Targeting nuclear transport pathways to overcome endocrine resistance and recurrence

Eylem Kulkoyluoglu1, Kinga Wrobel1, Yiru Chen1, Jamie Holloway2, Yosef Landesman3, Partha S. Ray4,5,6,7, Alexander E. Lipka8, Rebecca L. Smith9, Zeynep Madak-Endogan1

1Department of Food Science and Human Nutrition, UIUC, Urbana, IL
2Karyotypic Therapeutics, Newton Massachusetts, USA
3Oncostrat Technologies, Urbana, IL, Department of Surgery, Department of Bioengineering, Interdisciplinary Health Sciences Institute
4Department of Crop Sciences, UIUC, IL
5Department of Pathobiology, College of Veterinary Medicine, UIUC, Urbana, IL

ABSTRACT

Currently, around 75% of patients with breast tumors test positive for estrogen receptor alpha (ERα) and are treated with endocrine therapies, such as tamoxifen. One-third of the breast tumors eventually become refractory, reducing the survival rate for affected patients. A combination of alternative endocrine therapies and kinase inhibitors is currently used in such patients. However, after an initial period of therapy response, these tumors relapse in a more aggressive form. Further, the alternative therapies are not optimal in terms of pharmacological properties, are poorly tolerated, and have side-effects that severely decrease quality of life of the patient. Thus, there is a critical need for novel, targetable, mechanism-based therapeutic strategies that (1) re-sensitize ERα (+) tumors to endocrine therapies, and (2) include diagnostic methods to select patients likely to benefit from this approach.

Our objective in this study is to validate a group of nuclear transport genes as biomarkers for endocrine resistance, and to evaluate their inhibition as a novel means to enhance the effectiveness of endocrine therapies. Our central hypothesis is that high expression of these genes in ERα (+) tumors serve as a viable biomarker for risk of endocrine therapy failure. We focused on XPO-1, the major nuclear export protein, which exports ERK5 from the nucleus to the cytoplasm and we used selinexor (KPT-330), the inhibitor of XPO-1, which is already used in clinical trials for solid and hematological cancers. Our experiments show that estradiol induces nuclear localization of ERK5, which otherwise would contribute to increased invasiveness and metastatic potential in the cytoplasm. Selinexor (KPT-330) increases ERK5 nuclear localization in tamoxifen resistant breast cancer cell lines. Our hypothesis is that selexinexor in the cell nucleus and blocking its recycle into the nucleus by selinexor is directly associated with the improved transcriptional responses to endocrine therapies. The nuclear export pathways have not previously been implicated in the development of endocrine resistance, and given the need for better strategies for selecting patients to receive endocrine therapies and improving therapy response of relapsed ERα (+) tumors, our findings show high and significant promise for uncovering the role of these pathways and demonstrating their utility in reducing cancer recurrences.

RESULTS

Nuclear transport gene signature is upregulated in BT474 cells (Luminal B type) compared to MCF-7 cells (Luminal A type).

In clinical tumor samples, XPO-1 mRNA is higher in Luminal B subtype breast tumors.

Overexpression of XPO1 in Tamoxifen resistant MCF-7 cells increases activation of pro-proliferative kinase signaling pathways and cell proliferation.

XPO-1 inhibitor, KPT 330 (Selinexor) decreases cell proliferation in combination with 4-OH-Tamoxifen in both Tamoxifen sensitive MCF-7 cells and Tamoxifen resistant BT474 cells.

CONCLUSION

Overall, results of our studies should validate XPO1 as a target whose inhibition should enhance the effectiveness of endocrine therapies in breast cancer subtypes that are more refractory to endocrine therapies. Validation of XPO1 inhibition as a cancer treatment will lead us to devise, in the future, clinical trials for combination of two clinical therapeutic agents, 4-OH-Tamoxifen and KPT 330 (Selinexor) for therapy resistant breast cancers.