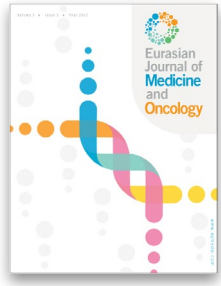
EJMO

DOI: 10.14744/ejmo.2019.21089
EJMO 2019;3(4):246–250



Review

H19: A Regulatory Biomarker with Prognostic Value in Leukemias

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Abstract

There are pieces of evidence indicating the important role of long noncoding RNAs (lncRNA) with transcription factors and their effect on gene expression at transcription and epigenetic levels. The possible role of lncRNAs in humans have been investigated the involvement of H19 in cancers, including leukemia. H19 inhibits the transcription of IGF-2 receptor via miR-675 and thereby regulates IGF-2 signaling. In chronic myeloproliferative disorders (CMPD), bone marrow cells of patients express H19 in significantly lower levels than healthy samples, and the reduced expression of H19 through IGF-2 reinforces the growth signal. H19 plays a regulatory role in maintaining the proliferation and self-renewal abilities of HSCs. This molecule also influences the pathogenesis of leukemia due to its role in increasing the proliferation and regulating the quiescence of stem cells. Accordingly, it may be possible to consider H19 as a prognostic biomarker for myeloid disorders. In this review, the probable regulatory role of H19 as a prognostic biomarker with a variable role dependent upon disease context will be discussed.

Keywords: H19, Long noncoding RNA, Leukemia, prognostic, regulatory

Cite This Article: *Ghanavat M, Khodadi E, Sadegh Pezeshki SM, Shahjahani M, Shahrabi S. H19: A Regulatory Biomarker with Prognostic Value in Leukemias. EJMO 2019;3(4):246–250.*

Leukemia is a blood cell malignancy with bone marrow involvement and can be lymphoid or myeloid depending on the involved cell line. The basic pathogenesis of leukemia has not been completely recognized. Leukemia is divided into acute and chronic types according to disease progression, and there are pieces of evidence suggesting the relationship between long noncoding RNAs (lncRNA) and leukemia.[1]

lncRNAs, which are not able to encode proteins, are a group of noncoding RNAs (ncRNAs) transcribed by RNA polymerase II attracting much attention over the past decade. Several studies have indicated the important role of lncRNA interactions with transcription factors and their impact on gene expression in transcript and epigenetic levels.[1] In mammals, the expression of a majority of genes is controlled by genetic imprinting process, and a number of lncRNAs (e.g. the transcript of H19 gene) are involved in the regulatory imprinting process.[2] Research has elucidated the biological roles of lncRNAs, including the transcript of H19 gene in humans and has pointed to their potential role in cancers such as leukemia.[3–6] This review mentions the biological role of H19 in humans, especially

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Submitted Date: July 21, 2019 **Accepted Date:** October 14, 2019 **Available Online Date:** November 13, 2019

its relationship with the production of blood cell lineages, as well as its involvement in biology of hematopoietic stem cell (HSCs). Afterwards, the potential role of H19 as a prognostic biomarker in leukemia and the possible function of this biomarker in new therapeutic strategies for leukemia will be highlighted.

H19: History, Biology, and Interactions

In the early third millennium, when sequencing results of the entire human genome were released for the first time, it turned out that a majority of human DNA did not encode proteins and that almost <10% of total RNA in the cell played a role in encoding for proteins.[7, 8] Non-coding RNAs can be divided into two groups based on the number of nucleotides: RNAs with <200 nucleotides and those with >200 nucleotides, including lncRNAs.[9] Non-coding genes appear to be generated through various mechanisms such as duplication of genes present in the existing genome sequences.[7] These new and important findings led the scientific community to seek to answer the question of the role of this large part of human genome and its specific biological function.

In the past decade, new lncRNAs, including H19, were discovered.[10] New findings concerning lncRNAs led to the idea that the existence of the transcripts of lncRNA genes, as well as their ratio relative to the entire genome, correlated with the complexity of an organism.[7] Although the exact role of these transcripts is still unknown, their significant role in human evolutionary processes cannot be ignored. On the other hand, the presence of various mutations in the regions harboring these transcripts has raised the possibility of their association with various diseases in recent years.[7, 11]

H19 is an imprinted gene of lncRNA family that is located on 11p15.5 locus along with another imprinted gene called IGF-2.[11] Studies have indicated the role of H19 in tumorigenesis, proliferation, apoptosis, and metastasis, and the association between the expression of this gene and cancer has been suggested.[12] H19 has a high expression level in embryonic tissues but its expression decreases after birth.[13, 14] The tumor suppressor role of H19 has been suggested, although its biological function seems to be related to embryonic development and embryonic tissues.[11] Apparently, H19 exerts its biological effects through the interaction with several factors in the body; for example, this lncRNA has been specified as a precursor of miR-675, which is involved in various malignancies such as liver and colorectal cancers.[4–14] MiRs form another group of non-coding RNAs that exercise their effects on gene expression in post-translational stages.[15] The effects of miRs and their significant roles have been shown in vital biological processes such as proliferation, cell differentiation, apoptosis, and hematopoiesis,[16] which, in addition to demonstrating the importance of non-coding RNAs in humans, suggest that miRs could mediate the effects of other regulatory factors such as H19 because of their involvement in the above-mentioned processes. The miR-675 seems to play a role in H19 regulation, which is mediated by signaling pathways such as EGR-1.[4] H19 is likely to inhibit the transcription of IGF-2 receptor via miR-675, and H19 is thus able to regulate IGF-2 signaling.[17] C-Myc is another transcription factor affecting H19, which has a regulatory effect on H19 together with p53 gene.[14] A study on gastric cancer, which showed that H19 expression was affected by c-Myc and that the changing expression of H19 was associated with cell proliferation in patients, confirmed the role of c-Myc and H19 in cancer.[5] However, the prognostic role of H19 transcript is not limited to gastric cancer. Studies in patients with lung cancer have also pointed to prognostic and diagnostic roles of this transcript and have concluded that increased H19 expression is associated with a poor prognosis in patients.[18]

After birth, H19 level in HSCs is higher than that in blood progenitors.[19] It is now known that the expression of H19 in HSCs is related to their quiescence state. If the expression of H19 is increased, the proliferation potential of HSCs is increased, but their self-renewal capacity is decreased.[17] Research has indicated that H19 is involved in the induction of commitment in blood lineages and that the lack of H19 may be associated with delayed maturation of different hematopoietic series.[20] Recently, a study has shown the regulatory role of H19 gene transcript in BM osteogenesis process.[21] Hypoxia is another factor contributing to the regulation of H19, which, similar to c-Myc, causes the upregulation of H19 expression.[9]

Considering the role of H19 in hematopoiesis and the importance of preserving self-renewal capacity of HSCs for hematopoiesis, precise mechanisms (which require further studies) should reasonably regulate H19 expression and its effect on HSCs in the bone marrow; on the other hand, the same role highlights the likelihood of H19 involvement in the pathogenesis of leukemia.

Expanding Role of H19 in Leukemias

While studying chronic myeloproliferative disorders (CMPD), researchers showed that bone marrow cells of patients had a significantly lower expression level of H19 than healthy samples and that the reduced expression of H19 increased the expression of IGF-2, which in turn led to an increase in growth signal. They also mentioned the involvement of loss of IGF-2 gene imprinting in Acute Myeloblastic

Leukemia (AML) and Chronic Myeloblastic Leukemia (CML), which resulted in changing expressions of IGF-2 and H19.[13] These findings suggest that high H19 levels can be interpreted as an indicator of good prognosis in patients with myeloproliferative disorders who have not entered the acute phase. Given the regulatory role of c-Myc for H19, studies have shown that the H19/c-Myc/Bcr-Abl signaling pathway is involved in leukemogenesis.[1] H19 gene seems to play a role in cell differentiation through JAK/STAT signaling pathway by inhibiting apoptosis in collaboration with Bcr-Abl oncogene.[12, 14] On the other hand, concentrating on this association has indicated that increasing H19 expression in CML blast phase is related with increased effectiveness of Bcr-Abl transcript during disease progression, a finding that emphasizes the poor prognosis of increasing H19 expression in CML blast phase.[12] Increased H19 expression can be interpreted as a likely biomarker of poor prognosis with regard to the above findings concerning the enhanced CML progression towards accelerated and blast phases.

Studies have shown the association between increased expression of LIN28B protein in JMML patients with changing H19 expression and have concluded that increased H19-mediated expression of LIN28B plays a role in the pathogenesis of JMML.[22] Lack of H19 gene imprinting in Adult T-cell Leukemia/Lymphoma (ATLL) has been observed in both acute and chronic states of this disease. According to this finding, the lack of H19 gene imprinting can be seen as a factor related to the initiation of disease.[23] Lack of H19 has also been reported with an increase in miR-138 levels.[21] Investigating the role of miR-138 in drug refractoriness of leukemic cells has shown that the upregulation of this miR is probably associated with resistance to drug in the applied cell line of HL-60.[24] It has also been previously reported that miR-138 is involved in p53-mediated cell programming.[25] Based on the above findings, we can assume that increasing H19 expression, which is indirectly mediated by downregulation of miR-138, reduces the drug resistance of leukemic cells and is likely to lead to a better response to treatment in patients; therefore, increased H19 levels can be indicative of the response to treatment in patients with leukemia.

However, unlike previous findings, a study has shown the upregulation of H19 gene in multiple myeloma (MM). Increased H19 expression is likely to be synergistically associated with NF-KB pathway to regulate the growth of malignant cells. The findings of this study consider the role of oncogene for H19 biomarker and attribute a variable regulatory role to this biomarker that is dependent upon the context of malignancy.[26]

With regard to the above findings, the study of interactions between c-Myc, H19, and Bcr-Abl is suggested to better appreciate their association with signaling of leukemic cells. Such studies will lead to a better understanding of molecular basis of leukemia, especially CML. Moreover, further information in relation to H19 signaling provides the opportunity to take advantage of it in new therapeutic strategies. Using the above findings, we can hypothesize that H19 levels in leukemic cells are associated with the drug resistance of these cells, and H19 can thus be introduced as a prognostic biomarker for leukemia. In general, given the reciprocal regulatory and imprinting relationships between H19 gene and IGF-2, we can expect that a higher H19 expression in myeloid disorders before transformation into acute states be associated with a better prognosis because a higher expression of H19 is assumed to suppress growth signaling in HSC cells and blood precursors.

Discussion and Future Perspectives

Recently, various lncRNAs such as H19 have been implicated in various diseases, including cancers and leukemias.[23, 27, 31–34] Therefore, much effort has been made to clarify the molecular interaction mechanisms of lncRNAs. Although the lncRNAs have only recently become attractive research subjects, there are increasing pieces of evidence suggesting the changing expressions of H19 in various cancers and leukemias, which raise the likelihood of the involvement of this gene in the pathogenesis of leukemia. Dysregulated methylation due to downregulation of H19 gene in JMML can be interpreted as indicative of a poor prognosis, and the association of H19 gene imprinting with the course of ATLL has also made a prognostic factor from H19. A correlation has been observed between increased expression of H19 in MM patients with the levels of some cytokines and NF-KB signaling pathway.[26] The study of interaction between H19 and NF-KB signaling would probably be a new approach to better understand the pathophysiology of disease. H19 and its expression could be considered as a prognostic biomarker given the regulatory relationship between IGF-2 and H19, as well as their reciprocal effects on signaling of myeloid leukemia (Fig. 1).

H19 plays a regulatory role to preserve the biological capabilities of HSCs, namely high proliferation and self-renewal capacities. In general, H19 is necessary to maintain the quiescence state of HSCs, but requires further research to completely understand its role.[17] Overall, the reduced expression of H19 via increasing signaling of IGF-2 mediated by miR-675 stimulates stem cell proliferation. On the other hand, following the reduction of H19 and through miR-138 factor upregulation, the potential resistance to drug is developed in leukemic cells. Furthermore, increasing expres-

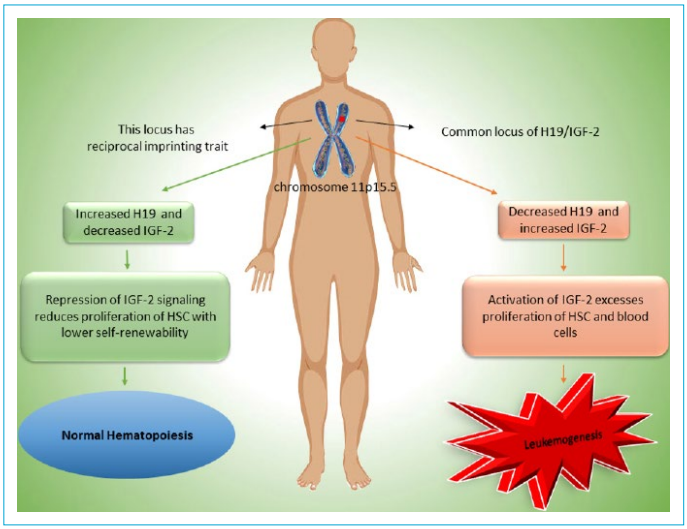

Figure 1. A possible relationship between H19/IGF-2 signaling and occurrence of Leukemia. In normal conditions, reciprocal imprinting causes a high expression of H19 while IGF-2 expression is low, which leads to reduced proliferation of HSC with lower self-renewability. However, in abnormal conditions, a low expression of H19 activates IGF-2, which results in leukemogenesis. Abbreviations: IGF-2: insulin-like growth factor–2, HSC: Hematopoietic Stem Cells.

sion of H19 also increases the effectiveness of Bcr-Abl oncogene transcript in CML during the blast phase.[4, 12, 14, 21, 24]

Tumor growth needs the telomerase (hTERT) reactivation. Studies have shown that the H19 is a potential candidate of telomerase regulation by using a microarray method. In addition, there was a link between H19 and hTERT expressions and H19 could inhibit telomerase function using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and quantitative telomeric repeats amplification protocol (qTRAP). This finding showed that the telomerase can be regulated by H19 and thus H19 can be targeted for therapeutic purposes in acute promyelocytic leukemia (APL).[35] New studies have found a strong relationship between H19 expression and patients' characteristics such as gender, white blood cells (WBCs), older age, and intermediate karyotype, FLT3-ITD, and DNMT3A mutations in AML patients. In addition, H19 expression was related to lower complete remission (CR) rate and shorter overall survival in these patients. H19 also showed a pro-apoptotic effect in leukemic cell HL60 its expression was positively related to downstream gene ID2 in AML patients. So, these findings showed that H19 was a prognostic biomarker, and H19/ID2 played a vital role in leukemogenesis and was a therapeutic target in AML.[36]

DDX43 expression increases the survival and colonel expansion and inhibits cell apoptosis in CML cell lines. Studies have shown that down-regulation of miR-186 leads to DDX43 up-regulation as its target gene, in which increase the progression of CML. DDX43 can upregulates the H19 expression by its demethylation and silencing and inhibit cell survival. This finding shows that regulating of H19 by DDX43 increase tumorigenesis and CML progression.[37]

These findings indicate the significant role of changing H19 expression in pathogenesis of leukemia. H19 seems to have a regulatory role in cancers, in addition to being a prognostic biomarker in leukemia. In this review, it has been shown that the changes in the expressions of H19 biomarker in chronic and acute phases of myeloid leukemia as well as increasing H19 expression in MM have a poor prognosis value and that H19 could be a prognostic factor in leukemia due to increased expression of it during tumorigenesis. Also, H19 can be a therapeutic target in AML and have an important role in CML progression. So, it can be suggested that H19 is a regulatory biomarker with prognostic role in leukemias.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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