AURKA and AURKB as potential targets to suppress early metastasis in triple-negative breast cancer in women of African ancestry.

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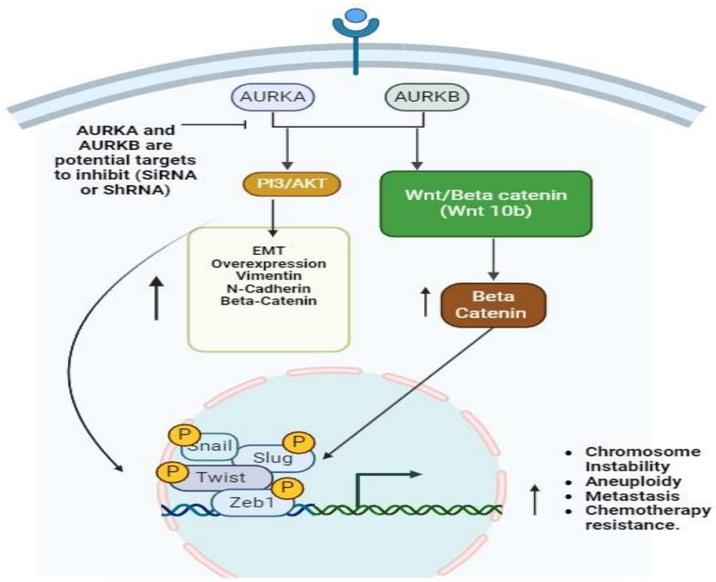
Abstract

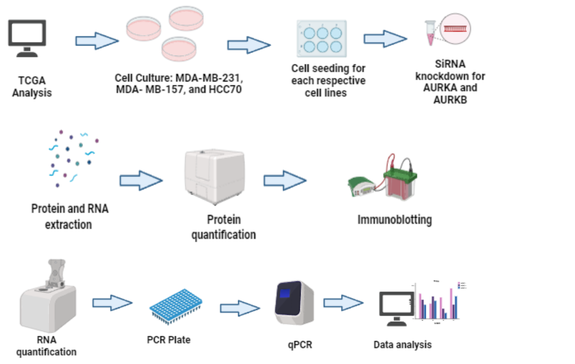
Hispanic/Latino women (H/L) and women of African heritage (non-Hispanic black, NHB, Black H/L, and Caribbean H/L) are more likely to be diagnosed at more advanced stages and with triple-negative breast cancer (TNBC). This contributes to poorer survival rates than non-Hispanic white women (NHW). TNBC lacks ER, PR, and HER2 receptors and cannot be treated with biological treatments. Mitotic kinases are proteins essential for centrosome and mitotic fidelity that are overexpressed in TNBC. That overexpression promotes centrosome amplification, chromosome instability, and early metastasis (the epithelial-to-mesenchymal transition (EMT), cell invasion, and migration). Our studies aim to inhibit the expression of mitotic kinases such as AURKA and AURKB in TNBC. We hypothesize that co-inhibiting AURKA and AURKB will decrease EMT biomarkers and therefore, early metastasis. Using The Cancer Genome Atlas database, we identified higher expression of AURKA and AURKB in NHB women compared to NHW women. SiRNA-mediated knockdown and immunoblotting with EMT biomarkers were performed using the MDA-MB-231 cells (NHW), MDA-MB-157 (NHB), and HCC70 (NHB) TNBC cells. The expression of AURKA and AURKB decreased in all cell lines compared to the control group, and EMT biomarkers such as N-cadherin and Vimentin decreased in MDA-MB-157. These results indicate the potential use of mitotic kinase inhibitors as therapies against TNBC. Ultimately, we will study the combined inhibition of AURKA and AURKB in different TNBC cell lines from NHB women.

Introduction

- Triple-negative breast cancer (TNBC) lacks progesterone (PR), estrogen (ER), and human epidermal growth factor (Her2) receptors and cannot be treated with biological therapies against these three receptors. NHB women and H/L women have a higher probability of being diagnosed with TNBC and at higher stages. This disparity contributes to a poor rate of survival in NHB women.
- In TNBC, overexpression of AURKA and AURKB culminates in centrosome amplification and chromosome instability. The overexpression of mitotic kinases associates with the expression of EMT biomarkers, such as N-cadherin, Vimentin, and β-catenin. In addition, overexpression of AURKA and AUKRB can lead to the activation of molecular pathways such as PI3/AKT and Wnt/β-catenin to promote EMT.
- To understand how AURKA and AURKB are potential targets against TNBC, we performed siRNA knockdown singly and in combination in TNBC cell lines derived from NHW women and NHBW. To measure the expression of AURKA and AURKB, EMT Biomarkers and transcription factors, immunoblotting and qPCR was performed.



Materials and Methods



AURKA and AURKB mRNA expression is increased significantly in NHB women compared to NHW women. Expression of AURKB is elevated in Basal/Triple-Negative Breast Cancer in NHB women and NHW women

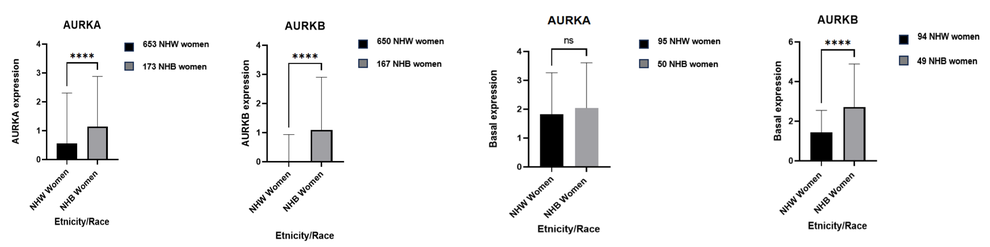


Figure 1: The TCGA database shows significant differences in the expression of AURKA and AURKB mRNAs in NHB women compared to NHW women. AURKB mRNA level is significantly different in NHB women compared to NHW women in Triple-negative breast Cancer.

Targeting AURKA in MDA-MB-231 (White Women) decreased the expression of Vimentin

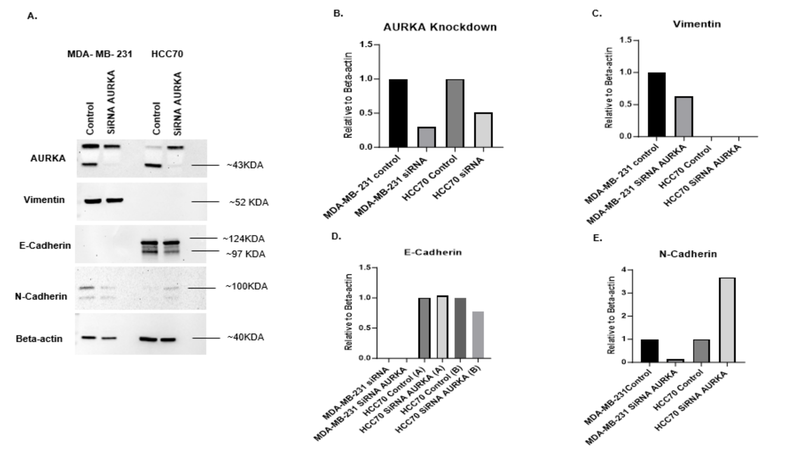


Figure 1: Expression of AURKA and EMT biomarkers after siRNA knockdown in MDA-MB 231 (NHW women) and MDA-MB-157 (NHB women). This preliminary data demonstrates how the expression of AURKA decreased after siRNA-mediated knockdown.

Targeting AURKB in MDA-MB-231 (White Women) and MDA-MB-157 (Black Women) decreased the expression of Vimentin

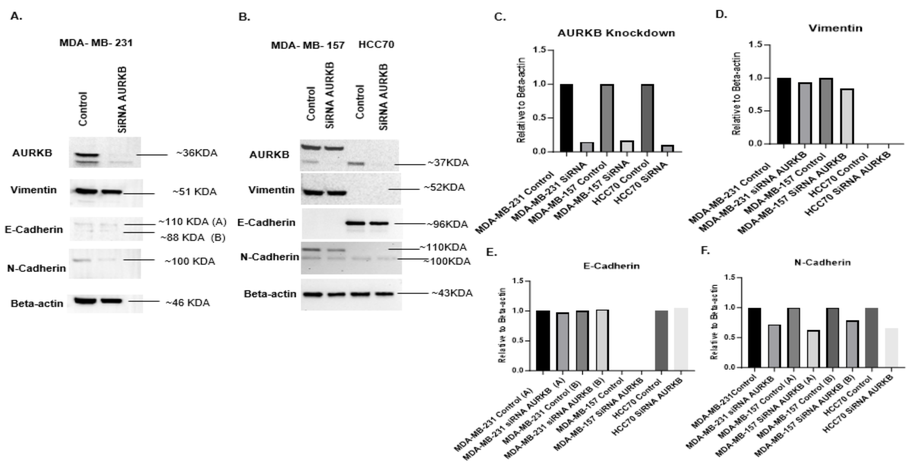


Figure 2: Expression of AURKB and EMT biomarkers after siRNA knockdown in MDA-MB 231 (NHW women), MDA-MB-157 (NHB women), and HCC70 (NHB women).
This preliminary data demonstrates how the expression of AURKB decreased. Also, it shows how targeting AURKB promotes a decrease in the expression of N-cadherin in MDA-MB-157 and HCC70, as well as Vimentin in MDA-MB-157.

Targeting both AURKA and AURKB singly and in combination in MDA-MB-157 (Black women) decreased mRNA levels of Vimentin and N-cadherin.

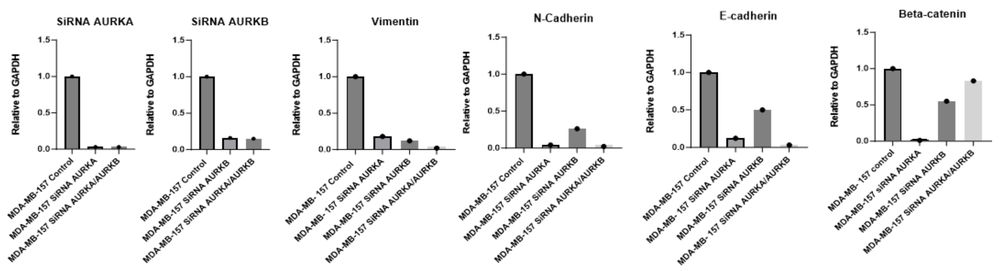


Figure 3 : Expression of AURKA, AURKB, and EMT biomarkers after siRNA knockdown in MDA-MB-157 (NHB women). This preliminary data shows how targeting AURKA and AURKB singly and in combination promotes a decrease in the expression of Vimentin and N-cadherin.

Targeting AURKA and AURKB in MDA-MB-157 singly and in combination the expression of different transcription factors such as Slug, Twist, Snail, and Zeb1

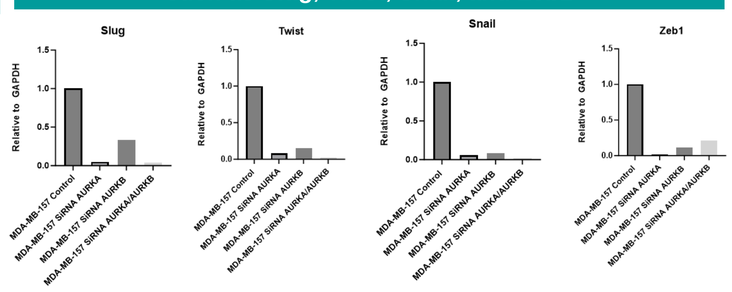
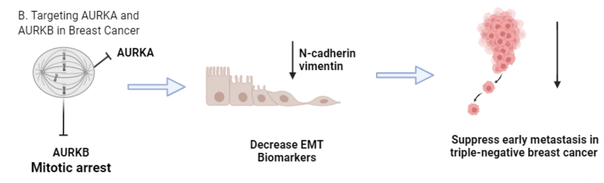


Figure 5: Expression of Transcription Factors after siRNA knockdown in MDA-MB-157 (NHB women). This preliminary data shows how targeting AURKA and AURKB singly and in combination promotes a decrease in the expression of different transcription factors such as Slug, Twist, Snail, and Zeb1.

Conclusion and Discussion

•The Cancer Genome Atlas (TCGA) database analyses revealed that AURKA and AURKB mRNA expression is elevated in women of African heritage. AURKA and AURKB may be future novel potential targets for triple-negative breast cancer treatment in NHB and H/L.
• Our preliminary results suggested that targeting both AURKA and AURKB in TNBC cell lines derived from non-Hispanic black women, decreases N-cadherin and Vimentin expression.
•Since overexpression of AURKA and AURKB can promote the activation of different EMT biomarkers, targeting these mitotic kinases will help suppress early metastasis. These outcomes will have a positive impact because they will elucidate how mitotic kinase plays a fundamental role in triple-negative breast cancer and how they can be a potential target to develop novel therapies against triple-negative breast cancer in Women with African heritage. Therefore, it will help decrease their elevated death rates.



Future Directions

- These results suggest that increased expression of mitotic kinases such as AURKA and AURKB contributes to breast cancer survival disparities in NHB women compared to NHW women. Therefore, we will study how the combined inactivation of mitotic kinases in different TNBC breast cancer cells derived from NHB women modulate cell growth, invasion, metastasis, and the epithelial-to-mesenchymal transition.
- We will also study the effects of co-inhibiting AURKA and AURKB in suppressing early metastasis in vivo models such as NGS female mice models.

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