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► To cite this version:

Maxence Mocquery-Corre, Julie Clachet, Alexandre Berquand, Cathy Hachet, Katia Savary, et al.. LRP-1 a key modulator of TBNC progression. Matrix Biology Europe (MBE) 2024, Sep 2024, Lyon, France. hal-04787198

HAL Id: hal-04787198 https://hal.science/hal-04787198v1

Submitted on 17 Nov 2024

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LRP-1 a key modulator of TNBC progression

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Introduction

Triple-negative breast cancers (TNBC) are a very aggressive subtype of breast cancer with high metastatic potential; they do not respond to hormone therapy and few targeted therapies are available. During metastatic dissemination, tumor cells undergo a cascade of events including invasion of surrounding tissues, followed by blood vessels intravasation and extravasation mechanisms. We focused on molecular deciphering mediated by the LRP-1 receptor (Low Density Lipoprotein Receptor-related Protein 1) in breast tumor progression using two cell lines of TNBC (HS578-T and 4T1) on which we performed a Knock-Out (KO) of the LRP-1 gene. These cell models have enabled us to study precisely the effect of LRP-1 on numerous key stages of carcinogenesis.



Figure 2: Pro-migratory effect of LRP-1 Receptor in breast cancer cell lines. HS578-T and 4T1 cells (WT and CR-LRP-1) were embedded in a 3D collagen gel migration model and monitored over 24 hours using videomicroscopy (1 image/20 min). Scatter plot represents three independents replicates with a total tracking of 860 cells.

4T1 WT

4T1 CR-LRP-1

100₇

Figure 3 : Pro-invasive effect of LRP-1 Receptor in breast cancer cell lines. HS578-T and 4T1 cells (WT and CR-LRP-1) were seeded into matrigelTM-coated inserts and incubated for 24 hours. Invasive cells were stained with crystal violet, and absorbance was measured at 560 nm Histogram represents the percentage of invasion (arbitrary fixed at 100% for the WT) of three independents replicates.

HS578-T WT

HS578-T CR-LRP-1

LRP-1 KO promotes the

inhibition of cellular migration

<u>3D collagen gel</u>





Figure 5: Evasion effect of LRP-1 Receptor in breast cancer cell lines. Left panel : representative photograph of escape areas in HS578-T and 4T1 cells (WT and CR-LRP-1). Right panel : Histogram displays the quantification of escape areas in HS578-T and 4T1 . (scale bar 500 µm).

necrotic zone of each spheroid section.

CNrs

✓ Different structural organisations \checkmark Sensitivity to hypoxia



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Figure 7 : Contribution of LRP-1 on tumor growth. 500,000 4T1 cells expressing LRP-1 (4T1-WT) or not (4T1 CR-LRP1) were injected into mammary fat pad of 7 weeks old BALB/C mice. As soon as tumors were palpables, measurements of tumor volume were realized twice a week using a caliper until 21st day post injection. (n=10mice, ** p<0.01).

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Conclusion

Taken together, our results highlight the role of LRP-1 in TNBC models via the regulation of migratory and invasive capacities as well as cell viability of tumor cells. These results were reinforced by in vivo experiments which demonstrate the pro-tumoral role of LRP-1. Proteomic analyses are ongoing to decipher the molecular pathways regulated by LRP-1.

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ACKNOWLEDGEMENTS : I would like to thank all those who contributed to this work such as mobycite (microscopic analysis). We also thank Nicole BOULAND for putting tumors into a cassette. Finally, we would like to thank CHAZÉE Lyse and AZIZ Abdel-Ilah for their help with cell culture.

Presented by : Mocquery-Corre Maxence Supervised by : Dr Devy Jérôme And Dr Thevenard-Devy Jessica

