Method of Inhibiting Tumor Cell Proliferation

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Technology description

A novel 19 amino acid peptide, within the ARF tumor suppressor protein, that reduces proliferation of mouse liver tumor cells and increases apoptosis of cells.

Liver cancer (HCC) is the fifth most common cancer in the world. A deadly disease, liver cancer will kill almost all who contract it within a year. In 1990, the World Health Organization estimated that there were about 430,000 new cases of liver cancer worldwide, and a similar number of patients died as a result of this disease.
HCC faces a substantial limitation of conventional cancer chemotherapy and radiotherapy. The nonselectivity of the available gene delivery systems also renders cancer gene therapy strategies potentially toxic to normal cell populations.
The complexity of the relevant gene and lack of clarity regarding its regulatory factors in respect to the gene expression controlling pathway for a specific tumor make it difficult to construct a selective gene therapy.
Recognizing the need for a targeted cancer therapy the researchers at UIC constructed a unique system, which makes it possible to examine the effect of FoxM1B protein and its relevant cascades for hepatocytecellular carcinomas (HCC).
They discovered that FoxM1B - forkhead box transcription factor – is essential for development of HCC. Using CRE-LOX technology, the researchers deleted the mouse FoxM1b gene selectively in hepatocytes and then induced liver tumors in these mice using hepatic carcinogens (Alb-Cre Foxm1b fl/fl).
The researchers found that inhibition of expression of FoxM1B prevented development of mouse HCC in response to chemically induced liver tumors. These mouse genetic studies indicate that FoxM1b is a therapeutic gene to inhibit proliferation and growth of liver tumor cells in mice.
The UIC investigators also showed that the FoxM1b transcription factor is a novel inhibitory target of the ARF tumor suppressor protein.
They defined a 19 amino acid peptide within the ARF tumor suppressor protein that was sufficient to inhibit FoxM1b transcriptional activity.
This ARF peptide was modified by addition of nine D-ARG to facilitate cellular uptake and converted this ARF peptide into a specific inhibitor of FoxM1 function in tissue culture cells. Mice with pre-existing hepatocelllular carcinomas were treated with daily injections of this membrane transducing ARF peptide for duration of 4 or 8 weeks.

This ARF peptide treatment significantly reduced proliferation of mouse liver tumor cells through the inhibition of FoxM1b activity. Furthermore, the researchers observed a selective 22% increase in apoptosis (programmed cell death) of mouse liver tumor cells without causing apoptosis of the normal surrounding liver tissue.
The invention provides methods for inhibiting tumor cell proliferation and stimulating tumor cell apoptosis by inhibiting FoxM1B activity with a membrane transducing ARF peptide.

Application area

Cancer therapy and prevention
Hepatitis B and C therapy

Advantages

Reduces tumor proliferation
Potentially prevents metastases
Limits the growth of the liver tumors
Selectively causes program cell death of the liver tumor cells
Serves as a potential therapy for hepatitis B and C viral infections of the liver

Institution

University of Illinois, Chicago

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com