Bioinformatics analysis for Lysyl Oxidases as therapeutic targets for breast cancer

Sofia Ramos1#, Sandra Ferreira1#, Nuno Saraiva1*, Ana S. Fernandes1*
[1]CBIOS, Universidade Lusófona's Research Center for Biosciences & Health Technologies, Campo Grande 376, Lisboa 1749-024, Portugal

Introduction

- LOX and LOXL 1-4 catalyze the cross-linking of elastin and collagen in the ECM [1,2]
- Promote of cell migration and formation of metastases [1, 2]
- Expression of LOX family enzymes is clinically correlated with increased metastasis and poor patient survival

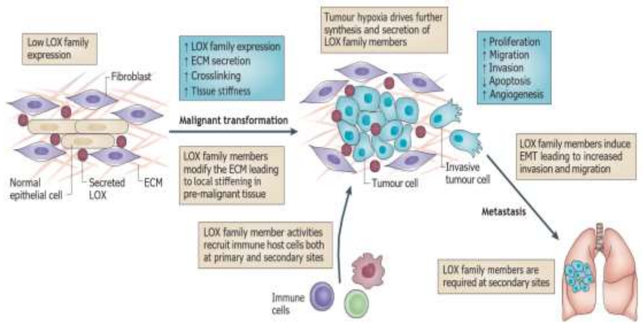

Figure 1. The role of the LOX family members in tumour progression (2)

Potential therapeutic targets to prevent breast cancer metastasis[3]

Importance of selectivity of LOX enzymes inhibitors is not yet clear

Goals and Approach

Explore the role of each LOX enzymes in breast cancer and its subtypes in survival of patients

Bioinformatic-based

Two TCGA-based platforms was used

TIMER2.0
- Association between expression of LOXs and the tumor infiltrates

GEPIA2
- Expression profile of LOXs and the impact of this expression on cancer patient survival
- Correlation between the expression of LOX enzymes and of those with other ECM-related genes

Referências
[1] Ferreira et al. *Antiox*, 2021
[2] Barker et al. *Nat Rev Cancer*, 2012
[3] Ahn et al. *Breast Cancer Res Treat*, 2013

LOX Family gene expression

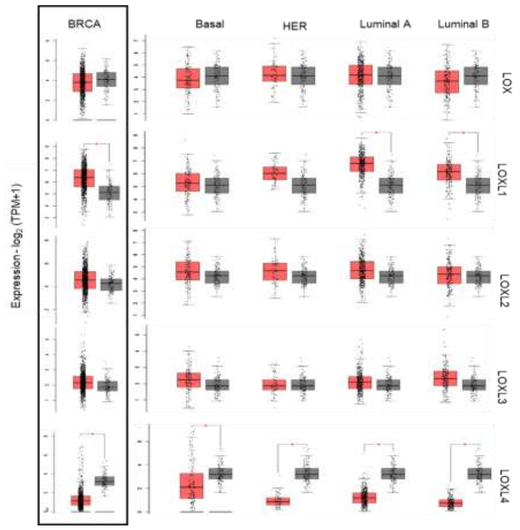

Figure 2. LOX family gene expression analysis. Comparative analysis between BRCA cancer (pink) and normal (grey) tissues and its subtypes

LOXL1, LOXL2, and LOXL3 have generally higher expression in cancer tissues vs normal tissues, while LOXL4 shows the inverse relationship.

The difference is more evident in Luminal-type B

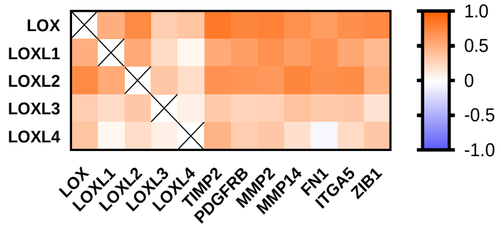

Figure 3. Correlations between LOX family genes and some ECM-related genes in BRCA patients.

Positive correlation between the expression of LOX, LOXL1, and LOXL2 and the expression of genes related with ECM. Correlation is much weaker for LOXL3 and LOX4.

Impact of LOX Family expression in patient survival

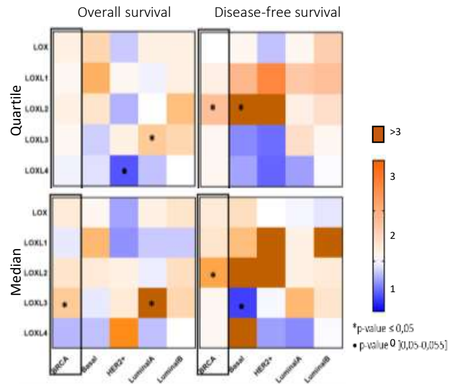

Figure 4. Impact of expression of LOX family genes in patient´s overall survival (OS) and disease-free survival (DFS). A Cox proportional hazard ratio (HR), using as cut-offs median and quartiles of expression of LOX family genes was used in BRCA and its subtypes.

Overexpression of LOXL1 has a negative impact on DFS in all subtypes

LOXL2 has a negative impact on DFS of basal and HER2+ subtypes.

Impact of LOXL3 on DFS is cancer subtype-dependent.

Downregulation of LOXL4 is associated with a reduction of DFS and overall survival in HER2+ patients.

LOXs expression and breast tumor infiltrates

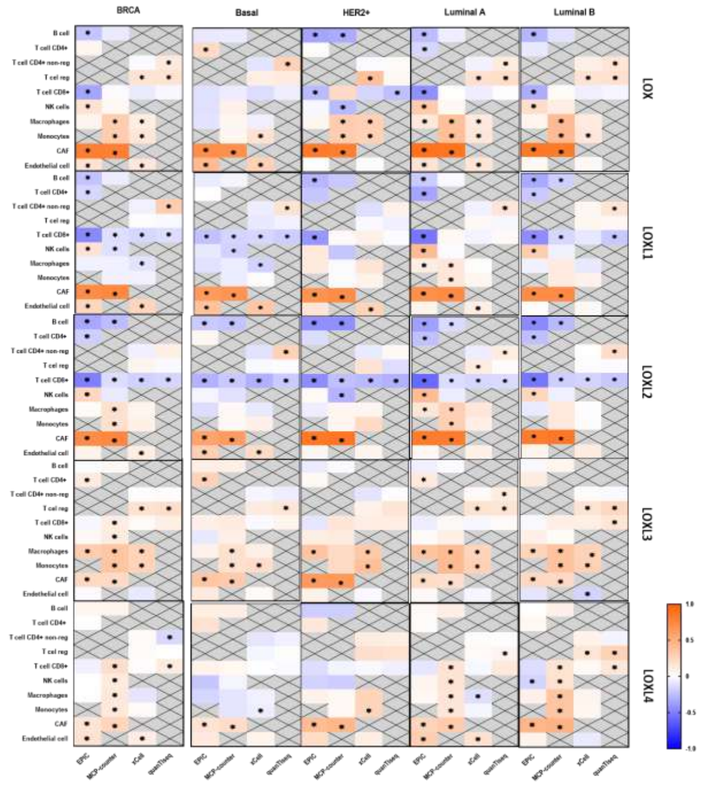

Figure 5. Relation of expression of LOXs and the breast tumor infiltrates. Blue gradient represents a negative correlation and orange gradient a positive correlation (*p<0,05).

Expression of LOXs is associated with higher CAFs in all BC subtypes. Stronger association for LOX, LOXL1 and LOXL2

Expression of LOX, LOXL1, and LOXL2 is associated with lower infiltration of B cells, T CD4, and T CD8 and with higher Treg

Less immunogenic tumors / worse prognosis?

This is not observed for LOXL3 and LOX4.

Main conclusions

- When designing LOX inhibitors for breast cancer treatment, it may be advantageous to block both LOXL1 and LOXL2, but not LOXL4.
- Impact of LOXL3 inhibition may vary with BC subtype (not problematic for luminal types; potentially harmful for HER2+).

Selectivity matters and should be taken into account in drug discovery process

Acknowledgement:
FCT-Foundation for Science and Technology, I.P., (UIDB/04567/2020 and UIDP/04567/2020). ILIND Grant Program Fazer+ (ILIND/F+/EI/01/2020).