1586

Heterogeneous dormant breast cancer cells leverage bone marrow cell plasticity at the single-cell level to drive metastasis initiation

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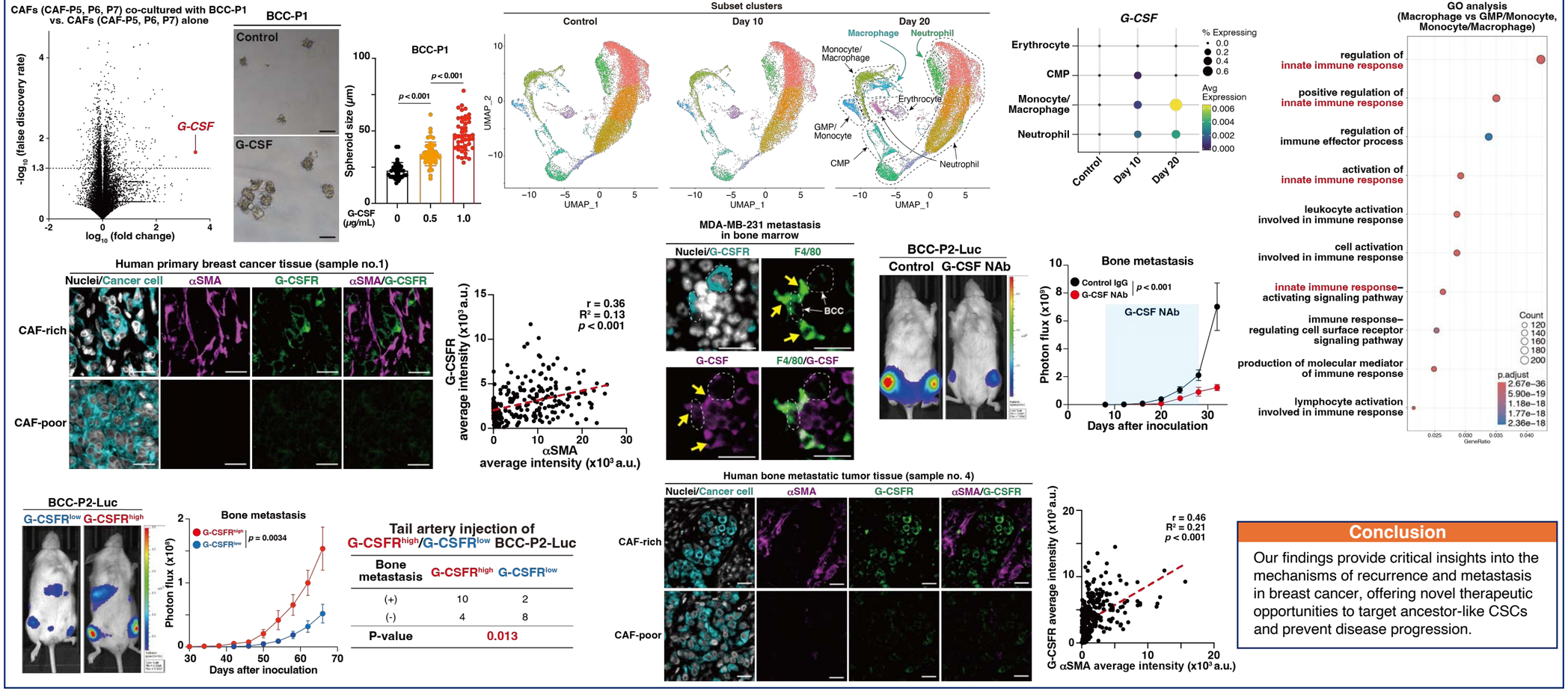
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Abstract

Breast cancer remains a leading cause of cancer-related deaths among women worldwide due to the high risk of recurrence and metastasis in triple-negative breast cancer (TNBC) patients. While bone metastasis is common, the molecular mechanisms driving its initiation remain poorly understood. We recently identified a subpopulation of cancer stem cells (CSCs) with ancestral features, marked by the FXYD domain-containing ion transport regulator 3 (FXYD3), a Na+/K+ pump component. These "ancestor-like CSCs" persist in breast tissues during neoadjuvant chemotherapy (NAC), linking them to drug-tolerant persisters (DTPs) and positioning them as critical therapeutic targets for preventing local recurrence (Li M, Gotoh N et al., J Clin Invest, 2023).

Despite this, the mechanisms underlying DTP dormancy in the bone marrow and their transformation into bone metastasis-initiating cells remain unclear. Given the stromal richness of TNBC tissues, we explored interactions between cancer-associated fibroblasts (CAFs) and breast cancer cells using a co-culture system. RNA-sequence analysis revealed a strong upregulation of granulocyte colony-stimulating factor (G-CSF) in co-cultured CAFs. Notably, we identified FXYD3+ and G-CSFR+ cancer cells as a distinct subpopulation of CSCs with bone metastasis initiation potential. To investigate the temporal-spatial dynamics of bone metastasis initiation, we performed single-cell RNA sequencing and immunofluorescent imaging using metastatic bone marrow from the patient-derived xenograft (PDX) models. These analyses revealed how bone metastasis-initiating CSCs exploit the plasticity of bone marrow cells to establish a CSC niche at the single-cell level.

Results



Conclusion

Our findings provide critical insights into the mechanisms of recurrence and metastasis in breast cancer, offering novel therapeutic opportunities to target ancestor-like CSCs and prevent disease progression.

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References
1. Li M, Gotoh N et al., J Clin Invest, 2023.

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