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Immunotherapeutic Approaches of Rheumatoid Arthritis and the Implication on Novel Interventions for Refractoriness

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Abstract

Rheumatoid arthritis is an autoimmune disorder involving the chronic inflammation of affected joints which lead to the distortion and eventually destruction of the articular tissues. Clinically, many therapeutic methods are being used for RA treatment. Non-steroidal anti-inflammatory drugs (NSAIDs), steroid, and disease-modifying anti-rheumatic drugs (DMARDs) are the three main categories of intervention approaches. Among which DMARDs, targeting mainly the release of pro-inflammatory cytokines, demonstrated high efficacy because of its direct drug action that alter the underlying disease mechanisms rather than simply to mediate symptoms relieve. However, the use of DMARDs also accompanying some unwanted adverse side effects, in particular, the development of refractoriness, which hampers the successful rate of treatment. In this chapter, the conventional RA drugs will be reviewed, focusing on the currently used and latest development of DMARDs. Novel methods that could improve RA pathogenesis will also be introduced. Because of the critical role of refractory RA, the progress of the disease to develop resistance to standard drug treatment will also be described. Finally, innovative RA therapeutic methods inspired by researches concerning the pathogenesis and contemporary treatments of RA will be discussed.

Keywords: rheumatoid arthritis, DMARDs, refractory, immunotherapy, immunosuppressive

1. Introduction

Around 0.5–1% of the world population is challenged by rheumatoid arthritis (RA) with patients afflicted by progressive articular destruction accounting for the commonest chronic systemic autoimmune disorder [1, 2]. RA is demonstrating prevalence in developed countries or urban areas [3] and is around three times more commonly found in female [4]. Apart from persistent synovitis, structural bone damages, and the eventual deformity of affected joints, 40% of the RA patients are also accompanied with extra-articular manifestations in multiple organs including kidney (glomerulonephritis), heart (atherosclerosis), and skin (small vessel vasculitis) [5, 6] critically compromising the quality of life [7]. Owing to the comparatively early disease onset (at the age between 30 and 50) [8], RA also implied increased individual and socioeconomic impact as a result of reduced work capacity and early unemployment [9–11].

Thus far, the etiology of RA is unclear and curing strategy is lacked. Environmental and genetic factors are considered as the main causes of increased risk of RA. Smoking is the strongest environmental stimuli that trigger the onset of RA. Both cohort and case-control studies demonstrated that the number and duration of cigarette consumption is positively correlated to RA risk in a dose dependent and irreversible manner [12, 13]. By contrast, the use of alcohol significantly reduced RA susceptibility in habitual drinkers when compared with non-drinkers or individuals consuming low level of alcohol [14, 15]. In the case of smoking-induced RA, the involvement of polymorphisms in genes mechanistically regulating the immunity, such as the human leukocyte antigen-DRB1 (*HLA-DRB-1*)-encoded type II major histocompatibility complex (MHC), is critical to more than half of such condition [7]. Of note, some of the disease-associated polymorphic variants of HLA-DRB-1 are specific to severe disease phenotypes, for example, more aggressive erosive disease and higher mortality [16]. Genetic involvement in RA is also suggested by the existence of shared epitope of RA-associated circulatory autoantibodies such as the IgG rheumatoid factor (RF) and antibodies recognizing the citrullinated peptide [7]. Although not all RA patients are positive for IgG- and citrullinated peptide-recognizing autoantibodies, the heritability rate of RA is approximately 40–65% for seropositive rheumatoid arthritis, and 20% for seronegative disease [17, 18].

The pathogenesis of RA is as complicated as the causation of the disorder, conventional therapeutic methods is not confined to the application of single pharmaceutical intervention. Instead, personalized treatment algorithms with the combinational use of different RA medications are required, which is highly dependent on individual patient and the stage of disease progression. Generally the drug used for RA can be classified into three categories: (1) non-steroidal anti-inflammatory drugs (NSAIDs); (2) glucocorticoid (steroid); (3) non-biological (synthetic origin)/biological disease-modifying anti-rheumatic drugs (DMARDs). The therapeutic effects of NASIDs like aspirin and Coxibs targeting the cyclooxygenase pathways, together with glucocorticoid acting via the cortisol receptor, are rapid which effectively alleviate the analgesic, pyretic, and inflammatory symptoms associated with RA [19, 20]. However, the effects of NASIDs are limited to symptoms relief and demonstrated no significant delaying effect on disease progression [21]. Glucocorticoids can slow down the progress of bone erosion resulted from cytokines-induced imbalance of local bone turnover under long-term treatment

with low dosage [22]. Unfortunately, the extensive side effects affecting the different organs outweighed such beneficial immunosuppressive property. As such, therapeutic compounds, for example the treat-to-target DMARDs, which control the inflammatory and destructive processes of RA is inevitable to the maintenance of persistent remission. Since, DMARDs is slow-acting drug which take 1 month to a year to be effective [23], NSAIDs/glucocorticoid are usually applied together with DMARDs to serve initially as moderator of pain and stiffness before the drug action of DMARDs commence.

Many DMARDs have previously been reported targeting various cellular signaling molecules or receptors related to the immunoregulatory machinery of RA. In this chapter, the currently employed, as well as newly exploited DMARDs will be described. The latest therapeutic strategies that can potentially be applied to RA intervention will also be updated. Eventually, insight provided by such methods that could innovate novel RA therapeutic development will be discussed.

2. Innate and adaptive immunity in the pathogenesis of RA

Inflammation and swelling of the synovial membrane, or synovitis, are the pathological features of RA. Both the innate and adaptive immunity are participating the disease pathogenesis through the orchestration of cellular communication between the two systems. The pathogenesis of RA is heterogeneous (**Figure 1**) and the exact triggering factors of the inflammatory
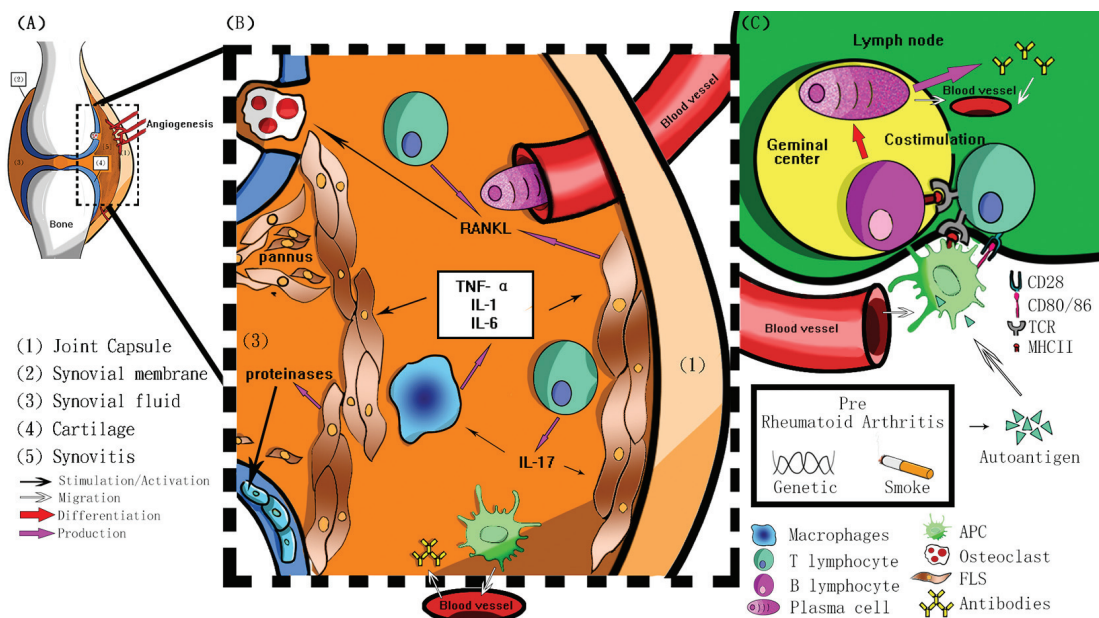
Figure 1. Cellular and molecular pathogenesis of RA: (A) Gross anatomical structure of the inflamed joint of RA. (B) The inflammatory synovium with cytokine signaling and cellular interactions underlying the RA pathogenesis indicated. (C) The involvement of lymph node in orchestrating the activation of immunocellular components involved in RA progression. TCR: T cell receptor; APC: Antigen presenting cells; FLS: Fibroblast-like synoviocyte; MHCII: Major hoistocompatibility complex class II.

response at the diseased joint are still unclear. In the inflammatory milieus, the synovial macrophages (SM) positioned at the cartilage–pannus junction is activated to secret the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1, and 6 (IL-1/IL-6). In fact, findings suggested that the SM are the key regulator of RA inflammation [24]. These cytokines then activate another important residential cell type, the fibroblast-like synoviocytes (FLS), in the synovium leading to hyperproliferation and the consequential formation of an abnormal layer of fibrovascular tissue called pannus. The pannus expresses the cytokine receptor activator of nuclear factor kappa-B ligand (RANKL) which together with the macrophage-released cytokines, stimulate the differentiation of osteoclast [25] to resorb the calcified bone matrix (i.e. bone erosion) via the secretion of acid and hydrolytic enzymes such as cathepsin K and matrix metalloproteinase-13 (MMP-13). In addition, the activation of FLS in pannus generates proteinases that are correlated to the destruction of cartilage [1, 26]. The activated FLS also migrate to other unaffected joints and induce inflammatory responses and bone and cartilage destruction [27].

Infiltrated antigen-driven CD4$^+$ lymphocytes and plasma cells (c.a. 50% and 5% of lymphocytes found in synovium, respectively) are also found in the inflamed joints. The RA joints are highly vascularized due to the inflammation-induced angiogenesis, and that the newly generated blood vessels facilitate the infiltration of the lymphocytes from the periphery. In the synovium, CD4$^+$ lymphocytes secreted a repertoire of cytokines, including IL-17, which further stimulate the expression of inflammatory mediators from SM and FLS supporting the persistent inflammatory environment of the affected joints. The plasma cells also involve in such process by the secretion of different cytokines. One of the activation routes of the infiltrated CD4$^+$ lymphocytes and plasma cells is via the cell-cell interaction with the antigen presenting cells (APC), for example dendritic cells (DC). Environmental factors, like smoking and genetic abnormalities and chronic inflamed RA tissues can induce the modification, including citrullination, of autoantigens, such as citrullinated self-proteins of vimentin, alpha-enolase, fibronectin, and type II collagen [28], which activated the APC to generate the surface MHC-peptide complex. The autoantigen-activated APC migrate to the secondary lymphoid organs (SLO) and stimulate the maturation of CD4$^+$ T lymphocytes via the MHC-peptide complex and co-stimulatory molecules, such as CD80/CD86, on the cellular surface [29]. B lymphocytes in the germinal center are then co-stimulated by the mature CD4$^+$ T lymphocytes to become plasma cells which produce the destructive autoantibodies, such as RF and anti-citrullinated protein antibodies (ACPAs) [30, 31]. These CD4$^+$ T lymphocytes, plasma cells, and autoantibodies eventually return to the RA joints mediating the destructive process of bone and cartilage and underpinning the chronic inflammatory response.

3. Conventional and current development of DMARDs for RA treatment

The intricate interaction between the immunocellular components during RA progression suggested that the effective regulation targeting the signaling mediators of such cellular communication or the physiology of the involved immune cells appeared as the key to successful RA therapy. Several FDA-approved DMARDs, for example Methotrexate, TNF antagonists,

Rituximab, and Tocilizumab, which modify the biologic responses are extensively used as immunotherapy for preventing immune attacks associated with RA in clinical settings.

3.1. Methotrexate (MTX)

MTX is among the quickest-acting DMARDs and represent the mainstay of DMARDs therapy. As a non-biologic DMARDs, MTX is produced through chemical synthesis which is structurally analogous to folate inhibitory targeting the dihydrofolate reductase (DHFR) [32] which is critical to the *de novo* synthesis of purine and pyrimidine, therefore, downregulate cellular proliferation and induce apoptosis. MTX-induced inhibition of DHFR also leads to the generation of resultant polyamines which is accumulated and converted into toxic ammonia and hydrogen peroxide by synovial mononuclear cells in RA patients functionally suppressing the stimulated T lymphocytes [33]. As expected, MTX suppress the proliferation and inhibit the turnover of inflammatory cells during RA treatment [34]. However, the mechanism of action of MTX is complex which is not merely mediated through limiting the growth and survival of the immunocellular components. MTX also target and inhibit 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leading eventually to the increased intra and extra-cellular levels of adenosine [35, 36], which contributed significant to adenosine-induced immunosuppression [37] as demonstrated by the inhibition of phagocytosis, secretion of TNF, IFN, IL2, IL12, expression of HLA expression, etc. [38–43]. Findings also evident the indirect anti-inflammatory and inhibited neutrophil chemotaxis effects of MTX signaling via the cyclooxygenases-2 (COX-2) and lipoxygenase pathways [44–46]. In the synovial tissue, MTX also indirectly inhibit the synthesis of metalloproteinase (MMP) and activate tissue inhibitor of MMP (TIMP) via cytokines (IL-1) modulation [47].

3.2. Tocilizumab (TCZ)

The monoclonal antibody TCZ, together with TNF and CD20 antagonists [48] which will be discussed later, represented the subcategory of biologic DMARDs, is produced through genetic engineering as contrast to the chemically synthesized non-biologic counterpart. The biologic DMARDs exhibit their therapeutic effect in a treat-to-target manner by modulating the various molecular pathways signaling the dysregulated immunity. As the first of its kind, TCZ specifically target the IL-6 receptor (IL-6R) by functioned as an antagonist [49] and is usually used when conventional treatment (e.g. MTX) [50, 51] and other biologic DMARDs (e.g. TNF antagonists) become irresponsive or tolerated [52]. However, TCZ also works with high efficacy when applied as monotherapy in early disease [53]. In the course of RA pathogenesis, serum and synovial tissue levels of IL-6 is elevated and is positively correlated to RA disease severity and radiological joint damage [54–57]. Mechanistically, IL-6 coupled with IL-6R triggering the Janus kinase (JAK) pathways [58] and activates the downstream effector functions of the different RA-associated immune cells. For example, IL-6 stimulates the plasmablasts to produce autoantibodies [59] and significantly regulates the differentiation process of T lymphocytes by enhancing T helper 17 (Th17)/regulatory T lymphocytes (Treg) balance skewed toward the Th17 profile [60]. In addition, IL-6 are involve in the proliferation and

production of MMP of FLS [56, 61] and differentiation of osteoclast [62], which lead to cartilage damages and bone resorption. TCZ can downregulate these RA-associated cellular responses by interacting with the IL-6R. New findings suggested that the therapeutic effects of TCZ can be mediated by lowering the serum level of IL-6, however, the underpinning mechanisms are yet to be defined [63].

3.3. TNF antagonists

Infliximab, etanercept, and adalimumab are the currently approved TNF antagonists being used clinically in RA treatment [23]. These type of DMARDs are sharing similar efficacy as MTX exhibiting rapid drug response [64, 65]. When compared with MTX, the mechanism of action of these inhibitors are more specific which target to the tumor necrosis factor receptor type 1 and 2 (TNFR1/TNFR2) signaling pathways mediated by the cytokine tumor necrosis factor-alpha (TNF-α) [64, 65]. Cells with monocytic origin are the main cellular components producing TNF-α [66], however, other immune cell types , for example lymphoid and mast cells, has also been reported to participate the secretory process [23]. During the course of RA pathogenesis, TNF-α serves as a strong chemoattractant for the tethering of neutrophils to the endothelial cells [67]. Also, TNF-α is the central regulator of the immunity which autocrinally and paracrinally repress the expression of other cytokines, such as IL-1, IL-6, IL-8, and granu-locyte colony-stimulating factor (G-CSF) [68]. Therefore, the blockage of TNF signaling with the use of TNF antagonists can molecularly suppress the pro-inflammatory progression of RA in a systemic sense. The three TNF antagonists are recombinant monoclonal antibodies that function by binding either to TNF-α (infliximab) or the corresponding receptor (etanercept and adalimumab). Clinically, the use of TNF inhibitors in conjugation with MTX at the initial stage of RA is associated with rapid disease remission [69].

3.4. Rituximab (RTX)

Similar to TCZ and TNF antagonists, RTX is a chimeric monoclonal antibody recognizing the antigen CD20 which is a transmembrane receptor expressed on the surface B lymphocytes during differentiation from the pre-B cell to memory B cell stages [70, 71]. As previously mentioned, B lymphocytes are contributing to the development of RA via the production of autoantibodies. The B lymphocytes also produce a spectrum of pro-inflammatory cytokines, including IL-6, IL-16, TNF-α, and lymphotoxin-β (LT-beta) [72, 73], which are pivotal to the perpetuation of inflammatory environment aggravating joint damage. Therefore, the use of RTX to deplete CD20$^+$ B lymphocytes suggested an effective therapeutic strategy for RA. The antibody binds to the cell surface protein CD20 and induces cell death toward the targeted B lymphocytes via three potential pathways: (1) Antibody dependent cell-mediated cytotoxicity (ADCC) which stimulates phagocytosis and cell lysis of CD20$^+$ lymphocytes by the binding of immunocellular components, such as macrophages, monocytes, and natural killer cells, via the Fcγ region of RTX [74, 75]; (2) Complement dependent cytotoxicity (CDC) by inducing mem-brane attack toward CD20$^+$ B lymphocytes resulted in cell lysis via the formation of rituximab-complement (C1q) complexes [76]; (3) Direct promotion of CD20$^+$ B cell apoptosis [77]. It is worth noting that, CD20 neither present on stem cells nor the antibody-secreting plasma cells which enhance the safety of the practical application of RTX. Although the monoclonal antibody

is approved for use in combination with MTX, current study reported that RTX is efficient and safe for managing RA patients without the presence of MTX [78].

3.5. The development of novel DMARDs

The mentioned FDA-approved DMARDs (both biologic and non-biologic) are demonstrating profound effects in RA intervention. Owing to the chronic nature of RA, however, patients are subjected to prolonged exposure of DMARDs resulted in the development of side effects and drug resistance. For the use of MTX, hepatic fibrosis or cirrhosis is one of the most severe side effects affecting the patients [33]. Skin and soft tissue infections and abnormal liver function are observed in patients treated with TCZ [53]. TNF antagonists have been reported to associate with adverse responses such as serious bacterial and opportunistic infections, and lymphoma [79–81]. RTX treatment is also plagued by severe skin reaction and infection [23]. Accordingly, researchers have been making efforts to improve the toxicity of classical DMARDs and to exploit of newer anti-rheumatic agents.

In 2007, a polypeptide-based novel TNF antagonist with amino acid sequence isolated from part of the pre-ligand assembly domain (PLAD) has been patented [82]. In the extra-cellular region of TNFR, PLAD is located at the position NH_2-terminal to the ligand binding domain essential for inducing receptors trimerization. The binding of the synthetic polypeptide to PLAD elicit inhibition to the formation of functional receptors complex and repress the down-stream signaling thereof. Such therapeutic peptide inhibitor is recognized by the immune system as "totally-self" and is highly specific instead of blocking immunocomponents in a global sense, therefore, avoiding undesirable immune reactions minimizing the appearance of potent adverse side effects [83]. A patent application of another 18-residue peptide targeted the secretory phospholipase A2 (sPLA2) has also been filed [84]. As a pro-inflammatory mediator, sPLA2 is found to be related to the onset and severity of RA in animal [85] and patients [86], respectively. The neovascularization process which is critical to the RA-associated hyperplasia of synovial tissue has been suggested as therapeutic target for the development of novel DMARDs as well. The cytokines that are significantly responsible for new blood vessel out-growth is vascular endothelial growth factor (VEGF) which also participates to vascular leakage [87]. VEGF inhibitory compounds, such as derivatives of quinazoline [88, 89], have been synthesized and can potentially be used for RA treatment. There are still many others new DMARDs, for example, the colony-stimulating factor (CSF) inhibitors, which target the key regulator of neutrophil production [90, 91]. All these compounds are potentially new therapeutic strategy with high efficacy and improved adverse effects. Investigation of the combinational use of these compounds with the classical DMARDs will also encourage the discovery of formulation against refractory RA for patients who respond poorly to conventional interventions.

4. Next-generation immunosuppressive strategies

In general, the described DMARDs directly inhibit the pro-inflammatory signaling molecules and their receptors. The ligand-receptor interaction is circumvented by the use of monoclonal

antibodies, synthetic peptides, or natural compounds. These therapeutic strategies tune down the cytokines machinery of the targeted cells or manipulate the cells that produce the cytokines lead eventually to RA remission. Theoretically, any immunosuppressive methods, not limited to interfering the ligand-receptor interaction process, can result in therapeutic effects toward RA and innovate the development of RA treatment.

4.1. Sphingosine-1-phosphate receptors (S1PRs) agonist

Antagonizing the recruitment of immunocellular components to reach the site of inflammation provided a clue to RA treatment. Chemokine receptors such as CCR5 and CXCR3 are playing significant roles in RA pathogenesis via the regulation of monocyte and T lymphocyte chemo-taxis [92, 93]. The use of inhibitors against these receptors has shown therapeutic efficacy toward RA treatments [94, 95]. Instead of blockage of immune cells from entering the inflammatory site, to enhance the homing of these cells could be another approach for controlling the inflammatory status of RA joints. Fingolimod (FTY720), an analog of sphingosine-1-phosphate (S1P) extracted from a vegetative wasp composed of the fruiting bodies of *Isaria sinclairii* and its parasitic host larva [96], is able to deplete lymphocytes from the circulatory and lymphatic systems [97, 98]. The mechanism of action involves the formation of phosphorylated FTY720 (FTY720-P) by sphingosine kinase 2 which agonistically stimulates the sphingosine-1-phosphate receptors (S1PRs). Located on the surface of lymphocytic cells, S1PR is internalized upon interaction with FTY720-P inhibiting lymphocytes egress from the secondary lymphoid tissues and thymus (lymphopenia). As such, the FTY720-treated lymphocytes are sequestrated in the lymph nodes, spleen, and thymus, which are not able to recirculate to peripheral inflammatory tissues. In fact, the migration of other immune cells are also regulated by the S1P-S1PRs axis, for example, dendritic cells (DCs) [99] and macrophages [100]. FTY720 is originally used for allotransportation to induce long-term graft acceptance [101] reflecting the pharmaceutical value of the immunosuppressive property of the compound. In fact, FTY720-induced lymphopenia has been proposed as a new therapeutic approach for RA as demonstrated in the adjuvant-induced arthritis (AIA) rat [102]. In a recent animal experiment using the collagen-induced arthritis (CIA) model, it was revealed that the migration profile of DCs is also modulated by FTY720 and is responsible for the beneficial effects of the treatment [103]. Most importantly, the normal function of the immune cells is preserved after FTY720 treatment [100, 104], suggesting the safety and practicality in the application of the compound.

4.2. Dendritic cell (DCs)-targeted therapeutics

As a key regulator of both the innate and adaptive immunity, DCs in the inflamed synovial tissues of RA plays a significant role in the pathomechanism. In RA patients, DCs are activated in response to pro-inflammatory cytokines stimulation, with up-regulated co-stimulatory molecule expression [105]. DCs also induce the differentiation of Th1 and Th17 cells via production of IL-12 and IL-23 [106]. Also, treatment with TNF-α inhibitors could reduce the number of activated DCs and inhibits its maturation, leading to improvement of the clinical symptoms of RA [107]. These observations support the strategy of targeting DCs for the treatment of RA. Accordingly, DCs with tolerogenic function has been proposed as therapeutic tool for RA

treatment, which specifically targets the pathogenic autoimmune response and simultaneously maintain the integrity of protective immunity [108]. In a randomized, unblinded, placebo-controlled, dose-escalation phase I study, tolerogenic DC therapy demonstrates promising results in RA patients without major adverse effects. However, administration of tolerogenic DC therapy should ideally be given to RA patient as early as possible, to avoid the establishment of autoimmunity desensitizing the RA treatment [109].

4.3. Manipulation of neuroimmune communication

The reciprocal effects of the nervous system on immunity have attracted high focus. The nervous system regulates inflammation via a variety of neurotransmitters, neuropeptides, and peripheral nerves. In general, activation of sympathetic nervous system may exhibit both pro-inflammatory and anti-inflammatory properties, whereas the para-sympathetic nervous system via the vagus nerve, exerts anti-inflammatory actions [110]. Subsequent research has identified the neuronal type $\alpha 7$-acetylcholine (Ach) receptor is necessary to regulate the anti-inflammatory effects mediated by the para-sympathetic nervous system [111]. Interestingly, the $\alpha 7$-ACh receptors are also widely expressed in immune cells and FLS [112, 113]. TNF-α expressed by the residential macrophages in spleen located in the red pulp and marginal zone can be repressed via the stimulation of vagus nerve mediated by nicotinic acetylcholine receptor subunit $\alpha 7$ [114]. Accordingly, administration of a specific $\alpha 7$-ACh receptor agonist showed effective inhibition of systemic inflammatory responses in CIA models [115, 116]. In animal models of neurological disorders, peripheral denervation suppressed joint inflammation in mice with AIA has also been demonstrated [117]. Recently a clinical trial consolidated that vagal nerve stimulation (VNS) could be therapeutically feasible in RA. VNS refers to the technique of manually or electrically stimulates the vagus nerve, which has been approved more than a decade ago by the FDA for the treatments of severe and recurrent unipolar and bipolar depression [118], as well as pharmaco-resistant epilepsy [119]. The potential use of VNS for insomnia, anxiety, etc., have also been reported [120]. Clinical relevance of VNS in RA was debuted in 2012 in which a volunteer patient with surgically implanted pacemaker-like nerve stimulator successfully halted the joints attack with remarkable symptoms recovery [121]. It was proved to be a result of VNS-stimulated inhibition of peripheral blood production of TNF, IL-1β, and IL-6 in a later clinical study [122]. Such achievement posited the alternative use of computerized device in RA treatment as compared to the traditional biological or chemical pharmaceutics

4.4. Cell-based therapy

The modulation of disease pathogenesis by the delivery of cellular materials to patients has been proposed as promising intervention method for many incurable conditions [123]. The application of mesenchymal stem cells (MSCs) is the prototype among the various types of cell-based therapy, which illustrated another possibility of managing RA without using the biological or chemical pharmaceutics. MSCs are capable of bypassing the sanction of immune system upon transplantation [124, 125] conferring the practicality *per se* to act as potential allograft by abolishing the concomitant requirement of immunosuppressant drugs. A recent

randomized, single-blind, placebo-controlled phase Ib/IIa clinical trial has been established to evaluate the safety and tolerability of intravenously administrating the Cx611, a preparation of allogeneic expanded adipose-derived MSCs (eASCs), in patients with refractory RA [126]. Results demonstrated that patients were having good response and generally well tolerated the infused Cx611 without evidence of dose-related toxicity at the dose range and time period studied. The precise mechanisms mediating the beneficial effects of Cx611 is not clear, it could be associated with the interruption of T lymphocytes and SLF pathophysiology including inhibited cellular proliferation and inflammatory cytokines production, enhanced generation of anti-inflammatory cytokines, and antigen-specific T lymphocytes [127–129]. The allogeneic nature of Cx611 in this study circumvents the limitation of using patient-specific clinical grade stem cell product with unstable availability during manufacture making itself an "off-the-shelf" therapeutic product [130]. Provided that, the isolation and expansion procedures of MSCs are comparatively easy, which further secured their supply during immediate need [123]. On top of that, the limited replicative lifespan of MSCs provided additional safety by avoiding the formation of unwanted malignancy [123].

5. From intervention to innovation: Implication of conventional and emerging RA therapies on the exploitation of novel immunosuppressive strategies against refractoriness

Conventional DMARDs, both the non-biologic and biologic types, are able to achieve clinical remission or reduce disease activity status for RA. Nevertheless, the unmet need in the treatment of RA remains high because of substantial number of RA patients do not response sufficiently to the currently available regimens. Therefore, remission of disease is not always achieved and refractory cases are very common [131, 132]. The causes of refractory RA are multifaceted varying depend on individual, patient-tailored management approach is presented to determine whether persistence of signs and symptoms is based on the inflammatory disease activity, and the role of comorbidities [133]. Owing to the complexity in etiology of refractory RA, it is difficult to summarize a single picture that can comprehensively depict the underpinning cellular responses and molecular pathways. Here in this section, some of the possible causative factors that may responsible for the development of resistance against standard RA treatment are to be listed. Ingenious intervention methods for refractory RA as inspired by the increasingly understanding of the disorders will also be discussed.

5.1. P-glycoprotein (P-gp)-mediated drug resistance

P-gp, also known as multidrug resistance protein 1 (MDR1) or CD243, is an important membrane pumps for the cellular removal of foreign substances. In patients with refractory RA and high disease activity, overexpression of P-gp on lymphocytes can cause resistance to anti-rheumatic drugs through efflux of intracellular drugs [134]. Recent studies further showed that high expression level of P-gp found in FLS of refractory RA patients is the potential mechanism for multidrug resistance in RA treatment [135]. Also, activated B lymphocytes with elevated P-gp expression seems to be associated with drug resistance, disease activity, and

destructive arthritis with extra-articular involvement in RA [136]. Overcoming drug resistance by using P-gp inhibitor could sensitize the response to DMARDs in patients with refractory RA further support the role of P-gp in the development of refractoriness [137].

5.2. Autoantibodies-mediated refractoriness

Although the direct association of autoantibodies and refractory RA is enigmatic, RA patients with more severe disease and a worse prognosis are seropositive for RF and ACPAs [138, 139]. Patients with unsatisfactory responsiveness toward conventional DMARs, in particular MTX, resumed clinical improvement after TNF antagonists treatment through the manipulation of autoantibodies level, which represent a promising therapeutic method for refractory RA to other treatment options [140–142]. In a one-year prospective study with the use of adalimumab (monoclonal anti-TNF-α antibody), MTX-resistant patients are clinically benefited from the treatment in terms of decreased tender/swollen joint counts, erythrocyte sedimentation rate, and C-reactive protein values associated with RF and ACPAs titer reduction [143]. Treatment using another monoclonal antibody infliximab against TNF-α also demonstrated clinical efficacy toward patients who do not respond to DMARDs by decreasing the serum levels of RF and ACPAs [144]. Of note, the efficacy of TNF antagonists is correlated to the titers of both RF and ACPAs. The higher the autoantibodies titer, the lower is the clinical response of the anti-TNF-agents [145]. These findings strongly suggested that autoantibodies generation during the course of RA pathogenesis may lead to the progression to refractoriness.

5.3. Role of cytokines in refractory RA development

Regardless the profound effects of TNF antagonists in refractory RA treatment, many patients either do not respond or relapse after initially responding to these agents [146]. Recent study revealed that the responsiveness of anti-TNF-α agents in RA patients depend on high blood level of granulocyte–monocyte colony-stimulating factor (GM-CSF) and low blood level of IL-17. Circulatory lymphocytes from most anti-TNF-α responder patients produced higher levels of GM-CSF than non-responder patients, whereas non-responsiveness to anti-TNF-α is associated with high IL-17 levels suggest that the responsiveness of TNF-α inhibitors is likely to be driven by different inflammatory pathways [146].

5.4. Current drugs and therapeutic approaches for refractory RA

As MTX is the first-line and frequently used DMARD, it is one of the most studied compounds for RA therapy. Information concerning the development of and the method to overcome drug resistance of MTX is well documented. Only about 40-60% of RA patients compromise with the MTX monotherapy [147]. Combination therapeutic approaches are commonly adopted and found effective in clinic, especially with MTX combined with other anti-arthritic agents. For instance, CsA, sulfasalazine, LEF, doxycycline, and HCQ individually combined with MTX demonstrated good efficacy in clinic, whereas triple DMARD therapy (MTX-sulfasalazine-chloroquine) and step-up combination of four DMARDs (MTX-CsA-HCQ-prednisone) are also applied in clinical treatment of RA [147–149]. However, a new synthetic small-molecule DMARD called iguratimod was recommended to treat RA patients who showed inadequate response to

MTX-CsA-HCQ-prednisone treatment [147]. Another immunosuppressive drug, tacrolimus (TAC) was found to be a promising therapeutic option for refractory RA patients despite treatment with anti-TNF therapy combined with methotrexate [150]. Later study further demonstrated the new oral triple combination therapy using TAC with MTX and mizoribine (MZR), this oral triple therapy might be safe and economical for clinical practice in effective against refractory RA [151]. Unfortunately, combination therapy is not always working and drug-resistant cases are still commonly found in refractory RA patients [147]. Therefore, the search of novel therapeutic strategies to combat refractoriness of RA is still urged.

5.5. Innovative therapeutic strategies for refractory RA with clinical potential

As mentioned in the earlier section, the use of monoclonal anti-CD20 antibody RTX is one of the approved conventional therapeutic methods for RA for the co-treatment with MTX. A randomized, double-blind controlled clinical trial indicated the potent efficacy of low dose RTX in RA refractory to first-line DMARD, MTX [148]. In addition, a recent clinical study has evaluated the impact of RTX on patient-reported outcomes (PROs) in a US-based observational cohort of patients with active RA refractory to TNF-α antagonist. Results demonstrated that patients with long-standing refractory RA experienced improvements in PROs 1 year after initiating RTX [152]. Another clinical study further revealed that RTX-based B cell depletion therapy is effective in refractory RA and systemic lupus erythematosus (SLE) [153]. Together with the role of CD20$^+$ plasma cells in autoantibodies production, deletion of B lymphocytes with specific identity of surface antigen appeared to be a prominent therapy for tackling refractory RA. In 2017, a new kind of immunotherapy, namely chimeric antigen receptor (CAR)-T cell therapy, has been approved by FDA for the cancers of acute lymphoblastic leukemia and advanced lymphomas [154], which provide insight to the exploitation of novel tool for B lymphocytes removal. The concept of CAR-T cell therapy involves the genetically engineering of autologous T lymphocytes to express a chimeric antigen receptor of target. Accordingly, expressing the CAR that recognized CD20 for RA therapy, in principal, can preserve the same effects as monoclonal anti-CD20 antibody. Another surface antigen CD19 has also been suggested as a promising marker for targeting B lymphocyte in RA [155] , which can also serve as another CAR-T cell therapeutic target. The humoral responses of B lymphocytes isolated from RA patients are repressed by the administration of the monoclonal anti-19 antibody XmAb5871 which facilitate the engagement of CD19, B cell antigen receptor, and Fcγ receptor IIb inhibitory receptor [156]. When compared with the passive administration of monoclonal antibody, CAR-T cells are benefited from its tissue biodistribution property because of their extravasate capacity [157], active responses to chemokine signaling [158], and the secretory ability of proteolytic enzymes [159]. Also, the self-amplification property of CAR-T cells enhance their *in vivo* persistence after adoptive transfer [160, 161].

On the other hand, the therapeutic effects toward RA by S1P-induced lymphopenia and VNS suggested the development of intervention methods by means of systemic regulation of the immunity. Intriguingly, the gut-associated lymphoid tissue (GALT) represent the largest mass of lymphoid tissue in the human body, which is an immune hub intimately communicating with

residential microbiome to maintain the homeostatsis of different organs [162]. The involvement of gut microbiome in the systemic dysregulation of host immunity in different disease as a result of disturbed phyletic distribution or amount in the gut environment has aroused tremendous attention. Evidence associating gut microbiome and RA has recently been documented based on the characterization of the expansion of rare lineage intestinal microbes in RA [163]. Also, a metagenome-wide association study (MGWAS) suggested that the dysbiosis of gut microbial detected in RA is associated with clinical indices, which can be partly normalized after DMARDs treatment [164]. These information tempted us to ask if the application of pharmaceutic or health care supplement which manipulate the microbiome physiology could be potential RA therapeutic approach for providing more effective treatment with fewer side effects [165]. Chinese herbal medicine (CHM) appeared to be an ideal pharmaceutical method accordingly, since the philosophy of traditional Chinese medicine (TCM) emphasized on the maintenance of holistic balance of the human body which is best fit to the idea of managing local inflammation via the regulation of systemic immune system. In addition, CHM is natural constituents of herbal plant, and have been used for centuries, which is comparatively safe for clinical trial. In China, the country with wide application of CHM, medicinal compounds extracted from herbal plant has been using as folk remedy to manage RA for a long time. Many herbal formulated drugs targeting RA are prescribed in clinics, for example, Qingfu Guanjiesu capsule and Zhengqing Fengtongning tablet exploited by our group are demonstrating good clinical efficacy. The single molecule sinomenine is the main bioactive component constituting the above two pharmaceutics, which can successfully inhibit the proliferation of activated lymphocytes [166]. Our recent studies further suggested that the mechanism of action of sinomenine is cell type-oriented and is targeting multiple signaling pathways. Sinomenine suppresses the proliferation of FLS by regulating α7nAChR expression [167]. It also downregulates the expression of mPGES-1, which lead to the alleviation of arthritic inflammation [168]. Of note, sinomenine inhibits mPGES-1 transcription without affecting prostacyclin (PG)I2 and thromboxane (TX)A2 synthesis, therefore, lowering the risk of cardiovascular complication upon treatment. As yet, report documented CHM usage in RA by targeting gut microbiome is scarce. However, it is suggested that CHM can maintain the homeostasis of the gut ecosystem mainly via two processes [169]: (1) metabolic manipulation of the administrated CHM by gut microbiota; (2) gut microflora-targeted modulation of physiological conditions. The possibility of practising CHM to manipulate gut microbiota has been demonstrated in a recent case study using the decoction Du-Shen-Tang containing ginseng polysaccharides and ginsenosides [170]. The administration of Du-Shen-Tang, after gut microbiota-involved metabolism, was able to recover the pathologically ablated gut microbiota and specifically stimulated the growth of the commensal *Lactobacillus spp*. and *Bacteroides spp*. As such, CHM that could similarly modulate the gut-microbes as polysaccharides and ginsenosides decotion, may enhance the immune system and ultimately intervent the refractory condition.

6. Conclusion

Although a lot of intervention methods are available for the treatment of RA, they often come along with drug resistance upon unavoidable persistent administration. In addition, the

long-term usage of RA drugs is often associated with various side effects which complicated the treatment performance. Therefore, the search for novel therapeutic approaches is needed so as to explore more effective RA medication. Such new drugs could enlarge the pharmaceutical scope of choices for refractory cases by acting as monotherapeutic agent or being used in combination with other conventional RA drugs. Of note, the novel findings related to the control, or more precisely, the regulation of local joint inflammatory profile via systemic immune system deserved more attention and in-depth investigation. Since, researches in such orientation could provide information not just for the cure of RA, but also, hopefully, could help to achieve the goal of disease prevention.

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Conflict of interest

Vincent Kam Wai Wong and Liang Liu are co-corresponding authors of this chapter. We request to indicate this information in the final version.

Dedication

This chapter is dedicated to adorable Gwyneth and her gorgeous mother for contributing to the manuscript with their laughter.

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