Identification of Combinations of Targets for Claudin-Low Triple Negative Breast Cancer Reversion

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Tumor reversion is the biological process by which tumor cells lose a significant fraction of their malignant phenotype. It has been observed spontaneously and explored as a therapeutic approach both *in vivo* and *in vitro* over the past century. In particular, tumor reversion has been achieved in the Claudin-Low Triple Negative Breast Cancer (CL TNBC) cell line, MDA-MB-231. Claudin-low tumors have high relapse and low survival rates due to their metastatic tendencies and decreased response to cytotoxic drugs, creating the need for new therapeutic strategies. This project aims to apply optimal control theory to identify combinations of therapeutic targets for claudin-low tumor reversion *in silico.* An intracellular signaling network was constructed with multi-omics data for the CL TNBC cell line MDA-MB-231. A structure based control method for nonlinear dynamic systems called Feedback Vertex Set Control was applied to the network to identify driver nodes. The attractor landscape of the network was estimated using a topological signal flow analysis (SFA) via the signal propagation algorithm. *In silico* screenings of FC node perturbations were run using SFA to identify putative concerted targets for CL TNBC reversion, those nodes whose concerted perturbation resulted in an attractor in the basin of attraction for a normal breast cell.

Claudin-Low Triple Negative Breast Cancer (CL TNBC) tumors are characterized by high rates of metastasis and decreased response to cytotoxic drugs. This results in high relapse rates, low survival rates, and the need for new therapeutic strategies. One such strategy is tumor reversion, the biological process by which tumor cells lose a significant fraction of their malignant phenotype. Tumor reversion has occurred spontaneously and experimentally both *in vitro* and *in vivo* throughout the past century, in particular with the CL TNBC cell line MDA-MB-231. This project aims to apply optimal control theory to identify combinations of therapeutic targets for Claudin-Low tumor reversion *in silico*. An intracellular signaling network was constructed with multi-omics data for MDA-MB-231. Then a structure-based attractor-based control method for nonlinear dynamic systems developed by Mochizuki and Zañudo, Feedback Vertex Set Control (FC), was applied to the network. FC assumes that the targets to control are attractors and that perturbations can be directly applied to network nodes in order to identify driver nodes whose perturbation can steer the network from any attractor to any other observable attractor. The attractor landscape of the network was estimated and *in silico* perturbation screenings of the driver nodes were run based solely on the network topology, using a topological signal flow analysis (SFA) via the signal propagation algorithm. Nodes whose concerted perturbation resulted in an attractor in the basin of attraction of a normal breast cell were deemed potential reversion targets as they prompted the switch from a malignant to normal-like phenotype.

has been observed spontaneously and experimentally as a therapeutic strategy both *in vivo* and *in vitro* over the past century. Tumor reversion is the biological process by which tumor cells lose a significant fraction of their malignant phenotype, and has been achieved in CL TNBC cell lines.

This method assumes that the targets to control are attractors and that perturbations can be directly applied to nodes.

We were successfully able to identify XX potential combo targets where are majority of the targets were already known individually in literature but this is the first time they’ve been identified together…

Claudin-low triple negative breast cancer (CL TNBC) is a subtype of breast cancer displaying a low expression of tight junction proteins Claudin 3,4, and 7, as well as the cell adhesion molecule E-Cadherin. These tumors have a high rate of relapse and a low survival rate due to their metastatic tendencies and decreased response to cytotoxic drugs.

Although tumor reversion is a rarely explored therapeutic approach, it has been observed both *in vivo* and *in vitro* over the past century.

With the network we will apply structure based control method called ….

Nonlinear dynamic system

This takes the structure of the network. Since its nonlinear, it assumes that the targets to control are the attractors and the perturbations can be directly applied to nodes.

These tumors are prone to the epithelial to mesenchymal transition as well as exhibiting stem-cell characteristics, but unlike most tumors, they are characterized by low proliferation rates. This leads to high rates of metastasis and decreased response to cytotoxic drugs, resulting in a poor prognosis and the need for new treatment options.

Combinations of nodes were considered putative reversion targets if the attractor resulting from their concerted perturbation fell into the basin of attraction for a normal breast cell, thus reverting the cell from a malignant to a normal-like phenotype.

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