Journal of Blood Disorders

Open Access

Austin Publishing Group

Special Article - Acute and Chronic Myeloid Leukemia

Some Reasons to Deeper Investigate the Vascular Niche in Acute Myeloid Leukemia

Gottardi M[1]*, Conconi MT[2], Gherlinzoni F[1] and Di Liddo R[2]

[1]Hematology, Ospedale Ca' Foncello, Italy

[2]Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Italy

***Corresponding author:** Gottardi M, Hematology, Ospedale Ca' Foncello, Piazza Ospedale 1, 31100 Treviso, Italy

Received: July 24, 2017; **Accepted:** August 01, 2017; **Published:** August 09, 2017

Editorial

Likely other solid and liquid cancers, Acute Myeloid Leukemia (AML) is characterized by a high grade of intratumoral heterogeneity [1]. Furthermore, bone marrow biopsies from AML patients show a complex ecosystem wherein cancer cells interact directly and indirectly with Tumor Microenvironment (TME) that comprises stromal, endothelial, hematopoietic and other infiltrating cells immersed in extracellular matrix. Within the tumor niche, both survival and functionality of leukemic cells are significantly affected by cell-cell, cell-matrix and cell-extrinsic factors interactions. According to the clonal evolution model, the vast majority of tumor cells propagate and drive tumor growth, thus any cancer treatment is traditionally aimed to suppress whole cancerous populations. In contrast, the Cancer Stem Cell (CSC) hypothesis, firstly reported in AML [2], associates the control of the tumor growth, the drug resistance and, finally, the recurrence of the disease to a rare population of cells characterized by self-renewal and stem cell properties [3]. According to this hypothesis, cancer cells could be divided into two subsets that are discriminated by their functionality, proliferative capacity, and clonogenic activity, and include, respectively, a relatively well-differentiated subset forming the bulk of tumor, and a smaller and less differentiated one containing clonogenic CSCs. A growing body of evidence demonstrates that CSCs are endowed with unique biologic properties, including dormancy and drug or radiation resistance, that are determinant for escaping the therapies and promote the eventual relapse of the disease. Thus, the main translational repercussion of the CSC hypothesis is the definition of therapies targeting the self-renewal of the stem-cell compartment for obtaining cancer exhaustion.

Using a pioneering approach with immunodeficient SCID mice, Dick and colleagues attributed the leukemia-initiating activity of primary human AML cells to the $CD34^{+}CD38^{-}$ subpopulation [2] that were, consequently, named Leukemia-Initiating Cells (L-ICs). As the normal Hematopoietic Stem Cells (HSCs) share the same immunophenotypic cues, the L-ICs have been suggested to arise from functionally altered HSCs. Likely normal HSCs, also L-ICs preferentially reside in the BM endosteal region, are cell cycle–quiescent and resist to chemotherapy *in vivo* [4]. Interestingly, recent studies also focused attention on the potential of TME to initiate stem cell-like program in cancer cells [5] suggesting that every tumor cell may function similarly to CSC/L-IC cells under inductive microenvironmental influences. HSC niche is generally divided into two compartments: a hypoxic endosteal bone marrow niche, that is developed within cancellous/trabecular bone and a vascular niche characterized by higher oxygen tension. The former is believed to maintain the HSCs in a quiescent state, especially during bone marrow repair. Hypoxia, that has been demonstrated to preserve the stemness of HSCs through the stabilization of the master transcriptional regulator of hypoxia response (HIF-1α), is a prominent feature of BM microenvironment in different hematological malignancies, such as leukemia [6]. A growing body of evidence suggests that HIF-1α promotes the quiescence of leukemic cells residing in the endosteal niches, thus contributing to the persistence of a minimal residual disease [7]. Finally, it has been demonstrated that hypoxia is able to activate a stemness genomic signature in cancer cells through the up-regulation of some genes such us *OCT-3/4*, *NANOG*, and *SOX2* [8], two of which were used by Takahashi and Yamanaka to generate induced Pluripotent Stem cells (iPS) from fibroblasts [9]. Based on numerous studies reporting the functional role of the endosteal niche as L-IC supportive microenvironment, therapies interfering with the endosteal localization of blasts have been proposed as a valid strategy for AML treatment. Unlike the endosteal niche, the vascular niche is characterized by both high oxygen tension and numerous cytokines stimulating proliferation and differentiation [10]. In the past, the induction of cell dormancy has been assumed as a peculiar characteristic of endosteal niche. In contrast, several studies have recently demonstrated that the vascular niche exerts an active role in regulating HSCs proliferation, differentiation but also self-renewal and quiescence, mainly through the interaction with phenotypically and molecularly unique perivascular cells, known as CXCL12-Abundant Reticular (CAR) cells [11,12]. In particular, the peri-arteriolar CARs have been shown to induce a more quiescent state of HSCs [13] and to protect them from genotoxic insults. There is compelling evidence that an increased bone marrow Micro Vessel Density (MVD) is associated to AML. As MVD is restored to physiological conditions when a complete remission of AML is induced by chemotherapy [14], a strong correlation could be hypothesized between the process of angiogenesis and AML progression [15]. The influence of leukemia cells on vessel hyperplasia essentially derives from the secretion of several pro-angiogenic factors such as Vascular Endothelial Growth Factor A (VEGFA) and Angiopoietin-1 (Ang-1) [16,17] that, overall, cause the dilatation of vessels and a reduced pericyte coverage [16]. As the inadequate pericyte coverage is demonstrated to negatively affect the structure of the capillary wall and the blood flow [18], in the advanced stages of AML even the vascular niche could paradoxically become a hypoxic niche favoring the quiescence and the chemoresistance of the leukemic cells. Besides, the growth factors such as VEGFA and Ang-1 activate Endothelial Cells (ECs) for the expression of adhesion molecules such as VCAM- and ICAM-1 (P-and E-selectin) on their

Citation: Gottardi M, Conconi MT, Gherlinzoni F and Di Liddo R. Some Reasons to Deeper Investigate the Vascular Niche in Acute Myeloid Leukemia. J Blood Disord. 2017; 4(2): 1046.

surface, leading to an increased adhesion of leukemia cells to ECs and providing a fertile niche for the propagation of more aggressive clones. Furthermore, the tight interaction between blasts and ECs also reduce the susceptibility of leukemic cells to chemotherapy eventually selecting drug-resistant subpopulations [19]. Recently, more attention has been focused either on the characterization of the niche extrinsic factors involved in the physical interactions among leukemic and endothelial cells or on the possible integration of AML cells into the vascular niche [20]. In that regard, Cogle and colleagues have shown in both patients and xenograft models that human AML cells first localize to the vasculature and then closely integrate into vascular endothelium, eventually fusing with ECs. These vascular tissue-associated AML cells (V-AML) differentiate into phenotypically and functionally defined endothelial-like cells and, worthy of note, show a significant reduction in their proliferative activity. Interestingly, the Authors demonstrated that these V-AML give rises to leukemia once transplanted. Thus, all these data suggest that endothelium may serve as a reservoir for AML and may represent a previously unrecognized site of a hidden, not detectable, minimal residual disease, consisting of quiescent and chemo resistant cells responsible for disease relapses. It is believed that environment-mediated drug resistance is a transient state whereby LSCs are protected through signals from the niche, which eventually leads to the selection of secondary genetic changes and outgrowth of cells that acquired multiple mechanisms of pharmacologic resistance. These findings have generated novel approaches targeting the microenvironment supporting the LSC phenotype.

Among vascular regulatory peptides present in the vascular niche, Adrenomedullin (ADM) is a peptide with pleiotropic effects extending from blood pressure regulation to immune modulation. Moreover, ADM is implicated in tumor angiogenesis besides the survival, proliferation and invasion of cancer cells by autocrine/paracrine mechanisms. Recently, our group has demonstrated that ADM signaling could be involved in impaired cellular differentiation of myeloid leukemia cells by modulating both the expression of its cognate receptors RAMPs/CRLR and the activity of PI3K/Akt and ERK/MAPK signaling pathways [21]. When administered exogenously to *in vitro* cultures of HL60 promyelocytic leukemia cells, ADM was shown to exert a strong proliferative effect with minimal up-regulation in the expression level of differentiation markers**.** Notably, the experimental inhibition of ADM signaling with the inhibitor ADM22-52 promoted the differentiation of leukemic blasts towards monocytic and granulocytic lineages. The AML leukemic cells express platelet/endothelial cell adhesion molecule–1 (CD31) and CD38, two adhesion molecules that are essential for physical interaction of cells with micro environmental elements, i.e., CD31 on the surface of marrow endothelial cells (CD31/CD31 and CD38/CD31 interactions) and hyaluronate (CD38/hyaluronate interactions). As previously reported by Gallay et al. [22], an overexpressed CD31 on the cell membrane of leukemic cells (CD31/CD38 ratio >1) promotes a homotypic interaction with marrow endothelial cells, and thus a higher transendothelial migration. Unlikely, an excess of CD38 (CD31/CD38 ratio <1) promotes the entrapment of leukemic cells within the bone marrow microenvironment through hyaluronate adhesion. The immunophenotypic characterization of marrow leukemic cells from 78 AML patients highlighted a correlation with the expression levels of CD38 and evidenced an excess of CD31 in peripheral leukocytes. Based on the relative expression of CD31/CD38 observed in HL-60 cells, our group speculated that high ADM levels in bone marrow vascular niche could increase physical interaction with endothelial cells and the trans-endothelial migration of leukemia cells while decreased ADM levels might increase cell retention in the bone marrow micro environment by up regulating CD38 [21]. From a therapeutic point of view, the inhibition of ADM signaling could have a significant impact in the treatment of AML, as already demonstrated for the endotoxic shock [23] and the expansion of keratinocytes, fibroblasts [24] and adrenal cortical cells [25].

In conclusion, the vascular niche can behave as an L-IC supportive microenvironment and consequently may represent an attractive target for selective therapies. To our opinion this is the main, among other, reason to deeper investigate the vascular niche in AML.

References

1. Kreso A, Dick JE. Evolution of the cancer stem cell model. Cell Stem Cell. 2014; 14: 275-291.
2. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997; 3: 730-737.
3. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001; 414: 105-111.
4. Ishikawa F, Yoshida S, Saito Y, Hijikata A, Kitamura H, Tanaka S, et al. Chemotherapy-resistant human AML stem cells home to and engraft within the bone-marrow endosteal region. Nat Biotechnol. 2007; 25: 1315-1321.
5. Vermeulen L, De Sousa E Melo F, van der Heijden M, Cameron K, de Jong JH, Borovski T, et al. Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. Nat Cell Biol. 2010; 12: 468-476.
6. Benito J, Zeng Z, Konopleva M, Wilson WR. Targeting hypoxia in the leukemia microenvironment. Int J Hematol Oncol. 2013; 2: 279-288.
7. Matsunaga T, Imataki O, Torii E, Kameda T, Shide K, Shimoda H, et al. Elevated HIF-1α expression of acute myelogenous leukemia stem cells in the endosteal hypoxic zone may be a cause of minimal residual disease in bone marrow after chemotherapy. Leuk. Res. 2012; 36: e122-e124.
8. Koh MY, Lemos R Jr, Liu X, Powis G. The hypoxia-associated factor switches cells from HIF-1α-HIF-2α dependent signalingpromoting stem cell characteristics, aggressive tumor growth and invasion. Cancer Res. 2011; 71: 4015-4027.
9. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126: 663-676.
10. Lo Celso C, Fleming HE, Wu JW, Zhao CX, Miake-Lye S, Fujisaki J, et al. Live-animal tracking of individual haematopoietic stem/progenitor cells in their niche, Nature. 2009; 457: 92-96.
11. Butler JM, Nolan DJ, Vertes EL, Varnum-Finney B, Kobayashi H, Hooper AT, et al. Endothelial cells is essential for the self-renewal and repopulation of Notch-dependent hematopoietic stem cells. Cell Stem Cell. 2010; 6: 251-264.
12. Sugiyama T, Kohara H, Noda M, Nagasawa T. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity. 2006; 25: 977-988.
13. Kunisaki Y, Bruns I, Scheiermann C, Ahmed J, Pinho S, Zhang D, et al. Arteriolar niches maintain haematopoietic stem cell quiescence. Nature. 2013; 502: 637-643.
14. Padró T, Ruiz S, Bieker R, Bürger H, Steins M, Kienast J, et al. Increased angiogenesis in the bone marrow of patients with acute myeloid leukemia. Blood. 2000; 95: 2637-2644.
15. Shih TT, Hou HA, Liu CY, Chen BB, Tang JL, Chen HY, et al. Bone marrow angiogenesis magnetic resonance imaging in patients with acute myeloid

leukemia: peak enhancement ratio is an independent predictor for overall survival. Blood. 2009; 113: 3161-3167.

16. Weidenaar AC, ter Elst A, Koopmans-Klein G, Rosati S, den Dunnen WF, Meeuwsen-de Boer T, et al. High acute myeloid leukemia derived VEGFA levels are associated with a specific vascular morphology in the leukemic bone marrow. Cell Oncol (Dordr). 2011; 34: 289-296.

17. Müller A, Lange K, Gaiser T, Hofmann M, Bartels H, Feller AC, et al. Expression of angiopoietin-1 and its receptor TEK in hematopoietic cells from patients withmyeloid leukemia. Leuk Res. 2002; 26: 163-168.

18. Jain RK. Normalizing tumor vasculature with antiangiogenic therapy: A new paradigm for combination therapy. Nat Med. 2001; 7: 987-989.

19. Poulos MG, Gars EJ, Gutkin MC, Kloss CC, Ginsberg M, Scandura JM, et al. Activation of the vascular niche supports leukemic progression and resistance to chemotherapy. Exp Hematol. 2014; 42: 976-986.

20. Cogle CR, Goldman DC, Madlambayan GJ, Leon RP, Al Masri A, Clark HA, et al. Functional integration of acute myeloid leukemia into the vascular niche. Leukemia. 2014; 28: 1978-1987.

21. Di Liddo R, Bridi D, Gottardi M, De Angeli S, Grandi C, Tasso A, et al. Adrenomedullin in the growth modulation and differentiation of acute myeloid leukemia cells. Int J Oncol. 2016; 48: 1659-1669.

22. Gallay N, Anani L, Lopez A, Colombat P, Binet C, Domenech J, et al. The role of platelet/endothelial cell adhesion molecule 1 (CD31) and CD38 antigens in marrow microenvironmental retention of acute myelogenous leukemia cells. Cancer Res. 2007; 67: 8624-8632.

23. Mazzocchi G, Albertin G, Nussdorfer GG. Adrenomedullin (ADM), acting through ADM (22-52)-sensitive receptors, is involved in the endotoxin-induced hypotension in rats. Life Sci. 2000; 66: 1445-1450.

24. Albertin G, Carraro G, Parnigotto PP, Conconi MT, Ziolkowska A, Malendowicz LK, et al. Human skin keratinocytes and fibroblasts express adrenomedullin and its receptors, and adrenomedullin enhances their growth in vitro by stimulating proliferation and inhibiting apoptosis. Int J Mol Med. 2003; 11: 635-639.

25. Rebuffat P, Macchi C, Malendowicz LK, Nussdorfer GG. Up-regulation of adrenomedullin gene expression in the regenerating rat adrenal cortex. Int J Mol Med. 2007; 20: 551-555.

J Blood Disord - Volume 4 Issue 2 - 2017
ISSN 2379-8009 | www.austinpublishinggroup.com

Citation: Gottardi M, Conconi MT, Gherlinzoni F and Di Liddo R. Some Reasons to Deeper Investigate the Vascular Niche in Acute Myeloid Leukemia. J Blood Disord. 2017; 4(2): 1046.