Peptides for treating cancer

A team of the scientists at National Chemical Laboratory (CSIR-NCL), Pune led by Dr. M.I. Khan* isolated a novel peptide that could play an important role in treating or preventing cancer. The peptide, called cysteine protease inhibitor, isolated from *Streptomyces* inhibited the migration of cancer cells.

Cysteine Protease plays significant role in various pathological conditions such as cancer metastatis, osteoporosis etc. Compounds having inhibitory activity against cysteine protease have been shown to work as drugs in these pathological conditions.

Microbes and plants have been the most efficient and convenient source of natural bioactive compounds. Novel secondary metabolites continue to be isolated from Actinomycetes. Their biological activities and chemical structures show a wide range of diversity. Taking into consideration all this understanding, the Actinomycetes were explored in order to isolate small molecular mass cysteine protease inhibitor.

During the course of investigation a novel peptide (736-842 Da) was isolated which has Cathepsin K and L inhibition activity in nanomolar range. Cysteine proteases play an important role in cell migration and tumour metastasis. The compounds which possess their inhibition without harming the healthy tissues are of great significance, having potential to be developed as effective antimetastatic drugs for tumour therapy. A small molecule cysteine protease inhibitor, CPI-2081 (compound 1), a mixture of two novel pentapeptides, compound 1 a and compound 1 b, was isolated from *Streptomyces* species NCIM2081. It was found that compound 1 significantly inhibits tumour cell migration.

The effect of CPI-2081 was also investigated on osteoclast differentiation. The results suggest that CPI inhibits osteoclast differentiation without any toxic effect on osteoclast precursors. A novel modified peptidic thiol protease inhibitor (CPI-2081) was isolated from actinomycete *(Streptomyces sp* NCIM2081) which exhibit Ki in nanomolar (<100 nm) range and it can inhibit the tumour cell migration without any cytotoxic activity. Also, the CPI is able to inhibit the RANKEL induced osteoclast differentiation without having considerable cytotoxic effect. Among all kinds of sources for natural bioactive compounds; actinomycetes always had a competitive edge over others with respect to their ability to produce bioactive small molecules for drug development

The scientists determined the inhibitory constant (Ki) which is an important parameter that shows the potency of inhibitory compounds; it is the concentration required to produce half maximum inhibition. The initial kinetics of substrate hydrolysis inhibition by compound 1 revealed that substrate hydrolysis decreased as a function of concentration of compound 1 in a dose dependent manner displaying the IC_{50} value of 36.9± 1.8 nM. Dixon plot demonstrated the competitive mode of association of compound 1 with papain, showing Ki value of 49.14±2.45 nM, which is close to IC_{50} value.

The peptide needs to be chemically synthesized and evaluated for its anti metastatic and anti – osteoporotic activities. It also needs to be evaluated in other pathological conditions where cysteine proteases are known to be involved. This low molecular weight peptide inhibitor has potential to be developed as a significant drug molecule.

Most of these inhibitors have several disadvantages like cytotoxicity, allergic reactions, low absorptivity etc.

Commenting on the work, Prof. Alexei Degterev from Department of Biochemistry, Tufts University School of Medicine, Boston said that "Efficient inhibition of cysteine proteases remains an important goal of medicinal chemistry. Multiple cathepsins as well as other cyteine proteases are important targets in drug discovery against cancer and other diseases. Analyses of actimomycetes products have historically provided an excellent source of diverse biologically active molecules. Dr Khan's group has used this approach to discover a new inhibitor of cysteine proteases in *Streptomyces* fermentation broth. They present an in depth characterization of the main inhibitory substance, peptide Compound 1. Using papain as a reference enzyme, they demonstrated nanomolar inhibition by Compound 1. Furthermore, the authors went on to show inhibition of migration of three different aggressive tumor cell lines by this molecule. This work reveals a new class of potential inhibitors of cancer metastasis".

Prof Alexei further said that, "It would be very interesting to learn in the future the cellular targets of this molecule in cancer cells and the activity of this molecule in mouse metastasis models. Another promising direction may be development of peptidomimetic analogs of Compound 1 to improve pharmacological properties of this molecule in vivo, including cell permeability and stability. These molecules could turn out to be promising new anti-cancer agents, inhibiting cancer metastasis without significant dose-limiting toxicity."

The work was carried out in collaboration with National Centre for Cell Science, Pune.

Further reading

, Structure, and Functional Elucidation of a Modified Pentapeptide, Cysteine Protease Inhibitor (CPI-2081) from *Streptomyces* Species 2081 that Exhibit Inhibitory Effect on Cancer Cell Migration, Jay Prakash Singh, Sudarsan Tamang, P. R. Rajamohanan, N. C. Jima, Goutam Chakraborty, Gopal C. Kundu, Sushma M. Gaikwad, and Mohamad I. Khan, *J Medicinal Chemistry*, 2010, **53**, 5121-5128.

* - Dr. M.I. Khan died prematurely in November 2010 at the age of 53. Dr Khan joined NCL in May 1990. He contributed significantly to the area of Protein chemistry, Glycobiology, Enzymology and Biophysics and published over 120 research papers in the international peer-reviewed research journals.

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