

Studies on MAGI1 as a suppressor in Breast cancer

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Breast cancer is a heterogeneous disease comprising several subtypes with different therapeutic and prognostic implications. For this reason, an accurate diagnosis is crucial for the choice of the right therapeutic strategy. For instance, luminal A breast cancer subtype is estrogen sensitive and it is essentially treated with anti-hormonal therapy. In contrast, patients with luminal B subtype that become estrogen insensitive and develop resistance to hormonal therapy would consequently better benefit from chemotherapy.

MAGI1 is a member of the membrane-associated guanylate kinase (MAGUK) family and it is known to be a tumor suppressor in different cancers such as colon cancer. Human database mining revealed that breast cancer patients bearing tumors with high expression of MAGI1 have a better survival, especially in luminal A and hormone receptor positive breast cancer subtype. Therefore, we hypothesize that MAGI1 plays a role in estrogen-dependent breast cancer subtype and breast cancer metastasis.

In order to study the role of MAGI1 in breast cancer, we performed *in vivo* studies with two syngeneic models of breast cancer in Balb/c mice: luminal ER+ non-metastatic 67NR cells and triple negative highly metastatic 4T1 cells. MAGI1 is moderately expressed in the non-metastatic cell line 67NR and is expressed at low levels in 4T1 cells. Downregulation of MAGI1 in 67NR and overexpression of MAGI1 in 4T1 renders cells more and less metastatic to the lungs, respectively. *In vivo* assays further indicated that the above-mentioned effects on metastasis are due to differences in extravasation capacity. In particular, MAGI1 affects actin dynamics and the loss of MAGI1 promotes filopodial-like protrusion formation and impairs focal adhesion turnover.

We also demonstrated that MAGI1 is a gene upregulated by estrogen and MAGI1 presence is permissive for estrogen receptor signaling in human MCF7 breast cancer cell line. Consequently, downregulation of MAGI1 renders MCF7 cells insensitive to estrogen as they fail to upregulate estrogen-regulated genes such as Progesterone and BRCA1.

These results suggest that MAGI1 expression is downregulated upon tumor progression and it is negatively associated with metastatic potential. Moreover, MAGI1 loss upon tumor progression might be related to a more aggressive and proliferative luminal B breast cancer subtype and might predict estrogen receptor signaling independence hence resistance to anti-hormonal therapy.

Jury:

Prof. Dr. Curzio Rüegg (thesis supervisor)

Dr. Albert Santamaría Martínez (internal co-examiner)

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Prof. Dr. Michael Walch (president of the jury)