The Biology of Metastatic Breast Cancer: Circulating Tumor Cells, Physical Constraints, and Temporal Regulation

Introduction

Metastatic breast cancer (MBC) remains the primary cause of breast cancer–related mortality, largely due to its complex, multistep dissemination process and resistance to conventional therapies. Central to metastasis is the behavior of circulating tumor cells (CTCs) (Diamantopoulou et. al 1), which detach from the primary tumor, survive mechanical and immune stresses in circulation, and colonize distant organs. Recent advances in physical biology, single-cell transcriptomics, and chronobiology have reshaped current understanding of metastatic progression, revealing that metastasis is not only biologically heterogeneous but also physically constrained and temporally regulated. This article synthesizes recent findings on the physical properties of CTCs, their molecular heterogeneity, and the surprising influence of sleep-associated circadian dynamics on metastatic spread.

Circulating Tumor Cells as Drivers of Metastatic Progression

CTCs represent a rare but clinically significant population of tumor cells that mediate the transition from localized disease to systemic metastasis. (Orrapin et al). Although millions of tumor cells may enter circulation daily, only a small fraction survive to form secondary lesions, underscoring the selective pressures imposed by the circulatory system. CTCs must endure sheer stress, immune surveillance, and oxidative damage, while retaining the capacity for extravasation and colonization (Orrapin et. al). These constraints favor phenotypically plastic cells capable of rapid mechanical adaptation and transient epithelial–mesenchymal transition (EMT).

Notably, CTCs are not a homogeneous population. Clusters of CTCs, rather than single cells, exhibit markedly higher metastatic potential, partly due to enhanced survival signaling and protection from sheer forces (Orrapin et. al). In breast cancer, clustered CTCs often retain partial epithelial characteristics, challenging the assumption that complete EMT is required for metastasis. This hybrid phenotype enables both motility and intercellular adhesion, facilitating efficient dissemination.

Physical Biology of Circulating Tumor Cells

The physical properties of CTCs play a critical role in determining metastatic efficiency. Compared to normal blood cells, CTCs are generally larger, stiffer, and less deformable, characteristics that increase their likelihood of becoming mechanically trapped in capillary beds (Orrapin et. al). While this mechanical arrest was once thought to be a passive process, emerging evidence suggests that CTCs actively exploit vascular bottlenecks to initiate extravasation. Shear stress within the bloodstream further acts as a selective force, eliminating mechanically fragile cells while enriching for those with reinforced cytoskeletal structures. Breast cancer CTCs demonstrate adaptive cytoskeletal remodeling, allowing them to withstand hemodynamic forces that would otherwise induce apoptosis (Philips et. al). These findings

highlight metastasis as a process governed not only by genetic mutations but also by biophysical fitness.

Molecular Heterogeneity Revealed by Single-Cell RNA Sequencing

Single-cell RNA sequencing (scRNA-seq) has revolutionized the study of CTC biology by uncovering extensive transcriptional heterogeneity within metastatic populations. Analyses of breast cancer CTCs reveal distinct subpopulations associated with stemness, immune evasion, and therapy resistance (Orrapin et. al). Importantly, these transcriptional programs often coexist within the same patient, complicating treatment strategies.

CTCs frequently express stem-cell–associated genes such as *ALDH1* and *SOX2*, supporting the notion that metastatic competence is linked to self-renewal capacity rather than proliferative rate alone (Orrapin et. al). Additionally, scRNA-seq data demonstrate dynamic shifts in gene expression as CTCs transition between circulation and colonization, emphasizing metastasis as a reversible and adaptive process.

From a clinical perspective, this heterogeneity undermines the predictive value of bulk tumor biopsies. Precision medicine approaches that incorporate longitudinal CTC profiling may therefore provide a more accurate representation of metastatic risk and therapeutic vulnerability.

Circadian Regulation and Sleep-Associated Metastatic Acceleration

One of the most unexpected recent findings in breast cancer metastasis is the role of sleep and circadian rhythms in regulating CTC dissemination. Using mouse models and human patient samples, Diamantopoulou et al. demonstrated that the majority of metastatic spread occurs during the sleep phase rather than during active periods. Breast cancer CTCs collected during sleep exhibited higher proliferative capacity and increased metastatic potential compared to those collected while awake (Diamantopoulou et al.).

This phenomenon appears to be hormonally mediated, with circadian fluctuations in melatonin and glucocorticoids influencing tumor cell release and survival. These findings challenge longstanding assumptions about constant metastatic risk and raise critical questions regarding the timing of therapeutic interventions. Chronotherapy (administering treatments at biologically optimal times) may thus represent an underexplored strategy for limiting metastatic progression in breast cancer.

Implications for Treatment and Future Research

Together, these findings suggest that metastatic breast cancer cannot be fully understood through genetic analysis alone. Physical constraints, transcriptional plasticity, and circadian timing collectively shape metastatic success. Therapeutic strategies targeting CTC clusters, mechanical adaptability, or time-dependent dissemination may offer novel avenues for intervention.

Future research should integrate biophysical modeling, single-cell profiling, and longitudinal patient monitoring to capture the dynamic nature of metastasis. In particular, incorporating circadian biology into clinical trial design may improve both efficacy and patient outcomes.

Conclusion

Metastatic breast cancer emerges from the convergence of biological heterogeneity, physical selection, and temporal regulation. Circulating tumor cells act as the central mediators of this process, adapting mechanically, transcriptionally, and hormonally to overcome systemic barriers. By reframing metastasis as a dynamic and context-dependent phenomenon, current research opens the door to more nuanced and effective therapeutic strategies aimed at preventing the lethal spread of breast cancer.

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