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Role of Bone Marrow in the Pathogenesis of Rheumatoid Arthritis

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovial proliferation. Thus, joints in RA consist of massive proliferating synovium, forming an invading tissue termed pannus, which results in the destruction of cartilage and bone. One of the most important histologic characteristics of the synovium in RA includes cellular proliferation in the lining layer as well as in the sublining layer (Tak, 2004). In the lining layer, both type A and type B synoviocytes, alternatively called intimal macrophages and fibroblast-like synoviocytes, respectively, are found to proliferate (Tak, 2004). In the sublining layer, there is infiltration of a variety of cells, including dendritic cells (DC), lymphocytes, plasma cells, and polymorphonuclear leukocytes. Notably, lymphoid cluster in RA synovium sometimes forms pseudo-germinal center, consisting of CD20+ B cells in the center surrounded by CD4+ T cells (Tak, 2004; Hirohata, 2004). In the synovium of RA, neovascularization is usually accompanied by lining cell proliferation and inflammatory cell infiltration (Firestein, 1999). In fact, lining cells and inflammatory cells have been found to produce angiogenic growth factors (Koch, 1998). It should be noted, however, that the synovium of RA also showed neovascularization in the areas without either lining cell proliferation or inflammatory cell infiltration, suggesting that the neovascularization might be one of the primary abnormal features that are most proximal to the etiology of RA (Hirohata & Sakakibara, 1999).

A number of studies have suggested that abnormal activation of normal joint constituents, such as synovial lining cells, play a pivotal role in the synovial hyperplasia in RA (Shiozawa & Tokuhsa, 1992). However, increasing attention has emerged to the role of bone marrow in the pathogenesis of RA. The present article overviews an update on the role of bone marrow in the pathogenesis of RA.

2. Bone marrow and type A synoviocytes (intimal macrophages) in RA

2.1 Abnormalities in peripheral blood monocytes in RA

We previously showed that peripheral blood monocytes in patients with active RA are already activated to express higher densities of CD14 (Shinohara et al.,1992). It is also suggested that peripheral blood monocytes in patients with RA may have intrinsic abnormalities as evidenced by the enhanced expression of FcγR, which is repeatedly observed regardless of the disease activity of RA (Shinohara et al.,1992). It has been also demonstrated that CD14, FcγRI and FcγRII are involved in the regulation of various

functions of monocytes, including the production of cytokines (Krutmann et al.,1990) and the expression of adhesion molecules (Lauener et al.,1990). Therefore, the observed abnormalities in our studies suggest that the recruitment of RA peripheral blood monocytes may result in further activation and adhesion of these cells in the synovial tissues, thus contributing to extending the rheumatoid disease process.

2.2 Accelerated generation of CD14+ monocyte-lineage cells from the bone marrow

Although previous studies have suggested a role of dysregulated proliferation of synoviocytes in synovial hyperplasia (Lafyatis et al.,1989), it was found that rheumatoid synovium had rarely evidence of mitosis, and that only 4% of rheumatoid synovial cells showed uptake of thymidine (Harris Jr.,1993). Thus, there has been no evidence for accelerated or dysregulated in situ proliferation of synoviocytes in rheumatoid synovium.

We have disclosed that the spontaneous generation of CD14+ cells from bone marrow CD14-progenitor cells was accelerated in RA patients compared with control patients (Hirohata et al.,1996). Moreover, the expression of HLA-DR on the bone marrow-derived CD14+ cells was also accelerated in RA patients compared with controls, confirming the accelerated maturation of macrophages in RA bone marrow. Consistently, CD14+ CD16+ blood monocytes with high expression of chemokine receptors and CD54 were found to be increased in active RA (Kawanaka et al., 2002). It should be also pointed out that the expression of a variety of chemokines and adhesion molecules is enhanced in vascular endothelium and fibroblast-like synoviocytes in the RA synovium (Oppenheimer-Marks & Lipsky,1998; Patel et al.,2001; Kanbe et al.,2002), possibly facilitating the entry of such CD14+ CD16+ blood monocytes into the synovium. These observations strongly support the hypothesis that the accelerated generation of CD14+ cells from bone marrow progenitor cells and the accelerated maturation of such CD14+ cells into tissue-infiltrative CD16+ monocytes before entry into the joint might play an important role in the pathogenesis of RA.

2.3 Evidence for recruitment of cells from systemic circulation in RA

It is noteworthy that accelerated angiogenesis has been demonstrated in RA synovium (Harris Jr.,1993), which might facilitate the recruitment of bone marrow-derived monocytes as well as lymphocytes into the synovium. In fact, the transendothelial migration of monocytes in RA synovium can be frequently observed under electron microscopy (Fig. 1).

Of interest, the formation of synovium-like tissue was also observed at the site of non-union formed after bone fracture as well as in the pericardial lesions in an RA patient (Fig. 2). Since such formation of the synovium-like tissue took place in the place without original synovial tissues, it is suggested that all the constituents of the newly formed tissue might be recruited from the systemic circulation. Finally, proliferative synovial tissues usually disappear at the site of bony ankylosis and total immobility. These observations strongly support the hypothesis that the accelerated generation and continuous recruitment of bone marrow-derived cells might play a critical role in the synovial hyperplasia in RA, thus accounting for the discrepancy between the marked synovial hyperplasia and the lack of evidence for accelerated proliferation of synoviocytes.

3. Origin of type B synoviocyte

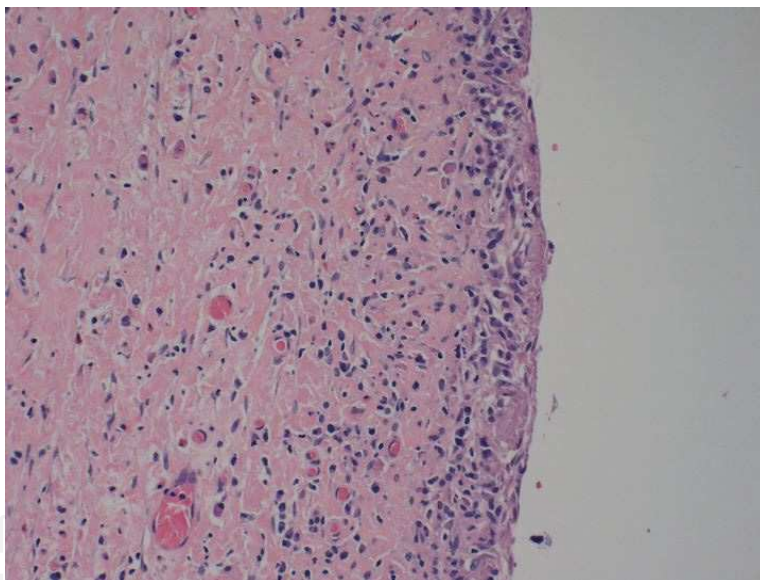
3.1 Origin of type B synoviocytes

Type B synoviocytes, which are called fibroblast-like synoviocytes, have the morphologic appearance of fibroblasts as well as the capacity to produce and secrete a variety of factors,



Monocyte-like cells are shown by arrow heads.
(Electron microscopy, the scale bar at the right-bottom corner indicates 5 μm)

Fig. 1. Transendothelial migration of monocyte into RA synovium.



(Hematoxylin and eosin, original magnification x25)

Fig. 2. Synovium-like tissue at pericardium lesion in an RA patient

including proteoglycans, cytokines, arachidonic acid metabolites, and matrix metalloproteinases (MMPs), that lead to the destruction of joints (Firestein,1996). Unlike intimal macrophages, the precise origin of type B synoviocytes remains unclear, although they are thought to arise from the sublining tissue or other support structures of a joint (Firestein,1996). On the other hand, a number of studies have shown that peripheral blood dendritic cells (DC) accumulate in the synovium, where they undergo phenotypic and functional differentiation in situ (Zvaifler et al.,1985; Thomas et al.,1994). It has been also shown that synovial DC gradually lose their distinct morphologic appearance and become indistinguishable from fibroblasts in vitro (Hendler et al.,1985). Moreover, Kyogoku et al. identified the presence of DC-like cells that strongly express major histocompatibility

complex (MHC) class II antigens and interact with T lymphocytes, in the sublining layers of the RA synovium (Kyogoku et al.,1992). They also showed that the sublining DC-like cells proliferate and differentiate into type A as well as type B synoviocytes to replace the lining layers (Kyogoku et al.,1992).

3.2 Generation of type B synoviocytes from bone marrow CD34+ cells in RA

Since it was shown that DC are derived from bone marrow CD34+ cells (Reid et al.,1992; Szabolcs et al.,1995; Chen et al.,2004), it was also likely that type B synoviocytes might be induced from bone marrow progenitors. In this regard, we previously demonstrated that bone marrow CD34+ cells from RA patients have abnormal capacities to respond to tumor necrosis factor- α (TNF- α) and to differentiate into fibroblast-like cells (FLC) producing MMP-1, suggesting that bone marrow CD34+ cells might generate type B synoviocytes and thus could play an important role in the pathogenesis of RA (Hirohata et al.,2001). Thus, CD34+ cells from the bone marrow of RA patients differentiated into cells with fibroblast-like morphology, which expressed prolyl 4-hydroxylase, in the presence of stem cell factor (SCF), GM-CSF, and TNF- α , much more effectively than CD34+ cells from the bone marrow of control subjects (Hirohata et al.,2001).

3.3 Capacity of bone marrow DC to differentiate into type B synoviocytes

We have recently demonstrated that bone marrow plasmacytoid DC (pDC) as well as myeloid DC (mDC), irrespective of their origin from RA bone marrow or osteoarthritis (OA) bone marrow, have prominent capacity to differentiate into FLC producing MMP-1 especially under influences of TNF- α (Hirohata et al.,2011). Of note, depletion of pDC from RA bone marrow CD34+ cells significantly diminished their capacities to differentiate into FLC, which were restored by addition of pDC in a dose-response manner (Hirohata et al.,2011).

It should be pointed out that generation of FLC from RA bone marrow CD34+ cells or pDC was correlated with MMP-1 levels in culture supernatants (Hirohata et al.,2001; Hirohata et al.,2011). On the other hand, it has been demonstrated that cadherin-11 is abundantly expressed in type B synoviocytes (Chang et al.,2010) compared with lung or dermal fibroblasts (Vandooren et al.,2008). Accordingly, the FLC induced from RA and OA bone marrow pDC expressed comparable amounts of cadherin-11 mRNA to RA and OA synovial FLC (Hirohata et al.,2011). These results indicate that DC are one of the progenitors of type B synoviocytes irrespective of RA or OA and suggest that bone marrow CD34+ cells might differentiate into type B synoviocyte-like cells via DC, since DC have been demonstrated to originate from CD34+ cells (Reid et al.,1992; Szabolcs et al.,1995; Chen et al.,2004). It is also likely that expansion of immature DC from bone marrow CD34+ cells might be upregulated in RA compared with in OA, accounting for the enhanced capacity of RA bone marrow CD34+ cells to differentiate into FLC upon stimulation with TNF- α , although further studies are required to confirm this point.

3.4 Recruitment of type B synoviocytes and their precursors into RA joints: Role of DC

It is thus suggested that the presence of abnormal precursors within the bone marrow progenitor cells might play an important role in the pathogenesis of RA by providing a repopulating reservoir of type B synoviocytes, as has been also suggested in other recent studies (Sen et al.,2000). Notably, the numbers of mDC and pDC have been found to be significantly decreased in RA peripheral blood, whereas both mDC and pDC are present in

synovial fluid from RA (Jongbloed et al.,2006). In fact, previous study showed that pDC are recruited to RA synovial tissues and contribute into the local inflammatory environment (Lande et al,2004; Cavanagh et al.,2005). Recent studies have disclosed that the characteristic clinical phenomenon of destructive arthritis spreading between joints is mediated, at least in part, by the transmigration of activated RA synovial fibroblasts (Lefèvre et al.,2009). Thus, RA synovial fibroblasts showed an active movement from human RA synovial tissue or human cartilage-sponge complex containing RA synovial fibroblasts implanted into the SCID mouse to the naive cartilage implanted at the contralateral flank via the vasculature, leading to a marked destruction of the target cartilage (Lefèvre et al.,2009). The movement of DC-like cells from the sublining layer to the lining layer in RA synovium (Kyogoku et al.,1992) and the presence of DC in synovial fluid (Jongbloed et al.,2006; Lande et al,2004) strongly suggest that DC might be also released from the joint to the systemic circulation via draining veins. Since bone marrow pDC as well as mDC have capacities to differentiate into type B synoviocyte-like cells, it is possible that DC, as precursors for synovial fibroblasts, also contribute to the spread of destructive arthritis between joints in RA.

4. RA as a disease of antigen-presenting cells

A number of studies have demonstrated that RA is strongly associated with HLA-DR4 or DR1 (Nepom,2001), which are involved in the presentation of antigens to T cells. These results suggest that the antigen presentation involving HLA-DR4 or the shared epitope might play a critical role in the development of synovitis in human RA. In fact, the interactions between DC and T cells, possibly through MHC class II antigens, have been disclosed in the sublining layers of the RA synovium (Kyogoku et al.,1992). If the antigens presented by APC to T cells are perpetuating antigens, such as autoantigens or antigens of persistently infected virus, that are presented through MHC class II molecules, continuing activation of APC might take place. Further studies to explore such antigens that involve persistent interactions between APC and T cells would be still important for the complete understanding of the pathogenesis of RA.

As highlighted above, bone marrow derived monocytes and DC have been shown to be the precursors of type A synoviocytes and type B synoviocytes, respectively. It is therefore suggested that RA might be a disease of dysregulated activation of antigen-presenting cells (APC), leading to synovial proliferation. Lymphocytes activation in the synovium can also be triggered by the activation of APC, accounting for activation of T cells and B cells in the synovium. Triggering with arthritogenic antigens, followed by dysregulated generation of APC from the bone marrow might result in persistent recruitment of APC into the synovium.

5. Bone marrow abnormalities and angiogenesis in RA

A number of studies indicated that neovascularization is crucial to the synovial hyperplasia in RA (Koch,1998; Hirohata & Sakakibara,1999). Postnatal neovascularization has been attributed to so-called angiogenesis, a process characterized by the sprouting of new capillaries from preexisting blood vessels (Folkman & Shing,1992). However, recent studies have demonstrated that endothelial progenitor cells of bone marrow origin play a significant role in the de novo formation of capillaries without preexisting blood vessels, so-called vasculogenesis (Asahara et al.,1997; Gehling et al.,2000; Bhattacharya et al.,2000; Lin et al.,2000).

We also showed that RA bone marrow CD34+ cells have enhanced capacities to differentiate into endothelial cells in relation to synovial vascularization (Hirohata & Yanagida et al.,2004). Therefore, bone marrow CD34+ cells might contribute to synovial neovascularization by supplying endothelial precursor cells and, thus, play an important role in the pathogenesis of RA.

Neovascularization of the synovium is not unique to RA. It has also been observed in OA synovium and has been shown to play an important role in the development of new cartilage and mineralization (Brown et al.,1980; Giatromanolaki et al.,2003; Haywood et al.,2003). Of note, recent studies have revealed that levels of expression of the angiogenic factors VEGF and platelet-derived endothelial cell growth factor are increased in RA as well as in OA, relative to normal subjects, whereas the presence of an activated synovial vasculature was high only in RA (Giatromanolaki et al.,2003). Moreover, the vascular activation by VEGF/KDR was significantly lower in OA than in RA patients, although the activation of the hypoxia inducing factor α (HIF α) pathway was comparable in OA and RA patients (Giatromanolaki et al.,2003). These observations suggest the presence of intrinsic abnormalities in synovial endothelial cells in RA patients. Of note, we have disclosed that the expression of VEGFR-2/KDR mRNA in RA bone marrow CD34+ cells was significantly higher than that in OA bone marrow CD34+ cells (Hirohata & Yanagida et al.,2004). It is therefore likely that the differences in VEGF/KDR vascular activation in bone marrow CD34+ cells might result in differences in their capacity to generate endothelial progenitor cells between RA and OA patients (Koch et al.,1994; Giatromanolaki et al.,2001).

It has been shown that decreased numbers and impaired function of endothelial progenitor cells (EPCs) resulting in defective vasculogenesis are associated with RA, leading to premature atherosclerosis (Herbrig et al., 2006; Pakozdi et al., 2009). On the other hand, it has been recently disclosed that EPCs can be differentiated into 2 subpopulations, EPCs of monocytic versus hemangioblastic origin, which have been denoted as early-outgrowth and late-outgrowth EPCs, respectively (Jodon de Villeroché et al, 2010). More importantly, late-outgrowth EPCs have been found to be increased and have higher colony formation capacity in the active stage of RA. It is therefore likely that hemangioblastic EPC-dependent vasculogenesis might be associated with active inflammation and accelerated atherosclerosis in RA.

6. Abnormal gene expression in bone marrow CD34+ cells in RA

6.1 RA and hematopoietic stem cell transplantation

Although autologous hematopoietic stem cell transplantation (HSCT) has been used to treat severe RA in limited case reports (Joske,1997; Durez et al.,1998), a study with greater numbers of patients have disclosed that recurrence of RA is frequent after the autologous HSCT (Snowden et al.,2004; Bingham & Moore, 2004). Such frequent recurrence after autologous HSCT clearly indicates that abnormalities in bone marrow stem cells persist after the treatment. It has been proposed that bone marrow CD34+ progenitor cell reserve and function are defective in RA probably due, at least in part, to a TNF- α mediated effect, because significant restoration of the disturbed hematopoiesis was obtained following anti-TNF- α treatment (Papadaki et al.,2002; Porta et al.,2004). It should be noted, however, that blockade of TNF- α is not curative for RA in spite of its epoch-making impact on treatment of RA (Feldmann & Maini,2001). Thus, recurrence of RA is noted after discontinuation of blockade of TNF- α or even during anti-TNF- α therapy (Feldmann & Maini,2001). It is

therefore likely that intrinsic abnormalities that were not secondary to the influences of TNF- α might be present in bone marrow progenitor cells, leading to recurrence of RA. In fact, although abnormal regulatory networks in the immune response and cell cycle categories were identified in bone marrow mononuclear cells from RA patients (Lee et al., 2011), it is possible that such changes might be secondary to systemic inflammation, presumably due to proinflammatory cytokines. In this regard, beyond its role in angiogenesis, the demonstration of the abnormal expression of VEGFR-2/KDR mRNA in RA bone marrow CD34+ cells (Hirohata & Yanagida et al., 2004) have brought an impact as the first evidence for the intrinsic abnormality in RA bone marrow.

Mesenchymal stem cells (MSCs) have been shown to have potent anti-inflammatory and immunomodulatory properties through suppression of Th1/Th17 response and induction of Treg response (Macdonald et al., 2011). However, it remains unclear whether MSC therapy is beneficial for treatment of RA.

6.2 Nuclear factor kappa B1 (NF κ B1)

As mentioned above, bone marrow CD34+ cells from RA patients have abnormal capacities to respond to TNF- α and to differentiate into FLC producing MMP-1, suggesting that abnormalities in bone marrow CD34+ cells might play a role in the pathogenesis in RA (Hirohata et al., 2001). TNF- α is one of the first triggers to be found effective for the activation of NF κ B (Müller-Ladner et al., 2002). Of note, we have recently demonstrated that RA bone marrow CD34+ cells showed enhanced expression of NF κ B1 (p50), silencing of which resulted in prevention of their differentiation into FLC (Hirohata et al., 2006).

6.3 FK506-binding protein5 (FKBP5)

Nakamura et al. recently disclosed that the expression of several genes including amphiregulin (AREG), chemokine receptor 4 (CXCR4), and FK506-binding protein 5 (FKBP5), was augmented in bone marrow mononuclear cells from RA patients compared with those from OA patients (Nakamura et al., 2006). Interestingly, FKBP5 was found to be involved in nuclear translocation and activation of NF κ B by degradation of inhibitor of NF κ B alpha (I κ B α) in a human megakaryoblastic leukemia cell line (Bouwmeester et al., 2004; Komura et al., 2005). It is therefore suggested that the up-regulated expression of both NF κ B1 and FKBP5 mRNAs in bone marrow CD34+ cells from RA patients might be involved cooperatively in their abnormal responses to TNF- α to differentiate into type B synovocyte-like cells.

Although the expression of mRNAs for AREG, CXCR4 and FKBP5 has been shown to be augmented in RA bone marrow mononuclear cells (Nakamura et al., 2006), only FKBP5 mRNA expression was significantly upregulated in bone marrow CD34+ cells from RA (Matsushita et al., 2010). Therefore, it is suggested that the up-regulation of the expression of mRNAs for AREG and CXCR4 in RA bone marrow mononuclear cells might be sequelae of systemic inflammation of RA. By contrast, the up-regulation of FKBP5 mRNA expression in RA bone marrow CD34+ cells might not be secondary to systemic inflammation, but a primary abnormality in bone marrow CD34+ cells (Matsushita et al., 2010). It has been previously shown that TNF- α enhanced NF κ B1 mRNA expression in bone marrow CD34+ cells from healthy individuals (Hirohata et al., 2006). However, TNF- α did not enhance FKBP5 mRNA expression in bone marrow CD34+ cells from healthy individuals (Matsushita et al., 2010). It is therefore confirmed that apart from NF κ B1, the enhanced

FKBP5 mRNA expression in RA bone marrow CD34⁺ cells is not secondary to systemic inflammation of RA.

6.4 Krüppel like factor 5 (KLF-5)

Krüppel like factor 5 (KLF-5), a zinc finger-containing transcription factor, activates many genes, including platelet-derived growth factor (PDGF) A/B, plasminogen activator inhibitor-1, inducible nitric oxide synthase and VEGF receptors (Shindo et al.,2002; Nagai et al.,2005). KLF-5 has been shown to cooperate with NFκB1 to activate PDGF-A gene expression (Nagai et al.,2005; Aizawa et al.,2004), which might be involved in synovial fibroblast-like cell proliferation (Ohba et al.,1996). KLF-5 mRNA expression in bone marrow CD34⁺ cells was significantly higher in RA patients than in OA patients (Hirohata et al.,2009). It is thus likely that the upregulation of VEGFR-2/KDR mRNA expression might be secondary to the enhanced KLF-5 mRNA expression in RA bone marrow CD34⁺ cells. Of note, TNF-α enhanced NFκB1 mRNA expression, but not KLF-5 mRNA expression, in bone marrow CD34⁺ cells from normal individuals (Fig.3) (Hirohata et al.,2009).

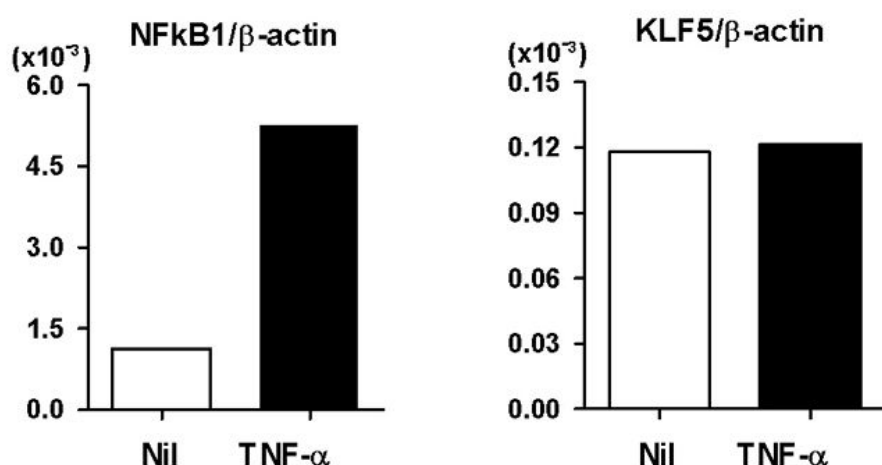


Fig. 3. Effect of TNF-α on the expression of mRNAs for NFκB1 and KLF-5 in bone marrow CD34⁺ cells from a healthy donor

Previous studies also demonstrated that the suppression of KLF-5 by silencing RNA resulted in a reduction of NFκB1 mRNA in IEC6 cells stimulated with lipopolysaccharide, indicating that KLF-5 is an upstream regulator for NFκB1 mRNA expression in IEC6 cells (Chanchevalap et al.,2006). Taken together, it is most likely that the upregulation of KLF-5 mRNA expression might lead to the enhanced expression of NFκB1 mRNA in bone marrow CD34⁺ cells, but not vice versa, in RA. In addition, the upregulation of KLF-5 mRNA as well as NFκB1 mRNA in RA bone marrow CD34⁺ cells might result in their abnormal capacities to differentiate into FLC. Although it is strongly suggested that KLF-5 might be an upstream regulator of NFκB1 mRNA in bone marrow CD34⁺ cells, further studies to explore the mechanism of abnormal expression of KLF-5 mRNA in BM CD34⁺ cells and its relation with FKBP5 would be important.

7. Conclusion

As summarized in Fig.4, accumulating evidence has been provided for the involvement of bone marrow in the pathogenesis of RA. Thus, all the constituents in the proliferating synovial tissues might be supplied from bone marrow CD34+ cells. Apparently, RA bone marrow CD34+ cells have abnormal mRNA expression for several genes, possibly resulting in abnormal differentiation of monocytes and DC. Moreover, it is strongly suggested that DC, as precursors for synovial fibroblasts, might also contribute to the spread of destructive arthritis between joints in RA (Hirohata et al.,2011; Lefèvre et al.,2009).

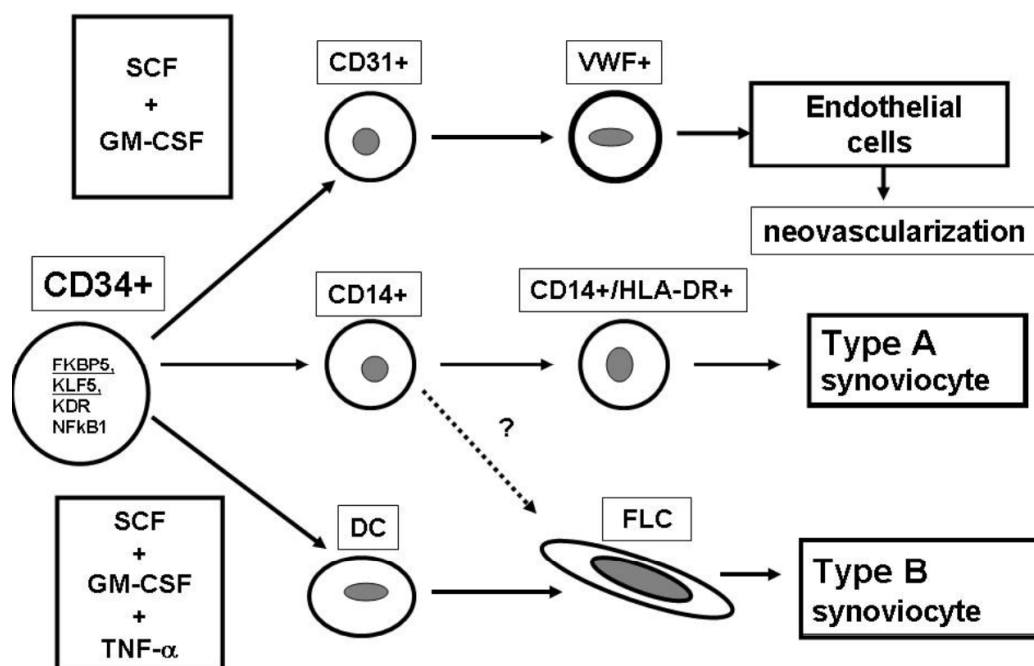


Fig. 4. Schema for the suggested role of bone marrow in the pathogenesis of RA

In the past decade, the importance of TNF- α in the pathogenesis of RA has come to be increasingly appreciated (Feldmann et al.,1996). We have revealed that CD34+ cells from bone marrow of RA patients have abnormal responsiveness to TNF- α (Hirohata et al.,2001). However, the precise sequelae of abnormal responses of CD34+ cells from bone marrow of RA patients to TNF- α remain unclear. KLF-5 might upregulate the expression of mRNAs for NFkB1 and VEGFR-2/KDR, whereas FKBP5 might enhance activation of NFkB, resulting in further upregulation of NFkB1 mRNA expression. Further studies that explore in detail the mechanism of abnormal expression of the genes, especially KLF-5 and FKBP5, in CD34+ cells from bone marrow of RA patients would be helpful in gaining a complete understanding of the etiology as well as the pathogenesis of RA. In this regard, we showed previously that GM-CSF-stimulated bone marrow CD34+ cells from 3 of 8 RA patients, but none from 7 OA patients, gave rise to spontaneous transformation of highly purified B cells of Epstein-Barr virus (EBV)-seronegative healthy donors, whereas neither GM-CSF-stimulated bone marrow CD34+ cells alone nor highly purified B cells alone gave rise to spontaneously transformed B cell lines (Hirohata et al.,2000). All the transformed B cell lines

were positive for EBV-DNA. It is therefore possible that EBV might be involved in abnormalities in RA bone marrow CD34+ cells. Further studies to investigate the role of EBV in bone marrow abnormalities in RA would be interesting.

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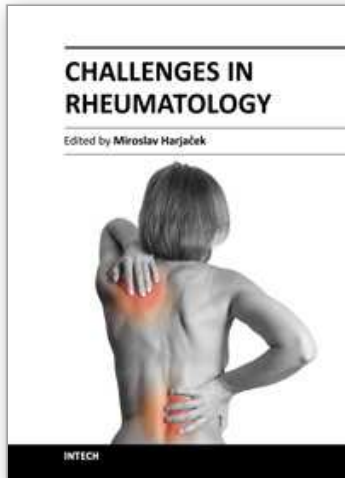
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Challenges in Rheumatology

Edited by Dr. Miroslav Harjacek

ISBN 978-953-307-848-9

Hard cover, 190 pages

Publisher InTech

Published online 22, December, 2011

Published in print edition December, 2011

Rheumatology is a subspecialty of medicine that focuses on the biology, cause, diagnosis and the treatment of a variety of musculoskeletal and other systemic diseases. The field of rheumatology is expanding rapidly and several very exciting developments have occurred during the recent years. Firstly, there has been a new dramatic understanding of the nature of inflammation and the possibility of specifically regulating the aberrant immune inflammatory response. Secondly, an understanding of pathogenesis has led to the development of new, more targeted therapies. Challenges in Rheumatology has assembled an impressive group of international experts who have studied specific aspects of certain rheumatic diseases and have extensive experience either in pathophysiology, or with the in-depth diagnosis and/or management of rheumatic patients. They communicate their knowledge and experience to the reader in chapters that are conveniently organized as pathophysiology, clinical manifestations and diagnosis of selected rheumatic diseases, medical and perioperative orthopedic management, and the economic impact of rheumatic diseases. We hope that this book will help trainees become better physicians and scientists, and that it will help practicing rheumatologists to provide better care, and ultimately, improve the quality of life of our patients.

How to reference

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Shunsei Hirohata (2011). Role of Bone Marrow in the Pathogenesis of Rheumatoid Arthritis, Challenges in Rheumatology, Dr. Miroslav Harjacek (Ed.), ISBN: 978-953-307-848-9, InTech, Available from: <http://www.intechopen.com/books/challenges-in-rheumatology/role-of-bone-marrow-in-the-pathogenesis-of-rheumatoid-arthritis>

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