Use of the dendritic cell marker, B and T lymphocyte attenuator, to identify functionally distinct subsets of human CD1c+ dendritic cells

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Abstract

Background Dendritic cells specialise in initiating adaptive immune responses. The CD1c+ subset in human beings is proposed to excel at CD4+ T cell priming. An equivalent population in mice has been shown to be heterogeneous and contain functionally distinct monocyte-related and conventional dendritic cell-related subpopulations. We aimed to examine whether analogous diversity exists in human beings using the conserved conventional dendritic cell marker, B and T lymphocyte attenuator (BTLA), which exhibits bimodal expression on CD1c+ dendritic cells.

Methods BTLA–CD1c+ and BTLA+CD1c+ dendritic cells were flow-sorted from peripheral blood. Gene expression (NanoString, Seattle, WA, USA), cytokine production after stimulation with lipopolysaccharide and R848 (Luminex, eBioscience, San Diego, CA, USA), and naive CD4+ T cell polarisation capacity (allogeneic mixed lymphocyte reaction assay) were compared. Their potential to differentiate into Langerhans cells (by culturing in granulocyte macrophage colony stimulating factor [GM-CSF] plus BMP7) and osteoclasts (by culturing in macrophage colony stimulating factor plus RANKL) in vitro was assessed. Their relative proportions in healthy blood and rheumatoid arthritis synovial fluid were compared by flow cytometry.

Findings CD1c+BTLA– dendritic cells had higher expression than CD1c+BTLA+ dendritic cells of typical monocyte genes (*CD14*, *FCGR2A*, *S100A8*, *S100A9*); they preferentially promoted interferon γ (mean 17·79% [SE 3·69] *vs* 7·21 [1·20], p=0·0094), interleukin (IL) 17 (5·10% [0·96] *vs* 2·30 [0·77], p=0·0015), and GM-CSF-producing T cells (34·39% [8·65] *vs* 18·31 [7·16], p=0·0066) and produced more IL1β (2517 pg/mL [241] *vs* 702·6 [206·4], p<0·0001) and IL18 (71·7 pg/mL [4·97] *vs* 48·07 [3·11], p=0·0016). CD1c+BTLA+ dendritic cells had higher expression than CD1c+BTLA– dendritic cells of conventional dendritic cell genes (*CLEC9A*, *CD24*, *KIT*) and preferentially promoted IL4-producing T cells (15·7% [2·06%] *vs* 11·7 [1·65], p=0·0059) and CD25hiFOXP3+ regulatory T cells (Tregs) (15·09% [4·18] *vs* 9·26 [2·48], p=0·0346). CD1c+BTLA– dendritic cells had greater potential to differentiate into tartrate-resistant acid phosphatase positive multinucleated osteoclasts whereas CD1c+BTLA+ dendritic cells preferentially differentiated into langerin+CD1a+ Langerhans cells. The ratio of CD1c+BTLA– to CD1c+BTLA+ dendritic cells was significantly higher in rheumatoid arthritis synovial fluid than in peripheral blood (3·76 [0·64] *vs* 1·11 [0·10], p<0·0001).

Interpretation CD1c-expressing dendritic cells have been regarded as a single population but these data demonstrate underlying complexity. CD1c+BTLA– dendritic cells support T helper (Th) 1 cell and Th17 cell responses and possess osteoclast potential. CD1c+BTLA+ dendritic cells support Th2 cell and Treg responses and possess Langerhans cell potential. The bulk CD1c+ population has previously been manipulated to produce vaccine and tolerogenic dendritic cell therapies in cancer and autoimmunity, but more refined targeting could potentially improve their efficacy.

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Contributors
All authors designed the experiments and analysed the data. GR and PM performed the experiments.

Declaration of interests
We declare no competing interests.

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