Proceedings International
Platinum Open Access Journal (ISSN 2668-6384)

Proceedings, Abstract
Volume 5, Issue 1, 2023, 16
https://doi.org/10.33263/Proceedings51.016

The Dual Role of Tumor Necrosis Factor alpha (TNF-α) in 3D Breast Cancer Cell Migration †

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† Presented at 2nd Edition of the OncoHub Conference – Connecting Scientists and Physicians for Next Generation Cancer Management, Poiana Brașov, Brașov, 21-23 September 2022

Received: 10.12.2022; Accepted: 20.12.2022; Published: 5.01.2023

Abstract: TNF-α is one of the most important pro-inflammatory cytokines found in the breast tumor microenvironment, strongly influencing the fate of the tumor. It can trigger signals for cell proliferation, survival, and invasion, but also for apoptosis, depending on the specific cellular context and the molecular traits that characterize each cell line or tumor. However, the significance of TNF-α signaling in breast cancer (BC) metastasis remains unclear due to its dual role in shaping the malignant phenotype. Therefore, we evaluated the cellular and molecular effects of BC cell migration in response to TNF-α. The migration capacity of seven BC cell lines was evaluated in 3D microfluidic devices, and their migration capacity (migration speed, migration persistence, and percentage of migratory cells) was associated with their molecular signature. The gene expression of 715 genes was correlated (rho > ±0.7; $p < 0.05$) with the migratory phenotype. TNF-α was found to be one of the most important upstream regulators of the signaling networks in which these 715 genes participate, suggesting its involvement in cell migration. To assess the impact of TNF-α signaling on the BC migration capacity, two different strategies were employed in four diverse BC cell lines (T47D, MDA-MB-468, BT549, and MDA-MB-231): either rhTNF-α was administrated on cells, or the TNF-α-receptor TNFR1 was silenced by siRNA. In each experimental setting, the cell migration capacity was evaluated in microfluidic devices, while the molecular effects triggered by the treatment were monitored by RT-qPCR. According to our results, TNF-α stimulates the migration of triple-negative, mesenchymal-like BC cells that are also characterized by high *TNFR1* expression but inhibits the migration of epithelial-like cells in which *TNFR1* expression is low. Furthermore, 12 genes stood out as key regulators of the BC cell migration capacity under the influence of TNF-α signaling.

Keywords: breast cancer; TNF-α; 3D cell migration; microfluidic technology.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.