Kheir, P. Jagust, M. Schoenhals, et al., MYC/PGC-1α balance determines the metabolic phenotype and plasticity of pancreatic cancer stem cells, Cell Metab. 22 (2015) 590–605.
[56] P.C. Hermann, B. Sainz Jr., Pancreatic cancer stem cells: a state or an entity? Semin. Cancer Biol. 53 (2018) 223–231 Elsevier.
[57] A.S. Cazet, M.N. Hui, B.L. Elsworth, S.Z. Wu, D. Roden, C.-L. Chan, et al., Targeting stromal remodeling and cancer stem cell plasticity overcomes chemoresistance in triple negative breast cancer, Nat. Commun. 9 (2018).
[58] H. Dianat-Moghadam, M. Heydarifard, R. Jahanban-Esfahlan, Y. Panahi, H. Hamishehkar, F. Pouremamali, et al., Cancer stem cells-emanated therapy resistance: implications for liposomal drug delivery systems, J. Control. Release 288 (2018) 62–83.
[59] W. Zhang, J.-M. Zhao, J. Lin, C.-Z. Hu, W.-B. Zhang, W.-L. Yang, et al., Adaptive fibrogenic reprogramming of osteosarcoma stem cells promotes metastatic growth, Cell Rep. 24 (2018) 1266–1277 (e5).
[60] H.T. Tzeng, C.C. Su, C.P. Chang, W.W. Lai, W.C. Su, Y.C. Wang, Rab37 in lung cancer mediates exocytosis of soluble ST2 and thus skews macrophages towards tumor-suppressing phenotype, Int. J. Cancer 143 (2018) 1753–1763.
[61] L. Chen, S. Wang, Y. Wang, W. Zhang, K. Ma, C. Hu, et al., IL-6 influences the polarization of macrophages and the formation and growth of colorectal tumor, Oncotarget 9 (2018) 17443.
[62] D. Iliopoulos, H.A. Hirsch, G. Wang, K. Struhl, Inducible formation of breast cancer stem cells and their dynamic equilibrium with non-stem cancer cells via IL6 secretion, Proc. Natl. Acad. Sci. (2011) 201018898.
[63] B. Sainz, S. Alcala, E. Garcia, Y. Sanchez-Ripoll, M.M. Azevedo, M. Cioffi, et al., Microenvironmental hCAP-18/LL-37 promotes pancreatic ductal adenocarcinoma by activating its cancer stem cell compartment, Gut 64 (2015) 1921–1935 (gutjnl-2014-308935).
[64] B. Sainz, B. Martín, M. Tatari, C. Heeschen, S. Guerra, ISG15 is a critical microenvironmental factor for pancreatic cancer stem cells, Cancer Res. 24 (2014) 7309–7320.
[65] N. Takebe, L. Miele, P.J. Harris, W. Jeong, H. Bando, M. Kahn, et al., Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update, Nat. Rev. Clin. Oncol. 12 (2015) 445.
[66] Z. Castaño, T. Marsh, R. Tadipatri, H.S. Kuznetsov, F. Al-Shahrour, M. Paktinat, et al., Stromal EGF and IGF1 together modulate plasticity of disseminated triple negative breast tumors, Cancer Discov. 3 (2013) 922–935 (CD-13-0041).
[67] J. Chou, J.H. Lin, A. Brenot, Kim J-w, S. Provot, Z. Werb, GATA3 suppresses metastasis and modulates the tumour microenvironment by regulating microRNA-29b expression, Nat. Cell Biol. 15 (2013) 201.