DBT-CDFD scientists find molecule with potential to kill colon cancer cells

New Delhi, Aug 6: Researchers at the Department of Biotechnology’s Centre for DNA Fingerprinting and Diagnostics (DBT-CDFD) have discovered a molecule that showed the potential to specifically kill colon cancer cells. It is a small molecule inhibitor of human histone deacetylase, SIRT1. It is called 4bb. The scientists investigated its effect on viability of colon cancer cells and its molecular mechanism of action to understand how it works within the cell to stop growth of colon cancer cells.

In human cells, to fit into a tiny nucleus, DNA, which is a long genetic material, is wrapped around beads made of histone proteins. This complex of DNA and the 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 - the program by which proteins are formed within a cell. Such changes are called epigenetic changes.

Cancer is a major health problem world over. Currently available drugs are not satisfactory as they cause traumatic side effects. Therefore, there is an urgent need for development of more specific and relatively non 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.

Scientists are considering enzymes called Sirtuins, which are class III NAD-dependent deacetylases, as another set of targets for cancer therapeutics as their levels increase in many cancers. As these are enzymes, inhibition of their deacetylase activity can allow re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells.

However, no sirtuin inhibitor has 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.

4bb has been found to be a significantly more potent SIRT1 inhibitor than β-naphthols such as sirtinol, cambinol in vitro. 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 has shown 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 caspasess. 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 methytransferase inhibitor or HDAC inhibitor. In addition, determination of the molecular basis of anti-tumor effect will help in understanding the functions of Sirtuins in cancer formation.

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 Nahi, E. V. Venkat Shivaji Ramarao, Navneet Bunge, Gopalakrishnan Bulusuc, Manojit Pal and Devyani Haldar” was published in journal “Biochemical and Biophysical Research communications”.

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