

Novel Therapeutic Targets in Rheumatoid Arthritis

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ABSTRAK

Rheumatoid arthritis (RA) merupakan salah satu penyakit autoimun yang paling kerap di dunia. Walaupun tidak dapat disembuhkan, terdapat ubat-ubatan yang dapat mengawal aktiviti penyakit ini dan mengurangkan kerosakan sendi. Beberapa sitokin, enzim dan pelbagai protein didapati memainkan peranan dalam proses penyakit RA. Tapak jalan sitokin adalah sasaran ubat-ubat yang khas untuk penyakit RA. Walaupun terdapat pelbagai jenis ubat untuk merawat RA, terdapat sebilangan pesakit yang masih tidak respon kepada ubat-ubatan yang sedia ada. Maka, pencarian untuk ubat yang baru dengan mekanisme tindakan yang berbeza untuk RA adalah suatu usaha yang berterusan. Artikel ini bertujuan mengkaji molekul-molekul yang berpotensi menjadi sasaran rawatan untuk penyakit RA. Penghalang tirosin kinase limpa, kolina kinase, galectin 3 dan faktor-teraruh hipoksia mempunyai potensi sebagai rawatan untuk RA. Rawatan sel yang meningkatkan paras tritetraprolin juga mungkin bermanfaat.

Kata kunci: faktor-teraruh hipoksia, galectin 3, kolina kinase, rheumatoid arthritis, tirosin kinase limpa, tristetraprolin

ABSTRACT

Rheumatoid arthritis (RA) is the most common chronic systemic autoimmune disease worldwide. Although incurable, there are available therapies to effectively control the disease activity and minimize the joint damage. Numerous cytokines, enzymes and other forms of proteins have been implicated in the disease process of RA. In general, pharmacological therapies in RA target cytokine pathways. Despite a wide variety of disease modifying antirheumatic drugs (DMARD), a significant proportion of patients remain refractory to the available therapies. Hence, the search for newer drugs with different modes of actions is an ongoing process. The present review aimed to explore novel therapeutic targets in RA based on data from the literature. Inhibitors of spleen tyrosine kinase, choline kinase, galectin 3 and hypoxia-inducible factor may have a promising role in the

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treatment of RA. Besides, cell based therapies which may enhance the levels of systemic tristetraprolin could be beneficial in RA.

Keywords: choline kinase, galectin 3, hypoxia-inducible factor, rheumatoid arthritis, spleen tyrosine kinase, tristetraprolin

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the peripheral small and large joints. The estimated worldwide prevalence of RA is 1%. The most common complication of this disease is joint deformity which restricts the mobility of the affected joint or limb (Di et al. 2011). RA is a heterogenous disease with a complex pathogenesis and its etiology remains largely unknown. Numerous cytokines, enzymes and other forms of proteins have been implicated in the disease process of RA (Sakthiswary et al. 2016). Targeting these molecules is pivotal in controlling the disease activity and retarding the progression of the disease.

In the past, physicians embraced a “start low, go slow” approach with regard to RA treatment; consisting of physical therapy and non-pharmacological interventions, followed by the use of non-steroidal anti-inflammatory drugs (NSAIDs), and later the introduction of a single disease modifying antirheumatic drug (DMARD). The past few decades have seen a remarkable paradigm shift in the therapeutic armamentarium of RA; from conventional synthetic DMARDs to biologic DMARDs and more recently targeted synthetic

DMARDs which are the janus kinase inhibitors (Hur et al. 2015; da Mota et al. 2015). The current treatment strategy in RA focuses on timely and aggressive definitive treatment with DMARDs either singularly or often in combinations.

Despite a wide variety of approved medications for RA, a significant proportion of patients remain refractory to the available therapies. Hence, the search for newer drugs with different modes of actions is an ongoing process. The RA research agenda is geared towards discovering novel therapeutic targets. This review summarizes some of the latest potential molecular and cellular targets in the treatment of RA (Table 1).

NOVEL THERAPEUTIC TARGETS IN RHEUMATOID ARTHRITIS

SPLEEN TYROSINE KINASE

Spleen tyrosine kinase (Syk) is a cytoplasmic enzyme that is an important mediator of immunoregulation involving macrophages, neutrophils, mast cells, and B cells. Syk plays a pivotal role in the signaling of activation of both the Fc and B-cell receptors. Syk is present in abundance in the synovial tissues

of patients with RA. Activation of Syk triggers the production of cytokine and metalloproteinase (Cha et al. 2006).

In rodent models of inflammatory arthritis, fostamatinib disodium, an oral selective inhibitor of Syk demonstrated potent anti-inflammatory activity, suggesting a role for Syk inhibition in the treatment of RA (Brasemann et al. 2006). In a phase 2 study by Weinblatt et al. (2008), oral Syk inhibitor at doses of 100 mg twice daily and 150 mg once daily were superior to placebo in reducing RA disease activity at month 6 of the clinical trial. The same group of researchers found that at 12 weeks there was a significant reduction in the serum levels of biomarkers namely interleukin-6 and matrix metalloproteinase 3 in the two groups that received 100 mg twice daily and 150 mg twice daily as compared with the groups that received placebo or the 50-mg dose of oral Syk inhibitor.

Coffey et al. (2013) through an *ex vivo* study reported that Syk inhibitors exhibited tremendous potency in suppressing BCR mediated B-cell activity in whole blood from RA patients who received stable doses of methotrexate therapy. Of note, the B-cell functional response in RA is influenced by a variety of cytokines and JAK/STAT signaling. Despite the remarkable clinical efficacy in RA, Syk inhibitors were found to significantly elevate systolic and diastolic blood pressures (Kitas et al. 2014).

A meta-analysis on fostamatinib (Kunwar et al. 2016) revealed that the drug was effective in achieving ACR20, ACR50 and ACR70 responses compared to placebo ($p=0.0004$,

$p<0.00001$, and $p<0.00001$, respectively).

CHOLINE KINASE

Choline kinase which is a phosphotransferase enzyme that mediates the conversion of choline to phosphocholine (Bernard 2014); is a treatment target in malignancies. As the synovium in RA shares similar characteristics with malignancies i.e. abundance of cytokines and oxygen radicals, it is tempting to speculate that choline kinase inhibition may control RA disease activity through suppression of the fibroblast-like synoviocytes (Guma et al. 2015). This notion was supported by a murine study with an arthritis model which demonstrated decreased severity of arthritis with choline kinase inhibition (Guma et al. 2015).

Based on metabolomics studies, there was a correlation between choline levels and inflammation in RA (Young et al. 2013). Choline kinase blockade resulted in robust reduction of interleukins 6 and 8; which were secreted by the fibroblast-like synoviocytes (Friday & Fox 2016). The selective small-molecule; ICL-CCIC-0019 is a novel inhibitor of choline kinase which decreases the mitochondria function and citrate synthase expression (Trousil et al. 2016). Likewise, bispyridinium cyclophanes are potential templates for the inhibition of human choline kinase (Conejo-Garcia et al. 2005).

HYPOXIA-INDUCIBLE FACTOR

RA is characterized by hypoxic microenvironment of the affected joints (Ng et al. 2010). In RA synovium as well as in the rheumatoid arthritis synovial fibroblasts (RASFs), there is overexpression of hypoxia-inducible factor-1 (HIF-1 α) (Giatromanolaki et al. 2003). HIF-1 α is a transcription factor that is expressed by many cells. It gains transcriptional activity leading to the expression of genes which trigger angiogenesis (Westra et al. 2010). HIF-1 α potentiates several cytokines such as IL-8, IL-33 and matrix metalloproteinase which contribute to joint inflammation and damage (Hu et al. 2013). Besides, HIF-1 α triggers toll like receptor-induced inflammation in RA (Hu et al. 2014).

HIF-1 α enhances the activation of the signaling pathways of IL-33 expression which perpetuates inflammation in RA. Furthermore, it mediates the migration and recruitment of leucocytes i.e. monocytes, T and B lymphocytes in the rheumatoid joints (Ceradini et al. 2004). Hu et al. (2014) showed that HIF-1 α played a bridging role between the hypoxic and innate immune responses.

Several agents were identified to have HIF-1 α inhibitory properties. There are small molecules that inhibit HIF-1 α at the protein level and inhibitors of HIF-1 α dimerization, DNA binding and transcriptional activity (Xia et al. 2012). Examples of small molecules that inhibit HIF-1 α are the PI3K/Akt/mTOR inhibitors, EZN-2968, camptothecins, 2ME2 and analogs, Hsp90 inhibitors, histone deacetylase (HDAC) inhibitors and thioredoxin inhibitors (Xia et al. 2012). Rapamycin, has been shown to

lower cellular levels of HIF-1 α (Hudson et al. 2002). Acriflavine inhibits HIF-1 dimerization by binding to the PAS-B subdomain of HIF-1 α and HIF-2 α (Lee et al. 2009) whereas polyamides and echinomycin inhibit the DNA binding capacity of HIF-1 α (Dervan & Edelson 2003; Olenyuk et al. 2004). Furthermore, agents that were noted to inhibit HIF-1 α transcriptional activity include chetomin, bortezomib and amphotericin B (Zhong et al. 2000; Isaacs et al. 2002; Gradin et al. 1996). To date, there are no clinical trials of RA with the aforementioned agents. Hence, the role of HIF- α inhibitors in the treatment of RA remains theoretical.

GALECTIN 3

Galectins play key roles in inflammatory diseases and malignancies (Ohshima et al. 2003). The systemic effects may differ across the various types of galectins. For instance, decreased galectin 1 (Rabinovich et al. 2000) and increased galectin 3 expression (Jeng et al. 1994), have been associated with autoimmune diseases. Previous studies have suggested novel links between synovial activation and galectin 3 in RA (Neidhart et al. 2005). Galectin 3 binding protein messenger RNA (mRNA) was increased in RA synovial fibroblasts. Galectin 3 expression was more prominent in the synovium of RA patients compared to patients with osteoarthritis (Seki et al. 1998).

Galectin 3 may be found in the skin, cartilage, synovium and macrophages (Perillo et al. 1998). It has a profound role in cellular homeostasis and appears to have proinflammatory,

Table 1: Summary of Novel Therapeutic Targets in Rheumatoid Arthritis

Therapeutic target	Mode of Action	Molecular regulation	Agents (inhibitors)
Spleen Tyrosine Kinase	Activation of both the Fc and B-cell receptors	matrix metalloproteinase 3, IL-6	fostamatinib disodium
Choline kinase	Mediates the conversion of choline to phosphocholine	fibroblast-like synoviocytes	ICL-CCIC-0019, bispyridinium cyclophanes
Hypoxia-inducible factor-1 α	Controls expression of genes which trigger angiogenesis Mediates the migration and recruitment of leucocytes	IL-8, IL-33, and matrix metalloproteinase	PI3K/Akt/mTOR inhibitors, EZN-2968, camptothecins, 2ME2 and analogs, Hsp90 inhibitors, histone deacetylase (HDAC) inhibitors and thioredoxin inhibitors
Galectin 3	Synovial activation	synovial fibroblasts	GR-MD-02
Tristetraprolin	Promotes mRNA degradation causing reduction in TNF levels	TNF	p38 MAPK inhibitors

IL: interleukin; TNF: tumour necrosis factor; MAPK: mitogen-activated protein kinase

chemotactic and anti-apoptotic properties (Jeng et al. 1994).

In a clinical study (Issa et al. 2017), galectin-3 did not correlate with clinical disease activity indices such as tender , swollen joint counts or DAS28 (disease activity score based on 28 joints), but correlated positively with MRI erosion of the joints and anti-citrulinated cyclic peptide (anti-CCP). This finding suggested that galectin-3 had an association with joint destruction in RA.

In the recent years, several galectin-3 inhibitors were studied using animal models and in vitro studies of malignant cells with promising results (Glinsky et al. 2009; Glinskii et al. 2012; Lin et al. 2009). Despite the accumulating evidence on the deleterious effects of galectin 3 in RA, galectin 3 inhibitors have not been studied in RA.

TRISTETRAPROLIN

Tristetraprolin (TTP) is an inducible, widely expressed protein with 2 zinc finger domains which are RNA binding sites. TTP is produced in response to gene expression in fibroblasts and other cells following a wide variety of stimuli (Ma & Herschman 1991). TTP binds to TNF mRNA and promotes mRNA degradation with sequential reduction in TNF levels (Carballo et al. 1998). In animal studies, TTP-deficient mice developed severe chronic inflammatory arthritis. These findings suggest that increased levels of TTP have protective effects against inflammatory disease (Patial et al. 2016).

TTP gene is underexpressed in the synovium of RA patients. Synovial tissue from patients with elevated acute phase reactant i.e. serum C-reactive protein (CRP) tended to have a low

TTP to TNF gene expression ratio (Tsutsumi et al. 2004). Taken together, appropriate expression of the TTP gene may be crucial in controlling the disease activity in RA. In a clinical study (Sugihara et al. 2007), the TNF gene was overexpressed and the TTP gene was underexpressed in patients with RA compared to healthy control subjects. This may imply that the imbalance between TNF and TTP genes expression may trigger the development of RA.

Hence, TTP is a promising therapeutic target in RA. Gene and cell based therapies could cause systemic elevations of TTP. A previous study with an experimental periodontitis model showed that adenovirus-delivered TTP had therapeutic effects (Patil et al. 2008).

CONCLUSION AND FUTURE PERSPECTIVES

Due to the complexity of the disease process in RA, there is a wide range of therapeutic targets for this chronic disease. These targets are molecular structures that are involved in the pathogenesis of RA especially in the cascades of inflammation, angiogenesis and apoptosis.

This discovery of novel therapeutic targets has opened new doors and paved the way for more treatment avenues in RA. Further clinical research is warranted to provide convincing evidence on the efficacy of these novel agents.

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