Reassessing Th1 *versus* Th17.1 in sarcoidosis: new tricks for old dogma

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While enhanced IFN-gamma expression remains a principal feature of sarcoidosis, its origin may involve factors beyond Th1 http://ow.ly/qtyB30i48bU

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Immunologically, sarcoidosis has been classically defined by the presence of a Th1-dominant environment localised to sites of disease, characterised by overexpression of interferon (IFN)γ and Th1-promoting interleukin (IL)12 and IL18 [1]. Accordingly, the downstream effects of enhanced Th1 are also observed in sarcoidosis, such as the expression of Th1-associated chemokines (MIG/CXCL9, IP10/CXCL10, ITAC/CXCL11, MCP1/CCL2, MIP1α/CCL3, MIP1β/CCL4, RANTES/CCL5) and their respective receptors (CXCR3, CCR5). Conversely, the presence of augmented Th2 has never been firmly documented in the sarcoidosis lung.

The recent manuscript by Broos *et al.* [2] contributes to an emerging refinement of these classical observations. By assessing the surface expression of Th1-associated and Th17-associated chemokine receptors, they demonstrate that T-cells bearing a surface Th17.1 phenotype have a majority presence in the sarcoidosis lung (bronchoalveolar lavage) and adjacent mediastinal lymph nodes (MLN). Using this approach, they also appear on the surface (no pun intended) to identify a diminished presence of a Th1 phenotype in sarcoidosis lung and a lack of correlation of Th1 with clinical status (remitting *versus* chronic disease). In fact, their study associates Th17.1 with chronic active sarcoidosis, and the authors propose that examination of Th17.1/Th1 ratio could serve as a prognostic indicator of disease course.

However, the authors also cite a potential difference between their data and that reported by Kaiser *et al.* [3], who reported that Th17.1 was associated with disease remission in Scandinavian patients experiencing Löfgren syndrome (acute sarcoidosis). The differences between these two manuscripts is not likely to result from patient populations that are distinguished by clinical phenotype and genetics, but rather the methods used to define helper T-cell subsets.

The Scandinavian study examined the expression of transcription factors associated with Th1 and Th17 function, respectively Tbet and RORγt [3]. From this perspective, measuring intracellular expression of Tbet+RORγt+ defined a higher Th17/Th1 ratio at the cellular level. These cells expressed higher IL17 and lower IFNγ, and this functional phenotype was associated with favourable disease outcomes in patients

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with acute sarcoidosis. This observation appears to be congruent with the accepted dogma that relevant clinical endpoints in sarcoidosis correlate with the expression of IFNγ [4].

And therein lies the difference: defining helper T-cell subsets by function (Kaiser *et al.* [3]) *versus* by surface phenotype (Broos *et al.* [2]). While the surface phenotype of Th17 cells (CCR6+ CCR4+ CXCR3−) maps directly to a functional phenotype (IL17 expression), the function of cells bearing a Th17.1 surface phenotype (CCR6+ CCR4− CXCR3+) is less distinct as this identifies a mix of cells that are either dual-functional (IL17+IFNγ+) or mono-functional (IL17−IFNγ+) IFNγ-expressing cells (figure 1 and Broos *et al.* [2], supplementary figure E1). Results from *in vitro* experiments suggest that double positive (DP) cells (CCR6+ CCR4+ CXCR3+) are distinctly dual-functional (IL17+IFNγ+) [5], possibly representing an ephemeral population of Th17 cells that are transitioning to a functional Th17.1 phenotype in the presence of differentiation factors including IL12 and tumour necrosis factor (TNF)α [6]. Arguably, the authors have previously shown data that a majority of effector T-cells with a Th17.1 phenotype were monofunctional expressing IFNγ and very few (<5%) expressed IL17 [5].

Both the Kaiser *et al.* [3] and Broos *et al.* [2] studies, however, reaffirm that the dominant T-cell phenotype localised to sites of disease express IFNγ consistent with a functional Th1-phenotype, and both studies agree that T-cells with a functional Th17 phenotype (IL17 expression alone) represent a minority of T-cells recruited to the lung in sarcoidosis. CCR6+ Th17 cells may be well-suited for recruitment to sites of granulomatous inflammation in sarcoidosis, in part, through the engagement of chemokines including CCL20 [7]. The majority of Th17 cells would be transformed to non-classical Th1 cells by the local cytokine milieu with abundant IL12 and TNFα found in the sarcoidosis lung. These observations provide a rationale to support the use of anti-TNF therapies for sarcoidosis, but also provide reasons for investigating treatments targeting the Th17 pathway [8]. Although seminal knowledge regarding Th17 associated this T-cell phenotype with autoimmunity, it is the plasticity of Th17 cells, specifically their

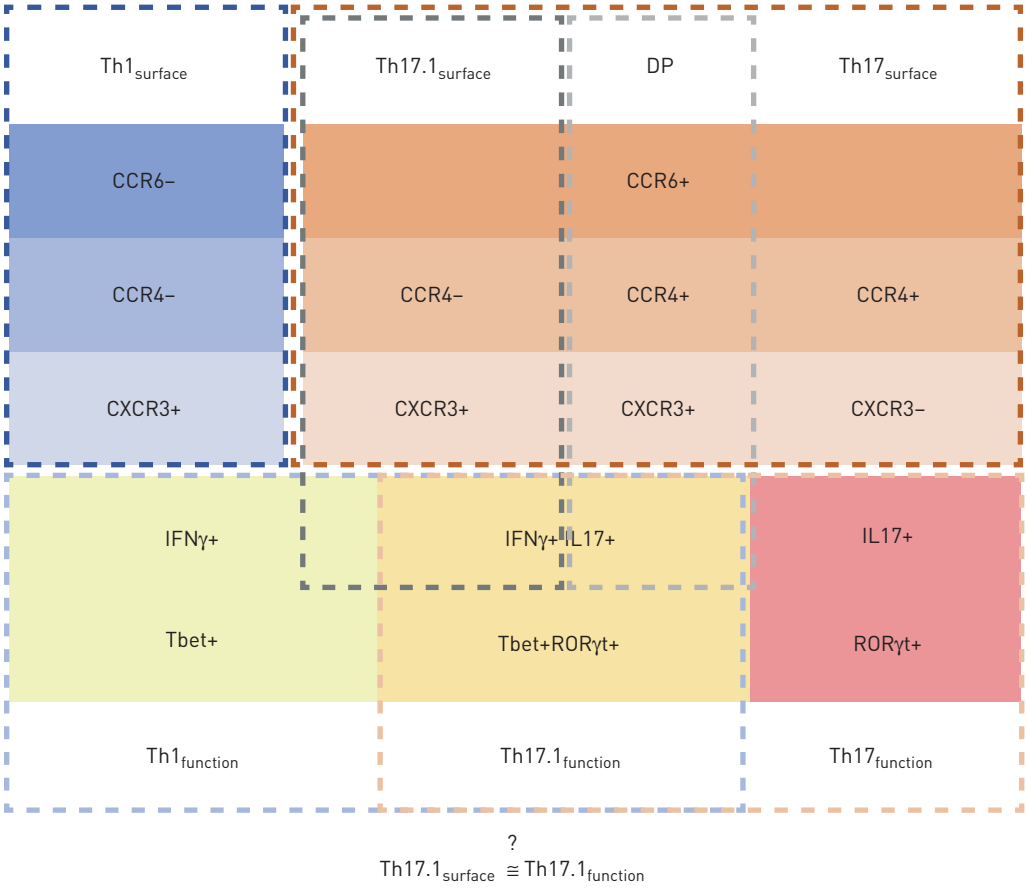

FIGURE 1 Cytometric form *versus* function: Schematic of T-helper (Th)1 and Th17 T-cell subsets as defined by surface-expressed chemokine markers (top half; blue and brown columns) and as defined by intracellular-expressed functional markers (bottom half; yellow, orange, and red columns). DP: double positive; IFN: interferon; IL: interleukin.

ability to transform to non-classical Th1 cells at sites of disease, that may indicate a wider role for this proinflammatory T-cell phenotype in granulomatous disorders other than sarcoidosis [9, 10].

In the end, the manuscript from Broos *et al.* [2] contributes to a growing body of knowledge deciphering the role of Th17 in sarcoidosis. Enhanced expression of IFNγ remains the principal immunological characteristic of sarcoidosis [11], but future studies will be necessary to determine whether the lineage of IFNγ-expressing cells (classical Th1 cells *versus* non-classical Th1/Th17.1 cells) influence end-points in sarcoidosis, including imparting differences in disease pathogenicity (*i.e.* maintaining granulomatous inflammation) [12], serve as an index of clinical status, predict response to treatment, and whether expression of IL17 trumps IFNγ as a biomarker for disease activity in sarcoidosis.

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