Understanding breast cancer resistance to chemotherapy: Characterization of cancer cell sub-populations in residual and relapsed tumors

Tumor recurrence fueled by residual tumor cells having survived chemotherapy represents the principal cause of breast cancer treatment failure. Triple-negative breast cancer (TNBC) is a heterogeneous disease at both molecular and cellular level, and the presence of different tumor cell sub-populations is likely the reason for this heterogeneity and for the incomplete response to neoadjuvant chemotherapy observed for most TNBC. To identify and isolate tumor cell sub-populations that resist to chemotherapy, we used a panel of 45 antibody-fluorochrome conjugates in combination with multi-parameter flow cytometry to screen for the expression of a set of cell surface markers in residual tumor cells that survive chemotherapy. This set of markers represented both proteins involved in stem cell function and proteins known to be over-expressed in stem cells or cancer stem cell sub-populations. As a source of tumor samples, we used a panel of TNBC patient-derived xenografts (PDXs). Those tumor models are known to preserve the morphology, molecular characteristics and drug response profile of the original patient tumors. We used TNBC PDX models to reproduce in vivo-chemotherapy-induced tumor regression and relapse.

Abstract #
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A.

In vivo induction of PDX tumor regression and re-growth with adriamycin / cyclophosphamide chemotherapy

B. PDX tumor dissociation

C. Immunofluorescence staining

Tumor Dissociation Kit, Human (Miltenyi Biotec)

D. Gating strategy for flow cytometry-based cell surface marker expression analysis

E. Sample gating

F. Debris exclusion

G. Live cell exclusion

H. Dead cell exclusion

I. Screening channels

J. Probes

K. Population settings

L. Data analysis

M. Scatterplot

N. FlowJo

O. Data presentation

P. Data interpretation

Q. Data validation

R. Data publication

S. Data archiving

T. Data sharing

U. Data dissemination

V. Data impact

W. Data utilization

X. Data reuse

Y. Data citation

Z. Data replication

Selection of candidate markers for molecular and functional characterization

Cell surface marker expression before and after A/C chemotherapy: average of four different TNBC PDX models

Molecular and functional analyses of sorted tumor cell sub-populations

mRNA and miRNA expression analyses

In vivo tumor initiation and drug response assays

In vitro sphere formation and drug cytotoxicity assays

Candidate markers

One common marker enriched in residual tumor cells

No common marker depleted in residual tumor cells

Untreated tumors
Residual tumors
Recurrent tumors
Pre-treatment tumors
Residual tumors
Recurrent tumors

% of marker-positive cells for each marker tested

100 %
50 %
25 %
0 %

HBCx-17
HBCx-10
HBCx-6

HBCx-14

HBCx-14

HBCx-17
HBCx-10
HBCx-6

HBCx-14

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HBCx-6

HBCx-14

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