Mini Review

Functional change of synoviocytes and mesenchymal stromal cells through adipogenesis: A possible model of pannus and bone edema formation in rheumatoid arthritis

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The biology of fibroblast-like cells is important in understanding of pathogenesis of rheumatoid arthritis (RA). Fibroblast-like synovial cells (FLSs) is major component of pannus in inflamed joint, and mesenchymal stromal cells (MSCs) is thought to be in bone edema, a recently reported RA lesion in bone marrow that is detectable by MRI. It is interesting that MSCs share many characteristics with FLSs. Both types of cells can secrete cytokines, and differentiate into mesenchymal lineage cells such as osteoblasts, chondrocytes, and adipocytes. In this review, we discuss the possible contribution of the adipogenesis insufficiency of FLSs or MSCs to the development of synovial hyperplasia and bone edema in RA.


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Introduction

It is important to observe the pathological hallmarks of rheumatoid arthritis (RA) to understand the pathogenic mechanism of the disease. In addition to synovial hyperplasia in inflamed joints, which is a well-known characteristic of the disease, bone edema was recently identified as a pathological change in RA bone marrow detected by magnetic resonance imaging (MRI). Even though the lesions are separated from each other by bone cortex, both lesions have similar cellular components, including monocytes, osteoclasts, and fibroblasts. It is also noteworthy that changes in fat tissue are evident in both lesions. Namely, synovial hyperplasia seems to invade surrounding fat tissue and bone edema replaces fat tissue with non-fat tissue. However, it is not understood how fat tissue is replaced with other cells in joint or bone marrow and how the aberrant replacement of fat tissues affect the clinical course of RA.

Fibroblasts in synovial hyperplasia are called fibroblast-like synovial cells (FLSs). FLSs are regarded as a thera-
Adipogenesis of FLSs and RA

In 2001, De Bari et al. reported that FLSs differentiate into mesenchymal lineage cells such as osteoblasts, chondrocytes, and adipocytes. These discoveries paved the way to tissue engineering technology using FLSs to repair damaged joint structure in RA patients. Another application of the phenomena is to induce FLS differentiation in vivo to alter the cellular characteristics of FLSs to ameliorate RA. In this regard, we attempted to induce the adipogenesis of FLSs using troglitazone, a synthetic PPARγ ligand. Troglitazone induces adipogenesis of FLSs as well as the established adipogenesis induction method introduced by De Bari et al.

We examined whether the inflammatory milieu in rheumatoid synovial tissues affects the adipogenesis of FLSs. We tested the effects of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and IL-1/β on a troglitazone-mediated FLS adipogenesis system. Troglitazone-induced adipocyte differentiation of FLSs was effectively inhibited by TNF-α and IL-1/β. This can be explained by the report by Suzawa et al., which stated that MSC adipogenesis can be blocked by a signal via nuclear factor-κB (NF-κB)-inducing kinase (NIK)-mediated NF-κB activation. Interestingly, IFN-γ also inhibits the adipogenesis process of FLSs. These findings indicate that the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway also plays a role in inhibiting the adipogenesis of FLSs.

One of the striking changes in FLS function is that the secretion of IL-6 is significantly reduced after the adipogenesis of the cell. In addition, the production of IL-8 and matrix metalloprotease-3 (MMP-3) in troglitazone-differentiated adipocyte-like FLSs is diminished. These functional changes in FLS can be explained by decreased NF-κB nuclear activity induced by TNF-α in troglitazone-differentiated adipocyte-like FLSs compared to non-treated ones. Since NF-κB is an important transcription factor for IL-6, IL-8, and MMP-3 expression, these transformations of FLSs are very favorable for the regression of RA. It is important that the differentiation of FLSs into adipocyte-like cells is not stable, because the production of IL-6, IL-8, and MMP-3 is restored 8 days after the withdrawal of troglitazone; this means that FLSs return to an undifferentiated or active state without differentiating stimulus.

Adipogenesis of MSCs and RA

A recent histological examination of bone edema revealed that adipose tissue, a major cellular component of bone cavity, is replaced by inflammatory cells such as monocytes, fibroblasts, and osteoclasts. More importantly, the extent of bone edema is related to the prognosis of RA. Therefore, it is expected that bone edema plays roles in inflammation and the destruction of joint in RA. These findings about bone edema also give rise to 2 questions: (1) how does bone edema emerge in bone marrow, and (2) how does the lesion contribute to the disease progression of RA?

MSCs are spindle-shaped adherent cells that can be enriched from bone marrow. The most remarkable characteristic of these cells is their ability to differentiate into mesenchymal lineage cells such as osteoblasts, adipocytes, and chondrocytes. Besides this, MSCs can maintain their multipotency even after their expansion in vitro. Interestingly, recent studies show that MSCs modulate the activities of T, natural killer, and dendritic cells. This suggests the therapeutic potential of MSCs for treating RA. However, it remains unclear whether MSCs are beneficial for RA therapy, because the cells are also implicated to have pathogenic roles in RA.

We examined whether cytokines block MSC adipogenesis, as is observed in FLSs. As a result, the adipogenesis of MSCs was dramatically reduced by culture with TNF-α, IL-1/β, IL-6, or transforming growth factor β (TGFβ). These data suggest that the inflammatory milieu inhibits the adipogenesis of MSCs as is observed in FLSs; a variety of
The Impact of Adipogenesis Inhibition in RA

Inflammatory cytokines block the adipogenesis of both FLSs and MSCs. This finding implies that inflammation contributes to the replacement of adipose tissue with vigorously proliferating FLSs and MSCs, which may lead to the formation of synovial hyperplasia or bone edema. It is important that these pathological changes already appear at the early stage of RA. Our data suggest that the inflammation that triggers the onset of RA may also block the adipogenesis of FLSs and MSCs to form synovial hyperplasia or bone edema.

Interestingly, one arthritis model mouse exhibits a phenotype consistent with this hypothesis. MSCs obtained from IL-1 receptor antagonist knockout mice (IL-1ra^{-/-}), an arthritis model mouse, exhibit altered self-renewal and differentiation ability^{25}. Interestingly, the population of MSCs with adipogenic potential decreases prior to the onset of arthritis. In addition, the adiposity of the IL-1ra^{-/-} mouse decreases prior to arthritis. Thus, it is possible that inflam-
The reduced migration capacity of MSCs after adipogenesis compared to undifferentiated MSCs is another important finding. It is thought that inflammatory cells and proliferating synovial cells in inflamed joints break cortical bone to generate bone edema\(^2\). We propose that MSCs also have the potential to initiate this cortical breaking from the bone cavity toward the joint cavity, because they can vigorously migrate and secrete IL-6. Taken together, it is possible that a bidirectional cortical break can occur in RA in which synovial cells stimulate MSCs and vice versa. In this scenario, treatments targeting RA lesions must explore bone edema. Our model is demonstrated in Figure 2.

**The Potential of Adipogenesis Induction for RA Treatment**

The marked induction of IL-8 in MSCs after adipogenesis compared to that observed in undifferentiated MSCs\(^2\) completely contradicts the results described in our previous study using FLSs\(^1\). This can be explained by the difference in cells or the adipogenesis induction system used. We used adipogenesis induction medium containing indomethacin, IBMX, insulin, and dexamethasone for MSC adipogenesis. In the previous study on FLSs, we induced the adipogenesis of FLS using troglitazone, a synthetic PPAR\(_\gamma\) ligand. The synthetic PPAR\(_\gamma\) ligand, which is proven in arthritis model mouse to be a potent anti-rheumatic drug\(^5\), may be a better choice for inducing the adipogenesis of FLS and MSC because it can inhibit both IL-8 and IL-6 production\(^4\).

**Conclusion**

We discussed the possibility that MSCs may be a component of bone edema as well as a potent therapeutic target that deserves exploration. Accordingly, we propose "adipogenesis induction in FLSs and MSCs in the treatment of early-stage RA" as a future study. An existing group of drugs can induce MSCs adipogenesis; synthetic PPAR\(_\gamma\) ligands are now widely used to treat diabetes and can induce FLSs and MSC adipogenesis. Using these compounds may diminish inflammatory lesions during the early stage of RA such as synovial hyperplasia and bone edema, blocking their progression to persistent and established joint-destructing lesions.

Further basic and clinical research is also desired to determine whether bone edema can be an indicator for an affirmative treatment in RA.
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Conflict of interests

None

References


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