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Interleukin 7-induced lymphoid neogenesis in arthritis: recapitulation of a foetal developmental programme?

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Summary

Chronic inflammatory diseases such as rheumatoid arthritis (RA) are associated with the *de novo* formation of organised lymphoid tissue in a subpopulation of patients. The aberrant expression of cytokines and chemokines by stromal cells plays an important role in recruitment and survival of effector cells of the immune system and the development of ectopic tertiary lymphoid organs (TLOs). TLOs may promote the persistence of inflammation and the recognition of self antigens. Recent studies in man and mice now indicate that interleukin 7 (IL-7) is implicated in the formation of TLOs and progression of chronic inflammation.

Key words: Interleukin 7; arthritis; inflammation; lymphoid tissue inducer cell; tertiary lymphoid organ

Introduction

IL-7 is a cytokine that uses the common gamma chain (γc) and the IL-7 receptor α (IL-7Rα) chain for signalling. It is primarily expressed by epithelial and stromal cells of various organs such as the thymus, bone marrow, intestine and skin [1]. IL-7 is required for T lymphocyte development and homeostasis in man and mice but only in mice it has an additional function in B cell development (figure 1). Apart from its role in differentiation and survival of lymphocytes, studies in knockout mouse models have identified IL-7 as a critical cytokine regulating secondary lymphoid organ (SLO) development. A specialized subset of IL-7R-expressing haematopoietic cells named "lymphoid tissue inducer" (LTi) cells has been identified as a key player in generating lymph nodes (LNs) and Peyer's patches (PPs) [2–5]. LTi cells form cellular aggregates with local stromal cells and interact via adhesion and TNF family member molecules. During this haematopoietic/mesenchymal crosstalk, the production of cytokines, chemokines and adhesion molecules leads to the recruitment of leukocytes and the organisation into lymphoid compartments.

It is well established that the development of SLOs is completed after birth. Chronic inflammation, however, is commonly associated with the *de novo* formation of ectopic lymphoid organs

Abbreviations

APRIL	a proliferation induced ligand
Blys	B lymphocyte stimulator
DC	dendritic cell
GC	germinal center
IFNγ	interferon γ
IL-7	interleukin 7
IL-7R	interleukin 7 receptor
JAK3	janus-activating kinase 3
LN	lymph node
LTαβ	lymphotoxin αβ
LTβR	lymphotoxin β receptor
LTi	lymphoid tissue inducer
MIP 1β	macrophage inflammatory protein β
NOD	non-obese diabetic
PP	Peyer's patch
RA	rheumatoid arthritis
RANKL	Receptor activator of nuclear factor κB ligand
SLO	secondary lymphoid organ
Th	T helper
TLO	tertiary lymphoid organ
TNF	tumour necrosis factor
VCAM-1	Vascular adhesion molecule 1

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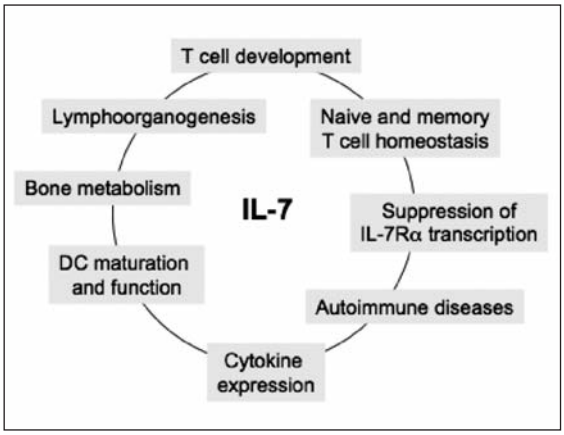

Figure 1

IL-7 has multiple effects on haematopoietic cells through induction of cytokines, survival and developmental signals. IL-7 is critical for the development of human T cells and for the homeostatic turnover of naïve and memory T cells. It also plays a role in dendritic cell (DC) development, maturation and function. Moreover, it is important in bone metabolism, during lymphoorganogenesis and can have an influence on autoreactive T cells leading to autoimmune diseases.

named "tertiary lymphoid organs" (TLO). The molecular mechanisms underlying the transformation of inflammatory infiltrates into TLOs are not completely understood, but studies in mice indicate that lymphoid organ development during ontogeny and inflammation shares some common features (figure 2). In both chronic inflammation and organogenesis, the activation of stromal cells leads to the release of molecules that regulate the recruitment, proliferation and survival of leukocytes. The establishment of a niche for incoming leukocytes is mediated by the collaboration of extracellular matrix components, adhesion molecules, cytokines and chemokines. Tumour necrosis factor (TNF) and lymphotoxin αβ (LTαβ) expressed by haematopoietic cells are critical cytokines acting on mesenchymal stromal cells and vascular endothelial cells and promote the establishment of lymphoid niches. Despite the success of anti-inflammatory treatment in RA, TLOs still persist. In this review we will highlight the role of IL-7 in SLO and TLO development and discuss its function in the progression of RA.

Development and remodelling of secondary lymphoid organs

SLO development in mice is orchestrated by LTαβ$^+$ LTi cells, which express CD4, c-Kit (CD117) and IL-7Rα (CD127), originate from the foetal liver and circulate during early foetal life before they enter peripheral tissues [6]. At sites of LN and PP anlagen, LTi cells interact with local lymphotoxin β receptor (LTβR)$^+$ mesenchymal organizer cells thereby inducing the expression of lymphoid chemokines such as CCL19, CXCL13 and CCL21 by the organizer cells and the colonisation with mature leukocytes [6]. In the absence of LTi cells or if components of the LTβR signaling pathway are blocked, LNs and PPs do not develop. Similarly, the formation of LNs and PPs is impaired in mice lacking lymphoid chemokines and chemokine receptors. This led to the current concept of a haematopoietic/mesenchymal crosstalk required for the formation and organisation of lymphoid tissue. Once SLO development has progressed to a stage where functional lymphoid compartments are established, signals via TNF family member molecules and chemokines help maintain a T cell/B cell segregation and germinal center (GC) reaction during immune responses [7].

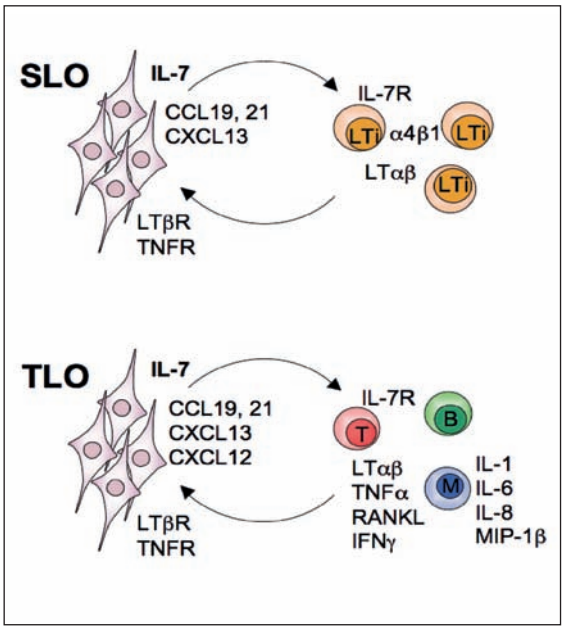

Figure 2

SLO and TLO development share common features. Chemokines, IL-7 and growth factors are provided by mesenchymal stromal cells (spindle formed). Haematopoietic cells (LTi cells, T cells, B cells, macrophages) produce cytokines and integrins, which promote stromal cell differentiation.

Mice lacking IL-7, IL-7Rα or Janus-activating kinase (JAK) 3, a signaling component of the IL-7R, have severe defects in LN and PP development suggesting a critical role of IL-7 in lymphoorganogenesis [8–10]. The precise nature of the signals provided by IL-7 was unsolved until now. We have recently shown that IL-7 induced the expression of LTαβ on LTi cells and amplified LTi cell numbers through inhibiting apoptosis [11]. In mice overexpressing IL-7 ubiquitously, lymphoid organs were hyperplastic and additional PPs and LNs were found. Ectopic LNs were connected to the lymphatic system and most probably developed from budding lymph sacs. The ectopic LNs were fully functional and supported normal T cell dependent B cell responses and GC reactions. Altogether, these data show that IL-7 is operative in the development of normal and ectopic lymphoid organs through increasing LTi cell number.

The development of SLOs during human ontogeny is a largely unexplored field and cells with LTi function have not been identified yet. In patients with JAK3-deficiency, RAG deficiency or X-linked agammaglobulinaemia, LNs are hypoplastic and formation of GCs does not occur [12] indicating that mature lymphocytes contribute to SLO organisation.

It is generally accepted that the developmental programme for SLO formation is completed after birth. In patients with chronic post-inflam-

matory and post-traumatic lymph stasis, however, the neogenesis of LNs from intralymphatic aggregates has been reported [13]. Inflammation and immune responses in LNs lead to fibroblast reticular cell hyperplasia followed by contraction after resolution of the immune activation. It is a matter of current research if the process of stroma hyperplasia and contraction during infection is triggered by molecular mechanisms that are also operative during the development of SLOs. Interestingly, a subset of adult $CD4^+CD3^-$ cells resembling foetal LTi cells was found to accumulate in reactive LNs of Helminth infected mice [14] and in the spleen of lymphocytic choriomeningitis virus-infected mice [15]. Adult $CD4^+CD3^-$ cells share some phenotypic marker with foetal LTi cells and appear to play a role in splenic organisation and immune responses [16]. Therefore, it is possible that LTi cells have a broader function as previously thought and act as inducers of lymphoid tissue during foetal and adult life.

Tertiary lymphoid organs in rheumatoid arthritis: role of IL-7

Chronic inflammatory diseases such as autoimmune diseases, chronic infections and chronic graft rejection are commonly associated with the formation of TLOs. These tissues resemble SLOs with segregation into T and B cell zones, dendritic cells (DCs), GCs, follicular dendritic cells, lymphatic vessels and high endothelial venules. Transgenic mice overexpressing lymphoid chemokines (CXCL13, CCL19, CCL21) or TNF family member molecules (LTαβ) under the control of a tissue-specific promoter, develop site-specific TLOs (for review see [17]). These data suggest that TLO development during chronic inflammation recapitulates a molecular programme used during foetal lymphoid organ development. The anatomical similarities between SLOs and TLOs have led to the hypothesis that TLOs provide the environment for generating chronic adaptive immune responses that contribute to disease progression. This concept was confirmed by investigating chronic organ transplant rejection in mouse and man where TLO formation promoted B and T cell mediated allograft rejection [18, 19].

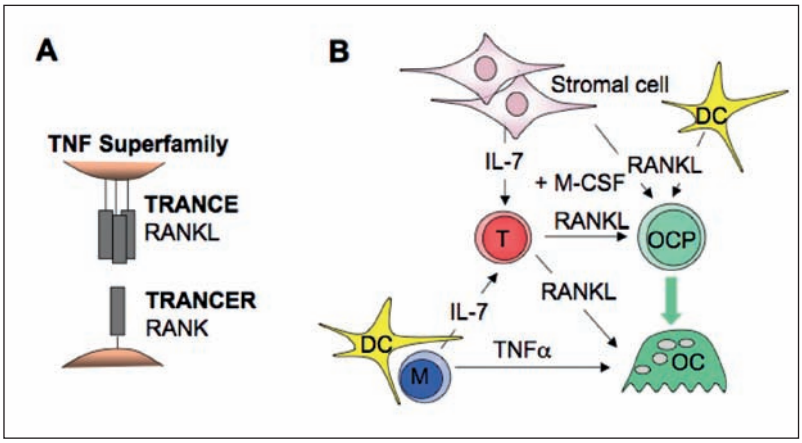

Figure 3

A. Receptor activator of nuclear factor κB ligand (RANKL, also named TRANCE) binds to its receptor RANK (also named TRANCER), a member of the TNF receptor superfamily.
B. IL-7-driven production of RANKL by T cells increases the pool of osteoclasts either indirectly by differentiation of osteoclast progenitors or directly by osteoclast proliferation. (DC: dendritic cell, M: macrophage, T: T lymphocyte, OCP: osteoclast progenitor, OC: osteoclast, TNFα: tumour necrosis factor α, M-CSF: macrophage colony stimulating factor).

RA is an autoimmune disease characterised by chronic inflammation of the joints leading to progressive destruction of cartilage and bone [20]. B cells, T cells, macrophages, synovial cells and endothelial cells producing proinflammatory cytokines are considered to be involved in the pathogenesis of RA. In contrast to the transient recruitment of leukocytes during the early phase of inflammation, in many but not all patients with established RA, fibroblast activation and hyperplasia lead to the establishment of TLOs in synovial lesions [21]. Fifty percent of patients form T/B cell aggregates, and half of them have synovial tissues containing B cell follicles with GCs [22, 23]. B cells isolated from these ectopic GCs undergo antigen-driven clonal expansion and somatic hypermutation [24] leading to memory B cells and autoantibody-producing plasma cells. The increased levels of B cell survival factors such as B lymphocyte stimulator (BLyS) and APRIL found in RA patients may further enhance these B cell responses [25]. Some T cells found in inflamed joints of RA patients have a diverse autoreactive T cell receptor repertoire [26]. Collectively, GCs in the synovia of RA patients may collect self-antigens, which can be presented to the adaptive immune system and stimulate autoreactive T and B cell responses.

There is evidence that the development of TLO in the synovia of RA patients is, analogous to SLO development, coordinated by the interaction of incoming $LT\alpha\beta^+$ haematopoietic cells with stromal cells (fibroblasts, endothelial cells). The activation of the LTβR signaling pathway in synovial fibroblasts and endothelial cells may lead to the inappropriate secretion of chemokines, growth and survival factors for leukocytes and the establishment of lymphoid structures. This concept is further supported by the fact that synovial tissues of RA patients overexpress LTα, LTβ, CXCL12, CXCL13, CCL21, and VCAM-1 [22, 23]. These molecules are also essential for the development of SLOs. Recent studies in a chronic arthritis mouse model reveal that in the absence of corresponding chemokine receptors (CXCR5, CCR7), TLOs fail to form followed by a signifi-

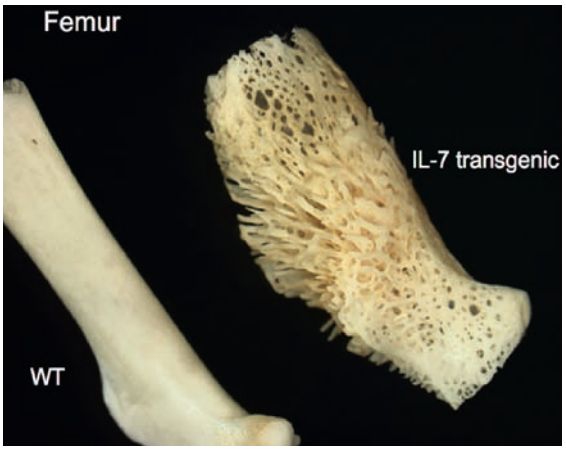

Figure 4

Femur of wild type (left) and IL-7 transgenic (right) mouse. IL-7 overexpression leads to osteolysis, lacuna formation and contraction in length.

cantly reduced joint destruction [27]. This strongly suggests that TLO development can contribute to the progression of the disease.

In RA patients, synovial fluid levels of IL-7 are strongly elevated [28, 29]. Fibroblasts, macrophages, endothelial cells and DCs in the synovia of RA patients produce IL-7 [30] (figure 3B). Interestingly, gene expression of RA synovia reveals that increased levels of IL-7, IL-7R and IL-7R signalling molecules are associated with the presence of TLOs [23]. The activation of the IL-7R signalling pathway may therefore play a role in TLO development analogous to its role in SLO development. Our studies in mice in which IL-7 overexpression induces the development of additional normal and ectopic lymphoid organs strongly support this paradigm of an IL-7-dependent mechanism of TLO formation [11].

Apart from a role in lymphoid tissue development, IL-7 is operative in bone loss through increased osteoclastogenesis mediated by T cells producing TNFα and the receptor activator of nuclear factor kB ligand (RANKL) [31, 32]. Both generalised and focal bone loss is found in patients with RA [33]. Higher levels of RANKL are detectable in synovial tissue of RA patients with active synovitis [34]. Activated T cells and RA stromal cells produce RANKL, which induces activation of RANK-expressing osteoclast progenitor cells and mature osteoclasts [35] (figure 3). Thus, studies in RA patients and animal models for arthritis highlight a role of IL-7 in secreting osteoclastogenic molecules. In line with this, in our IL-7 overexpressing mouse model, we observed a progressive osteolysis and bone remodelling irrespective of the gender (figure 4). Macroscopically we did not find signs of joint inflammation indicating that IL-7 alone is not sufficient to trigger the development of arthritis. It remains to be investigated whether IL-7 overexpressing mice are more susceptible to the development of experimentally induced arthritis. Altogether, IL-7 may have a dual function in the pathogenesis of RA through inducing TLO development and disturbing the bone metabolism. In addition, the local release of IL-7 in RA lesions might be the driving force for leukocyte survival and differentiation into potentially harmful effector cells. This is supported by the findings that synoviocytes from patients with RA stimulate the proliferation of Th1 cells through IL-7 [29, 36] and that IL-7-primed arthritogenic Th1 cells produce IFNγ and TNFα [28]. IL-7 also promotes cytotoxic T cell and Th2 responses [37]. Moreover, IL-7 can induce the secretion of IL-1α, IL-1β, IL-6, IL-8, macrophage inflammatory protein (MIP)-1β and TNFα by human monocytes [38–40]. The overexpression of TNFα in animals leads to the formation of TLO and the development of chronic arthritis, which may explain only one of the multiple mechanisms of TNF in the pathogenesis of the disease [41]. In turn, TNFα promotes the production of IL-7 by RA fibroblasts [36]. Despite considerable success in treatment of RA with anti-TNFα, a substantial proportion of patients do not respond and IL-7 persists upon anti-TNFα treatment [42] . In patients with RA refractory to anti-TNFα agents, the selective depletion of CD20-positive B cells with anti-CD20 antibodies (Rituximab) significantly reduces the activity of the disease in the majority of the patients [43–45]. Rituximab-treatment is more effective than switching to an alternative anti-TNF agent [46] suggesting that B cells have additional pathogenic functions in RA. The mechanisms, by which B cell depletion leads to a clinical improvement of RA, may rely on the effector function of B cells in antigen-presentation to T cells, the secretion of cytokines and the formation of TLO. This is supported by the finding that in rheumatoid synovium, LTβ-producing B cells are critical for T cell activation, production of IFNγ and IL-1β and formation of ectopic GCs [22, 47]. IL-7 can induce the expression of LTβ, which is critical for the development of ectopic GCs [11]. Finally, the induction of IL-7 by a TNF-independent mechanism can further contribute to establish T cell responses in TLOs. Therapeutic blockade of local IL-7 release or neutralisation of IL-7 protein may therefore have beneficial effects in established RA, but systemic immunosuppressive effects should also be taken into consideration. Altogether, TLO development in inflammatory RA shares some striking features with SLO development in mouse models. It is initiated by infiltrating haematopoietic cells, which activate local stromal cells. As a consequence of LTβ-dependent signals provided by haematopoietic cells, the stroma produces factors, which in turn help to establish and maintain inflammatory infiltrates. The local release of IL-7 may promote the chronic stimulation and survival of immune cells and the establishment of TLO that accounts for the progressive destruction of the tissue.

IL-7 and other autoimmune diseases

A role of IL-7/IL-7R in disease progression has also been proposed for other autoimmune diseases in humans or mouse models such as colitis [48], multiple sclerosis [49], diabetes [50], psoriasis [51] and sialitis in NOD mice [52]. Increased levels of systemic IL-7 where reported to directly sustain autoreactive T cell responses. Evidence for this comes from studies in mice where systemic IL-7 was essential for persistence of colitis [53]. The local release of IL-7 in chronically inflamed organs, however, may help establishing TLOs as previously discussed. In Sjögren's syndrome, the dysregulated expression of lymphoid chemokines together with the formation of TLOs has been observed [54, 55]. It is likely that conversion of fibroblasts into lymphoid stroma in the salivary gland is supportive of the high-affinity autoantibody production and the high incidence of B cell lymphomas associated with Sjögren's syndrome. Whether human LTi cells exist and contribute to TLO development in autoimmune diseases is still an open question but advances in engineering new models to study human haematopoietic progenitor cells may provide some tantalising clues. Altogether, autoimmunity is a multistep process requiring proinflammatory cytokines, growth factors, release of self-antigen and a *micromilieu* supporting the expansion and survival of self-reactive lymphocytes. Cytokines such as IL-7 may not only play an essential role in sustained T cell responses but also in establishing the microenvironment for chronic autoimmune responses.

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