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IIT Indore discovers treatment of Fragile X-associated tremor

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Indian Institute of Technology Indore has discovered three small molecules that could potentially be used for the therapeutic purpose of Fragile X-associated tremor/ataxia syndrome (FXTAS), a progressive neurological and neuromuscular disorder.

A team led by Dr Amit Kumar, head, department of Biosciences and Biomedical Engineering, IIT Indore has found three chemical compounds that significantly reduce the trinucleotide repeats RNA associated neuronal cells cytotoxicity and restored normal cell viability, in the preliminary studies.

The team included Arun Kumar Verma, Eshan Khan, Subodh Kumar Mishra. This study has been published in the journal Molecular Neurobiology, Springer.

There is still no effective medicine available in the market for the treatment of FXTAS. Currently, management of FXTAS is limited to symptomatic treatment of psychiatric and behavioural problems.

The research team.

FXTAS patients face balance problems while walking called ataxia and shaking of hand on grabbing anything called intention tremor. They also have symptoms of memory loss, autonomic dysfunction, cognitive decline, seizure, and Parkinsonism.

FXTAS disorder affects 1 in 4000 males and 1 in 6000 - 8000 females worldwide and usually begin at the age of 58 to 60 years. It is caused by the specific type of mutation in the DNA sequence of a gene called fragile X mental retardation 1 (FMR1).

The mutation name is CGG trinucleotide repeats. The number of trinucleotide repeats in FXTAS patients is above 200 times as compared to the healthy person which is 55. This excess trinucleotide repeats cause cytotoxicity in neuronal cells that ultimately leads to degeneration of brain cells. Scientists have been continuously trying to rescue neuronal cell death caused by this mutation via chemical compounds.

Kumar said, "Trinucleotide repeats expansion is involved in the pathogenesis of more than 15 different neurological diseases. We hope our finding would help in developing therapeutics for Fragile X-associated tremor/ataxia syndrome disorder as well as for the other related diseases. In this research work, chemically synthesized small molecules were identified with less cytotoxicity and high binding affinity against CGG repeats RNA, mainly responsible for FXTAS disorder from the library of ~ 2500000 small molecules maintained by the National Cancer Institute (NCI), USA."

This study was conducted in three different steps. 1) Shape and chemical-based virtual screening against query molecule, Bisantrene. 2) Biophysical analysis of lead compounds with target RNA. 3) Analyse potency of lead molecules using diseased cellular models. These lead compounds were tested in both developed cellular models of FXTAS and patient-derived cell lines isolated from patients suffering from the disease. Three compounds at the end were found to be selective and specific against CGG repeat RNA and also more effective in cell-based studies. Importantly, these data are interesting but further validation is needed using suitable animal models.