In Rheumatoid Arthritis (RA) Decreases in Conventional Dendritic Cell Lineages are Associated with Adverse Measures of Myocardial Function and Expansions of Anomalous HLA-DR+ Myeloid subsets

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Abstract

Introduction

- Dendritic cells (DC) are highly plastic antigen-presenting cells (APC), considered to have a central role in initiating and regulating immune responses1 including T cell activation, an established pathophysiologic pathway in RA (Fig. 0). 2.

Prior studies showed, unexpectedly, numeric decreases of 'canonical' DC subsets [myeloid (mDC) and plasmacytoid (pDC) DC] in RA2. We suspected that the decrease of canonical DC may not be the only change within this highly plastic immunoregulatory compartment

- By defining a 'non-lymphoid candidate APC' DC superset inclusive of non-lymphoid cells with APC potential [HLA-DR+CD3+CD19-CD56+CD14+] we set out to test the hypotheses that in RA:

  1. The totality of non-lymphoid candidate APC would NOT decrease
  2. Non-lymphoid candidate APC would be characterized by the appearance of 'anomalous' phenotypes [not conforming to established definitions]
  3. That shifts within the APC compartment would be associated with clinical RA characteristics, including adverse measures of cardiovascular health

Methods

3) A further fraction of non-canonical APC was associated with lower EF (Fig. 3a). Lower canonical CD1c+ cDC percentages showed reciprocal associations with lower systolic function; increased aortic FDG uptake (Fig. 3b-c)

Results

1A) We confirm decreases of 'canonical' mDC subsets in RA (Fig. 1).

1B) RA DC subsets showed lower HLA-DR expression and higher CCR2 expression compared with controls. (Table 1)

2A) The total non-lymphoid candidate APC population was not decreased (Table 2).

2B) In RA, the non-lymphoid candidate APC superset included APC that clustered near canonical DC but did not meet currently accepted definitions (Fig. 2; a-e)

Conclusion

We found extensive perturbations in the non-myeloid APC compartment in RA:

1) A significant decrease and phenotypic alterations of 'canonical' mDC populations – most pronounced in the major CD1c+ subset – that included decreased HLA-DR and increased CCR2 expression suggestive of increased propensity to traffic to inflamed tissues

2) The concurrent emergence of anomalous non-lymphoid cells with antigen-presenting potential (HLA-DR+) that are candidate DC subsets. The largest population included CD14+ APC that showed a partial loss of CD1c expression resembling recently defined CD3 by Dutertre et al. 3) The association of adverse measures of cardiovascular health with changes of the DC compartment, including decreases of CD1c+ mDC, emphasize their potential clinical significance.

Functional analyses of the putative DC populations are needed.

Anomalous DC may be implicated in RA rendering the DC/T cell interface a potential therapeutic target in RA


References