

DBT-CDFD study finds a potential therapy for colon cancer

New Delhi, Feb 23: A research article titled “A novel SIRT1 inhibitor, 4bb induces apoptosis in HCT116 human colon carcinoma cells partially by activating p53” by Ananga Ghosh, Amrita Sengupta, Guru Pavan Kumar Seerapu, Ali Nakhi, E. V. Venkat Shivaji Ramarao, Navneet Bungc, Gopalakrishnan Bulusuc, Manojit Pal and Devyani Haldar of DBT-Centre for DNA Fingerprinting and Diagnostics (DBT-CDFD) was published in the journal “Biochemical and Biophysical Research communications”.



Here, a novel anti-cancer molecule (4bb) which specifically kills colon cancer cells was reported. It is a small molecule inhibitor of human histone deacetylase, SIRT1. The researchers investigated its effect on viability of colon cancer cells and molecular mechanism of action (i.e. understanding how it works within the cell to stop growth of colon cancer cells).

In human cells, to fit our long genetic material, DNA into tiny nuclei, it is wrapped around beads made of histone proteins, this complex of DNA and protein is called Chromatin. Chromatin structure can be altered by chemically modifying the DNA and the histone proteins by acetylation, methylation etc. These modifications do not change the composition of the DNA. However, they can change gene expression i.e. the program by which proteins are formed within a cell. Such changes are called Epigenetic changes.

Cancer is a major health problem world over. Existing drugs are not satisfactory as they are not very specific and cause traumatic side effects. There is an urgent need for development of more specific and relatively less toxic drugs. Epigenetic therapeutics of cancer such as inhibitors of DNA methyltransferases and histone deacetylases (class I and classII) are already being used in combination with the standard cytotoxics with encouraging results. The

Sirtuins (class III NAD-dependent deacetylases) are being considered as important targets for cancer therapeutics as their level increases in many cancers.

As these are enzymes, inhibition of sirtuin's deacetylase activity allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. However, no sirtuin inhibitors have entered into the clinic yet as an anticancer agent. The NAD⁺-dependent protein deacetylase SIRT1 is an important target for epigenetic therapeutics of colon cancer as increase in its level is associated with cancer progression. SIRT1 represses tumor suppressor, p53 function via deacetylation, promoting tumor growth. Therefore, inhibition of SIRT1 activity is of great therapeutic interest for the treatment of colon cancer.

In vitro, 4bb is a significantly more potent SIRT1 inhibitor than β -naphthols such as sirtinol, cambinol. The viability of colon cancer cells reduces with increasing concentration of 4bb, but does not affect the viability of normal dermal fibroblasts depicting cancer cell specificity. Further, 4bb treatment increased p53 acetylation, Bax expression and induced caspase 3 cleavage suggesting that the death of HCT116 colon cancer cells occurs through the intrinsic pathway of programmed cell death (apoptosis).

Overall, the study presents 4bb as a new class of human SIRT1 inhibitor and suggest that inhibition of SIRT1 by 4bb induces programmed cell death of colon cancer cells at least in part via activating p53 by preventing p53 deacetylation, increasing Bax expression and inducing caspases. Therefore, this molecule provides an opportunity for lead optimization and may help in development of novel, nontoxic epigenetic therapeutics for colon cancer. This would aid in the development of novel Sirtuin inhibitor as a potential anti-cancer drug either by itself or in combination with cytotoxics and other epigenetic drugs such as methyltransferase inhibitor or HDAC inhibitor. In addition, determination of the molecular basis of anti-tumor effect will help in understanding of functions of Sirtuins in cancer formation.

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