Epigenetic Drugs: A Hope to Treat Cancer

Mehrdad Asghari, Mehdi Mohebbi, Abdolnasser Rafi

Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Department of Laboratory Sciences, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran.

INTRODUCTION

Epigenetic includes a wide range of reversible changes that regulate gene expression. Simple structure of DNA which has been gained by tissue-specific epigenetic changes occur, which provide the possibility to achieve a wide range of phenotype for a simple and sketch structure of DNA. Our understanding of the biological function of mammalian epigenetic has increased but still there is a long way to be completed and fully understood but our information regarding the impact of epigenetic rate changes and internal environmental factors, is very low. We have some evidences which suggest changing in DNA methylation and histone modifications play a key role in pathogenesis of many complex diseases. Regulation of the Epigenetic status can be a good potential for diseases treatment. transcriptional repression through epigenetic happens in a wide variety of tumors and tumor suppressor genes, genes related to cell cycle, DNA repair genes and genes involved in metastasis invasion. It has been shown in many of these genes that the genes re-expression in tumor cells suppresses cell growth or can cause changes in cell sensitivity to anti-cancer therapy (Brown, 2002). Although this proved to be heredity, but their reversibility, has opened many hopeful windows for treatment (Marks, 2001).

Some presented compounds can cause the gene reverse silent mode. Most of these small molecules compounds have pharmacological properties which quickly received by the tumor. Although we are facing with many challenges in Delivering Gene Therapy to Reverse Genetic Silencing ahead DNA methylation is an epigenetic alteration which is the addition of a methyl group to cytosine ring of position 5 in CpG nucleotides in DNA CpG islands usually occurs within the promoter region (Hendrich, 1999). Hypermethylation of DNA in promoter region causes gene expression silent. There are different areas that methylation occurs, including extensive areas of repetitive DNA sequences, such as centromeres and Transposons (Wang, 2004) (which are involved in chromosome stability), non-coding regions (Varambally, 2008) (Enhancer regions, miRNA) and within genes (Guenther, 2007). It is also important to mention that about 60% of promoter region include Cpg islands (Bird, 2002).

The key molecules that can cause DNA methylation are methyl transferase. DNMT1 makes methylation in new DNA synthesis during and after cell division and its deletion cause apoptosis as it was fatal in mice during...
embryonic development (Endres, 2001). More recently it has been reported that the amount of its activity for Hemi-methylated DNA is many times more for Unmethylated DNA. They are used for Unmethylated DNA methylation against DNMT3A, 3B but are not preferred. DNMT2 has been cloned in vitro. Although these enzymes place in the same category of enzymes and have second catalytic characteristics but may have different roles in tumor development: DNMT3A deletion can stimulate and grow the tumor (Gao, 2011) in the other hand, DNMT3B deletion can stop tumor creation through the deployment and activation of tumor suppressor genes that have got silent earlier (Nosho, 2009; Linhart, 2007).

Epigenetic Drugs:

Increased methylation patterns in CpG Islands of tumor cells would be seen in normal cells rarely. This template creates new treatments for specific purposes. Today, the major considerations are on the treatment through Methylation, Reverse-as a tool to suppress the growth of tumors or cancer treatment or change sensitivity to it (Costello, 2001; Strathdee, 2002). New evidence shows that when these genes are expressed again (by induction) can do these two objectives. But the most important question that must be taken in DNMT1 extending is that: is DNA methylation inhibition can be toxic to normal cells? (Because methylation is essential for growth, so it has been shown in studies that DNMT deletion is fatal for rats during the period of fetal) The answer is that although the DNA methylation of an adult tissue might not have up to the extent of toxicity to death except when some oncogenes will be off. In fact, genetic and pharmacogenetics potion to reduce toxicity has not been intoxicated for DNMTs activity too much.

Two categories of chemical compounds containing the DNMT inhibitor enzyme and HDAC under clinical trials and research in recent years are before it.

Table 1: Types of epigenetic drugs:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-aza-cytidine (azacitidine),</td>
<td>Nucleoside DNMTIs</td>
</tr>
<tr>
<td>5-aza-2-deoxycytidine (decitabine),</td>
<td></td>
</tr>
<tr>
<td>5-fluoro-2-deoxycytidine,</td>
<td></td>
</tr>
<tr>
<td>Zebularine</td>
<td></td>
</tr>
<tr>
<td>RG108</td>
<td>Non-Nucleoside DNMTIs</td>
</tr>
<tr>
<td>MG98</td>
<td>Antisense Oligonucleotides</td>
</tr>
</tbody>
</table>

DNMTIs Nucleoside concatenate into DNA through covalent reaction with DMNTs, it can inactive them. They do this process quietly and create disable DNA-protein (Lyko, 2005). Non-Nucleoside DNMTs by connecting to catalyst DNMTs area block them directly. Also Antisense Oligonucleotides can cause suppress the DNMTsexpression with connecting to mRNA. Until recent years the seven categories of the HDACI have also expanded which four kinds of them are under clinical consideration (Crea, 2011).

Table 2: HDAC inhibitors:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid,</td>
<td>Aliphatic acids</td>
</tr>
<tr>
<td>Sodium phenylbutyrate,</td>
<td></td>
</tr>
<tr>
<td>Pivaloyloxymethyl butyrate,</td>
<td></td>
</tr>
<tr>
<td>Vorinostat</td>
<td></td>
</tr>
<tr>
<td>Romidepsin</td>
<td>Cyclic peptides</td>
</tr>
<tr>
<td>Belinostat,</td>
<td></td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Hydroxamic acids</td>
</tr>
<tr>
<td>Entinostat,</td>
<td></td>
</tr>
<tr>
<td>Mocetinostat</td>
<td>Benzamides</td>
</tr>
</tbody>
</table>

Despite the diversity of their structure, they are in common to inhibit of HDACs and accumulation of acetylation in histones.

Clinical Application of Epigenetic Drugs in Cancer:

The inherent flexibility and reversibility of the epigenetic genome creates interesting opportunities for new treatments of the complex disease. There are a number of medications are introduced that have already reached the stage of approved with specific indications as well as new medications that have been produced over the course of the investigation and little toxicity. Today, making sensitive resistant tumors to the cancer patients with routine medicines and epigenetic drugs used to take 90% of research focus.

Targeting DNA Methylation:

DMNT inhibitors are one of the first and main epigenetic drugs. Azacytidine and decitabine took the FDA approval for the treatment of Myelodysplastic syndrome in the early 20th century. And also, it will replace nucleoside during DNA proliferation which will disable DNMT and causes DNMTs degradation. Despite
careful targeting DNMTIs (Schneider-Stock, 2005) it must be used in the low dose and by selecting proprietary gene expression, the side effects must be minimized (Kelly, 2010).

Phase III trials patients with MDS, which decitabine or azacitidine compared with placebo response rates 30% higher than the placebo group with high survival (3.10 months) and 9% had a complete response (Kantarjian, 2006; Silverman, 2002). In comparison with routine treatment, patients who had received, the disease to acute myeloid leukemia (act) and had fewer deaths. Phase III trial azacitidine which analyzes prescription status in MDS patients at high stage have shown that the survival of their causes (Fenaux, 2009).

In addition to MDS, DNMTIs also have an important clinical application in AML. In different clinical trials, in a number of phases II, 24-52% of patients had a complete response and in higher age’s patients with this condition has been better prognosis (Blum, 2010; Cashen, 2010). The main toxicity category suppression of myeloid leukemia (including neutropenia and thrombocytopenia) is nausea and vomiting. In a study on the model of rat xenograft, shown that treatment with low dose decitabine causes the gene MLH1 reactivate (Plumb, 2000). MLH1 protein in susceptibility to a number of chemotherapy drugs such as carboplatin, temozolomide, epirubicin involved. So decitabine administered with chemotherapy in clinical practice seems to be very useful.

Cameron et al have reported that concomitant use decitabine with HDACI (trichostatin A) causes reactivation of gene expression of MLH1 and TIMP3 synergism effect on colorectal cancer cell lines (Cameron, 1999). An important point is that the use of drugs should be considered de methyl is as gene silencing constantly and its effect is not stable as they can be treated with other medications when patients become resistant to be used temporarily. As can be seen, these are some of the applications of de methyl drugs that are nonspecific and have provided very positive results in the context of wider research groups. Potential for improvement is the following: the duration of treatment with azacitidine and decitabine and their important molecular effects (gene affecting key) (Kelly, 2010) and minimizing side effects.

Two of the newest DNMTIs consist of S110 which is caused by the release of intracellular decitabine (Yoo, 2007) and CP-4200 azacitidine changes elaidic acid is obtained from (Brueckner, 2010), the impact of high temozolomide in different cell lines and mouse models have been shown and they are waiting for clinical research. Neomycin A specific inhibitor of DNMT-3B is shown that it activates tumor suppressor genes (Kuck, 2010).

**Targeting Histone Acetylation/Deacetylation:**

Active area related to the Zn are the best target for HDACs inhibitors. Except for Class 3, HDACs (sirtuin) that are dependent on NAD⁺ (Saunders, 2007; Rodriguez-Paredes, 2011).

Impact of HDAC inhibitor seems to be G1 stimulating or the cell cycle arrest in G2/M which cause cell differentiation and apoptosis. The impact of these drugs as well as their toxicity is not specific to histone and it is reported that another, it targets the other target groups such as P53, heat shock protein 90 and other proteins that change the status of the Acetylation (Federico, 2010). Varinostat and romidepsin could gain the rate of response to the treatments above 30% in front of T-cell lymphoma (CTCL) surface phase in trial II (Olsen, 2007; Piekarz, 2009) and gained FDA approval for use in the 2000’s .

Side effects include diarrhea, increased cholesterol and anemia for varinostat and severe fatigue and nausea, cardiac toxicity for romidepsin is reported (Federico, 2010; Lane, 2009). With the high being tolerant towards routine chemotherapy drugs, fatigue and burnout is so intense that the HDAC inhibitor treatment continue to cause in excess of 30% of the patients as well.

Despite all these problems, there is a lot of enthusiasm for research for development and testing of various trial for this class of drugs other than epigenetic drugs. Panobinostat is one of other drugs from this class, which is used in several hematologic malignancies. Last trial Phase II for Hodgkin's lymphoma in 129 patients showed a reduction of tumor response in 74% and the median survival was 9 and 6 months (Younes, 2012). Phase III trial with panobinostat and bortezomib for multiple myeloma being done (Kelly, 2010). Similarly, the Mocetinostat, specific HDAC inhibitor in Phase II trial classes 1 and 5 of Hodgkin lymphoma, follicular lymphoma and B-cell lymphoma infiltration finder is ongoing (Olsen, 2007; Younes, 2011; Garcia-Manero, 2008; Mack, 2010). The reason of doing all trial for lymphoma is Hodgkin's lymphoma which is a high response rate of 38% (Younes, 2011).

**Conclusion:**

After nearly 30 years in various clinical trials yet a little impact has been reported on solid tumors. This is likely due to the use of high doses in a short time (Schrum, 2006). For example DNMTI the impact that low doses over several days (Lübert, 2001) and in different cycles consumed (Issa, 2005; Oki, 2007). This leads to cell survival and gene profile changes at the same time and in the desired cell differentiation, cell proliferation and increased apoptosis is low (Jones, 1980). In contrast, high doses can induce synergetic effects. Under these conditions, cell growth inhibition due to DNA synthesis by anti-metabolic activity occurs not epigenetic effects. Many trial made or epigenetic drugs as single agent in solid tumors to examine Maximum Tolerated Dose (MTD) of the patients in the advanced stages of cancer, so that they can be used to assess the impact of
epigenetic them. The result of such trials high toxicity and anti-tumor function of the DNMTIs and HDACIs (Van Groeningen, 1986; Abele, 1987; Newman, 2002; Vansteenkiste, 2008). In the other hand, uses of mentioned agents with low dose and in early stage of disease cause activation of tumor suppressor genes. However, this effect is unstable, it can use with other agents. In this context, researchers are still a long way ahead and many studies are needed.

REFERENCES


