Abstract
A major question concerning the immunopathology of rheumatoid arthritis is why the disease is localized to particular joints. A possible explanation could be the presence within the synovium of cells that foster inflammation or easy accessibility of the synovium to migratory disease enhancing cells. Within both the bone marrow and the synovium, fibroblastic stromal cells play an important role in supporting the differentiation and survival of normal cells, and also contribute to the pathologic processes. Among fibroblastic stromal cells in synovial tissue and bone marrow, nurse-like cells are a unique population having the specific capacity to promote pseudoemperipolesis (adhesion and holding beneath) of lymphocytes, and also the ability to promote the growth and function of some populations of lymphocytes and monocytes. Nurse-like cells could therefore contribute to the immunopathogenesis of rheumatoid arthritis, and may contribute to the localization of inflammation within specific joints. The present review considers the evidence that supports these possibilities.

Introduction
Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by immunologically enhanced inflammation and damage to articular structures [1,2]. Rheumatoid synovium is a site of intense inflammation, with active involvement by various populations of infiltrating lymphocytes, myeloid cells, and resident synovial fibroblasts or synoviocytes [1]. One question that has not been addressed is why RA preferentially affects certain joints. Although the explanation for the localization of rheumatoid inflammation to particular joints is not clear, one possibility relates to the presence within the synovium of resident cells that can promote inflammation. In addition, cells that can be induced to migrate from adjacent bone marrow structures may contribute to the local facilitation and propagation of inflammation and bone damage. The present review will focus on one such population, the nurse-like cells (NLCs) that populate the rheumatoid synovium and bone marrow.

Fibroblastic stromal cells in bone marrow and synovial tissue
Initially, to examine the relationship between the epiphyseal bone marrow and synovial tissue, we employed the animal model of collagen-induced arthritis [3]. Fibroblastic stromal cells (FSCs) in the bone marrow of Lewis rats were labeled with a fluorescent probe or 3HTdr and were examined for their migration at the onset of arthritis [4]. Accompanying the induction of polyarthritis, a large number of labeled FSCs in bone marrow were found to migrate into the joint cavity through canals observed in the bare zone of the joint (Figure 1), and then to proliferate in the synovial tissue. Based on these findings, we have studied FSCs of RA patients, comparing the characteristics of FSCs from bone marrow and FSCs from synovial tissue [5-7].

Nurse-like cells found in bone marrow and synovial tissue
Among the FSCs derived from the bone marrow and synovium of RA patients, a population of NLCs was identified by the capacity to carry out pseudoemperipolesis. The

Review
Mesenchymal stromal cells
Nurse-like cells reside in the synovial tissue and bone marrow in rheumatoid arthritis
Takahiro Ochi1, Hideki Yoshikawa2, Tomoko Toyosaki-Maeda3 and Peter E Lipsky4

1Sagamihara National Hospital, Sagamihara, Kanagawa, Japan
2Department of Orthopaedic Surgery, Osaka University Medical School, Suita, Osaka, Japan
3Department of Immunology, Shionogi Research Laboratories, Shionogi & Co. Ltd, Osaka, Japan
4National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD 20892, USA

Corresponding author: Takahiro Ochi, t-ochi@sagamihara-hosp.gr.jp

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BST-1 = bone marrow fibroblastic stromal cell antigen 1; FSC = fibroblastic stromal cell; GM-CSF = granulocyte/macrophage colony-stimulating factor; HLA = human major histocompatibility antigen; IFN = interferon; IL = interleukin; mAb = monoclonal antibody; NLC = nurse-like cell; RA = rheumatoid arthritis; RANKL = receptor activator of NF-κB ligand; TNF = tumor necrosis factor; TRAP = tartrate-resistant acid phosphatase.
Receptor activator of NF-κB (RANK) is involved in the differentiation of osteoclasts from myeloid precursors in a process known as pseudoemperipolesis (adhesion and holding beneath). In vivo, such thymic nurse cells were thought to support the development and expansion of thymocytes and to also play a role in positive/negative selection of T cells in mouse and rat thymus. A very similar capacity to interact and support the maturation of some population of lymphocytes and monocytes was noted for FSCs of bone marrow [5,7] and for FSCs of synovial tissue [6,7] of RA patients, suggesting that the NLC function of FSCs could contribute to the pathophysiology of RA [7].

We established RA-NLC clones with the ability to promote pseudoemperipolesis from bone marrow [5] and synovial tissue [6] of RA patients. These RA-NLC clones were determined to be of mesenchymal origin, given that they expressed vimentin but not cytokeratin. They did not exhibit desmosomes or classical junctional complexes, both of which are characteristic features of epithelial cells. Elongated and branching mitochondria were present in the cytoplasm of the clones, and caveolae, which are unique to cells of mesenchymal origin, were present on the surface [5,6].

NLCs have a number of unique functional activities that could contribute to rheumatoid inflammation. Among these activities are their ability to promote antibody production by B cells, the capacity to protect lymphocytes from apoptosis, the ability to secrete large amounts of cytokines and chemokines that could promote the accumulation and activation of lymphocytes and monocytes, and their unique capacity to promote the differentiation of osteoclasts from myeloid precursors in a receptor activator of NF-κB/receptor activator of NF-κB ligand (RANKL)-independent manner [10].

Multipotent mesenchymal stem cells from bone marrow were also found to exist in the synovial membrane [11-14]. Those cells were shown to have multipotency to develop into various cells such as cartilage, bone, fat, and muscle. Although it is currently unknown whether these cells can differentiate into NLCs, RA-NLCs are a more differentiated population. Multipotential mesenchymal stem cells from the synovial fluid and bone marrow of patients with inflammatory and degenerative arthritis were reported to be negative for CD45 and to be positive for D7-FIB, CD13, CD105, CD55, and CD10 [13]; these mesenchymal stem cells therefore have a very different phenotype from that of RA-NLCs mentioned in the following.

Function of the NLCs was reminiscent of thymic nurse cells [8,9], which have the capacity to interact with populations of thymic cells and gather them beneath their cell bodies in a process known as pseudoemperipolesis (adhesion and holding beneath). In vivo, such thymic nurse cells were thought to support the development and expansion of thymocytes and to also play a role in positive/negative selection of T cells in mouse and rat thymus. A very similar capacity to interact and support the maturation of some population of lymphocytes and monocytes was noted for FSCs of bone marrow [5,7] and for FSCs of synovial tissue [6,7] of RA patients, suggesting that the NLC function of FSCs could contribute to the pathophysiology of RA [7].

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Surface phenotype of rheumatoid arthritis nurse-like cells

RA-NLC clones from bone marrow and synovial tissue [5-7] expressed CD29, CD44, CD49c, CD54, CD106, and HLA-A, HLA-B, and HLA-C (class I major histocompatibility complex), but did not express CD1a, CD18 (LFA-1), CD35, CD40, CD154, or CD56. RA-NLCs constitutively expressed CD106 after long-term culture in the absence of cytokine stimulation. Constitutive expression of CD106 appears to be a characteristic appearance of nurse cell lines, permitting them to be distinguished from fibroblasts [7]. Human dermal fibroblast also expressed CD29, CD49c, CD54, and class I major histocompatibility complex, whereas constitutive expression of CD106 was minimal. IFNγ (100 U/ml) stimulation of RA-NLCs induced expression of CD40 and HLA-DR (class II major histocompatibility complex), but not expression of CD35 or CD154. The surface phenotype of RA-NLCs was therefore similar to that of FSCs derived from synovial tissue and bone marrow cells from non-RA controls. Namely, the phenotype of NLCs derived from osteoarthritis patients and human skin nurse cells was similar to that of RA-NLCs. Enhanced expression of CD106 and CD157 by IFNγ (mentioned below) was the characteristic observation in RA-NLCs and was different from human dermal fibroblasts [7].

Expression of CD106 by RA-NLCs was modestly enhanced by culture with normal peripheral B cells, and was markedly enhanced by IFNγ. In contrast, expression of CD106 by human dermal fibroblasts was much less marked after stimulation with IFNγ or by culture with peripheral B cells. One of the features of NLCs is their capacity to promote the survival of B lymphocytes [5-7]. Such B-cell survival was reduced by a blocking anti-CD106 mAb to the same level as B cells cultured in medium alone.

One notable product of NLCs is human bone marrow fibroblastic stromal cell antigen 1 (BST-1). This product was originally cloned from a human bone marrow FSC cell line by surveying for any unknown factors [15], supporting the FSC-dependent growth of the murine pre-B-cell line DW34. A new growth factor was identified, having the ability to enhance DW34 cell growth, and it was designated BST-1 [16]. Human BST-1 is expressed in various tissues and cell...
Cytokine production by nurse-like cells of RA patients

RA-NLCs produced numerous cytokines [5-7]. RA-NLCs from both bone marrow and synovial tissue produced detectable levels of IL-6, IL-8, and granulocyte/macrophage colony-stimulating factor (GM-CSF), and the production of IL-6 and IL-8 was quite robust. RA-NLCs from bone marrow but not synovial tissue produced IL-7, whereas RA-NLCs from synovial tissue produced granulocyte colony-stimulating factor and a greater amount of IL-6. Regulation of the production of cytokines was examined by co-culture of RA-NLCs from synovial tissue in direct contact with B cells. Secretion of IL-6, IL-8, granulocyte colony-stimulating factor, and GM-CSF was markedly increased by co-culture with B cells. IL-1β and TNF were only detected in the supernatants after co-culture with B cells. The effect of co-culture with B lymphocytes on the secretion of cytokines and immunoglobulin production by the B cells were examined under various culture conditions [5-7] (Table 1). After co-culture with B cells, the levels of IL-6, IL-8, granulocyte colony-stimulating factor, GM-CSF, and the levels of IgM were increased, and IL-1β and TNF were detected. Direct contact with the B-cell clone was required for RA-NLCs to produce IL-1β and TNF and higher levels of the other cytokines.

Inhibition of spontaneous apoptosis of lymphocytes and the effect of adhesion molecules

RA-NLCs were found to promote lymphocyte viability. Although peripheral blood B cells cultured in medium alone rapidly died, culture of B cells with RA-NLCs markedly increased the B-cell viability. The loss of viability of B cells cultured alone related to the induction of apoptosis, whereas co-culture of B cells with RA-NLCs substantially blocked their apoptosis. The mechanism of the prevention of apoptosis of B cells involved the contact-dependent upregulation of Bcl-xL by RA-NLCs [19].
Expression of MMP-2, MMP-9, and MMP-12 was increased in both TRAP(+) mononuclear and multinucleated cells after differentiation by culture with RA-NLCs, and these cells could induce cartilage degeneration in vitro by a mechanism that was completely blocked by inhibitors of MMP-2 and MMP-9. Although MMP-2 expression was significantly increased in TRAP(+) mononuclear cells, expression of MMP-9 and MMP12 was also higher in TRAP(+) multinucleated cells [27]. Of note, both TRAP(+) mononuclear and multinucleated cells differentiated by culture with RA-NLCs specifically expressed MMP-12 [27], whereas multinucleated cells expressing MMP-12 were clearly found near the bone erosions (S Yamane, M Maeda-Tanimura, Y Shimaoka, M Yukioka, T Toyosaki-Maeda, S Ishida, N Yamane, Y Tsuruta, T Itoh, N Fukui, et al., unpublished observation). RA-NLCs were therefore found to promote the differentiation of CD14(+) monocytes in a characteristic two-step differentiation process into multinucleated osteoclast-like cells with the capacity to degrade bone and cartilage.

Although TNF [28], IL-1 [29], macrophage colony-stimulating factor, and RANKL [30] are very important factors for developing osteoclasts, the RANKL-independent two-step differentiation of CD14(+) monocyte supported by RA-NLCs [10,26] may be an alternative pathway to develop multinucleated osteoclast-like cells specifically in RA. Beside the destruction of bone tissue by osteoclasts or osteoclast-like cells, we could confirm that FSCs from RA patients inoculated in vivo showed aggressive behavior, invading cartilage as reported previously [31-33], although we have not yet confirmed that pure RA-NLC lines have such function.

**Comparison of the properties of RA nurse-like cells and fibroblast-like synoviocytes**

A considerable amount of work has characterized another population of cells found in the rheumatoid synovium, namely fibroblast-like synoviocytes. The cells are thought to play a role in rheumatoid pathogenesis, especially because of their capacity to contribute to tissue damage [31-33]. RA-NLCs, however, have a number of specific attributes that suggest they may play a unique role in RA pathogenesis (Table 2).

**Mechanisms of progressive proliferation of fibroblastic stromal cells specifically found in joint**

To explain the remarkable proliferation of synovial tissue in the RA patient, various mechanisms have been reported such as the involvement of protooncogenes [34], inflammatory cytokines [35], and perturbations of Fas-mediated apoptosis [36]. As a mechanism specifically found in the synovial space but not in the bone marrow, we found that the interference with Fas-mediated apoptosis could upregulate specifically the growth of synovial FSCs [37,38]. In this regard, soluble Fas ligand was found to inhibit competitively the Fas–Fas ligand-mediated apoptosis [37] of FSCs bearing Fas. The levels of human soluble Fas ligand in synovial fluid from RA patients were found to be significantly higher than those from osteoarthritis patients.
In contrast, soluble Fas ligand was not detected in the peripheral blood, and also not in bone marrow blood in RA patients [38]. This mechanism, therefore, could at least partially upregulate the FSC growth in synovial tissue, but not in bone marrow.

**Conclusion**

A specific population of FSCs, RA-NLCs reside in both the bone marrow and synovium of RA patients and have the functional capacity to interact with lymphocyte and monocyte populations, inducing cellular differentiation and biologic activities that mimic pathophysiological features of rheumatoid inflammation. These findings suggest that RA-NLCs may play an essential role in the development of local immune and inflammatory responses in the synovium and the bone marrow. RA-NLCs could therefore be central elements in the pathologic events in RA and might be appropriate targets for therapeutic intervention in RA.

**Competing interests**

The authors declare that they have no competing interests.

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**Table 2**

Comparison of the properties of rheumatoid arthritis nurse-like cells and fibroblast-like synoviocytes

| Property                                      | Rheumatoid arthritis nurse-like cells | Fibroblast-like synoviocytes |
|----------------------------------------------|--------------------------------------|-----------------------------|
| Pseudoemperipolesis                          | +                                    | –                           |
| Constitutive expression of CD106             | +                                    | –                           |
| Enhanced expression of CD106 and CD157 by IFNγ | +                                    | –                           |
| Promote B-cell differentiation               | +                                    | –                           |
| Promote differentiation of osteoclast-like cells from CD14(+) monocytes | +                                    | –                           |
| Inhibit lymphocyte apoptosis                 | +                                    | –                           |

**References**

1. Eisenberg RA, Cohen PL: The role of immunologic mechanisms in the pathogenesis of rheumatic disease. In Primer on the Rheumatic Diseases. 10th edition. Edited by Schumacher HR, Klippel JH, Koopman WJ. Atlanta: Arthritis Foundation; 1993:27-35.

2. Genant HK: Radiology of rheumatic diseases. In Arthritis and Allied Conditions. 9th edition. Edited by McCarty DJ. Philadelphia: Lea & Febiger; 1979:70-130.

3. Trentham D, Townes A, Kang A: Autoimmunity to type II collagen: an experimental model of arthritis. J Exp Med 1977, 146: 857-868.

4. Nakagawa S, Toritsuka Y, Wakisita S, Denko K, Tomita T, Owaki H, Kimura T, Shino K, Ochi T: Bone marrow stromal cells contribute to synovial cell proliferation in rats with collagen induced arthritis. J Rheumatol 1986, 23:2098-2103.

5. Tomita T, Takeuchi E, Toyosaki-Maeda T, Oki H, Kaneko M, Takano H, Sugamoto K, Ohtono K, Suzuki R, Ochi T: Establishment of nurse-like stromal cells from bone marrow of patients with rheumatoid arthritis: indication of characteristic bone marrow microenvironement in patients with rheumatoid arthritis. Rheumatology 1999, 42:221-228.

6. Takeuchi E, Tomita T, Toyosaki-Maeda T, Kaneko M, Takano H, Hashimoto H, Sugamoto K, Suzuki R, Ochi T: Establishment and characterization of nurse cell-like stromal cell lines from synovial tissues of patients with rheumatoid arthritis. Arthritis Rheum 1999, 42:221-228.

7. Shimaoka Y, Attrep JF, Hirano T, Ishihara K, Suzuki R, Toyosaki T, Ochi T, Lipsky PE: Nurse-like cells from bone marrow and synovium of patients with rheumatoid arthritis promote survival and enhance function of human B cells. J Clin Invest 1998, 102:606-618.

8. Wekerle H, Ketelsen UP: Thymic nurse cells – a bearing epithelium involved in T-lymphocyte differentiation? Nature 1980, 283:402-404.

9. Wekerle H, Ketelsen UP, Ernst M: Thymic nurse cells. Lymphoepithelial cell complexes in murine thymuses: morphological and serological characterization. J Exp Med 1980, 161: 925-944.

10. Toyosaki-Maeda T, Takano H, Tomita T, Tsuruta Y, Maeda-Tanimura M, Shimaoka Y, Takahashi T, Iton T, Suzuki R, Ochi T: Differentiation of monocytes into multinucleated giant bone-resorbing cells: two-step differentiation induced by nurse-like cells and cytokines. Arthritis Res 2001, 3:306-310.

11. De Bari C, Dell’Accio F, Tytazonowski P, Luyten FP: Multipotent mesenchymal stem cells from adult human synovial membrane. Arthritis Rheum 2004, 44:1928-1942.

12. De Bari C, Dell’Accio F, Vanlauwe J, Eyckmans J, Khan IM, Archer CW, Jones EA, McGonagle D, Mitsiadias TS, Pitulis C, Luyten FP: Mesenchymal multipotency of adult human periosteal cells demonstrated by single-cell lineage analysis. Arthritis Rheum 2006, 54:1209-1221.

13. Jones EA, English A, Henshaw K, Kinsey SE, Markham AF, Emery P, McGonagle D: Enumeration and phenotypic characterization of synovial fluid multipotent mesenchymal progenitor...
cells in inflammatory and degenerative arthritis. *Arthritis Rheum* 2004, 50:817-827.

14. Jones EA, English A, Kinsey SE, Straszynski L, Emery P, Ponchel F, McGonagle D: Optimization of a flow cytometry-based protocol for detection and phenotypic characterization of multipotent mesenchymal stromal cells from human bone marrow. *Cytom Part B (Clin Cytom)* 2006, 70B:391-399.

15. Kaisho T, Oritani K, Ishikawa J, Tanabe M, Muraoka O, Ochi T, Hirano T: Human bone marrow stromal cell lines from myeloma and rheumatoid arthritis that can support murine pre-B-cell growth. *J Immunol* 1992, 149:4088-4095.

16. Kaisho T, Ishikawa J, Oritani K, Inazawa J, Tomizawa H, Muraoka O, Ochi T, Hirano T: Elevated levels of the soluble form of bone marrow stromal cell antigen 1 in the sera of patients with severe rheumatoid arthritis. *Arthritis Rheum* 1996, 39:629-637.

17. Lee BO, Ishikawa K, Denno K, Kobune Y, Itoh M, Muraoka O, Kaisho T, Sasaki T, Ochi T, Hirano T: Bcl-xL expression by B cells in a CD49/CD29-CD106-dependent mechanism. *Proc Natl Acad Sci USA* 1994, 91:5325-5329.

18. Ishihara K, Hirano T: B-1/CD157 regulates the humoral immune responses in vivo. *Chem Immunol* 2000, 75:239-255.

19. Hayashida K, Shimaoka Y, Ochi T, Lipsky PE: Rheumatoid synovial stromal cells inhibit apoptosis and up-regulate Bcl-xL expression by B cells in a CD49/CD29-CD106-dependent mechanism. *J Immunol* 2000, 164:1110-1116.

20. Takeuchi E, Tanaka T, Umemoto E, Tomita T, Shi K, Takaki K, Suzuki R, Ochi T, Miyaoka M: VLA-4-dependent and -independent pathways in cell contact-induced proinflammatory cytokine production by synovial nurse-like cells from rheumatoid arthritis patients. *Arthritis Res* 2002, 4:1-8.

21. Burger JA, Tsukada N, Burger M, Zvaifler NJ, Dell’Aquila M, Kipps TJ: Blood-derived nurse-like cells protect chronic lymphocytic leukemia B cells from spontaneous apoptosis through stromal cell-derived factor-1. *Blood* 2000, 96:2655-2663.

22. Tsukada N, Burger JA, Zvaifler NJ, Kipps TJ: Distinctive features of ‘nurselike’ cells that differentiate in the context of chronic lymphocytic leukemia. *Blood* 2002, 99:1030-1037.

23. Nishio M, Endo T, Tsukada N, Ohata J, Kitada S, Reed JC, Zvaifler NJ, Kipps TJ: Nurselike cells express BAFF and APRIL, which can promote survival of chronic lymphocytic leukemia cells via a paracrine pathway distinct from that of SDF-1α. *Blood* 2005, 106:1012-1020.

24. Burger JA, Zvaifler NJ, Tsukada N, Firestein GS, Kipps TJ: Fibroblast-like synoviocytes support B-cell pseudoemperipolesis via a stromal cell-derived factor-1 and CD106 (VCAM-1)-dependent mechanism. *J Clin Invest* 2001, 107:305-315.

25. Ohtani J, Zvaifler NJ, Nishio M, Boyle DL, Kalled SL, Carson DA, Kipps TJ: Fibroblast-like synoviocytes of mesenchymal origin express functional B functional B cell-activating factor of the TNF family in response to proinflammatory cytokines. *J Immunol* 2005, 174:864-870.

26. Tsuibo H, Udagawa N, Hashimoto J, Yoshikawa H, Takahashi N, Ochi T: Nurse-like cells from patients with rheumatoid arthritis support the survival of osteoclast precursors via macrophage colony-stimulating factor production. *Arthritis Rheum* 2005, 52:3819-3828.

27. Tsuibo H, Matsui Y, Hayashida K, Yamane S, Maeda-Tanimura M, Nampei A, Hashimoto J, Suzuki R, Yoshikawa H, Ochi T: Tartrate resistant acid phosphatase (TRAP) positive cells in rheumatoid synovium may induce the destruction of articular cartilage. *Ann Rheum Dis* 2003, 62:196-203.

28. Boyce BF, Li P, Yao Z, Zhang Q, Badell IR, Schwartz EM, O’Keefe RJ, and Xing L: TNFα and pathologic bone resorption. *Keio J Med* 2005, 54:127-131.

29. Wei S, Kitaura H, Zhou P, Ross P, Teitelbaum SL: IL-1 mediates TNF-induced osteoclastogenesis. *J Clin Invest* 2005, 115:282-290.

30. Saitenbery-Kermanach N, Cohen-Solal M, Bessis N, De Vernejoul MC, Boissier MC: Role for osteoprotegerin in rheumatoid inflammation. *Joint Bone Spine* 2004, 71:9-13.

31. Gay S, Gay RE, Koopman WJ: Molecular and cellular mechanism of joint destruction in rheumatoid arthritis: two cellular mechanisms explain joint destruction? *Ann Rheum Dis* 1993, 52:39-47.

32. Firestein GS: Invasive fibroblast-like synoviocytes in rheumatoid arthritis. Passive responders or transformed aggressors? *Arthritis Rheum* 1996, 39:1781-1790.