Circulatingstromalcells in blood are a sensitive biomarker in a variety of invasive solid tumours but absent in healthy individuals and uncommon in non-malignant conditions

ABSTRACT

Peripheral blood allows for the recovery of various cancer associated circulating stromal cells, including Cancer Associated Macrophage-Like cells (CAMLs). CAMLs are phagocytic-myeloid cells that derive from an immunological response to tumor presence which emanate from primary tumors. Using a filtration platform we analyzed the peripheral blood of untreated newly diagnosed cancer patients (n=279) for the presence of CAMLs as a blood based biomarker for the presence of malignancy. In parallel, we screened patients with newly diagnosed non-malignant diseases, i.e. lupus, cysts, etc. (n=32), as well as healthy control samples (n=65). We found that CAMLs are highly prevalent (94%) in the circulation of cancer patients, uncommon in non-malignant conditions (26%) and absent in healthy individuals (0%).

RESULTS

Anonymized peripheral blood were taken from 279 cancer patients after confirmation of invasive malignancy (stage I (n=63), stage II (n=65), stage III (n=66), stage IV (n=55) and unstaged non-metastatic (n=30) from patients with pathologically confirmed breast (n=50), esophageal (n=29), lung (n=65), prostate (n=29), and pancreas cancers (n=43), Renal Cell Carcinoma (n=18), Hepatocellular carcinoma (n=15), Head & Neck (n=6), Neuroblastoma (n=10), Sarcoma (n=9), and Other (n=5). Further, anonymized blood was taken from patients with confirmed untreated non-malignant conditions including benign breast masses (n=22), Lupus (n=11), benign prostatic hyperplasia (n=5), and viral infection (n=1); or from healthy control volunteers (n=65). CAMLs were isolated from whole peripheral blood by the CellSieve™ microfiltration technique and defined as enlarged, multicellular nuclei with cytokeratin and/or CD45/CD14 positive.

Figure 1. Isolation and identification of CAMLS by size and nuclear size
(a) CAMLS are easily identified under 10X magnification from a prostate patient
(b) Under 40X magnification the large polyploid nuclear structure can be seen (DAPI). These cells are usually positive for CD45 and weakly positive for cytokeratin

Figure 2. Percentage of patients with CAMLS by Stage or Cancer

Figure 3. AUC chart-patients with carcinoma vs healthy control or carcinoma vs benign

INTRODUCTION

CAMLs are specialized myeloid polyploid cells transiting the circulation of patients with various types of solid malignancies and appearing in all stages of cancer1-4. However, while CAMLs are easy to identify by their large size and polyploid nucleus (Fig. 1), their expression of multiple heterogeneous markers have defied conventional characterization and have made study difficult using most isolation technologies. Size exclusion is a technique for isolating large cells from peripheral patient blood irrespective of their surface marker expression. CellSieve™ microfilters are size exclusion membranes which efficiently isolate CAMLs and circulating tumor cells (CTCs) from whole blood, making it possible to study both cell types in conjunction with and in relation to malignant disease.

CONCLUSIONS

Using combination of clinical studies, we found CAMLs (a Circulating Stromal Cell subtype) are a sensitive blood biomarker specific to patients with confirmed malignancy.

CAMLs were uncommon in non-malignant conditions and absent in healthy individuals.

CAMLs appear to be a sensitive and specific blood based biomarker for persons with solid tumors.

REFERENCES


Funding Sources

This work was supported by R01-CA154624 and U01CA214183 from the National Cancer Institute, KG100240 from the Susan G. Komen Foundation, and the U.S. Army Research Office (ARO) and the Defense Advanced Research Projects Agency (DARPA) (W911NF-14-C-0098). The content of the information does not necessarily reflect the opinion or the policy of the US Government.