Inducing Oxidative Stress Using Biotin Receptor Targeted Organometallic Compounds on Cancer Cells

Tate Truly*, Dr. Marianne Burnett,Dr. Kayla Green**, and Dr. Giridhar Akkaraju*,**

Department of Biology*, Department of Chemistry**, Texas Christian University, Fort Worth, TX

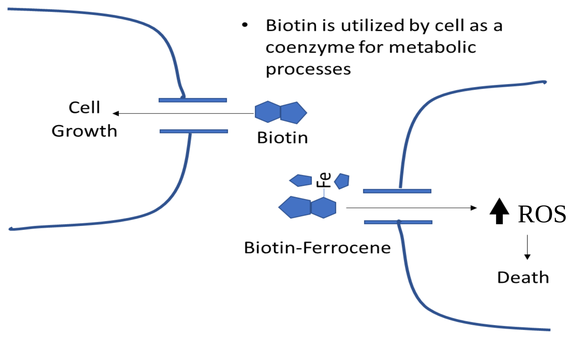
Abstract

Cancer is a collection of diseases primarily characterized by aberrant cellular proliferation and is one of the leading causes of death worldwide. Current therapies such as chemotherapy kill rapidly dividing cells without differentiating between cancer and normal cells. This lack of cancer specificity results in negative side effects including hair loss, fatigue, anemia, susceptibility to infection and nausea. To combat these side effects, the development of targeted therapies that try to target cancer specific features to increase therapeutic selectivity has been revolutionary to the advancement of cancer therapy. One unique aspect of cancer is their high metabolic rate which generates a higher requirement for sugars and vitamins involved in metabolism. One important vitamin is biotin (Vitamin B7) which functions as an important cofactor for enzymes involved in gluconeogenesis, fatty acid synthesis and amino acid metabolism. To increase the absorption of biotin and maintain their high metabolic and proliferation rate, some cancers overexpress the biotin receptor. One consequence of the high metabolic rate found in cancer is the generation of reactive oxygen species (ROS) which can trigger apoptosis at high levels. Ferrocene is an organometallic compound that has previously been shown to generate ROS in cells. Thus, our project is interested in utilizing ferrocene to induce oxidative stress and selectively targeting cancer cells by conjugating ferrocene to biotin. Therefore, our group has generated a library of ferrocene-biotin conjugates to test their ability to selectively enter cancer cells and generate ROS. Experiments were conducted utilizing ferrocene and a variety of conjugates (C1, C2, C3, 2) in both cancer (MCF-7) and non-cancer cells (HEK293).

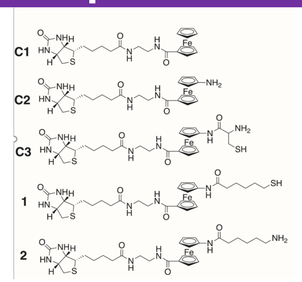
Hypothesis

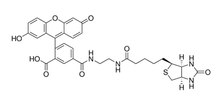
Conjugating ferrocene and ferrocenyl-derivatives to biotin will result in increased absorption in cancer cells which will result in increased ROS and cell death.

Mode of Action



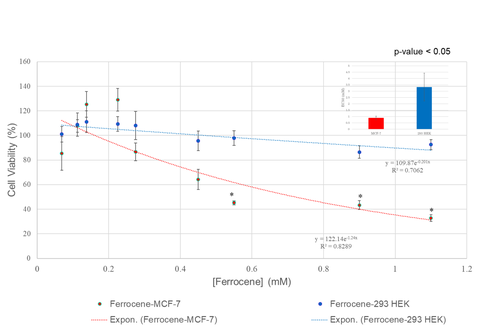
Compounds

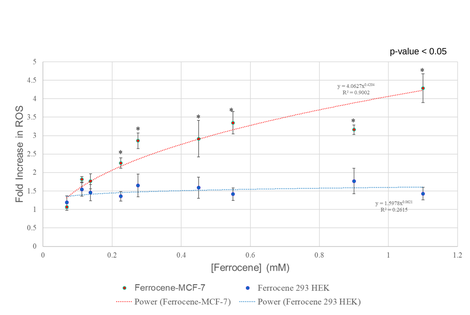


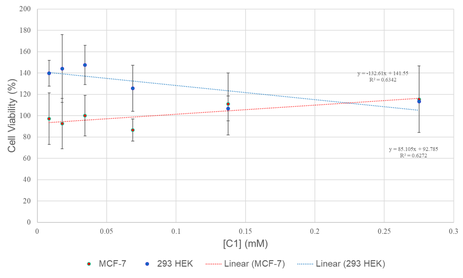


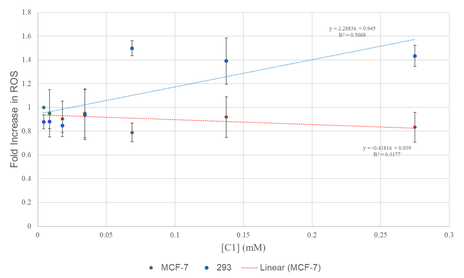
Synthesized by Dr. Green and Marianne Burnett, Department of Chemistry

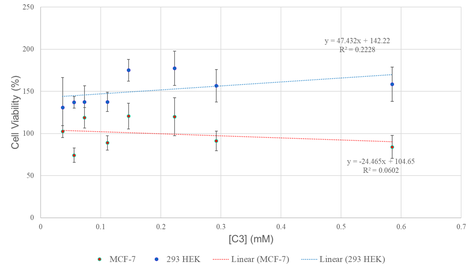
Results

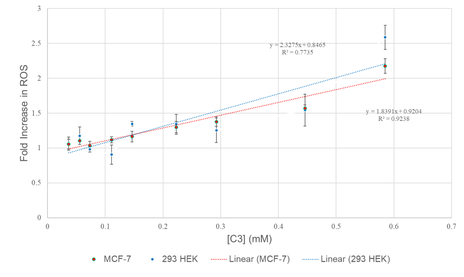


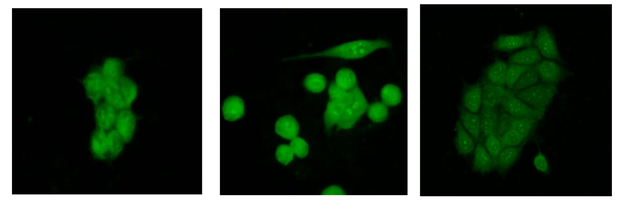












293 HEK Hela MCF-7

Discussion

Due to the increased metabolic rate in cancer, cancer cells are prone to the production of free radicals ROS. Compounds such as ferrocene have shown to increase levels of ROS and cell death in cancer cells in comparison to non-cancer cells. Furthermore, cancer cells' requirement of biotin and overexpression of the biotin transporter provides a novel mechanism for targeted cancer treatment. The overexpression of the biotin transporter allows for an increased efficiency of absorption of biotin in cancer cells. By conjugating ferrocene, ferrocenyl derivatives and biotin it is predicted that there will be an increased absorption of the compounds by cancer cells and will result in higher levels of ROS and cell death.

Conclusions

- Ferrocene exhibits selective toxicity towards cancer cells
- Ferrocene generates elevated levels of ROS in cancer cells
- Ferrocene-biotin conjugates C1 and C3 are not toxic in cancer cells
- Biotin does not enter MCF-7 and Hela cancer cells with a higher efficiency

SciCom Let's Talk Science

TCU College of Science & Engineering reSEaRCh Science and Engineering Research Center