Deciphering tumor heterogeneity and therapeutic vulnerabilities in rare metaplastic breast carcinoma: insights from the Gold Cohort

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Scientific abstract

Background and Rationale. Metaplastic breast cancer (MpBC) is a rare but highly aggressive subtype of breast cancer (BC), histologically defined by the coexistence of at least two distinct cellular phenotypes. These include carcinomatous components (e.g., squamous) and mesenchymal elements such as osseous, chondroid, or spindle morphologies, reflecting metaplastic differentiation. MpBC is associated with the poorest prognosis among BC subtypes; however, it remains unclear whether its unfavorable clinical outcomes are driven by its marked cellular heterogeneity, which may underlie divergent therapeutic responses.

Objectives. The main aims of this project are to apply genomic and spatial transcriptomic profiling to dissect MpBC heterogeneity and identify novel therapeutic vulnerabilities with translational potential.

Methods and Results. Through the Marathon of Hope Cancer Centres Network (MOHCCN), we collected and sequenced over 180 rare breast cancer subtypes (Cohort 15), including 9 MpBC tumors in Quebec. To address the rarity of MpBC, we established a Canada-wide MpBC research network, enabling coordinated specimen collection and sequencing across Canada. To date, we sequenced more than 30 MpBC tumors and implemented advanced spatial transcriptomics (Visium HD, 10x Genomics) in 15 cases. We found that transcriptional heterogeneity closely aligns with spatially distinct histological features. Notably, specific MpBC cell populations display unique expression programs that may represent new therapeutic targets.

Conclusions and Anticipated Impact. Our findings demonstrate that MpBC is characterized by profound intratumoral heterogeneity, which is reflected both histologically and transcriptionally. The identification of spatially distinct subpopulations with potentially targetable pathways highlights the importance of integrating spatially resolved transcriptomic into MpBC research. A deeper understanding of MpBC biology may uncover actionable targets and guide rational combinatorial treatment strategies, ultimately improving outcomes for patients with this rare and lethal disease.

Plain language abstract

Background and Rationale. Metaplastic breast cancer (MpBC) is a very rare but particularly aggressive form of breast cancer. Unlike more common breast cancers, MpBC tumors are made up of different types of cells, including those that look like regular breast cancer cells and others that resemble bone, cartilage, or connective tissue. This unusual mix of cell types may explain why MpBC does not respond well to standard treatments and why patients often face worse outcomes compared to other breast cancer subtypes.

Objectives. Our goal is to better understand how MpBC tumors develop and behave by studying their unique cell composition. By doing this, we aim to discover new weaknesses in these cancers that could lead to more effective treatment options in the future.

Methods and Results. Through the Marathon of Hope Cancer Centres Network (MOHCCN), we collected and analyzed over 180 rare breast cancers in Quebec, including 9 cases of MpBC. Because MpBC is so uncommon, we built a national Canadian network to bring together samples from across the country, including British Columbia, Ontario, and Alberta. Using advanced genomic technologies that allow us to analyse different spatial regions of the tumor, we have uncovered tumor heterogeneity and differential drug sensitivity.

Conclusions and Anticipated Impact. Our research shows that MpBC tumors are composed of heterogeneous cells that may each respond differently to treatment. By mapping these differences, we can begin to identify new ways to treat this rare and difficult disease. In the long term, this work may lead to more personalized and effective therapies for patients with MpBC, improving their chances of survival.