Condensed title:

Peripheral decrease and migratory phenotype of CD1c$^+$ myeloid dendritic cells are associated with adverse cardiac function in RA *C Geier*

Full title:

Peripheral decrease and enhanced migratory phenotype of a subset of blood myeloid dendritic cells (CD1c$^+$ mDC) are associated with adverse measures of cardiac function in patients with Rheumatoid Arthritis (RA)

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Background

Heart failure (HF) is more common in rheumatoid arthritis (RA) and associated with evidence of myocardial inflammation. Dendritic cells (DC) are a heterogeneous group of immune modulatory cells but their role in the context of HF in RA is unclear.

Hypothesis

The importance of DC in regulating immune responses led us to consider that a DC subset may be driving RA-associated HF. We hypothesized that in the peripheral blood this DC population would feature an activated phenotype (increased HLA-DR expression) and increased migratory capacity (CCR2 expression) and would be associated with markers of left ventricular (LV) dysfunction.

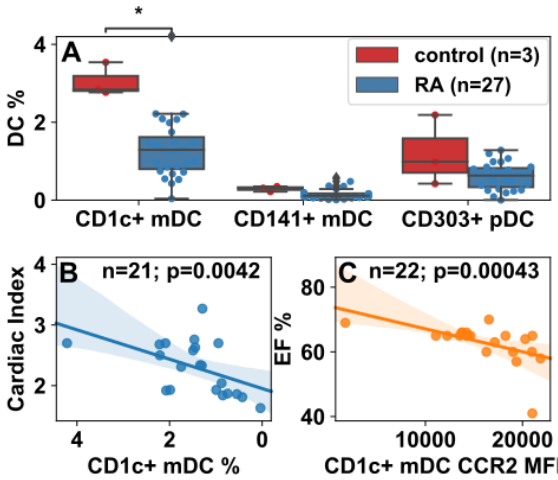
Methods

27 RA patients without clinical HF and 3 healthy donors underwent immunophenotyping; DC from peripheral blood mononuclear cells (PBMCs) were stained with a cocktail of fluorochrome-antibody conjugates designed to define three subsets (1)***CD141+ myeloid (mDC)*** [Lin$^-$(CD3$^-$ CD19$^-$CD56$^-$),DR$^+$,CD11c$^+$,CD141$^+$] (2)***CD1c$^+$ mDC*** [Lin$^-$,DR$^+$,CD11c$^+$,CD1c$^+$] and (3)***CD303$^+$ plasmacytoid pDC*** [Lin$^-$,DR$^+$,CD11c$^+$,CD1c$^+$]. For each subset HLA-DR and CCR2 expression were recorded as median fluorescence intensities (MFI).

Relative frequency was calculated based on proportion of DC subsets to the sum of lymphocytes and monocytes and compared between RA and controls using Mann-Whitney *U* (MWU) testing. The correlations of DC subsets and their DR/CCR2 expression profile with cardiac function, assessed by echocardiography and Positron-Electron-Tomography (PET), were calculated using Spearman correlation coefficients.

Results

Circulating CD1c$^+$ mDC were remarkably decreased in RA (mean 1.29% [IQR 0.78%-1.62%] vs controls (2.84%, [IQR 2.83% - 3.19%]); p=0.011). Frequencies of CD141$^+$ mDC and CD303$^+$ pDC subsets were not different (Fig 1A).



A lower percentage of CD1c$^+$ mDC was negatively correlated with cardiac index (corr=0.597; p=0.0042. Fig 1B).

Unexpectedly, HLA-DR expression in the CD1c+ DC subset was lower in RA whereas CCR2 expression was numerically higher (mean MFI 16247 vs 13394; not shown). In RA, CCR2 expression on CD1c+ DC was associated with lower Ejection Fraction (EF) (corr=-0.6853; p=0.00043. Fig 1C).

Figure 1. ***Frequency of DC subsets and their association with select cardiac parameters****. (A) Relative frequency of DC subsets in the peripheral blood. (B) Correlation between CD1c$^+$ mDC frequency and Cardiac Index. (C) Association between CCR2 expression of CD1c$^+$ subset and Ejection Fraction.*

Conclusions

In RA without clinical HF, the decrease of peripheral CD1c$^+$ mDC is associated with adverse measures of cardiac function. Their decrease and association with increased CCR2 expression may reflect an increased propensity to migrate to the RA myocardium that precedes development of clinical HF. CD1c$^+$ mDC may be implicated in the pathogenesis of HF in RA.