Viewpoint

# Leukotrienes, mast cells, and T cells

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Unravelling the complex interactions that regulate the recruitment and subsequent cellular crosstalk between leukocyte subsets in inflamed synovium offers considerable therapeutic potential. In rheumatoid arthritis (RA), synovial membrane is characterised by T-cell infiltrates including both CD4 and CD8 subsets that occupy distinct domains within the tissue [1,2]. The former have attracted the most attention, given their proposed central role in the development and maintenance of acquired immune responses in the synovium. Their functional importance, however, has been critically reviewed, particularly in light of equivocal or negative outcomes in clinical trials in which CD4 T cells have been specifically targeted [1,3,4]. Thus far, only CTLA4-Ig has shown any clinical promise [5]. Although comprising up to 40% of the synovial T-cell compartment, CD8 T cells have received less attention. CD8 T cells are widely distributed throughout the synovial membrane and in synovial fluid, exhibit an activated phenotype and enhanced migratory activity, express proinflammatory cytokines, and contribute to formation of ectopic germinal centres in synovial tissues [1,6,7]. Recruitment of CD8 T cells to the synovial compartment has been considered a function of appropriate chemokine gradients, lymphocyte chemokine receptor expression, and activation of endothelial cells, expressing adhesion molecules.

Antigen-experienced CD8 T cells segregate into at least two populations in mice, namely central memory CD8 T cells (Tcm; $CD62L^{hi}$, $CCR7^{hi}$), which traffic primarily to lymphoid tissues, and effector memory CD8 T cells (Teff; $CD62^{lo}$, $CCR7^{lo}$), which migrate to nonlymphoid tissues [8]. Distinct populations can be generated *in vitro* using IL-15 and IL-2 to promote Tcm and Teff populations, respectively. Whereas CD62L and CCR7 have been attributed homing function for Tcm, the molecular basis for Teff recruitment to target tissues has not previously been understood. Ott and colleagues [9] now report an elegant series of experiments suggesting that mast-cell-dependent leukotriene $B_4$ ($LTB_4$) may subserve CD8 Teff recruitment to tissues. Mast-cell biology has assumed increasing prominence in theories of synovitis, providing a potential cellular link between humoral autoimmunity (B cells) and synovial inflammation [10]. The present observations provide a novel molecular mechanism for interactions between mast cells and T cells [9].

Using a transwell migration assay, Ott and colleagues observed that murine CD8 Teff cells but not Tcm cells migrated in response to soluble factor(s) released by FcεRI-activated, but not resting, bone-marrow-derived mast cells [9]. Importantly, migration occurred within minutes of mast-cell coculture, suggesting release of a preformed or rapidly synthesised factor. In control experiments, both Tcm and Teff migrated to CCL5 (RANTES [regulated upon activation, normal T-cell expressed and secreted]), indicating that Tcm cells were motile *in vitro*. Subsequent gene-chip expression array analysis comparing Tcm and Teff revealed higher expression of BLT1, a receptor for $LTB_4$, in Teff cells. Commensurate with a functional role for leukotrienes, the 5-lipoxygenase-activating enzyme inhibitor MK-886 inhibited mast-cell-induced Teff migration; and purified $LTB_4$, but not $LTC_4$, directly induced Teff directional migration in a bell-shaped dose–response curve typical of many chemokines. In contrast, centrally derived (lymph node) $CD122^{hi}$ Tcm cells were unable to migrate to $LTB_4$ unless first activated via the T-cell receptor in the presence of IL-2 to promote a Teff phenotype. Using the inhibitor CP-105696, $LTB_4$-induced Teff migration was shown to be dependent on BLT1 (high affinity) rather than BLT2 (low affinity). Finally, addition of pertussis toxin inhibited migration further, implicating BLT1 via activation of $G_i$-type G proteins. Together, these data strongly suggest that a novel function of tissue-activated mast cells could be to rapidly recruit Teff cells to tissues during the early phase of innate inflammatory responses.

Mast-cell presence and activation in synovium has been long described within inflammatory aggregates and adja-

IL = interleukin; $LTB_4$ = leukotriene $B_4$; RA = rheumatoid arthritis; Tcm = central memory T cells; Teff = effector T cells; TNF = tumour necrosis factor.

cent to the cartilage pannus junction, where they may be associated with cytokine expression [11,12]. Their potential effector function includes release of proinflammatory cytokines, chemokines, proteases, vasoactive amines (e.g. histamine) and arachidonate metabolites, including prostaglandins and leukotrienes. Mast cells could therefore promote downstream activation of mononuclear cells, chondrocytes, osteoclasts, and angiogenesis [11]. Such functional import has recently been elegantly demonstrated *in vivo*. Administration of serum from K/B×N mice failed to induce arthritis in Sl/Sl$^d$ or W/W$^v$ murine strains, which exhibit functional mast-cell deficiency. Importantly, mast-cell engraftment into W/W$^v$ recipients recovered the incidence of arthritis following serum transfer [10]. Therefore, by virtue of FcγR and complement receptor expression, activated mast cells could provide a cellular mechanism whereby autoantibodies in the appropriate tissue context could promote host tissue inflammatory damage.

The data from Ott and colleagues [9] now suggest that mast cells could significantly modify T-cell function not only through chemokine release but also via $LTB_4$. Indeed, since $LTB_4$ is also a potent inducer of neutrophil migration, these effects may have broader functional importance in synovium. $LTB_4$ antagonists are effective in reducing collagen- and cytokine-induced arthritis, and 5-LO-deficient mice exhibit reduced collagen-induced arthritis [13–15]. However, it is currently unclear whether $LTB_4$ occupies a sufficiently critical hierarchical position in effector mediator pathways to provide a therapeutic target, given the multiplicity of other chemokines present in synovial tissues to which synovial T cells and indeed other leukocyte subsets are responsive. Thus, although $LTB_4$ antagonism has proved to be of some clinical utility in pulmonary inflammation, it has yet to be properly tested in chronic human synovitis. Other important issues arise. It would be of interest to further define CD8 effector subpopulations in RA tissues and thereafter to determine which are $LTB_4$ responsive. Comparison with migratory activity to other chemokines prominent in synovial tissues will also be essential. More difficult is the question of testing the central role for mast cells in RA in the clinical context. Whereas mast-cell-focused therapies have not yet been specifically attempted, cytokine effector pathways including tumour necrosis factor α (TNFα) have already proven amenable to target – mast cells, however, may represent only a proportion of the TNFα competent cell sources in synovium. More specific approaches targeting mast-cell stabilisation or deletion are awaited. As always, the issue of cellular priority in the chronic, feedback-rich environment of the rheumatoid synovium will await further deductive biologic investigation.

## Competing interests

None declared.

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## Note

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