Potential of B-cell-targeting therapy in overcoming multidrug resistance and tissue invasiveness associated with P-glycoprotein expressing-B cell compartments

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ABSTRACT
Rheumatoid arthritis (RA) is a systemic autoimmune mediated inflammatory disease characterized by progressive joint damage and extra-articular organ manifestations. Among the effector pathways and cells involved in the development of RA, activated B cells play a pivotal role in the pathological process of RA. P-glycoprotein (P-gp), a member of ATP-binding cassette transporters, is induced on the cell membrane by certain stimuli. P-gp transports various drugs from the cytoplasm to the cell exterior, resulting in the development of drug resistance. P-gp expression on B cells appears in patients with RA as the disease activity increases, and treatment of these patients’ results in modification of over-expression of P-gp on activated B cells. Evidence suggests that P-gp expressing-activated B cells play important roles in the pathogenesis and treatment resistance in RA through the efflux of intracellular drugs and progression of infiltration in inflammatory lesions. Therapies designed to target activated B cells might overcome refractory RA. Identification of the subsets of peripheral activated B cells that express P-gp in RA patients might help the selection of suitable treatment strategy.

1. Introduction
Rheumatoid arthritis (RA) is a systemic autoimmune-mediated inflammatory disease characterized by progressive destructive polyarthropathy with occasional systemic organ involvement [1]. The treatment strategy centers on the control of immune abnormalities with disease modifying anti-rheumatic drugs (DMARDS) as soon as possible, to prevent progressive joint damage and extra-organ manifestations [2]. However, some patients do not respond adequately to such treatments.

Among various effector pathways and cells, activated B cells play pivotal role in the pathogenesis of RA. In RA patients, these cells produce autoantibodies and various inflammatory cytokines, infiltrate the synovial tissues and present antigens to T cells [3-5]. We reported previously that overexpression of P-glycoprotein (P-gp) on the pathologically activated B cells could lead to drug resistance and failure to control disease activity, especially in RA patients with high disease activity [6-9]. In patients with refractory inflammatory bowel diseases (IBD), other investigators also reported upregulation of P-gp on peripheral lymphocytes [10] and accumulation of highly activated plasmablasts in the peripheral blood [11].

P-gp is a member of the ATP binding-cassette-transporters with two ATP binding sites, and functions as an energy-dependent transmembrane efflux pump. P-gp transports multiple drugs of P-gp substrates from the cytoplasm to the cell exterior through a process involving ATP hydrolysis, thus reducing their intracellular concentrations (Table 1) [12-19]. In other words, overexpression of P-gp on activated B cells can lead to the development of multidrug resistance.

Apart from its role in drug resistance, experimental and clinical evidence suggests the involvement of P-gp in the migration of various cancer cells and inflammatory cells. Overexpression of P-gp is associated with enhanced invasiveness and poor prognosis, whereas P-gp-specific inhibitors reduce migration of breast cancer cells and leukemia cells [20-22]. The synovitis and RA-associated interstitial pneumonitis of patients with highly active RA show massive infiltration of C-X-C chemokine receptor 4 (CXCR4)-expressing P-gp⁺CD19⁺ B cells, together with the presence of CXCL12-expressing...
Furthermore, expansion of CXCR4 expressing activated B cells for refractory RA. The expression level of P-gp on B cells correlate with disease activity in patients with RA [6]. Furthermore, treatment with corticosteroids without methotrexate (MTX) enhances P-gp expression on CD19⁺ B cells in RA patients with high disease activity [6]. Thus, overexpression of P-gp on activated B cells is associated with poor control of disease activity in RA patients with highly active disease [6–9].

The P-gp⁺ B cell subset that co-expresses CXCR4 are closely related to RA disease activity and serious organ involvement [9]. The upstream CXCR4 gene contains a putative consensus Y-box-binding site (inverted CCAAT box) to which the MDR-1 transcription factor YB-1 can bind [30]. It remains unclear whether activation of YB-1 is directly involved in the upregulation of CXCR4 gene. However, a Syk-dependent IgD-BCR signal, which is triggered by actin cytoskeleton remodeling following CXCL12/CXCR4 axis activation, is initiated and results in induction of Ca²⁺ influx and activation of the ERK pathway [31]. This could lead to induction of P-gp expression through ERK pathway. Fragmented hyaluronan, one of inflammatory extracellular matrix, induces P-glycoprotein expression on lymphocytes through CD44 [32]. Colone et al. [20] reported that P-gp interacts with CD44 through the activation of the ERK and MAPK pathways and results in increase of the invasive behavior, associated with an increase in MMP production and proteolytic activity. CD44 did not increase the invasive behavior in the absence of P-gp. Thus, P-gp may cooperate with molecules involved in induction of own expression and result in increase of migration and invasive potential. P-gp⁺CXCR4⁺CD19⁺ B cells seems to have high-migration capacity and can enhance pathological lesions. In addition to B cells, plasmablasts also coexpress CXCR4 and CD19 [33]. Evidence suggests the involvement of CXCL12/CXCR4 axis in the migration of plasmablasts to the inflamed tissues [34] and the association of P-gp⁺CXCR4⁺CD19⁺ B cells with severe organ injury in RA patients [9,35]. The expression and binding capacity of CXCL12 are increased in the RA synovium in the presence of TNF-α, a cytokine known to induce P-gp [36,37]. In addition to RA, the CXCL12/CXCR4 axis also plays a role in the migration of inflammatory cells in other autoimmune diseases [35,38,39]. For example, marked accumulation of CXCR4⁺CD19⁺ B cells was reported in the inflamed mucosa of ulcerative colitis (UC) [38] and significantly high CXCR4 and CXCL12 mRNA levels were reported in bronchoalveolar lavages of pulmonary sarcoidosis [39].

CXCR4 is located in proximity to the IgD-B-cell antigen receptor (BCR), which colocalizes with the neovascular endothelial cells and fibroblasts [9]. Furthermore, expansion of CXCR4⁺P-gp⁺CD19⁺ B cells in the peripheral blood reflect serious organ involvement [9].

In this review, we discuss the relevance of P-gp-expressing activated B cells in treatment resistance and enhancement of tissue damage, and propose potentially effective treatments that target P-gp-expressing activated B cells for refractory RA.

### 2. Regulation of P-gp expression associated with enhancement of migration of B cells in RA

P-gp, also known as the ABC transporter subfamily B member 1 (ABCB1), is a 170-kDa product of the multidrug resistance-1 (MDR-1). P-gp is expressed congenerically on various endothelial cells, including the blood brain barrier, and on epithelial cells of various organs, including the gut, liver, kidney and pancreas and functions to protect cells from harmful toxic substances [8]. Whereas resting normal lymphocytes show only marginal expression of P-gp, overexpression of this glycoprotein can be induced upon activation of lymphocytes by various stimuli [8,23]. For example, P-gp expression on activated B cells is directly regulated by activation of the Y-box binding protein-1 (YB-1), a MDR-1 transcription factor. Translocation of the YB-1 results in transcription of MDR-1 gene, which is induced by activation of the ERK pathway [24–26] in response to immune stimuli, such as IL-6 [23] and TNF-α [8] which are associated with increased disease activity and play important pathogenic roles in inflammatory erosive arthritis in RA (Figure 1(A)) [5,27–29].
coreceptor CD19, and IgD-BCR, CD19 and CXCR4 are functionally linked during the induction of B-cell migration associated with CXCL12-mediated CXCR4 signaling [31]. The lipid rafts on the plasma membrane contain constitutively associated CD19 and P-gp molecules [40]. We have reported previously the presence of strong and significant correlation between the proportions of P-gp+CD27-IgD+CD19+B cells and P-gp+CXCR4+CD19+B cells in RA patients (Figure 2(A)). Figure 2(B) shows images from a representative patient with highly active RA and extra-articular involvement who showed expansion of P-gp+CXCR4+CD19+B cells and preferentially high P-gp expression on CD27 IgD+CD19+B cells. Therefore, majority of P-gp+CXCR4+CD19+B cells might contain P-gp+CD27 IgD+CD19+B cells. Thus, P-gp+CD27 IgD+CD19+B cells were also significantly increased in RA patients with extra-articular involvements (Figure 2(C)). Other studies also showed significant upregulation of P-gp expression on peripheral lymphocytes and accumulation of antigen-selected IgD-
only B cells in the bronchial mucosa of asthmatic patients with high serum IgD levels [41–43]. CD19<sup>+</sup> B cells expressing triplets of P-gp-CXCR4-IgD may enhance the migration activity followed by progression of infiltration in CXCL12-expressing inflammatory lesions.

In patients with RA, B cells start to express P-gp with the increase in disease activity, and the expression level on activated B cells is further enhanced in RA patients with high disease activity treated with corticosteroids but without MTX. Furthermore, the P-gp overexpression on activated CD19<sup>+</sup> B cells associated with CXCR4/IgD expression subsequently results in treatment resistance and progressive destructive arthritis with extra-articular involvements.

### 3. Potential of treatments targeting P-gp<sup>+</sup> B cell compartments in RA

As reviewed above, P-gp<sup>+</sup>CD19<sup>+</sup>B cells, especially those co-expressing CXCR4 and IgD, are pro-inflammatory activated B cells associated with drug resistance, disease activity and progression of inflammatory lesions in RA. Therefore, P-gp<sup>+</sup> B cells targeting therapies may be beneficial in the control of disease activity in refractory RA (Figure 1(B)).

#### 3.1. Conventional synthetic DMARDs

MTX is one of the anchor drugs used for the treatment of patients with RA. It acts by inhibiting the proliferation and differentiation of B cells and reducing the production of immunoglobulins, including rheumatoid factor [44]. MTX is known to reduce the activation of ERK and production of cytokines, including IL-6 and TNF-α [45,46]. Thus, MTX seems to inhibit both B cells activation and the ERK pathway and that such inhibition may result in downregulation of P-gp expression on B cells. In fact, MTX is reported to limit P-gp expression on B cells in patients with highly active RA [6],

![Figure 2. Relations among P-gp<sup>+</sup>CXCR4<sup>+</sup> B cells, P-gp<sup>+</sup>CD27IgD<sup>+</sup> B cells and RA organ involvement. (A) Correlation between the proportions of P-gp<sup>+</sup>CXCR4<sup>+</sup> B cells and P-gp<sup>+</sup>CD27IgD<sup>+</sup> B cells in RA patients. Statistical analysis was performed by Person’s correlation analysis. (B) Flow cytometric analysis identified P-gp<sup>+</sup>CD27IgD<sup>+</sup> B cells in the representative RA patient with rheumatoid vasculitis. Values at the top of each section are percentages of CD19<sup>+</sup>B cell subpopulations based on CD27/IgD classification. Flow cytometric analysis showed P-gp expression on each B cell subpopulation (blue lines). Data represent the percentages of P-gp-positively stained B cell subpopulations. Red: isotype-control FITC-conjugated anti-mouse IgG Ab. The number of CD27<sup>+</sup>IgD<sup>+</sup>CD19<sup>+</sup> B cells was lower than that was available for the histogram exhibition and P-gp expression analysis. (C) Flow cytometry for P-gp<sup>+</sup>CD27IgD<sup>+</sup>B cells in 17 RA patients, including 10 with (closed bar) and 7 without (hatched bar) organ involvement. Values are mean ± SD of independent experiments. "p < .05, by non-paired t-test. RA disease activity, as estimated by the SDAI score, was not significantly different between the two groups (with: 26.3% ± 8.5, without: 30.9% ± 12.3; p = .41). Organ involvement included interstitial pneumonia (n = 2), interstitial pneumonia with rheumatoid vasculitis (n = 3), Felty syndrome (n = 1), amyloidosis (n = 1) and lymphadenopathy (n = 1). (A–C) Specific antibodies used for staining and flow cytometric analysis, including MRK16 for P-gp (a specific mAb against P-gp; Kyowa Medex, Tokyo) with FITC-conjugated goat anti-mouse IgG mAb, cy-chrome-conjugated CD19 mAb, APC-conjugated CD27 mAb and PE-conjugated IgD and CXCR4 mAb (BD Biosciences Pharmingen).
as well as overcome steroid resistance in sarcoidosis [47].

Tacrolimus (TAC) acts as a calcineurin inhibitor and inhibits the differentiation of naive T cells into functional pd1⁺iCOS⁺Tfh-like cells, resulting in inhibition of Tfh-dependent B-cell proliferation and differentiation into plasma cells and transitional B cells [48]. TAC also acts as a P-gp competitive inhibitor with the potential of overcoming drug-resistance, similar to cyclosporine A [8,49]. We have demonstrated that treatment with TAC resulted in recovery of intracellular dexamethasone concentrations in IL-2-activated lymphocytes using doses lower than the trough level measured clinically when TAC is used as a calcineurin inhibitor (Figure 3). In fact, the presence of low concentrations of TAC in cultures of lymphocytes harvested from highly active RA patients, induced recovery of intra-lymphocytes dexamethasone concentrations [8]. The efficacy of TAC in the treatment of patients with RA depends on both the expression level of P-gp on lymphocytes and its inhibitory effect on the drug exclusion function of P-gp [49]. Thus, P-gp competitors, including TAC regulate P-gp-mediated drug resistance by recovery of intracellular P-gp substrates (Table 1). Other investigators also reported the efficacy of TAC in asthma and interstitial pneumonia associated with autoimmune diseases [50,51]. Patients with myasthenia gravis exhibit increased P-gp function in lymphocytes, particularly in refractory patients compared with corticosteroid-responders, whereas it is attenuated by TAC treatment [52,53].

3.2. Targeted synthetic DMARDs

B-cells are activated by signal transduction through common γ-chain cytokine receptors. Janus kinase (JAK) inhibitors, which impair signal transduction through the common γ-chain, inhibit plasmablast development, production of IL-6 and the secretion of antibodies from B-cells [54,55]. The majority of JAK inhibitors are substrates of P-gp (Table 1) [18,56]. In vitro studies demonstrated attenuation of the effects of JAK inhibitors in stimulated peripheral blood B cells [54]. Whereas, first anchor drug MTX is known to inhibit P-gp expression on B cells [6], thus, MTX might prolong the effects of combined JAK inhibitors by preventing P-gp-related attenuation of the effects. Actually, the combination of JAK inhibitors and MTX is especially effective in patients with refractory RA who otherwise respond poorly to biological DMARDs or conventional synthetic DMARDs [57,58]. Since B cell activation induced by IL-4 via JAK signaling aggravates experimental asthma, several clinical trials have highlighted recently the potential therapeutic benefits of inhaled JAK inhibitors in asthmatic patients [59,60].

3.3. Biological DMARDs

Biological DMARDs (bDMARDs) act extracellularly, and the molecular weights of bDMARDs greatly exceed the molecular weights of the substrates of P-gp which are ranged 300–2000 Da [61]. Therefore, bDMARDs inhibit lymphocyte activation without being affected by P-gp [8]. TNF antagonists and IL-6 blockers inhibit B cell trafficking towards inflammatory sites in RA [62]. The former group of agents also reduces P-gp expression on B cells in RA patients [6–9].

The use of TNF antagonists for the treatment of refractory RA with organ involvement is reported to result in elimination of P-gp⁺CXCR4⁺CD19⁺ B cells with subsequent control of the pathological process [9]. On the other autoimmune diseases, the clinical response to TNF antagonists in patients with
inflammatory bowel diseases (IBD) is reported to be obtained through the effects to B cells. The IL10-producing B cells of both ulcerative colitis and Crohn disease patients were reduced compared with those in healthy control patients and detected a significant increase in responding patients after treatment with infliximab, a TNF antagonist [63].

IgD$^{+}$CD27$^{-}$ B cell and activated B cell subsets in reported to be predominant in peripheral blood of sarcoidosis patients [64]. Treatment of patients with CNS sarcoidosis unresponsive to immunosuppressants, using infliximab resulted in improvement in imaging and clinical findings [65]. Other studies also reported the clinical benefits of tocilizumab, an IL-6 blocker, in RA patients, which induced/expanded B regulatory cells [66], and in SLE by restoration of B and T cell homeostasis, together with normalization of abnormal B and T cell subsets [67]. We analyzed the changes in P-gp expressions on B cells in RA patient responding to tocilizumab therapy. The RA patient with microscopic polyangiitis was treated with high-dose corticosteroid and intravenous cyclophosphamide pulse therapy during a period of 3 months but showed exacerbation of RA disease activity to DAS28 of 5.3 by prednisolone (PSL) tapering to 25 mg/day. She showed accumulation of peripheral P-gp$^{+}$CXCR4$^{+}$ B cells and P-gp$^{+}$IgD$^{+}$ B cells (Figure 4(A)). The treatment was switched to tocilizumab, in addition to oral PSL, and resulted in significant fall in peripheral P-gp$^{+}$CXCR4$^{+}$ B cells and P-gp$^{+}$IgD$^{+}$ B cells within 4 weeks (Figure 4(B)), together with improvement of synovitis to DAS28 of 3.6 and tapering to 15 mg/day of PSL and without relapse of microscopic polyangiitis. Treatment of patients with systemic lupus erythematosus (SLE) using tocilizumab resulted in inhibition of B cell differentiation and suppression of peripheral plasma cell compartments [68]. These findings were assumed to be mediated through downregulation of P-gp expression on activated B cells since tocilizumab blocks IL-6 as the P-gp inducer [23]. Tocilizumab was also found to reduce plasmablasts in peripheral blood, AQP4-IgG titers and relapse activity in at least some patients with neuromyelitis optica (NMO) who showed activation of B cells accompanied by production of AQP4-reactive IgGs [69].

Another B cell depletion therapy is the use of anti-CD20 monoclonal antibody (e.g. rituximab). This treatment is largely designed to deplete CD20$^{+}$ B cells, including pre-B cells, immature B cells, IgD$^{+}$ native B cells and memory B cells and results in impaired generation of CD20-plasmablasts and low titers of autoantibodies, such as rheumatoid factors and anti-citrullinated protein/peptide antibodies [70,71]. Adlowitz et al. [72] reported that RA patients who received B cell depletion therapy showed marked reduction of B cells-TNF
production and that such reduction correlated with reduction in memory B cells. B cell depletion and reconstitution may lead to improvement in immune complex-dependent synovitis by reduction of autoantibody production, and also long-term remission by reduced populations of pro-inflammatory activated B cells. Treatment with rituximab has been reported to be efficacious also in corticosteroids-resistant patients with pulmonary sarcoidosis, neurosarcoidosis and refractory NMO [64,73].

3.4. CXCR4 antagonists

CXCR4 antagonists significantly suppress delayed-type hypersensitivity induced by sheep red blood cells, and significantly reduce disease severity experimental collagen-induced arthritis in mice. The use of CXCR4 antagonists could be useful for RA-associated interstitial pneumonia. CXCR4 antagonists have been reported to significantly decrease dissemination of diffuse large B cell lymphoma (DLBCL) and suppress pulmonary metastasis from breast cancer and melanoma cells in mice [35,74]. CXCR4 antagonist synergistically enhanced the anti-proliferative/pro-apoptotic effect of rituximab on DLBCL cells and was suggested to improve treatment outcome for DLBCL patients [75]. CXCR4 antagonist ameliorated colonic inflammation in murine experimental IBD including DSS-induced colitis and IL-10 KO, accompanied by reduction in TNF production from mesenteric lymph node cells [76].

4. Conclusion

P-gp⁺CD19⁺ B cells that co-express CXCR4 and IgD are pro-inflammatory activated B cells that play a pathological role in the development of destructive arthritis with extra-articular involvement and the acquisition of P-gp-mediated multidrug resistance. Accordingly, measurement of the percentage of peripheral P-gp⁺CXCR4⁺IgD⁺CD19⁺ B cells may help in the recognition of drug resistance and disease severity, and help in the design of new treatment modality for RA patients with highly active disease.

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