EBioMedicine 35 (2018) 24

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Restoring the Long Noncoding RNA MEG3 Indicates a Potential Role for JAK-STAT Signaling in Chronic Myeloid Leukemia

Thomas L. Olson, Thomas P. Loughran Jr. *

University of Virginia Cancer Center, Charlottesville, VA 22903, USA

Chronic Myeloid Leukemia (CML) is associated with a somatic rearrangement, the Philadelphia chromosome [1], which results in the formation of a fusion gene between the breakpoint cluster (BCR) and Abelson murine leukemia viral oncogene homolog 1 (ABL1). As BCR-ABL is a constitutively active tyrosine kinase, the treatment of choice is one of several tyrosine kinase inhibitors (TKI), which have been shown to be quite effective in increasing the 5-year survival rate of this disease. There are many factors including side effects, patient dosing preferences, and molecular and clinical staging that determine the TKI of choice. Not all patients will tolerate a TKI and these also show lower efficacy in advanced stages of CML [2] including the accelerated phase (CML-AP) where cells multiply more rapidly and blast phase (CML-BP) that more closely resembles an acute leukemia. It is in this space of TKI intolerant or non-responsive CML that Li et al. have performed their work.

They expand on a previous finding that the long noncoding RNA (lncRNA) maternally expressed 3 (MEG3) shows decreased levels in CML [3]. In this manuscript they show a decrease of MEG3 transcript in cells from CML-AP and CML-BP patients and a concordant increase in methylation of the MEG3 promoter. Treatment with Chidamide, an HDAC inhibitor that has been evaluated to treat peripheral T cell lymphoma (PTCL) [4] was sufficient to remove this methylation and restore MEG3 levels. This led to reduced viability and increased apoptosis of CML-AP and CML-BP patient-derived cells. This treatment decreased the transcript and protein levels of several epigenetic modifier genes including DNMTs and an HDAC. miR-147 was also investigated, due to its predicted interaction with MEG3, and the two were shown to negatively regulate each other in transfected cell lines. It is unclear in what contexts this negative regulation is important. In CML patient cells and cell lines both MEG3 and mir-147 were shown to function similarly. Both demonstrated decreased expression in all CML stages and restoration of levels decreased proliferation and promoted apoptosis. They were also shown to decrease those same epigenetic modifiers influenced by Chidamide, thus suggesting they could be mediating the effects of Chidamide upstream of these proteins rather than being a downstream consequence of their epigenetic influence.

lncRNAs have been shown to directly interact with proteins among other functions [5] and the authors conducted RNA- pulldown and RNA immune precipitation to identify and confirm proteins bound by MEG3. DNMT1 and HDAC1, which were demonstrated in prior experiments to be reduced by MEG3 transfection, were shown to interact directly with MEG3 RNA. Additionally, they demonstrated and confirmed that MEG3 can bind to several members of the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway and that expression of MEG3 leads to a reduction in JAK-STAT signaling. Inhibition of STAT signaling leads to higher levels of MEG3 indicating the presence of a feedback loop.

JAK-STAT signaling is important for normal lymphocyte biology and is dysregulated in multiple cancers, but only frequently mutated in one [6]. These findings suggest a role for MEG3 in the regulation of JAK-STAT signaling and it should be examined in those cancers with active STAT signaling from unknown sources and alternatively to determine if regulatory function is maintained in the presence of mutation.

More broadly these findings put forth Chidamide, MEG3, mir-147 and existing JAK-STAT inhibitors as potential therapeutics for CML. Chidamide is already in use for PTCL and is orally available making it a promising choice. Alternatively, it is less clear how MEG3 or mir-147, being that they are RNAs, can be restored as a therapeutic intervention but these may prove to be useful markers of Chidamide response.

The authors declare no conflicts of interest.

References

[1] Nowell PC, Hungerford DA. Chromosome studies on normal and leukemic human leukocytes. J Natl Cancer Inst 1960;25:85–109.
[2] Soverini S, Mancini M, Bavaro L, Cavo M, Martinelli G. Chronic myeloid leukemia: the paradigm of targeting oncogenic tyrosine kinase signaling and counteracting resistance for successful cancer therapy. Mol Cancer 2018;17:49.
[3] Li Z, Yang L, Liu X, Nie Z, Luo J. Long noncoding RNA MEG3 inhibits proliferation of chronic myeloid leukemia cells by sponging microRNA21. Biomed Pharmacother 2018;104:181–92.
[4] Shi Y, et al. Chidamide in relapsed or refractory peripheral T cell lymphoma: a multicenter real-world study in China. J Hematol Oncol 2017;10:69.
[5] Wilusz JE, Sunwoo H, Spector DL. Long noncoding RNAs: functional surprises from the RNA world. Genes Dev 2009;23:1494–504.
[6] Koskela HL, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med 2012;366:1905–13.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.07.013.
* Corresponding author.
E-mail address: TL7CS@hscmail.mcc.virginia.edu (T.P. Loughran).

https://doi.org/10.1016/j.ebiom.2018.08.019