RADIOTHERAPY AND CHEMOTHERAPY

INTRODUCTION

Gastric cancer (GC) was recorded as the third leading cause of cancer-related deaths worldwide, and overall and disease-specific survival for these patients is poor. Thus, developing the GC treatment is twice as efficient. Our results showed an inverse relationship between the radiosensitizing effects and the AuNPs sizes. Moreover, the nature of the coating influenced the triggered cell death process. In case of PVP-coated AuNPs, the cell death was characterised by a radio-induced senescence in relation with a 1.5-fold increase of the reactive oxygen species production. In contrast, smallest PEG-coated AuNPs triggered post-RX mitotic catastrophes, leading to a decrease in cell growth, radioresistance and tumorigenicity as well as expression of gastric cancer stem cell (CSC) markers. GEF-X depletion was accompanied by a concomitant decrease in nuclear b-catenin and CD44 levels. Moreover, interactions between GEF-X and b-catenin were observed in the nucleus of GC cells.

CONCLUSIONS

Our results suggest for the first time a novel role of GEF-X in the self-renewal of CSCs, supporting its utility as an independent marker of GC progression. GEF-X depletion was accompanied by a concomitant decrease in nuclear b-catenin and CD44 levels. Moreover, interactions between GEF-X and b-catenin were observed in the nucleus of GC cells.

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GEF-X IS AN INDEPENDENT PROGNOSTIC FACTOR OF GASTRIC CANCER ASSOCIATED WITH CANCER STEM CELL DEVELOPMENT AND RADIORESISTANCE USING MULTI-OmICS DATA

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Introduction

Gastric cancer (GC) was recorded as the third leading cause of cancer-related deaths worldwide, and overall and recurrent survival after potentially curative gastrectomy for advanced gastric cancer remains poor. Thus, developing the GC targeting molecules in combination with adjuvant radiotherapy, or adjuvant chemotherapy following surgical resection is an important trend for GC treatment.

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STUDYING PATHWAY INTERACTIONS AND DYNAMICS TO PREDICT CELL RESPONSES TO CHEMOTHERAPEUTIC TREATMENT IN BREAST CANCER CELLS

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Introduction

Breast cancer is the most common cancer among women affecting about 1 in 8 women during their lifetime. In most cases, the treatment is surgery combined with chemotherapy such as anthracyclines, including Doxorubicin. Unfortunately, the chemotherapy is only working for 25% to 50% of the patients showing a need to predict the patient’s response to the treatment. Chemotherapeutic drugs are known to activate apoptosis via the activation of JNK, p38 and p53 pathway. However, little is known about the interaction between these pathways and how the drugs activate them.

My hypothesis is that dynamic behaviour and network interactions between JNK/p38 and p53 confer drug (in-)sensitivity and resistance.
To address this problem, my project merges molecular and computational approaches to answer these two questions:

- What are the activation dynamics and underlying network interactions?
- Can a mathematical model of this network predict drug responses?

**Material and methods** To study the mechanism of action of Doxorubicin, I compared MCF10A cells, a non-cancerous cells used as a control, with five different breast cancer cell lines. The level of cell death was measured via flow cytometry after 1 μM of Doxorubicin treatment. In parallel, the cells' molecular response to the treatment was assessed by monitoring phosphorylation of JNK and p38, and the total levels of p53 via Western blots after 1 μM of Doxorubicin treatment.

**Results and discussions** Comparing the above pathways in MCF10A and T47D identified differences on two levels: network connectivity and activation dynamics. Currently I am constructing a mathematical model using ordinary differential equations (ODE) to test whether the identified network structures can explain network activation dynamics and drug responses. This predictive model will be validated using mammospheres and breast cancer tumour samples.

**Conclusion** Modelling pathway interactions has already revealed correlation between the experimental data (Western blots) and the simulated outcome of Doxorubicin treatment in MCF10A cells. The next step is to explain the differential pathway connexions and dynamics in the various cell lines with different mutation pattern by using my mathematical model. By doing so, I hope to predict treatment response of other breast cancer cell lines, and ultimately patients, to develop a personalised treatment strategy.