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# 5-Azadeoxycitidine and Trichostatin A in FMR1 Gene Reactivation

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## Mini Review

Here we review the ways of chromatin modifications by 5-azadeoxycitidine and trichostatin A for gene reactivation. Therapeutic effects for different diseases treatment are discussed.

Many existing diseases are caused by suppression of specific gene expression. As an example, for oncological diseases these are tumor suppressor genes [1]. In case of Fragile-X syndrome, expression of FMR1 gene is suppressed. Nowadays numerous studies to search for any ways to reactivate genes using small molecules like 5-azadeoxycitidine, and trichostatin A which act on the whole genome are performed. Mechanisms, advantages and disadvantages of these methods are briefly described below.

First of all, we have to look closer the gene silencing system using FMR1 gene as an example to explain the gene reactivation mechanism. Methylation of CpG islands in promoter area is involved in regulation of gene expression and cell differentiation. Repeat expansion in FMR1 gene promotor area up to more than 200 triplets leads to recognition of CpG islands by DNA-methyltransferases (DNMT), it add methyl groups to cytosines in CGG-repeats, this serves as a signal for hetero chromatinization and for switching off the gene. Methylated cytosine becomes recognized by MeCP2 protein, who activates histone deacetylases (HDAC), which further remove acetyl groups from N-terminal domain of H3 and H4 histones at the methylated area, and this leads to chromatin condensation [2].

A number of studies showed a possibility of methylated FMR1 reactivation using 5-azadeoxycitidine-a cytidine analog. During DNA chain elongation 5-azadeoxycitidine becomes inserted in instead of cytidine and an irreversible covalently binding with DNA-methyltransferase 1 (DNMT1) occurs, because this enzyme tries to methylate a trivalent nitrogen in 5 position of pyrimidine ring. Thereafter during cell division a passive demethylation process takes place [3].

Simultaneous treatment of cell lines with 5-azadeoxycitidine and histone deacetylases inhibitors has leaded to greater gene reactivation. So, simultaneous treatment of mammal gland cell lines with 5-azadeoxycitidine, buthyrate and trichostatin A leaded to more efficient FMR1 reactivation then when only 5-azadeoxycitidine was used [4]. It should be noted that these substances can reactivate tumor suppressors too [5]. When treated simultaneously with 5-azadeoxycitidine and trichostatin A prostate cells showed increased estrogen receptor β expression and apoptosis. It was found that cell death is connected with estrogen receptor β expression elevation [6]. To investigate an influence of histone H3 lysine 9 acetylation and DNA methylation of P16, HMLH1 and MGMTgenes in ovary tumor cells, treatment with trichostatin A and 5-azadeoxycitidine was performed. This experiment showed that DNA demethylation has a better effect on gene reactivation than deacetylation [7]. A problem which arises when using 5-azadeoxycitidine for clinical treatment is its toxity. It is important to note that 5-azadeoxycitidine and deacetylase inhibitors action is not specific. It was determined using microarray screening of 10814 genes that 5-azacitidine acts on 51 gene, and trichostatin A-on 23 genes [8].

It was shown that4 weeks after 5-azadeoxycitidine treatment DNA methylation level in most of experimental cells increases again. In cell lines which showed gene reactivation recurrent gene suppression can be induced due to de novo appearing methyltransferases. It was shown too; that many cells after 5-azadeoxycitidine treatment undergo apoptosis because of numerous DNMT1-DNA adducts [9]. 5-azacitidine and 5-azadeoxycitidine have side effects. Patients treated with these chemicals had sickliness, vomit, diarrhea and neutropenia. This effect restricts maximal permissible doses of these chemicals and patients therapy duration.

Now a days, causes of such hereditive disorders as Fragile X syndrome are well studied. This causes lie in DNA methylation and histone deacetylation mechanisms. At the same time, generation of therapy methods for these diseases remains a substantial problem. Laboratory investigations presented data about chemicals, which are able to reactivate genes. However,

these agents cannot be put into clinical practice for a range of reasons: high cytotoxity or low reactivation capacity. That's why search of new drugs which allow to reactivate FMR1 gene is an actual problem. This is especially important considering that Fragile X syndrome is the most often cause of mental retardation, and such patients have difficulties in socialization owing to memory and learning problems and hyperactivity.

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