Cell-autonomous activation of the Interferon/STAT1 pathway in response to genotoxic therapy

Introduction

Triple negative breast cancer (TNBC) is a very aggressive subtype of breast cancer. It lacks expression of estrogen (ER) or progesterone (PR) receptors and over-expression of HER-2, hence it cannot benefit from current targeted therapies. Its metastatic propensity is higher than in other types of cancer. After chemotherapy, recurrence is frequently observed and is most often lethal for the patient. Xenotech has developed a panel of Patients Derived Xenograft models (PDX) from TNBC in order to study and better understand the mechanisms of response to treatment and recurrence.

Identification of a 21 gene SIGNATURE

- IFN/STAT1 pathway: STAT1, ST2, IFIT1, IFIT2, ISG15, MX1
- Other pathways: LAMPI (unpaired), PARP12, PARP1A (DNA repair)

- Signature observed ONLY in tumors responding to treatment
- Detectable 3 to 7 days after A/C, i.e. BEFORE the nodule phase

Results

- Stimulation of naïve MCF-7 cells by conditioned media induces:
  1. Transcriptional activation of ISRE and GAS luciferase reporter genes
  2. Transcriptional induction of IFN-stimulated genes

- Fold change of IFN-stimulated genes
- Fold difference (cond media/control)
- Fold induction to control

- m afo + siIFNAR1
- mafo + siNT
- control + siNT

- m afo + siIFNAR1 plays a central role in the induction of the IFN/STAT1 signature

- IFN/STAT1 pathway activation induced by genotoxicities may be both
- a predictive marker of response to treatment (at the signature level)
- involved in the persistence of residual cells facilitating cancer recurrence (at the individual gene level)

Conclusions

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