Are lymphomas result of aberrant epigenetic regulation of immune system? molecular insights and therapeutic prospects

Opinion

Epigenetic regulation of immune system function remains obscure at present. The uncontrolled growth of cells and tissues of the immune system results in a condition known as lymphoma, or Lymphoma cancer that originates from B or T cells. Until last decade malignancies were thought to arise mainly due to genomic alterations, but recently epigenetic modifications also have been found to be associated with cancers in addition to previously known causes. Epigenetic plays an important gene regulatory function in organ development or cell proliferation. Epigenetic constitutes heritable changes in gene expression that operates independent of changes in DNA. DNA methylation, RNA mediated silencing and histone modifications are the three important epigenetic aspects which interact with each other within the cell. Epigenetic alterations frequently caused by mutations in chromatin modifying enzymes and enzymes involved in DNA methylation, which impacts the accessibility of DNA for transcription factors. This results in altered expression of the respective gene leading to tumor genesis.

Lymphomas are of two types, Hodgkin’s and non-Hodgkin’s lymphoma (NHL). Most common non-Hodgkin lymphomas are Follicular lymphomas and diffuse large B-cell lymphomas. Though these two forms share many mutant alleles, the search for underlying cause for phenotypic difference showed that DNA methylation patterning plays a key role in hematopoietic development and that DNA methylation and expression signatures define molecular subtypes of diffuse large B-cell lymphomas. Patterns of abnormal DNA methylation was shown to vary depending on chromosomal regions, gene density and the status of neighboring genes. Abnormal DNA methylation is said to arise via two distinct processes:

a. Promoter DNA methylation gets perturbed by lymphomagenic transcriptional regulators in a target gene-specific manner, and

b. In the absence of CTCF insulator binding sites aberrant epigenetic states tend to spread to neighboring promoters.

There are many epigenetic modifications in lymphoma cells that are known to reprogram the epigenome leading to sustained proliferation and tumor progression. Activating point mutations occur in histone methyltransferase (HMT) enhancer of zeste homolog 2 (EZH2), a component of Polycomb repressive complex (PRC2) in GCB DLBCL (germinal center B-cell Diffuse large B-cell lymphoma) and FL (Follicular lymphoma). These mutations result in gain-of-function promotes trimethylation of H3K27 leading to inhibition of tumour-suppressor genes. EZH2 was highly expressed in NHL, including ALCL (anaplastic large cell lymphoma).

Hypermethylation of histone 3 lysine 4 (H3K4) by MLL (mixed-lineage leukemia) partially opposes the action of EZH2. MLL is a methyl transferase enzyme that in humans belongs to Trithorax-group protein (TrxG). MLL forms a complex with UTX a Demethylase of H3K27. Thus both EZH2 and MLL illustrates the role of epigenetics in Lymphomagenesis. CDKN2A/p16 gene CpG region hypermethylation is associated with non-Hodgkin lymphoma (NHL). Mutations in TET2 (Tet methylcytosine dioxygenase 2), IDH2 (Isocitrate dehydrogenase 2), and DNMT3A (DNA methyltransferase 3A) have been associated with both PTCL-NOS (peripheral T cell lymphomas, not otherwise specified) and AITL (angioimmunoblastic T cell lymphoma). Isocitrate is converted to alpha-ketoglutarate by IDH2. Mutations in IDH2 results in unintentional production of 2-hydroxyglutarate (2HG), inhibiting TET2 DNA methylase resulting in DNA hypermethylation leading to gene silencing.

The identification of mutations affecting epigenetic and transcriptional modifiers is very important to understand the molecular biology of lymphomas. There is a need to understand the role of epigenetic modification in lymphoma, which is of high clinical relevance. As these epigenetic modifications are amenable/reversed by drugs such as DNA methylation inhibitors and histone deacetylase (HDAC) inhibitors also known as “Epidrugs”. Physiological epigenetic landscape can be restored by using these epi-drugs thereby stopping uncontrolled cellular proliferation. Thus epidrugs can be thought as a therapeutic option. However, there is a need to determine biomarkers, that are essential to identify patients, who may benefit from epi-drug treatment. DNA methylation occurs at position 5 mediated by two types of DNA methyltransferases (DNMTs) namely...
de novo and maintenance methyltransferases. DNMTs catalyse the covalent addition of a methyl group from S-adenosyl- methionine to the C5 position of cytosine mainly in CpG islands in the pyrimidine ring of cytosines of CpG dinucleotides. Based on the extent of sequence similarity in the catalytic HAT (Histone acetyl transferase domain about 17 human HATs, divided into at least five families are known: HAT1 HATs, Gcn5/PCAF HATs, MYST HATs, SRC HATs and p300/CREB HATs. HAT families have distinct biological functions depending on their catalytic HAT domain. Based on phylogenetic analysis and sequence similarity to yeast factors, about 18 HDAC isoforms are been described in humans. They are grouped into four classes: class I (HDAC1, 2, 3 and 8), class IIa (HDAC4, 5, 7, and 9), class IIb (HDAC6 and 10), class III (SIRT1, 2, 3, 4, 5, 6 and 7) and class IV (HDAC11). Gene expression is influenced by HATs and HDACs in two different ways:

A. They alter histone acetylation patterns and modulate the structure of chromatin and influence the accessibility of regulatory proteins involved in transcription, and

B. Some non-histone proteins which regulate transcription such as transcription factors and signaling molecules are acetylated and there by influence transcription.

Histones can be methylated at arginine (R) and lysine (K) residues of H3 and H4 proteins. Either mono or demethylation can occur at Arginine. Lysine can accept one, two or three methyl groups. Thus, Methylation offers a great combinatorial potential compared to other histone modifications. Histone acetylation generally correlates with transcriptional activation, while histone methylation can lead to both transcriptional activation and inactivation depending on the modified residue and other simultaneous histone modifications. In many cases there are recurrent mutations in enzymes, such as chromatin modifiers such as HDACs (histone deacetylases) and DNA methyltransferases, which have lead researchers to think of novel inhibitors targeting these enzymes. Nucleoside analogs 5-aza-cytidine (5-aza-CR; Vidaza®; Celgene, NJ, USA) and deoxy derivative 5-aza-2’-deoxycytidine (5-aza-CdR; decitabine) are prominent inhibitors of DNMT (DNA methyltransferase) function. 5-aza-CR and 5-aza-CdR are administered parenterally. While derivatives of the above meant for oral administration, such as zebularine, are in preclinical studies. At molecular level, nucleoside analogs such as 5-aza-CR gets incorporated in DNA and RNA of proliferating cells and form covalent complexes with DNMTs. Thus, they inhibit propagation of DNA methylation during each round of replication by inactivating DNMTs. HDAC inhibitors are known to directly induce modifications in the cancer cell epigenome leading to restoration of relevant gene expression and changes in non-histone proteins. This consequently leads to growth arrest, promotion of differentiation and induction of apoptosis. Normal cells are relatively resistant to HDAC inhibitors compared to cancer cells. HDAC inhibitors interact with the catalytic domain of class I, II and IV HDACs and block the substrate recognition ability. Examples of HDAC inhibitors include trichostatin A (TSA), SAHA.

**Conclusion**

lymphoma personalized medicine would be greatly influenced by Pharmaco-epigenetics. Epi-drugs, inhibit or activate disease-associated epigenetic proteins for ameliorating or curing patients. As underlying molecular mechanisms of resistance to drugs are not understood yet, there is a need for identification of biomarkers for prediction of clinical outcome, to identify lymphoma patients who potentially benefit from a treatment with Epi-drugs. Increasing our scope and target ability of epigenetic alterations might help in determining the role of pharmaco-genomics or individualized medicine approaches in lymphoma clinical practice. Epigenetic modifications influence drug response and such modifications can be modulated by drugs. Monitoring epigenetic modifications can be carried out in the affected tissues. Body fluids are also amenable for monitoring epigenetic modifications. In spite of many advantages, epigenetic biomarkers implemented in the clinical setting are only a few. Interpretation of interplay between changes to the genome and epigenome poses a greater challenge and would improve the understanding of pharmaco-genomics approaches. Finally, understanding of both genetic biomarkers and epigenetic mechanisms in detail would help in prediction of drug response for an ultimate successful therapy for lymphomas.

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**Conflict of interest**

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**References**


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