## Miss. Paulina Fuentes PhD(c)

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## Uncovering the role of KLK4 in the progression of breast cáncer

Kallikrein-related peptidases (KLKs), a family of serine proteases, are being researched as potential cancer biomarkers. KLK4 has shown promise as a prognostic marker for various cancers, including breast cancer, where overexpression is associated with a poor prognosis. However, its precise mechanism in breast cancerprogression remains unclear.Breast cancer is a heterogeneous disease, with the luminal subtype (positive for estrogen receptor, ER+) being the most prevalent and with the best prognosis. However, over half of advanced ER+ breast cancers are intrinsically resistant to tamoxifen, and about 40% will acquire resistance during treatment. To better understand the role of KLK4 in ER+ breast cancer biology,we studied its effects on endothelial permeability and adhesion to extracellular matrix components, as well as exploring its role in tamoxifen resistance. Additionally, we investigated whether KLK4 could serve as a biomarkerfor luminal breast cancer. We utilized various in vitro approaches with estrogen-sensitive MCF-7 and tamoxifen-resistant MCF-7 TAMR breast cancer cell lines stimulated with rKLK4 (2-20 ng/ml), IL-8 (10-150 pg/ml), and/or tamoxifen(1-7.6 μM). Techniques such as Westernblotting, immunofluorescence, ELISA,permeabilization, MTT, and adhesion assayswere performed to analyze the role of KLK4 in breast cancer progression.

Our findings indicate that KLK4 may promote breast cancer progression by increasing vascular permeability and adhesion to extracellularmatrix components. Tamoxifen treatmentwas found to upregulate endogenous KLK4 levels, and we observed changes in KLK4 localization in tamoxifen-resistant cells compared with MCF-7 WT, from a cytosolic to a more nuclear pattern, an effect that may shed some light on its functional role. We also found that KLK4 may positively regulate an alternative, plasmatic membrane estrogen receptor called GPER-1 and the levels of aromatase, the enzyme involvedin estrogen synthesis. Although KLK signaling is mediated by protease-activated receptors (PARs), we have not observed changes in the PAR2 subtype, the most important subtype reported in breast cancer. Additionally, we found that rKLK4 and IL-8 increased KLK4 protein levels and secretion in MCF-7 cells, respectively. Finally, we found increased serum levels of KLK4 in ER+ breast cancer patients compared to healthy female participants in a pilot case-control studyin Chile's Los Rios region.In conclusion, while our study suggests that KLK4 may contribute to breast cancerprogression, further research is needed to clarify its specific role. Our results are significant because they provide insights into the biological implications of KLK4 in the ER+ breast cancer model, includingsome responses to tamoxifentreatment.

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## Biography:

**Paulina Fuentes** is a dedicated pharmaceutical chemist from Valdivia, Chile, who has been actively contributing to the private and clinical sectors for nearly a decade. In pursuit of her passion for medical sciences, she started her PhD in 2020 and is now fully immersed in her doctoral thesis, which seeks to unravel the complexities of breast cancer cell biology and drug resistance. Her research represents a significant challenge, but her unwavering commitment to improving patientoutcomes makes her a valuableasset to the scientific community.



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