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Tumor-Macrophage Fusion Cells detected in the circulation of metastatic breast cancer patients is prognostic for rapid progression and death

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ABSTRACT

Recently, it was described that macrophages and tumor cells can fuse to form tumor macrophage fusion cells (TMFs), detectable within primary tumors and patient's (pts) circulation. However, there are multiple pathways and subsequent subtypes of TMFs with limited data on the various TMF types, commonality in blood, and their clinical relevance. Here we evaluated n=122 metastatic breast cancer (mBC) blood samples for CTCs & TMFs. We describe numerous types of TMFs with vastly different fusion phenotypes, including 1) partial (i.e. some membrane interaction & both cells retaining their original phenotypes), 2) homodimeric (i.e. both cells with fused membranes & sharing cytoplasm), 3) cannibalistic (i.e. CTC within a CD14+ macrophage & cells retaining their individual phenotypes), 4) binucleated (i.e. both cells completely merge & becoming one cell with dual expression phenotypes), and 5) hyperploidy (i.e. multiple cells merge to form a large polyploid cell). As CTCs & TMFs are isolated in conjunction from a single blood sample, we evaluated both CTCs & all TMF subtypes to determine their prognostic and predictive values for aggressiveness of disease.

Figure 1. Diagram of the Different TMF Subtypes and Images of TMFs from Metastatic Breast Cancer Patient's Blood

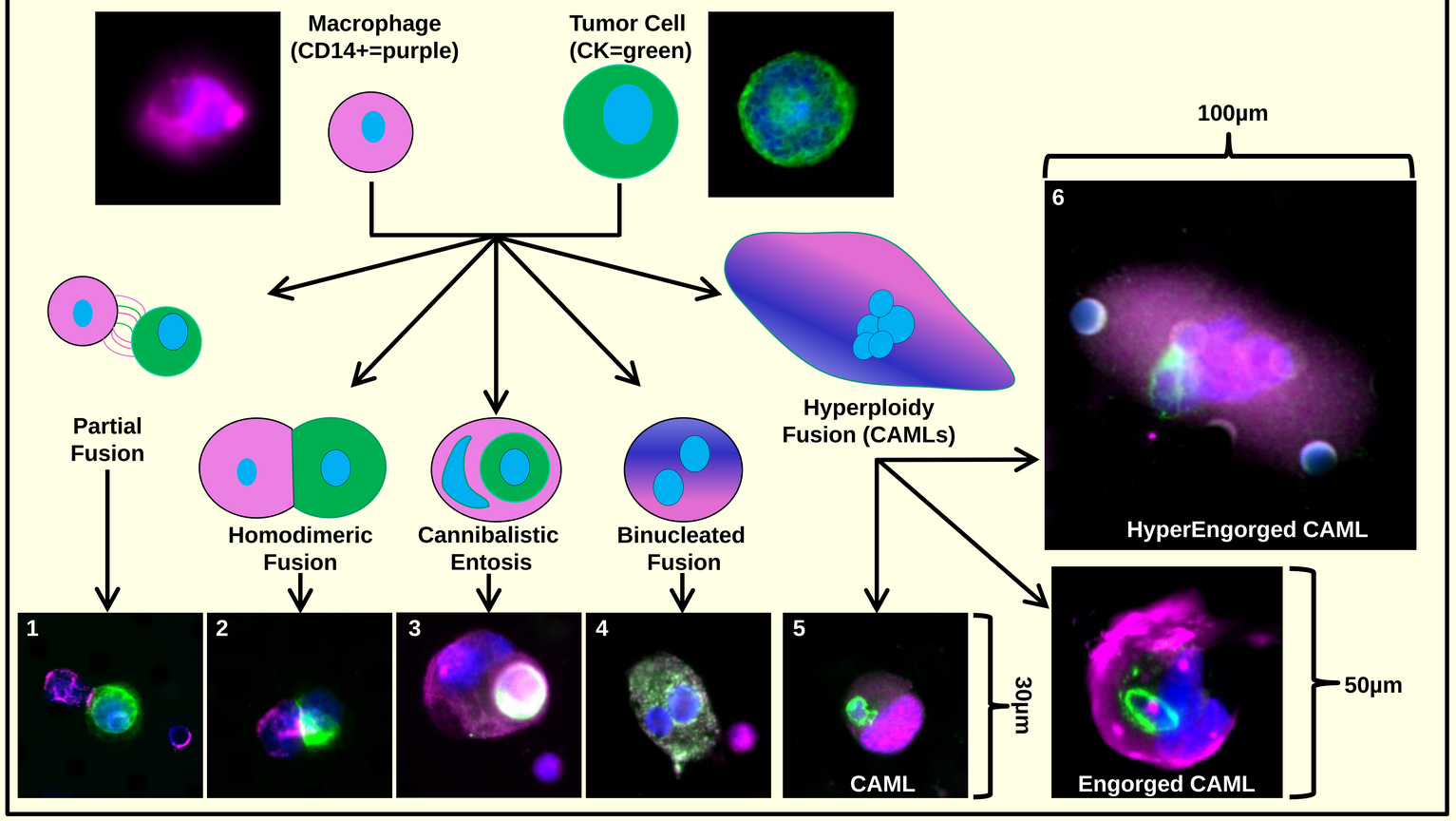


Figure 2. PFS of Patients with Any TMFs

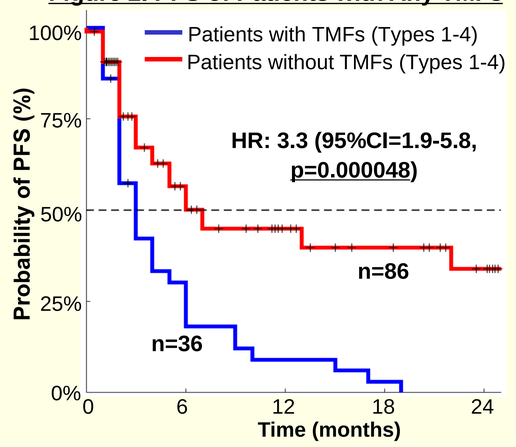
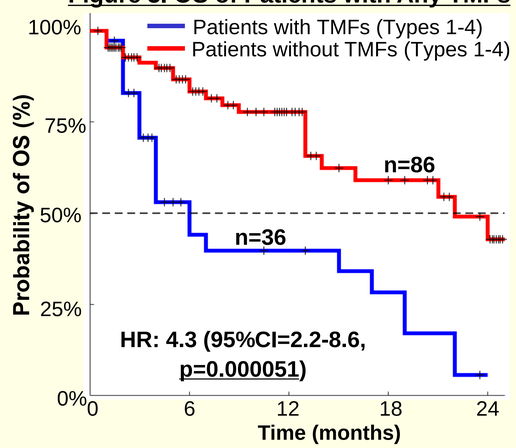


Figure 3. OS of Patients with Any TMFs



MATERIALS & METHODS

We categorized and enumerated the 6 forms of CTCs/TMFs: 1) Partial, 2) Homodimeric, 3) Cannibalistic, 4) Binucleated, 5) Hyperploidy, 6) and HyperEngorged, (**Fig. 1**) from a prospective pilot study using n=122 mBC pts that were starting new lines of treatment. Whole peripheral blood (7.5mL) was procured, filtered and stained using cytokeratin & CD45/CD14 to identify CTCs & TMFs. We compared the presence of the various types of TMFs & CTCs to pt's progression-free survival (PFS) and overall survival (OS) hazard ratios (HRs), analyzed by censored univariate analysis based on RECIST v1.1 over 24 months.

RESULTS

- CTCs were found in 39% of patients, partial fusion TMFs in 25%, homodimeric in 6%, cannibalistic in 0%, binucleated in 2%, & hyperploidy fusion cells (i.e. CAMLs) in 96%.
- Neither CTCs alone, binucleated TMFs, nor hyperploidy cells were prognostic for PFS or OS (**Table 1**).
- TMFs with partial or homodimeric fusion were prognostic for worse PFS & OS (**Table 1**).
- Combining patients with any TMFs into one group (minus hyperploidy TMFs) was highly significant for worse PFS and OS (**Figures 2 & 3**)

Table 1. Hazard ratio comparisons of CTCs, TMFs and CAMLs (Hyperploidy fusion cells)

HR(95%CI) p value	Any CTC	Partial Fusion TMF	Homodimeric TMF	Cannibalistic TMF	Binucleated TMF	Any TMF minus Hyperploidy	Hyperploidy (Any CAMLs)	HyperEngorged CAMLs (≥100µm)
Present vs Absent	47 vs 75	31 vs 91	7 vs 115	0 vs 122	2 vs 120	36 vs 86	117 vs 5	58 vs 64
PFS	1.7 (1.1-2.8) p=0.0506	3.0 (1.7-5.3) p=0.0005	8.0 (1.9-34.2) p=0.0156	N/A	1.9 (0.1-28.6) p=0.8375	3.3 (1.9-5.8) P<0.0001	3.3 (1.1-10.2) p=0.0735	1.5 (0.9-2.5) p=0.1395
OS	1.8 (1.0-3.2) p=0.0806	3.7 (1.8-7.4) p=0.0006	10.4 (1.7-64.4) p=0.0400	N/A	78.4 (08-7532.2) p=0.4787	4.3 (2.2-8.6) P<0.0001	3.0 (0.7-12.3) p=0.2381	1.6 (0.9-2.4) p=0.1939

CONCLUSIONS

- The study of TMFs is relativity limited and their existence is new in oncology.
- We detected and described TMFs in the blood of mBC pts, demonstrating an association with poor clinical outcomes.
- These data suggest a TMF involvement in the pathogenesis of cancer. Further understanding of their biology may be important in the study of tumorigenesis.

FUNDING SOURCE

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