Highly X-Ray Sensitive Iridium Prodrug Can Improve Cancer Radiochemotherapy

Zhennan Zhao, Pan Gao, Lin Ma, and Tianfeng Chen

Department of Chemistry, Jinan University, China

Abstract

Drugs that make cancer cells more sensitive to radiation are useful in cancer therapy. In this study, an iridium-based agent that can serve as a radiosensitizer was synthesized. The efficacy and mechanism of radiosensitization of the drug were analyzed. The results showed that the drug is an effective radiosensitizer, with a high sensitivity enhancement ratio (SER) of 10.35. These findings can advance the development of multifunctional radiosensitizers therapy.

Introduction

Radiosensitizers are agents actively used in cancer therapy.

The most commonly used radiosensitizers are platinum-based drugs but have limted limited efficacy in actively targeting cancer cells and pose a risk of genetic damage.

Cyclometalated iridium (Ir)-based drugs can serve as alternatives since they accumulate in the mitochondria of the cancer cells, but their cancer cell visualization and targeting capabilities need to be improved.

Goal

To synthezise a multifunctional Ir-based radiosensitizer that can effectively target and visualize cancer cells.

Methodology

Drug synthesis

Ir-NB consisted of four main components:

- An Ir(III) complex that provides a chemotherapeutic effect and luminescence to suppress and visualize cancer cells
- A nitrobenzol group, which is an electron acceptor that quenches the luminescence produced by the Ir(III) complex
- Acidity-sensitive imine bond is used as a pH responsive linker which links the nitrobenzol group to the Ir(III) complex
- A biotin group that can selectively deliver the drug to cancer cells linked to the Ir(III) complex by an ester bond

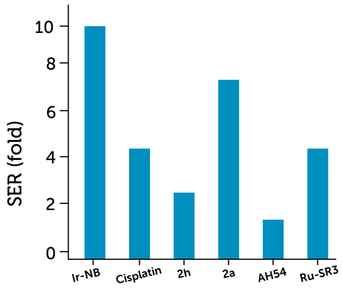
The properties of the drug were examined in vitro and in vivo using the A549 lung carcinoma cell line and the WI-38 normal cell line.

The effects of the drug on these cell lines are studied in combination with radiation therapy

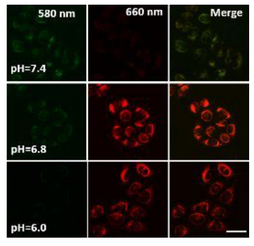
Results

Properties of the IR-NB

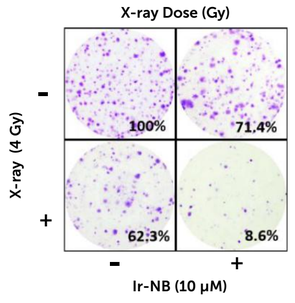
- Higher SER value (10.35) than other radiosensitizers
- Effective illumination and visualization of cancer cells
- Most effective in suppressing the growth of cancer cells in combination with radiotherapy
- High selectivity towards cancer cells and preferential accumulation in A549 cells, compared to WI-38



SER value of the synthesized drug Ir-NB compared to other radiosensitizers



Cancer cells illuminated by the Ir(III) complex under acidic condition

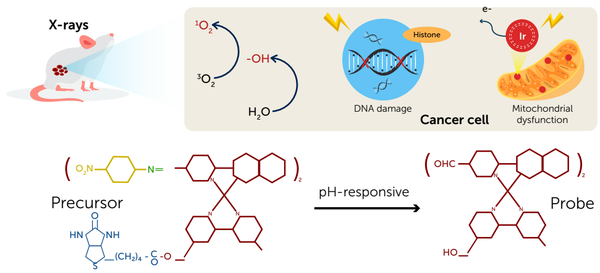


Colonies of A549 cancer cells Combined treatment suppresses the growth of cancer cells

Mechanism of radiosensitization

The biotin functional group targets the A549 cells, as these cells contain biotin receptors. In the acidic conditions of the cell, the imine bond breaks, releasing the Ir(III) complex from the fluorescence quencher and enhancing the luminescence of the Ir(III) complex.

The Ir(III) complex accumulates in the mitochondria of the cancer cells, triggering mitochondrial dysfunction (thus suppressing cancer cell growth).



On contact with cancer cells, the imine and ester bond of the precursor (Ir-NB) breaks and the Ir(III) complex (probe) enters the mitochondria of the cell

Conclusion

- IR-NB had a high SER value, allowing for lower radiation doses.
- IR-NB can be used for cancer cell visualization and targeting, potentially leading to fewer side effects than radiotherapy alone.

References

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