ID: 00968
Type: Oral Comunication
Topic: Tumor treatment

Targeting Myc in metastatic breast cancer by Omomyc: from proof-of-principle to pharmacological approach

Daniel Massó-Vallés[1] , Marie-Eve Beaulieu[1] , Toni Jauset[1] , Erika Serrano[2] , Sandra Martínez-Martín[2] , Laia Foradada[1] , Virginia Castillo[2] , Sílvia Casacuberta-Serra[1] , Mariano F. Zacarias-Fluck[2] , Génesis Martín[2] , Antonio Luque-García[2] , Marta Escorihuela[2] , Jonathan R. Whitfield[2] , Joaquín Arribas[2] , Laura Soucek[1]

1) Peptomyc SL, Barcelona, Spain 2) Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Introduction:

Breast cancer is a leading cause of cancer mortality in women due to the high frequency of metastatic disease, which, despite advances in therapeutic options, is still essentially incurable. The role of Myc in promoting tumorigenesis is beyond doubt, but there are contradictory reports in the literature on its role in the metastatic process. Using a Myc dominant negative termed Omomyc, we have demonstrated in various mouse models that Myc inhibition is a safe and effective therapeutic approach against several types of cancer, regardless of the tissue of origin or the driver oncogenic lesion.

Objectives:

So far, Omomyc has only been tested in primary tumors. However, since many steps of the metastatic cascade have been reported to depend on Myc, we hypothesized that Omomyc could be extremely effective in both the prevention and treatment of metastasis too.

Methodology:

We induced transgenic expression of Omomyc in a panel of 11 breast cancer cell lines and analyzed its effect on clonogenic capacity, proliferation, cell cycle progression, angiogenesis, migration and invasion. To characterize the effect of Omomyc expression in vivo we performed prevention and intervention studies in several mouse models of metastatic breast cancer: an orthotopic human cell line-derived model with surgical resection, a human cell-line derived lung colonization model and the MMTV-PyMT transgenic model. Omomyc expression was induced at different stages of the disease and tumor burden and metastatic spread were compared between groups at different time points. In parallel to this systemic modeling of Myc inhibition by transgenic expression of Omomyc, we are also validating the therapeutic utility of Omomyc-derived peptides as a pharmacological approach. To this aim, we assessed the cell penetrating capacity of the peptides in MDA-MB-231 cells by confocal microscopy and flow cytometry. To enhance its activity and to target metastases in vivo, Omomyc was conjugated with a metastasis-targeting sequence, and its efficacy compared with the one exerted by Omomyc alone in vitro. We selected the fusion peptide for in vivo studies and treated the orthotopic and lung colonization mouse models by several routes of administration.

Results:

Here we show that Omomyc expression has a dramatic effect on colony formation capacity in human breast cancer cell lines representative of all the molecular subtypes of the disease. In MDA-MB-231 cells, not only did it impair their proliferation but also migration, invasion and their capacity to induce angiogenesis, key aspects of the metastatic process.

We demonstrate that, in vivo, Omomyc reduces the growth of orthotopically-implanted human breast cancer cells in immunocompromised mice, induces regression of established metastases after primary tumor resection and impairs the development of lung metastases after tail vein injection. In the immunocompetent MMTV-PyMT transgenic model, Omomyc expression dramatically delays the formation and growth of mammary fat pad tumors, thereby preventing the appearance of lung metastases.

When the Omomyc peptide is administered exogenously, we observe remarkable growth inhibition that recapitulates transgenic expression of Omomyc. When conjugated with a metastasis-targeting sequence, its cell penetrating capacity is increased and causes abundant cell death in vitro. In vivo, treatment with the fusion peptide reduces growth of mammary primary tumors and lung metastases.

Conclusions:

We have demonstrated for the first time the applicability of Omomyc against metastasis, challenging the pre-established notion that Myc inhibition could potentiate, rather than inhibit, invasion. Finally, we have validated a metastasis-targeting fusion peptide as the first directly-deliverable Omomyc-based drug for the treatment of metastatic breast cancer, providing a new therapeutic opportunity for patients suffering from this dreadful and incurable disease.

[files191=2;500;500][fileShow][/files]