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Contact: cmtang@creatvmicrotech.com
301-983-1650

CXCR4 expression in tumor associated circulating cells of patients with pancreatic cancer is prognostic for progression and overall survival

Kirby P. Gardner[1,2], Susan Tsai[3], Mohammed Aldakkak[3], Stephen Gironda[2,4], Daniel L Adams[2]

[1] Rutgers University, Graduate School of Biomedical Sciences, Piscataway, NJ 08854 [2]Creatv MicroTech, Inc., Monmouth Junction, NJ 08852, [3] The Medical College of Wisconsin Milwaukee, WI 53226, [4] Wake Forrest School of Medicine, Winston-Salem, NC 27101

ABSTRACT

The chemokine receptor CXCR4 has been heavily implicated in the spread/mobility of many solid tumor cancers, such as pancreatic cancer (PC) based on its role in cancer cell chemotaxis and metastatic potential. To better elucidate CXCR4's role in the metastatic spread of PC, we examined its expression on circulating tumor cells (CTCs), epithelial to mesenchymal transition cells (EMTs), and cancer associated macrophage-like cells (CAMLs). In this pilot study, blood samples were procured from 30 PC patients prior to the start of therapeutic intent to evaluate CXCR4 in cell migration. High CXCR4 expression in CTCs, CAMLs, and EMTs was significantly related to their individual numbers in circulation. Patients with high CXCR4 expression in CAMLs, and EMTs, were significantly related to faster progression and worse survival, suggesting a relationship between CXCR4 and tumor cell migration into blood.

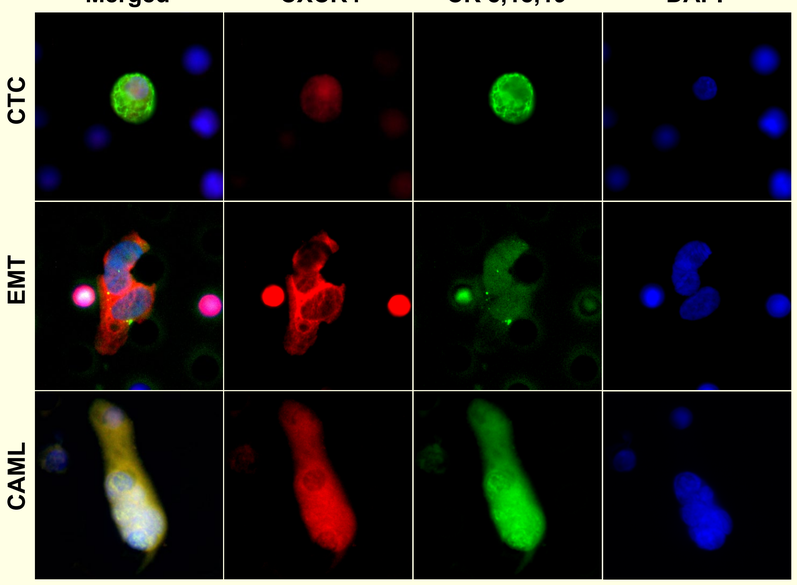

Figure 1. Example of CTC, EMT, CAML from a pancreatic cancer patient. CXCR4 expression (red) and Cytokeratin expression (green).

MATERIALS & METHODS

30 whole peripheral blood samples were drawn from untreated newly diagnosed PC pts referred for surgical resection prior to induction of therapy, from University of Wisconsin with IRB approval and written informed consent. Pts were recruited for a 2 year single blind prospective pilot study testing CXCR4 expression in CTCs, EMTs, and CAMLs in relation to numbers of cells in circulation. Pts were referred based on clinical resectability, with resectable (R) (n=11), borderline resectable (BR) (n=12), or locally advanced (LA)/metastatic (M) (n=7) . Blood samples (7.5mL) were taken prior to any neoadjuvant therapy. Blood samples were filtered by CellSieve™ filtration, and CAMLs quantified. In total, CTCs, CAMLs, and EMTs, were found in 60%, 97%, and 27% of PC patients, respectively. Analysis of CXCR4 on CTCs, EMTS and CAMLs were used to evaluate PFS and OS significance by log-rank testing.

INTRODUCTION

A partial cause of the high mortality of pancreatic cancer (PC) is the spread of the disease influenced by the involvement and spread of EMTs, CTCs, and PC[1,2,3]. A potential motility receptor that has been implicated in the spread of PC is the C-X-C chemokine receptor type 4 (CXCR4)[4]. Therefore, examining the expression of CXCR4 on CTCs, EMTs, and CAMLs may provide pertinent prognostic information, such as spread, progression, and survival.

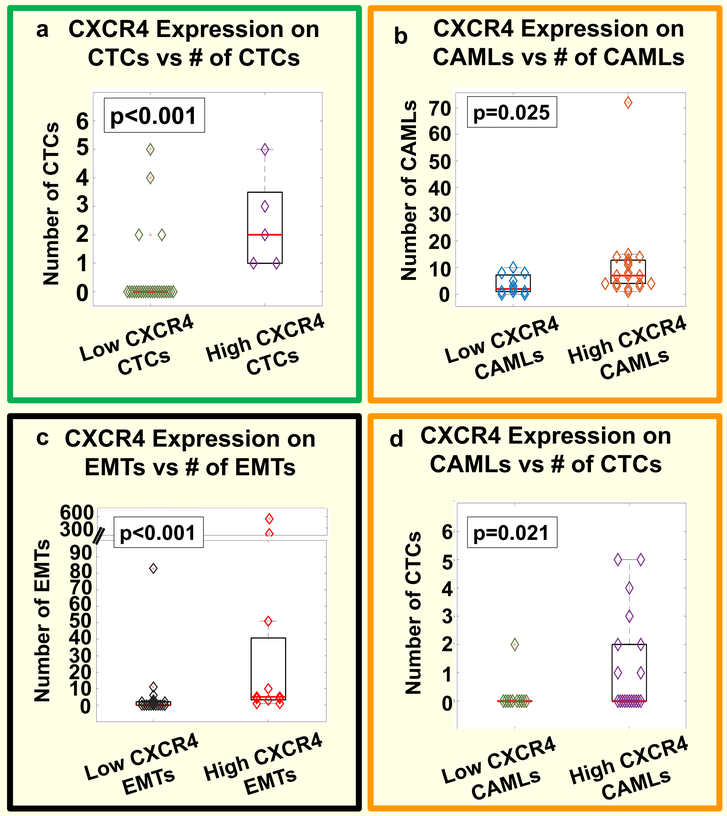

Figure 2: CXCR4 Expression on CTCs, CAMLs, and EMTs (Low vs High expression in patients). Wilcox Ranked sum. Error Bar=Std Dev. Red Bars=Median

RESULTS

- CXCR4 on CTCs, CAMLs & EMTs correlated with the respective numbers of these cells in circulation (**Figure 2a-c**)
- High CXCR4 in CTCs averaged 2.4 CTCs/7.5mL, vs 0.5 with low CXCR4 (**Figure 2a**)
- High CXCR4 in CAMLs averaged 10.8 CAMLs/7.5mL vs 3.5 with low CXCR4 (**Figure 2b**)
- High CXCR4 in EMTs averaged 69.9 EMTs/7.5mL, vs 5.8 with low CXCR4 (**Figure 2c**)
- Patients with high CXCR4 CAMLs had higher numbers of CTCs, averaging 1.2 CTCs, vs 0.2 CTCs in patients with low CXCR4 CAMLs (**Figure 2d**)
- High CXCR4 expression on CAMLs or EMTs was prognostic for both faster progression and worse survival **(Figure 3)**

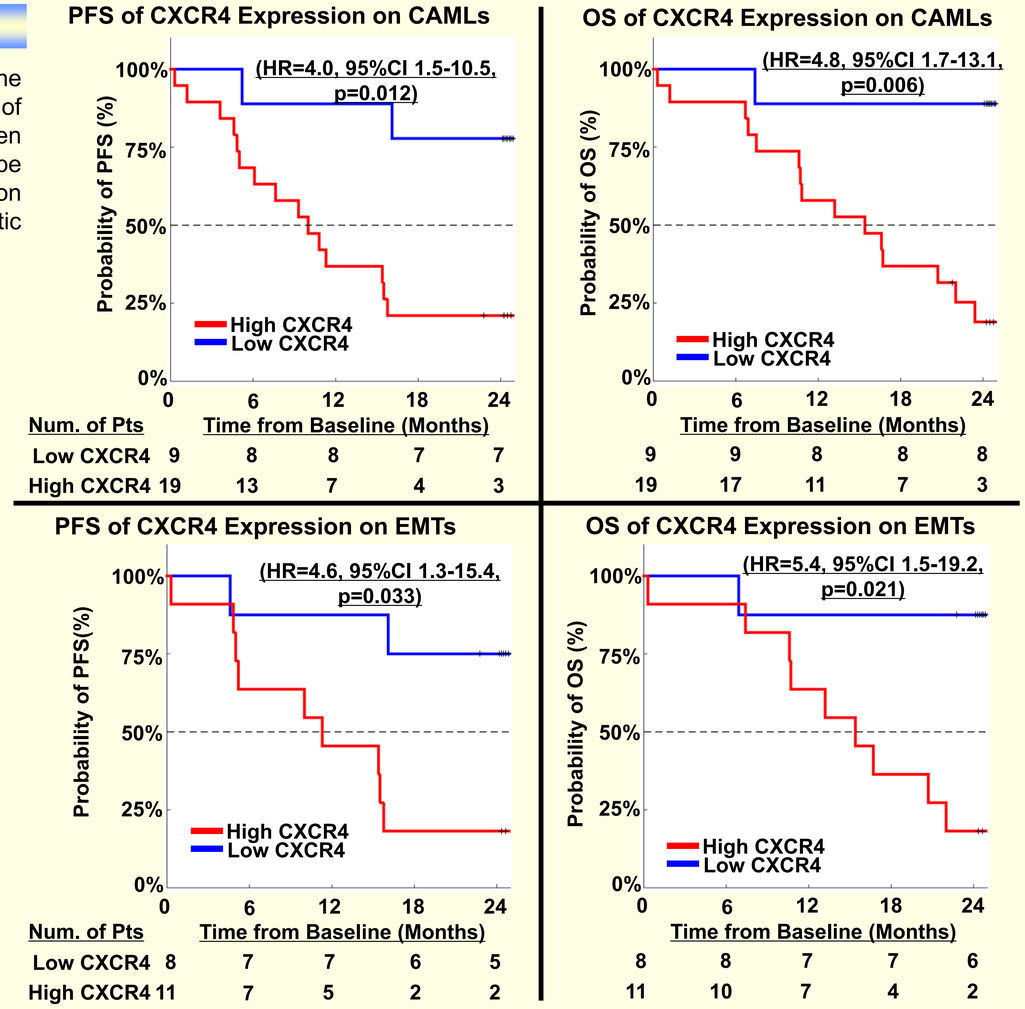

Figure 3: Kaplan-Meier graphs of PFS and OS for EMTs and CAMLs CXCR4 Expression

CONCLUSIONS

- High CXCR4 expression in either CAMLs or EMTs was correlated with faster progression and mortality (**Figure 3**).
- High CXCR4 expression in CTCs, CAMLs, and EMTs appears to correlate with their presence in circulation.
- CXCR4 expression in CAMLs appears related to number of CTCs in circulation.
- Cellular motility of CTCs into blood may be related to the CXCR4 pathway and may prove useful in guiding individualized treatments.

References

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