doi: http://dx.doi.org/10.11606/issn.1679-9836.v101i6e-174413 Rev Med (São Paulo). 2022 Nov-Dec;101(6):e-174143.

Review Article

Leukemic transformation of the hematopoietic stem cell microenvironment

Transformação leucêmica do microambiente das células-tronco hematopoiéticas

Maria Thereza Carvalho Rodriguez Guisande[1], Lorrany Junia Lopes de Lima[2], Gabriel Santos Costa[3], Jarbas Delmoutiez Ramalho Sampaio Filho[4], Matheus Rodrigues Lopes[5]

Guisande MTCR, Lima LJL, Costa GS, Sampaio Filho JDR, Lopes, MR. Leukemic transformation of the hematopoietic stem cell microenvironment / *Transformação leucêmica do microambiente das células-tronco hematopoiéticas.* Rev Med (São Paulo). 2022 Nov-Dec.;101(6):e-174413.

ABSTRACT: The microenvironment of hematopoietic stem cells is responsible for coordinating several events involved with the production of blood cells. This hematopoietic renewal is only possible thanks to the well-ordered interactions and signals that maintain tissue harmony. In leukemias, the control mechanisms break down and the leukemic transformation of the microenvironment occurs, thus favoring the neoplastic maintenance of blood tissue. From this perspective, this study aimed to investigate the microenvironment transformation process within the scope of cellular and molecular changes that support tumor progression. It is a narrative review article in which the Pubmed, SciELO, Cochrane Library, and MedLine databases were consulted in search of recent publications that addressed the proposed subject. The data obtained contribute to a more holistic understanding of leukemias. The leukemic transformation, either by primary mutations in the microenvironment components or through the sequestration of its normal functions by leukemia-initiating cells, is relevant for tumor establishment, progression, dissemination, and chemoresistance. Through the action of various components, this microenvironment supports leukemic stem cells and represents a promising path for developing new antileukemic therapies.

Keywords: Tumor microenvironment; Leukemia; Hematopoiesis; Stem Cells.

RESUMO: O microambiente das células-tronco hematopoiéticas é responsável por coordenar diversos eventos envolvidos na produção de células sanguíneas. Essa renovação hematopoiética só é possível graças às interações e sinalizações bem ordenadas que mantém a harmonia do tecido. Nas leucemias ocorre ruptura nesses mecanismos de controle e ocorre processo de transformação leucêmica do microambiente, de forma a favorecer a manutenção neoplásica do tecido sanguíneo. O objetivo deste estudo foi expor o processo de transformação leucêmica do microambiente, no âmbito das modificações celulares e moleculares sofridas para sustentar o tumor. Trata-se de um artigo de revisão narrativa e as bases de dados *Pubmed, SciELO, Cocrahne Library e MedLine* foram consultadas em busca de publicações dos últimos anos sobre o tema. Os dados apresentados contribuem para o entendimento holístico acerca das leucemias. A transformação leucêmica, seja por mutações primárias nos componentes do microambiente ou pelo sequestro de suas funções normais pelas células iniciadoras de leucemia, é relevante para que ocorra a instalação, a progressão, a disseminação e a quimiorresistência tumoral. Por meio da atuação de vários componentes este microambiente sustenta as células-tronco leucêmicas e representa caminho promissor para o desenvolvimento de novas terapias antileucêmicas.

Palavras-chave: Microambiente tumoral; Leucemia; Hematopoese; Células-tronco.

1. Universidade Federal do Vale São Francisco (UNIVASF), campus Paulo Afonso, BA. https://orcid.org/0000-0002-9125-5986. E-mail: guisande.m@gmail.com
2. Universidade Federal do Vale São Francisco (UNIVASF), campus Paulo Afonso, BA. https://orcid.org/0000-0003-3678-0101. E-mail: lorranyliima@hotmail.com
3. Universidade Federal do Vale São Francisco (UNIVASF), campus Paulo Afonso, BA. https://orcid.org/0000-0001-5696-4704. E-mail: costa.gabrielsantos@gmail.com
4. Universidade Federal do Vale São Francisco (UNIVASF), campus Paulo Afonso. BA. https://orcid.org/0000-0002-3637-3242. E-mail: jarbas.sampaiofilho@univasf.edu.br
5. Universidade Federal do Vale São Francisco (UNIVASF), campus Paulo Afonso, BA. https://orcid.org/0000-0002-3719-4131. E-mail: matheuslopesbio@gmail.com

Correspondence: Matheus Rodrigues Lopes. Universidade Federal do Vale São Francisco (UNIVASF) - Campus Paulo Afonso. Avenida da Amizade, s/nº, Sal Torrado. Paulo Afonso, Bahia, Brasil. CEP: 48605-780. E-mail: matheuslopesbio@gmail.com

INTRODUCTION

Governed by the functional capacity of cells and tissues, finitude is an intrinsic aspect of living organisms. Potential variations of these organisms occur until their death, involving stimuli of growth and development as well as loss and destruction. The main architects of these modifications are called stem cells.

Hematopoietic stem cells (HSC) are particularly associated with the origin and maintenance of blood components. Hematopoiesis, the process that forms blood cells, occurs through the proliferation, differentiation, and self-renewal of HSC cells in the bone marrow. However, the idea of their role solely for blood production has been replaced by a more holistic understanding of cell cooperation[2]. Several cells are related to HSC and are essential for hematopoietic homeostasis. This interaction is highly complex due to the dynamicity and transience of the elements of the hematopoietic niche[3].

Just as this model came to determine the physiology of the hematopoietic tissue, the possibility also emerged that it could be involved with disorders that affect blood cell production[4]. Several studies have highlighted the interactions between leukemic cells and their hematopoietic niche, corroborating the idea that changes and defects in the HSC microenvironment fatally result in blood disorders. It is, therefore, a two-way interaction mechanism: microenvironment-HSC[6].

The presence of a microenvironment capable of sustaining cancer development and progression was suggested to act in the background of this dysfunction, later called tumor microenvironment, which could be the cause or effect of malignant diseases[6,7]. Once this transformation occurs, the microenvironment becomes unable to sustain typical HSC cells, thus compromising hematopoiesis. To a greater or lesser extent, each cell and mechanism involved in blood production is sequestrated for leukemic activities of progression, dissemination, and therapeutic chemoresistance[8].

From this perspective, this study aimed to discuss the leukemic transformation process, from the structures and interactions that form the microenvironment of typical HSC cells to the modifications undergone by these cells in the tumor microenvironment.

METHODS

This is a narrative literature review. The searches were carried out in the *Pubmed, Scielo, Cochrane Library*, and *MedLine* databases. The descriptors used were "*tumor microenvironment,*" "*stem cells,*" *"leukemogenesis,"* and *"hematopoietic niche*". The Boolean operator AND was used in each database.

Initially, 441 articles whose titles were compatible with the objectives of this study were selected. After briefly reading their abstracts, 292 articles were excluded for not addressing the subject of this study or because they had a similar and more recent equivalent. Of the remaining 149 articles, 98 were excluded after full reading for showing no direct relationship with the objective of this review. As a result, a final sample of 51 articles was obtained.

Original articles, systematic reviews, and narrative reviews published from 2015 to 2020 in the national and international literature were selected. Only the data published as full articles were included. Articles with more than five years of publication were only included in exceptional cases when attributed great relevance with regard to the subject proposed.

RESULTS

Leukemic transformation of the microenvironment

The leukemogenesis process can be thought of based on two dichotomic models: the hierarchical and stochastic models. The first was proposed in 1997 by Bonnet and Dick, who described a hierarchical organization for the emergence of acute myeloid leukemia (AML)[9] (Figure 1).

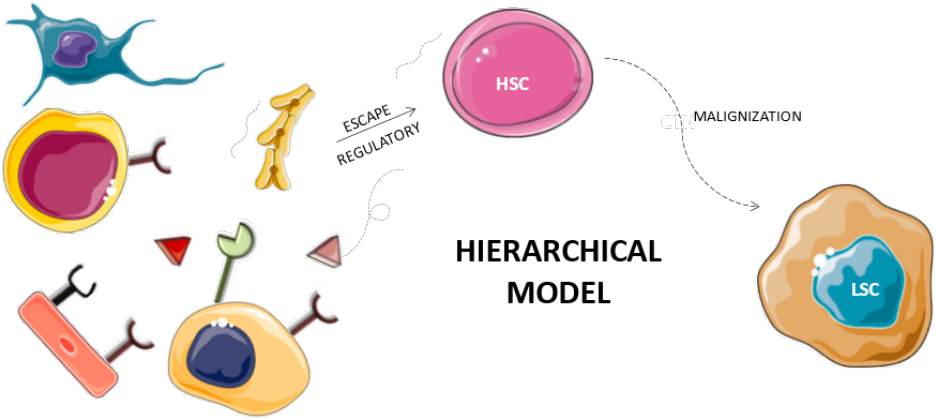

Figure 1. Hierarchical model depicting the leukemic transformation process. The phenotypically normal HSC cells, after escaping from physiological regulation functions in the microenvironment (shown on the left in the figure), can exert uncoordinated activities that direct them toward malignization, culminating in their transformation into LSC. HSC: Hematopoietic stem cells; LSC: Leukemic stem cells.

The second (stochastic) model admits that every cell within the tumor is equally subject to becoming a leukemia-initiating cell, facilitating the progression of this condition. This deterministic process would be associated with chance[10] (Figure 2).

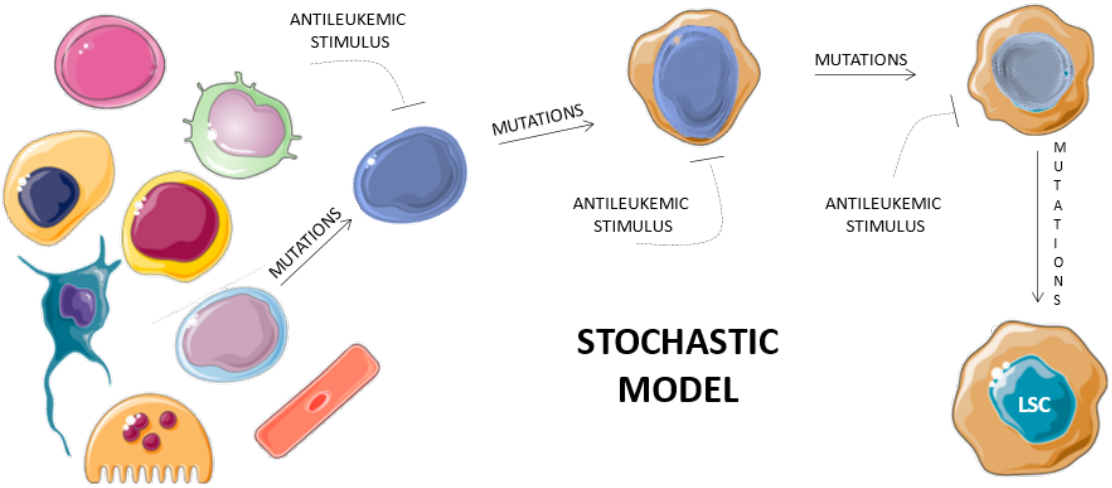

Figure 2. Stochastic model depicting the leukemic transformation process. Any cell within the bone marrow microenvironment, shown on the left of the figure, is equally susceptible to occasional mutations. When significantly modifying one of these cells, these mutations can turn it into a phenotypically atypical cell. In response to that, the typical cells of the microenvironment attempt to prevent progression through antileukemic stimuli. In order not to be eliminated, the atypical cell then needs to survive by acquiring resistance to these stimuli through successive mutations, which culminate in their progression into a leukemic stem cell. LSC: leukemic stem cell

Phenotypic plasticity refers to the ability of tumor cells to range between differentiated and undifferentiated states, with no established subgroup of stem cells[10]. From this perspective, a hierarchical model would only make sense if that hierarchical state implied a transient arrangement of cells that could soon alter their differentiation states. Therefore, a stochastic model would refer to the dynamicity with which hierarchical models reorganize depending on the stimuli. In both cases, leukemic stem cells (LSC) and their progenitors would be controlled by the microenvironment. As a result, at a given moment, the LSC could no longer phenotypically correspond to the cells that originated cancer[11].

Tumor heterogeneity also seems to be influenced by the diversity of genetic and epigenetic expression coordinated by the microenvironment. This heterogeneity apparently contributes to disease progression, impacts therapeutic efficacy, and interferes with patient survival. From this perspective, the heterogeneous remodeling that the microenvironment can exert on leukemic cells could be used as a parameter for the clinical course and serve as a prognostic predictor[12,13].

Leukemic cells can change this microenvironment by creating a leukemic microenvironment that acquires a significant role in the malignant progression of stem cells (Figure 3). Typical HSC, for example, when removed from their leukemic niche and transplanted into a healthy recipient, can have their self-renovation potential restored, verifying the defining role of the microenvironment in these cases[14].

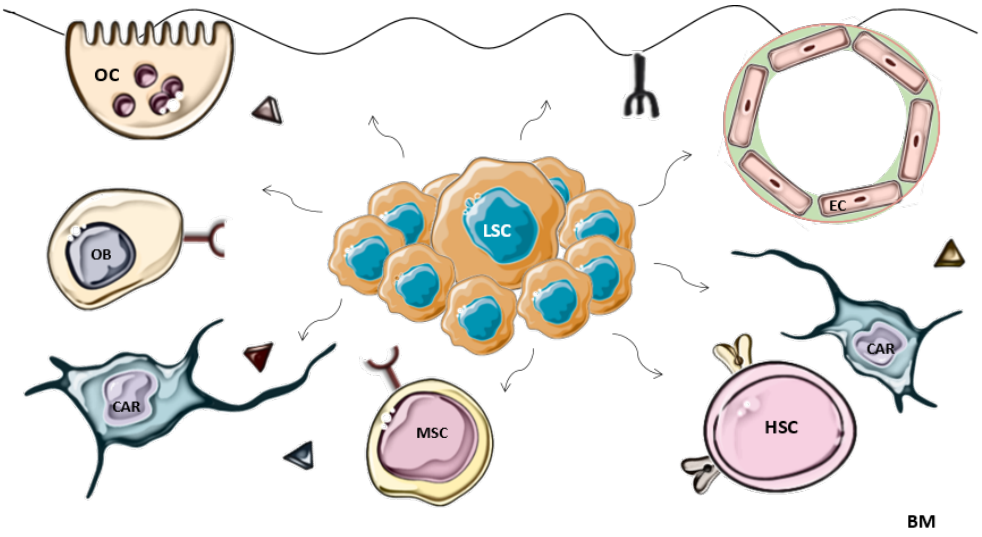

Figure 3. Leukemic transformation model of the HSC microenvironment. The leukemic stem cells, through regulatory stimuli, can sequestrate microenvironment components and subject them to leukemic transformation, thus working in favor of tumoral progression. CAR: CXCL12-abundant reticular; EC: endothelial cells; HSC: hematopoietic stem cells; LSC: leukemic stem cells; MSC: mesenchymal stem cells; BM: bone marrow; OB: osteoblast; OC: osteoclast

Cells

Leukemic stem cells

Leukemic stem cells are phenotypically different from both normal HSC and other LSC, depending on the patient in whom they are found. In their origin process, they derive from regular counterparts and/or leukemic progenitors that undergo phenotypic plasticity, acquiring the abilities of tumor stem cells. Among these, the characteristic intense proliferation and low differentiation stand out. Therefore, LSC represent the selective unit of a tumor, capable of preventing clonal exhaustion[15].

LSC-intrinsic mutations can conduce these cells toward a hyperproliferative and potent state under invasion and metastasis conditions. Therefore, the niche that previously served to maintain the quiescence of stem cells is reconfigured to withstand the dominant proliferation of the malignant counterpart. For that purpose, the LSC cells sequestrate the homeostatic mechanisms that regulate the HSC, using this niche to maintain them and escape from the cytotoxic effects of therapeutic interventions[16].

Mesenchymal stem cells (MSC)

MSC represent one of the cells of the niche that contribute to the leukemic microenvironment after LSC deregulation, especially through cell-to-cell contact, thus stimulating tumor progression with the promotion of the undifferentiated state. Furthermore, these cells can induce cancer proliferation and metastasis, favoring angiogenesis and immunosuppression. Several studies have reported that the interaction between MSC and malignant cells provides resistance to chemotherapeutic agents[17,18].

Osteolineage cells

Similar to the MSC, malignant cells can also reprogram osteoblasts so that these can compose a pro-inflammatory niche that supports the LSC. One such change is observed in the capacity to generate maintenance and retention factors for typical HSC cells. This support provided by osteoblasts to maintain the HSC in the normal niche is then provided to the malignant cells of the leukemic niche. Therefore, osteoblasts represent a supportive microenvironment to quiescent LSC and provide chemoresistance to therapy through tyrosine kinase inhibitors[19]. Furthermore, studies have highlighted that genetic dysfunction in osteoprogenitor cells is capable of causing an acute malignant process, thus corroborating the observation that leukemia both transforms the niche and can result from its modification[20].

Endothelial cells

Endothelial cells are important units for leukemia development. Their primary function is to regulate cell migration from the bone marrow to the blood. Furthermore, their adhesion molecules are relevant to stimulating progenitor HSC cells[21]. It has also been evidenced that endothelial cells with the same genetic anomalies as malignant cells are present in increased numbers in leukemia patients, consequently increasing the microvasculature that supports the leukemic niche, coordinated by the greater nutrient and oxygen demand[22].

Cancer-associated fibroblasts

Fibroblasts can also be transformed through LSC induction, thus becoming associated with cancer. Compared with normal states, these cells show increased proliferation rates, higher extracellular matrix production, and release of cytokines such as CXCL-12, VEGF, and PDGF[23]. Furthermore, cancer-associated fibroblasts stimulate the continuity of LSC through pathways such as WNT and Notch. Cancer-associated fibroblasts also increase the expression of LSC markers through the remodeling of the extracellular matrix by MMP2, 3, and 9[24].

Cells of the sympathetic nervous system

The role of the sympathetic nervous system was suggested after observing that leukemogenesis can be promoted through B2- adrenergic receptors in stromal cells of the niche, with damage to the sympathetic nervous system and infiltration of leukemic cells into the bone marrow. However, when not sequestrated by malignant cells, the sympathetic nervous system tends to protect the healthy microenvironment, responsible for the activation and rapid mobilization of HSC[25].

Leukemic cells seek to annul the action of the sympathetic nervous system so that this process can generate a loss of MSC and Schwann cells with the acceleration of the neoplastic process through the release of IL-1beta, responsible for generating neural damage[25].

Tissue status

Tissue hypoxia

The proportionally low vascularization within tumors can result in hypoxia, regulating a series of genes for stem cell development. LSC cells are better adapted than HSC to the hypoxic microenvironment. LSC location in the hypoxic niches can also minimize exposure to anti-tumoral therapies. Therefore, leukemic progression has been associated with the expansion of tissue hypoxia markers[7].

The most expressive marker is Hif-1α, involved in the upregulation of the receptor CXCR-4 in leukemic blasts and its ligand CXCL-12 in the endothelial cells of the hypoxic niche, facilitating the recruitment and retention of leukemic progenitor cells in the microenvironment. Furthermore, Hif-1α is related to the increase in angiogenesis for the reestablishment of an appropriate blood supply[26].

Immunomodulation

Immunosurveillance is one of the stages that leukemic cells need to overcome for tumoral progression. Leukemic blasts can induce the differentiation of monocytes into an M2-like type capable of suppressing the immune response[27]. This change is part of the process through which cancer cells release cytokines and chemokines capable of recruiting defense cells associated with the tumor, promoting the immunosuppression of cells associated with the protection of the host[28].

Cancer cells express the inflammatory profile of the tumoral environment capable of sustaining tumor proliferation and metastasis. Some inflammatory cytokines that participate in this regulation contribute to chronic inflammation, changing the functions of hematopoietic cells, dendritic cells, NK cells, and T cells. Furthermore, cytokines also modulate other aspects of the tumoral environment, promoting cancer degradation. For example, prostaglandin E2 acts in inflammation and can promote immune dysfunction and escape from immunosurveillance, whereas the cytokines IL-1beta, GM-CSF, IL-3, and TNF-alfa can increase the growth rates of leukemic cells in LMA[29].

Likewise, other tumoral cells that do not express the stem cell phenotype can secrete pro-leukemic cytokines, e.g., the IL-6 and IL-18 secreted by MSC, which can be involved in carcinogenesis[24].

Genetic modulation

Genetic modulation for leukemic transformation in the microenvironment is possible through lipid vesicles or microparticles called exosomes, secreted by cancer cells, mesenchymal stromal cells, macrophages, dendritic cells, B and T lymphocytes, mastocytes, and endothelial cells[30].

These exosomes are associated with the bidirectional transfer of mRNAs, microRNAs, and other proteins between malignant and adjacent cells, inducing genetic expression changes in the occupied niche. Furthermore, the serum content of exosomes associated with microRNA can be used as an AML-sensitive indicator through several disease biomarkers. As a result, the secretion of growth factors and the reprogramming of niche cells can be altered[31,32].

Adhesion molecules

Adhesion molecules are responsible for the cell-to-cell contact in the microenvironment. They are involved in the regulation of several cell processes, e.g., the morphogenesis of cell development, differentiation, inflammatory responses, angiogenesis, wound healing, tumor progression, and metastasis[33,34] (Figure 4).

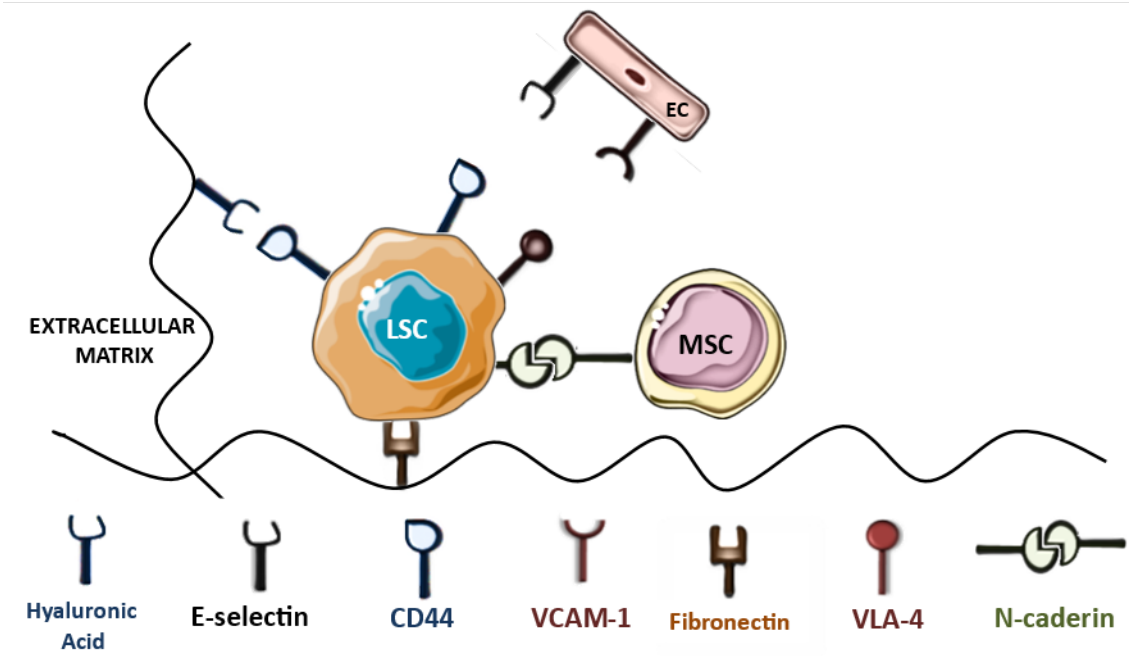

Figure 4. Model representing the main adhesion molecules in the leukemic microenvironment. Through various adhesion molecules, malignant cells can Interact with other cells and structures important for leukemic progression activities. EC: endothelial cells; MSC: mesenchymal stromal cells

Integrins play an important role in the fixation of leukemic cells in the microenvironment since the binding they promote can activate pro-survival signs. It is the case, for example, of the kinases associated with integrins, which can interact with beta integrins and activate the AKT pathway to promote the survival of leukemic cells[34,35].

N-cadherin is one such adhesion molecule involved with the tumoral microenvironment, playing a crucial role

in the self-renewal process of LSC cells[36]. CD44, in turn, is an important molecule in the regulation of homing, engraftment, and maintenance of the primitive states of LSC cells. Increased CD44 levels are also associated with AML[37,38]. Increased CD44 expression was also observed in the models of mice with chronic myeloid leukemia (CML), probably through the transcriptional regulator SCL/TAL1[39].

In healthy neutrophils, CD44 is not the main ligand with E-selectin. However, this profile changes in blast cells of acute leukemia, with greater interaction between CD44 and E-selectin, resulting in increased diversity in the expression and activity of adhesion molecules and affecting blast migration to the bone marrow and extramedullary tissues[38,40].

The adhesion molecule E-selectin is a relevant component in the vascular niche of HSC cells and is considered overexpressed in the endothelial sinuses of the AML microenvironment. It has also been shown that AML blasts release pro-inflammatory factors that increase the expression of E-selectin in the bone marrow endothelium, forming an endothelial protective niche for survival. In CML, one of its roles in the niche seems to be in the engraftment of leukemia-initiating cells. In both forms of leukemia, this molecule is relevant for the migration and repopulation of the bone marrow vascular niche[38,41,42].

The adhesion of leukemic blasts that express E-selectin in the vascular niche contributes to the survival of leukemic cells through favorable signs, e.g., Wnt activation[43]. In that regard, another study with mice observed that leukemic blasts, though the AKT/NF-κB signaling pathways, favored the expression of receptors in cells with a high binding potential to E-selectin and greater survival advantage to chemotherapy and disease relapse[42].

Similar to hyaluronic acid, fibronectin belongs to the extracellular matrix of the microenvironment and is produced by various cells. When present at metastasis sites, these cells increase fibronectin deposition, agglomerating hematopoietic cells in the new niche. In association, fibronectin-coated cells in the AML microenvironment are more resistant to apoptosis and show an increased survival rate[26].

Signaling molecules

Indoleamine 2,3-dioxygenase (IDO)

IDO is an enzyme involved in the metabolism of the amino acid tryptophan and is upregulated under inflammation conditions, e.g., leukemias. IDO seems to contribute to the differentiation of T cells responsible for the immunosuppression of defense cells. In addition, this enzyme is involved with the modification of the tumoral microenvironment through immunosurveillance escape mechanisms[44].

CXCL-12

CXCL-12 is important for various leukemic processes and is associated with HSC displacement in the normal microenvironment. Leukemic cells typically express CXCR-4, the binding receptor to the chemokine CXCL-12. Their interaction has shown to be especially relevant for the homing and lodgment of malignant cells in the niche and the activation of pro-survival signaling pathways[45].

The interaction between LSC and microenvironment via CXCL-12/CXCR-4 allows molecular exchange with the promotion of chemoresistance, resulting in patient relapse after chemotherapy[26].

Stem cell factor (SCF)

In the tumor microenvironment, the SCF is involved with stem cell migration to the detriment of CXCL-12. Leukemic progression implies increased stimuli for SCF production, and the homing of malignant cells occurs almost exclusively through SCF. The self-renewal, proliferation, and differentiation of typical HSC cells are compromised when subjected to SCF regulation by the tumor microenvironment. Also, the unregulated secretion of SCF inhibits the apoptosis of leukemic cells and allows their development through paracrine stimuli[26].

Vascular endothelial growth factor (VEGF)

Released by leukemic cells, the VEGF stimulates leukemic proliferation and endothelial cells through the stimuli to mitotic responses as well as survival, migration, and self-renewal responses. Moreover, this factor also inhibits apoptosis[46].

Highly metastatic tumors have a large number of VEGF receptors, probably due to the association between neo-angiogenesis and the metastatic potential of cancer[47]. VEGF receptors are also present in macrophages and endothelial cells of the target tissues of metastasis, inducing an increased expression of matrix metalloproteinases that contribute to forming the metastatic niche[48].

The VEGF seems to act by coordinating vascular permeability and stimulating the dilatation of lymphatic vessels through the synthesis of prostaglandins, benefiting the locomotion of tumor cells through the lymphatic network[48].

Stimuli for VEGF production are increased under hypoxic conditions. The stromal cells present in the tumor microenvironment form pre-angiogenic factors that stimulate the multiplication and migration of endothelial cells, resulting in the formation of new blood vessels responsible for increasing the oxygen supply and the nutrition of tumor cells[48,49]. Furthermore, increased plasma levels of VEGF and its receptor are correlated with a worse prognosis[47,49].

Hepatocyte growth factor (HGF)

The HGF belongs to the family of growth factors,

and there is evidence that its presence in the niche can regulate leukemia development. Released by activated human basophils, it is considered a pro-angiogenic factor, and its expression is related to increased blast growth and cell migration in the AML microenvironment. CML patients show increased HGF expression, probably because of basophilia, frequent during the accelerated phase of the disease. This fact is probably due to the loss or reduction of the transcription factor IKAROS in the leukemic blasts of the bone marrow[50].

A recent study with chronic lymphocytic leukemia (CLL) patients has shown that peculiar cell types from the bone marrow stroma, components of the tumor microenvironment, produce high HGF levels concomitantly to the increased expression of its transmembrane receptor, c-MET. The HGF/c-MET interaction contributes to the expansion of the leukemic clone and favors the pathogenesis of CLL[51].

DISCUSSION

The data shown in this review contribute to the holistic understanding of leukemias. Previously thought only through the optics of malignant stem cells, these neoplasias can be seen from a more complex organization perspective. The importance of the HSC microenvironment for this leukemic structuration is presented in a two-way manner: a modified microenvironment facilitates the appearance of neoplasias just as these progress from changes caused by them in the microenvironment. This process is called leukemic transformation[19,26], in which cells, adhesion molecules, factors, and signaling pathways have their functions sequestered in the service of malignant cells[6].

The healthy microenvironment tends to exert physiological regulations aiming to achieve hematopoiesis and hamper the development and progression of leukemia, corroborating the fact that only the changed microenvironment is permissive to cancer. Therefore, the mechanism used by malignant cells to compete with HSC consists of changing the regulatory expression of this niche[10,12]. It is inferred that the sequestration of the microenvironment only corrupts the intensity and destination of cell stimuli since the nature of the support is similar in both healthy and tumoral niches. The altered osteoblastic niche, for example, continues to promote LSC quiescence, which explains its participation in tumor chemoresistance[16]. Just as in normal hematopoiesis, endothelial cells are also used by leukemic cells to facilitate proliferation and dissemination to other tissues and organs[21,22].

The tissue status is also relevant for the leukemic microenvironment since hypoxia concomitantly represents a consequence of tumor growth and promotes adaptations in malignant cells to promote tumor resistance[7,26]. Furthermore, immunomodulation is important for cancer initiation and progression since it involves the leukemic transformation of immune cells, modifying their expression profile, and the activation of cytokines with a pro-leukemic profile[29].

Adhesion molecules allow the communication of malignant cells with the niche. This communication, in addition to being associated with the activation of various pro-leukemic signaling pathways, is also crucial for malignant cells to homing and lodgment to the microenvironment in order to allow malignant engraftment[38,41]. Regarding this communication, signaling molecules represent the main intercellular messengers, most of which promote several maintenance stimuli for leukemic cells. Furthermore, they are intimately involved with chemoresistance to therapy, neoangiogenesis, and the formation of the metastatic niche[44-49].

CONCLUSION

Leukemic transformation, either through primary mutations in the microenvironment components or the sequestration of its typical functions by leukemia-initiating cells, is relevant for tumor establishment, progression, dissemination, and chemoresistance. In addition, through the role of several components, this microenvironment sustains leukemic stem cells and represents a promising way to develop new anti-leukemic therapies.

Ethical aspects: The authors declare that no conflicts of interest exist

Author contributions: *Guisande MTCR* – participated in the conception of the study, research, data obtainment, and writing of the manuscript. *Lima LJL* and *Costa GS* - research, data obtainment, and writing of the manuscript. *Sampaio Filho JDR* – interpretation and critical review of the manuscript. *Lopes MR* - conception of the study, guidance, analysis, writing, and critical review of the manuscript.

REFERENCES

1. Daley GQ. Stem cells and the evolving notion of cellular identity. Philos Trans R Soc Lond B Biol Sci. 2015;370(1680):20140376. doi: http://doi.org/10.1098/rstb.2014.0376

2. Sugiyama T, Omatsu Y, Nagasawa T. Niches for hematopoietic stem cells and immune cell progenitors. Int Immunol. 2019;31(1):5-11. doi: http://doi.org/10.1093/intimm/dxy058

3. Vernot J-P, Bonilla X, Rodriguez-Pardo V, Vanegas ND. Phenotypic and functional alterations of hematopoietic stem and progenitor cells in an in vitro leukemia-induced microenvironment. Int J Mol Sci. 2017;18(2):199. doi: http://doi.org/10.3390/ijms18020199

4. Geyh S, Oz S, Cadeddu RP, Fröbel J, Brückner B, Kündgen A, Fenk R, et al. Insufficient stromal support in MDS results from molecular and functional deficits of mesenchymal stromal cells. Leukemia. 2013;27(9):1841-51. doi: http://doi.org/10.1038/leu.2013.193

5. Duarte D, Hawkins ED, Akinduro O, et al. Inhibition of endosteal vascular niche remodeling rescues hematopoietic stem cell loss in AML. Cell Stem Cell. 2018;22(1):64-77. e6. doi: http://doi.org/10.1016/j.stem.2017.11.006

6. Raaijmakers MH, Mukherjee S, Guo S, et al. Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. Nature. 2010;464(7290):852-7. doi: http://doi.org/10.1038/nature08851

7. Kumar B, Garcia M, Weng L, et al. Acute myeloid leukemia transforms the bone marrow niche into a leukemia-permissive microenvironment through exosome secretion. Leukemia. 2018;32(3):575-587. doi: http://doi.org/10.1038/leu.2017.259

8. Akinduro O, Weber TS, Ang H, et al. Proliferation dynamics of acute myeloid leukaemia and haematopoietic progenitors competing for bone marrow space. Nat Commun. 2018;9(1):519. doi: http://doi.org/10.1038/s41467-017-02376-5

9. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997;3(7):730-7. doi: http://doi.org/10.1038/nm0797-730

10. Quail DF, J Taylor M, Postovit LM. Microenvironmental regulation of cancer stem cell phenotypes. Curr Stem Cell Res Ther. 2012;7(3):197-216. doi: http://dx.doi.org/10.2174/157488812799859838

11. Chaffer CL, Weinberg RA. How does multistep tumorigenesis really proceed? Cancer Discov. 2015;5(1):22-4. doi: http://doi.org/10.1158/2159-8290.CD-14-0788

12. Kim JA, Shim JS, Lee GY, et al. Microenvironmental remodeling as a parameter and prognostic factor of heterogeneous leukemogenesis in acute myelogenous leukemia. Cancer Res. 2015;75(11):2222-31. doi: http://doi.org/10.1158/0008-5472.CAN-14-3379

13. Haas S, Trumpp A, Milsom MD. Causes and consequences of hematopoietic stem cell heterogeneity. Cell Stem Cell. 2018;22(5):627-638. doi: http://doi.org/10.1016/j.stem.2018.04.003

14. Hu X, Shen H, Tian C, et al. Kinetics of normal hematopoietic stem and progenitor cells in a Notch1-induced leukemia model. Blood. 2009;114(18):3783-92. doi: http://doi.org/10.1182/blood-2009-06-227843

15. Brown G, Sánchez L, Sánchez-García I. Lineage Decision-Making within Normal Haematopoietic and Leukemic Stem Cells. Int J Mol Sci. 2020;21(6):2247. doi: http://doi.org/10.3390/ijms21062247

16. Lopes MR, Pereira JK, de Melo Campos P, et al. De novo AML exhibits greater microenvironment dysregulation compared to AML with myelodysplasia-related changes. Sci Rep. 2017;7:40707. doi: http://doi.org/10.1038/srep40707

17. Cuiffo BG, Karnoub AE. Mesenchymal stem cells in tumor development: emerging roles and concepts. Cell Adh Migr. 2012;6(3):220-30. doi: http://doi.org/10.4161/cam.20875.

18. Jacamo R, Chen Y, Wang Z, et al. Reciprocal leukemia-stroma VCAM-1/VLA-4-dependent activation of NF-κB mediates chemoresistance. Blood. 2014;123(17):2691-702. doi: http://doi.org/10.1182/blood-2013-06-511527

19. Heath JL, Cohn GM, Zaidi SK, Stein GS. The role of cell adhesion in hematopoiesis and leukemogenesis. J Cell Physiol. 2019;234(11):19189-19198. doi: http://doi.org/10.1002/jcp.28636

20. Le PM, Andreeff M, Battula VL. Osteogenic niche in the regulation of normal hematopoiesis and leukemogenesis. Haematologica. 2018;103(12):1945-1955. doi: http://doi.org/10.3324/haematol.2018.197004

21. Goulard M, Dosquet C, Bonnet D. Role of the microenvironment in myeloid malignancies. Cell Mol Life Sci. 2018;75(8):1377-1391. doi: http://doi.org/10.1007/s00018-017-2725-4

22. Ladikou EE, Sivaloganathan H, Pepper A, Chevassut T. Acute myeloid leukaemia in its niche: the bone marrow microenvironment in acute myeloid leukaemia. Curr Oncol Rep. 2020;22(3):27. doi: http://doi.org/10.1007/s11912-020-0885-0

23. Junttila MR, de Sauvage FJ. Influence of tumour microenvironment heterogeneity on therapeutic response. Nature. 2013;501(7467):346-54. doi: http://doi.org/10.1038/nature12626

24. Cabarcas SM, Mathews LA, Farrar WL. The cancer stem cell niche - there goes the neighborhood? Int J Cancer. 2011;129(10):2315-27. doi: http://doi.org/10.1002/ijc.26312

25. Schmitt-Graeff AH, Nitschke R, Zeiser R. The hematopoietic niche in myeloproliferative neoplasms. Mediators Inflamm. 2015;2015:347270. doi: http://doi.org/10.1155/2015/347270

26. Wang A, Zhong H. Roles of the bone marrow niche in hematopoiesis, leukemogenesis, and chemotherapy resistance in acute myeloid leukemia. Hematology. 2018;23(10):729-739. doi: http://doi.org/10.1080/10245332.2018.1486064

27. Mussai F, De Santo C, Abu-Dayyeh I, et al. Acute myeloid leukemia creates an arginase-dependent immunosuppressive microenvironment. Blood. 2013;122(5):749-58. doi: http://doi.org/10.1182/blood-2013-01-480129

28. Kitamura T, Qian BZ, Pollard JW. Immune cell promotion of metastasis. Nat Rev Immunol. 2015;15(2):73-86. doi: http://doi.org/10.1038/nri3789

29. Binder S, Luciano M, Horejs-Hoeck J. The cytokine network in acute myeloid leukemia (AML): A focus on pro-and anti-inflammatory mediators. Cytokine Growth Factor Rev. 2018;43:8-15. doi: http://doi.org/10.1016/j.cytogfr.2018.08.004

30. Jaiswal R, Luk F, Gong J, Mathys JM, Grau GER, Bebawy M. Microparticle conferred microRNA profiles-implications in the transfer and dominance of cancer traits. Mol Cancer. 2012;11:37. doi: http://doi.org/10.1186/1476-4598-11-37

31. Corrado C, Raimondo S, Saieva L, Flugy AM, De Leo G, Alessandro R. Exosome-mediated crosstalk between chronic myelogenous leukemia cells and human bone marrow stromal cells triggers an interleukin 8-dependent survival of leukemia cells. Cancer Lett. 2014;348(1-2):71-6. doi: http://doi.org/10.1016/j.canlet.2014.03.009

32. Fernandes Q. MicroRNA: Defining a new niche in Leukemia. Blood Rev. 2017;31(3):129-138. doi: http://doi.org/10.1016/j.blre.2016.11.003

33. Mashreghi M, Azarpara H, Bazaz MR, et al. Angiogenesis biomarkers and their targeting ligands as potential targets for tumor angiogenesis. J Cell Physiol. 2018;233(4):2949-2965. doi: http://doi.org/10.1002/jcp.26049

34. Harjunpää H, Llort Asens M, Guenther C, Fagerholm SC. Cell adhesion molecules and their roles and regulation in the immune and tumor microenvironment. Front Immunol. 2019;10:1078. doi: http://doi.org/10.3389/fimmu.2019.01078

35. Sanchez VE, Nichols C, Kim HN, Gang EJ, Kim YM. Targeting PI3K signaling in acute lymphoblastic leukemia. Int J Mol Sci. 2019;20(2):412. doi: http://doi.org/10.3390/ijms20020412

36. Windisch R, Pirschtat N, Kellner C, et al. Oncogenic Deregulation of Cell Adhesion Molecules in Leukemia. Cancers (Basel). 2019;11(3):311. doi: http://doi.org/10.3390/cancers11030311

37. Quere R, Andradottir S, Brun A, et al. High levels of the adhesion molecule CD44 on leukemic cells generate acute myeloid leukemia relapse after withdrawal of the initial transforming event. Leukemia. 2011;25(3):515-26. doi: http://doi.org/10.1038/leu.2010.281

38. Spertini C, Baïsse B, Bellone M, Gikic M, Smirnova T, Spertini O. Acute myeloid and lymphoblastic leukemia cell interactions with endothelial selectins: critical role of PSGL-1, CD44 and CD43. Cancers (Basel). 2019;11(9):1253. doi: http://doi.org/10.3390/cancers11091253

39. Godavarthy PS, Kumar R, Herkt SC, et al. The vascular bone marrow niche influences outcome in chronic myeloid leukemia via the E-selectin-SCL/TAL1-CD44 axis. Haematologica. 2020;105(1):136-147. doi: http://doi.org/10.3324/haematol.2018.212365

40. Morath I, Hartmann T, Orian-Rousseau V. CD44: more than a mere stem cell marker. Int J Biochem Cell Biol. 2016;81(Pt A):166-173. doi: http://doi.org/10.1016/j.biocel.2016.09.009

41. Krause DS, Lazarides K, Lewis JB, von Andrian UH, Van Etten RA. Selectins and their ligands are required for homing and engraftment of BCR-ABL1+ leukemic stem cells in the bone marrow niche. Blood. 2014;123(9):1361-71. doi: http://doi.org/10.1182/blood-2013-11-538694

42. Barbier V, Erbani J, Fiveash C, et al. Endothelial E-selectin inhibition improves acute myeloid leukaemia therapy by disrupting vascular niche-mediated chemoresistance. Nat Commun. 2020 Apr 27;11(1):2042. doi: http://doi.org/10.1038/s41467-020-15817-5

43. Chien S, Haq SU, Pawlus M, et al. Adhesion of acute myeloid leukemia blasts to E-selectin in the vascular niche enhances their survival by mechanisms such as Wnt activation. Blood. 2013;122(21):61. http://doi.org/10.1182/blood.V122.21.61.61

44. Mansour I, Zayed RA, Said F, Latif LA. Indoleamine 2, 3-dioxygenase and regulatory T cells in acute myeloid leukemia. Hematology. 2016;21(8):447-53. doi: http://doi.org/10.1080/10245332.2015.1106814

45. Yanagisawa B, Ghiaur G, Smith BD, Jones RJ. Translating leukemia stem cells into the clinical setting: harmonizing the heterogeneity. Exp Hematol. 2016;44(12):1130-1137. doi: http://doi.org/10.1016/j.exphem.2016.08.010

46. Song M, Wang H, Ye Q. Increased circulating vascular endothelial growth factor in acute myeloid leukemia patients: a systematic review and meta-analysis. Syst Rev. 2020;9(1):103. doi: http://doi.org/10.1186/s13643-020-01368-9

47. Lu RM, Chiu CY, Liu IJ, Chang YL, Liu YJ, Wu HC. Novel human Ab against vascular endothelial growth factor receptor 2 shows therapeutic potential for leukemia and prostate cancer. Cancer Sci. 2019;110(12):3773-3787. doi: http://doi.org/10.1111/cas.14208

48. Ceci C, Atzori MG, Lacal PM, Graziani G. Role of VEGFs/VEGFR-1 Signaling and its inhibition in modulating tumor invasion: Experimental evidence in different metastatic cancer models. Int J Mol Sci. 2020;21(4):1388. doi: http://doi.org/10.3390/ijms21041388

49. Palodetto B, Duarte ASS, Lopes MR, Adolfo Corrocher F, Roversi FM, Soares Niemann F, Priscila Vieira Ferro K, Leda Figueiredo Longhini A, Melo Campos P, Favaro P, Teresinha Olalla Saad S. SEMA3A partially reverses VEGF effects through binding to neuropilin-1. Stem Cell Res. 2017;22:70-78. doi: http://doi.org/10.1016/j.scr.2017.05.012

50. Marone G, Gambardella AR, Mattei F, Mancini J, Schiavoni G, Varricchi G. Basophils in tumor microenvironment and surroundings. Adv Exp Med Biol. 2020;1224:21-34. doi: http://doi.org/10.1007/978-3-030-35723-8_2.

51. Giannoni P, Fais F, Cutrona G, Totero D. Hepatocyte growth factor: a microenvironmental resource for leukemic cell growth. Int J Mol Sci. 2019;20(2):292. doi: http://doi.org/10.3390/ijms20020292

Received: September 02, 2020
Accepted: May 27, 2022