



Editorial: Novel Drugs Targeting the Microenvironment and the Epigenetic Changes in Hematopoietic Malignancies

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Editorial on the Research Article

Novel Drugs Targeting the Microenvironment and the Epigenetic Changes in Hematopoietic Malignancies

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Starting with the first definition of epigenetics “to understand how the genotypes of evolving organisms can respond to the environment in a more co-ordinated fashion” originated in the research of Conrad Hal Waddington (1942) until current days, the field of epigenetics has evolved greatly (Dimopoulos and Gronbaek, 2019). We are now aware not only of the substantial contribution of the epigenomic patterns in development and homeostasis, but also of the profound implications of epigenetic alteration in disease pathogenesis (Stahl et al., 2016). Hematological malignancies light the way and provided proof-of-concept not only for the unraveling the role of epigenetic alterations in disease, but also for correcting these alterations and the clinical development of novel therapies (DNA hypomethylating agents and histone deacetylase inhibitors) for patients with myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML). Large scale studies of cancer cells show an epigenetic drift toward global hypomethylation with enhances chromosomal instability or intensified hypermethylation at CpG islands within the promoter of tumor suppressor genes and sustained tumorigenesis (Eden et al., 2003; Herman and Baylin, 2003; Karpf and Matsui, 2005; Esteller, 2008). On top of this, further research has shown that epigenetic mechanisms have deep implications for the establishment of cancer permissive microenvironments (Maio et al., 2015). The deploy of epigenetic alterations has been shown to hijack the mechanisms of immune surveillance in order to escape the antitumor immune responses (Cao and Yan, 2020). In this sense, by remodeling the tumor microenvironment, a combination between immunotherapy and epigenetic agents may provide clinical benefit for patients with incomplete responses to immunomodulatory agents (Villanueva et al., 2020). In addition, efforts are undertaken to understand the role of epigenetic alterations and tumor microenvironment in reshaping the metabolic fitness and chemoresistance of cancer cells (Carrar and Wellen, 2015; Forte et al., 2019). There is increasing evidence that the tumor

microenvironment is essential for maintaining malignant hematopoiesis. Since stromal elements (i.e., cancer-associated fibroblast, endothelial cells and other) do not exhibit somatic mutations, they are likely to be corrupted by the malignant cells via epigenetic driven events (Sylvestre et al., 2020). To this point, mesenchymal stromal cells from AML show focal points of DNA hypermethylation, but also global hypomethylation compared to their normal counterparts (von der Heide et al., 2017). Therefore, epigenetic therapy could benefit patients with hematological malignancies not only due to reprogramming the cancer cells, but also by rescuing the tumor microenvironment.

The Research Topic entitled *Novel Drugs Targeting the Microenvironment and the Epigenetic Changes in Hematopoietic Malignancies* covers recent advancements in our understanding of the role of the microenvironment in hematological malignancies. To this end, response to epigenetic drugs are presented within a cohort of juvenile myelomonocytic leukemia (JMML) cases that were molecularly annotated via targeted next generation sequencing (NSG). Treatment with 5-Azacytidine was well tolerated and had effective results in both *de novo* JMML and relapsed patients (Marcu et al., 2020). The authors are highlighting the paramount role of microenvironment not only in disease progression and treatment response, but also in the outcomes of bone marrow transplantation in these patients. These data emphasize the importance of establishing a healthy substrate for normal hematopoiesis in patients with MDS undergoing bone marrow transplantation. The article is expanding on the alterations that intervene in cancer associated stromal cells and how different therapies, including epigenetic agents can modulate the malignant environment (Teodorescu et al., 2020). The heterogeneity of the tumor microenvironment within AML is discussed with a focus on how unique immune profiles can serve as a surrogate distinct prognosis profiles for patients with hematological malignancies. Whether or not these changes are related to genetic and epigenetic events remains to be discussed (Antohe et al., 2020). The concept of minimal residual disease (MRD) in oncological hematology is presented within this research topic (Radu et al., 2020). In addition, DNA methylation patterns detected via revolutionary surface-enhanced Raman spectroscopy (SERS) are used as quantifiable biomarkers of circulating tumor cells in liquid biopsies (Turcas et al., 2020).

Although the critical influence of the epigenetic landscape on cancer cells survival and development has been recognized, so is its role in the establishment of supportive tumor environments. Nevertheless, the heterogeneous clinical response of hematological malignancies patients to epigenetic therapy suggests a complex relation between epigenetics and cellular behavior. Perhaps the newly emerging field of epitranscriptomics may provide the missing link between modulation of gene expression and the malignant phenotype. To this end, N⁶-methyladenosine (m⁶A) is the most common non-genetic alteration in mRNAs. M⁶A impacts RNA metabolism and thus, mediates aberrant gene expression seen in disease development (Chen et al., 2019). RNA methylation is mediated by m⁶A methyltransferases, removed by

demethylases and identified by m⁶A binding proteins, all of them recognized as “writers,” “erasers,” and “readers” respectively (Lan et al., 2019). The mechanism of RNA methylation in solid and hematological tumors is in its early years, without comprehensive clarification, and whatever this mechanism can surpass epigenetic changes is unknown. m⁶A enhances the translation of PTEN, BCL2, and c-MYC in AML (Vu et al., 2017), where YTHDF2 (m⁶A binding proteins) increases the expression of Tal1 (Li et al., 2018). On top, FMR1 (protein from the m⁶A binding complex) can bind multiple mRNAs to impair their translation and function (Edupuganti et al., 2017). However, how the entire RNA methylation machinery is functioning in cancer is still unknown; available data are showing distinct expression profiles of various “writers,” “erasers” and “readers” between cancer patients and distinct global m⁶A methylation profiles (Chen et al., 2019). The heterogeneity of these molecular profiles is demonstrating that RNA methylation is a dynamic process that can shift toward malignant favoring mechanisms, including during epigenetic treatment. Therefore, hematological patients that are non-responders to demethylating agents could be characterized by a dominant RNA methylation profile that favors the cancer phenotype or could present compensatory feedback mechanisms at the level of RNA to impede the modifications from the DNA induced by epigenetic therapy. Wide screening of different markers from the RNA methylation machinery could predict the eligible patients for epigenetic treatment, while analysis of the molecular background of the non-responder patients could offer new insights into the mechanisms of dynamic RNA methylation in cancer.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REFERENCES

- Antohe, I., Dascalescu, A., Danaila, C., Titieanu, A., Zlei, M., Ivanov, I., et al. (2020). B7-Positive and B7-negative acute myeloid leukemias display distinct T cell maturation profiles, immune checkpoint receptor expression, and European leukemia net risk profiles. *Front. Oncol.* 10, 264. doi:10.3389/fonc.2020.00264
- Cao, J., and Yan, Q. (2020). Cancer epigenetics, tumor immunity, and immunotherapy. *Trends Cancer.* 6 (7), 580–592. doi:10.1016/j.trecan.2020.02.003
- Carrer, A., and Wellen, K. E. (2015). Metabolism and epigenetics: a link cancer cells exploit. *Curr. Opin. Biotechnol.* 34, 23–29. doi:10.1016/j.copbio.2014.11.012
- Chen, X.-Y., Zhang, J., and Zhu, J.-S. (2019). The role of m6A RNA methylation in human cancer. *Mol. Cancer* 18 (1), 103. doi:10.1186/s12943-019-1033-z
- Dimopoulos, K., and Gronbaek, K. (2019). Epigenetic therapy in hematological cancers. *APMIS* 127 (5), 316–328. doi:10.1111/apm.12906
- Eden, A., Gaudet, F., Waghmare, A., and Jaenisch, R. (2003). Chromosomal instability and tumors promoted by DNA hypomethylation. *Science* 300 (5618), 455. doi:10.1126/science.1083557
- Edupuganti, R. R., Geiger, S., Lindeboom, R. G. H., Shi, H., Hsu, P. J., Lu, Z., et al. (2017). N(6)-methyladenosine (m6A) recruits and repels proteins to regulate mRNA homeostasis. *Nat. Struct. Mol. Biol.* 24 (10), 870–878. doi:10.1038/nsmb.3462
- Esteller, M. (2008). Epigenetics in cancer. *N. Engl. J. Med.* 358 (11), 1148–1159. doi:10.1056/NEJMra072067
- Forte, D., Krause, D. S., Andreeff, M., Bonnet, D., and Mendez-Ferrer, S. (2019). Updates on the hematologic tumor microenvironment and its therapeutic targeting. *Haematologica* 104 (10), 1928–1934. doi:10.3324/haematol.2018.195396
- Herman, J. G., and Baylin, S. B. (2003). Gene silencing in cancer in association with promoter hypermethylation. *N. Engl. J. Med.* 349 (21), 2042–2054. doi:10.1056/NEJMra023075
- Karpf, A. R., and Matsui, S. (2005). Genetic disruption of cytosine DNA methyltransferase enzymes induces chromosomal instability in human cancer cells. *Cancer Res.* 65 (19), 8635–8639. doi:10.1158/0008-5472.CAN-05-1961
- Lan, Q., Liu, P. Y., Haase, J., Bell, J. L., Huttelmaier, S., and Liu, T. (2019). The critical role of RNA m(6A) methylation in cancer. *Cancer Res.* 79 (7), 1285–1292. doi:10.1158/0008-5472.CAN-18-2965
- Li, Z., Qian, P., Shao, W., Shi, H., He, X. C., Gogol, M., et al. (2018). Suppression of m(6A) reader Ythdf2 promotes hematopoietic stem cell expansion. *Cell Res.* 28 (9), 904–917. doi:10.1038/s41422-018-0072-0
- Maio, M., Covre, A., Fratta, E., Di Giacomo, A. M., Taverna, P., Natali, P. G., et al. (2015). Molecular pathways: at the crossroads of cancer epigenetics and immunotherapy. *Clin. Cancer Res.* 21 (18), 4040–4047. doi:10.1158/1078-0432.CCR-14-2914
- Marcu, A., Colita, A., Radu, L. E., Jercan, C. G., Bica, A. M., Asan, M., et al. (2020). Single-center experience with epigenetic treatment for juvenile myelomonocytic leukemia. *Front. Oncol.* 10, 484. doi:10.3389/fonc.2020.00484
- Radu, L. E., Colita, A., Pasca, S., Tomuleasa, C., Popa, C., Serban, C., et al. (2020). Day 15 and day 33 minimal residual disease assessment for acute lymphoblastic leukemia patients treated according to the BFM ALL IC 2009 protocol: single-center experience of 133 cases. *Front. Oncol.* 10, 923. doi:10.3389/fonc.2020.00923
- Stahl, M., Kohrman, N., Gore, S. D., Kim, T. K., Zeidan, A. M., and Prebet, T. (2016). Epigenetics in cancer: a hematological perspective. *PLoS Genet.* 12 (10), e1006193. doi:10.1371/journal.pgen.1006193
- Sylvestre, M., Tarte, K., and Roulois, D. (2020). Epigenetic mechanisms driving tumor supportive microenvironment differentiation and function: a role in cancer therapy?. *Epigenomics* 12 (2), 157–169. doi:10.2217/epi-2019-0165
- Teodorescu, P., Pasca, S., Dima, D., Tomuleasa, C., and Ghiaur, G. (2020). Targeting the microenvironment in MDS: the final frontier. *Front. Pharmacol.* 11, 1044. doi:10.3389/fphar.2020.01044
- Turcas, C., Moisoiu, V., Stefanu, A., Jurj, A., Iancu, S. D., Teodorescu, P., et al. (2020). SERS-based assessment of MRD in acute promyelocytic leukemia?. *Front Oncol* 10, 1024. doi:10.3389/fonc.2020.01024
- Villanueva, L., Alvarez-Errico, D., and Esteller, M. (2020). The contribution of epigenetics to cancer immunotherapy. *Trends Immunol.* 41 (8), 676–691. doi:10.1016/j.it.2020.06.002
- von der Heide, E. K., Neumann, M., Vosberg, S., James, A. R., Schroeder, M. P., Ortiz-Tanchez, J., et al. (2017). Molecular alterations in bone marrow mesenchymal stromal cells derived from acute myeloid leukemia patients. *Leukemia* 31 (5), 1069–1078. doi:10.1038/leu.2016.324
- Vu, L. P., Pickering, B. F., Cheng, Y., Zaccara, S., Nguyen, D., Minuesa, G., et al. (2017). The N(6)-methyladenosine (m6A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells. *Nat. Med.* 23 (11), 1369–1376. doi:10.1038/nm.4416

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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