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Synovium Targeting Delivery of TNFα Blocker for Rheumatoid Arthritis Therapy – A Mini Review

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ABSTRACT

Tumor necrosis factor α (TNFα) blockers are proven to be potential suppressing agents for rheumatoid arthritis. Aside from showing significant effects in clinical treatment, they are also known as the top-selling biological agents. However, several systemic side effects related to infection and cancer are shown after treatments with systemic TNFα blockers. In order to reduce and overcome the side effects, a targeted delivery is then requested. Synovium or synovial membrane is considered as a promising delivery target because TNFα is highly accumulated within it. The current article reviews a number of strategies that might be applied in the synovium targeting delivery of TNFα blockers.

INTRODUCTION: RHEUMATOID ARTHRITIS, AN AUTOIMMUNE DISEASE ATTACKS JOINTS AND CARTILAGE

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of synovial joints leading to cartilage destruction and bone erosion (Belluci *et al.*, 2016; Chaudari *et al.*, 2016). It is commonly found in small joints such as hand and wrist. It also attacks other parts of the body, such as pulmonary and cardiovascular systems. The main clinical features of RA are swollen joints and hand tenderness. At the most severe stage, the RA might cause disability and premature mortality (Aletaha *et al.*, 2010; Mc. Innes and Schett, 2011).

The etiology of RA remains unclear. However, gene-like HLA and environmental risk factors have been showed to contribute to the disease pathogenesis (Belluci *et al.*, 2016). In 2016, Yarwood and colleagues reported more than 100 susceptible genetic loci involved in RA pathogenesis. Among them, *HLA II* gene encoding HLA-DBR was discovered to have significant involvement in RA pathogenesis. Those genetic loci are considered to be the main actors in RA development-starting as early as several years before the clinical symptoms appear. In an inductive environment, the susceptible genetic loci actively trigger autoimmune reaction then take the hidden potential RA stage to a higher stage of disease with obvious clinical symptoms (Yarwood *et al.*, 2016).

Environmental risk factors such as cigarette smoking, infection of microbes, early life exposures, and hygiene are reported to contribute to the RA development (Edward and Cooper, 2005; Liao *et al.*, 2009). Cigarette smoking increases oxidative stress in the body and modifies a specific amino acid sequence on HLA-DBR1. Thus, it is related to positive anti-citrullinated peptides antibodies (ACPAs)-RA instead of the negative ACPAs-RA (Chang *et al.*, 2014).

Microbial infection is also suspected to provoke RA emergence. *Porphyromonas gingivalis*, mycoplasma, parvovirus, and cytomegalovirus have been detected in the synovium (synovial membrane) and synovia (synovial fluid) of patients with RA (Li *et al.*, 2014).

On the other hand, the use of oral contraception

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suppresses the development of rheumatoid factor (RF), the first marker antibody that is known for RA. However, the protective effect of the oral contraception in RA progression is still uncertain (Liao *et al.*, 2009). In the early years of its discovery, RF was only identified as an immunoglobulin M (IgM), but later on, the other isotypes of immunoglobulin, e.g., IgA and IgE, were also considered as the RF (Herman *et al.*, 1986 and Hermann *et al.*, 1991).

THE IMPORTANCE OF TNFα IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

Pathogenesis of RA is started with stimulation of either B cell or T cell which is previously infected by an antigen, such as microbes present in synovial fluid (Robbins and Kumar, 1995). Therefore, the stimulated B cell produces an antibody such as IgG. In patients with RA, the IgG has lack of terminal galactose residues at the Fc region which is different with that of from patients with others chronic inflammation and healthy population (Roitt *et al.*, 1988). It is caused by the variation enzyme β-1,4-galactosyltransferase (GTase), an important factor for IgG galactosylation (Alavi and Axford, 1995). Subsequently, the RF binds to the RA typical-IgG to form immune complexes which are recognized as antigens inducing cytokines. Thus, RA is classified as an autoimmune disease (Robbins and Kumar, 1995).

The release of cytokines is regulated by macrophage-like synoviocytes (MLS), especially M1 macrophages. They secret cytokines such as TNFα, IL-1, IL-13, and IL-23. Another type of the MLS, M2 macrophages, are indirectly involved in cytokines secretion, yet act in phagocytosis, angiogenesis, and wound repair (Kennedy *et al.*, 2011; Laria *et al.*, 2016). The patients with RA are more sensitive in TNFα and its p75 receptor release than in patients with other chronic inflammation such as osteoarthritis because TNFα converting enzyme (TACE)—the main regulator in TNFα release is highly prevalent in that population only (Ohta *et al.*, 2001).

Among numerous cytokines involved in the pathogenesis of RA, TNFα and IL-1 play the superior roles in the disease progression. TNFα contributes to synovial inflammation, whereas IL-1 induces joints destruction (Toussirot and Wendling, 2004) (Figure 1). However, targeting TNFα in RA therapy is preferable to IL-1 because it allows the downregulation of other pro-inflammatory cytokines, including IL-1 (Feldman *et al.*, 2002). In addition, the epitope of TNFα is highly detected and localized in the synovial tissue of patients with RA, showing that TNFα is produced by active synovial lining cells (Husby *et al.*, 1988). It is commonly found in synovial tissue and fluid of RA and not prevalent in osteoarthritis or systemic lupus (Matsuno *et al.*, 2002). From an in vitro study, it is known that TNFα was able to induce production of other cytokines e.g. IL-1 and IL-6. On contrary, IL-6 did not induce production of the TNFα. Besides, in an in vivo study, TNFα showed the stronger effect to trigger synovial inflammation than IL-6 did (Matsuno *et al.*, 2002).

TNFα independently induces inflammation in RA even in the absence of other pivotal cytokines, like IL-1, but not contrariwise. However, it does not directly influence joint destruction and bone erosion-the clinical manifestation of RA (Matsuno *et al.*, 2002). TNFα provokes the production of IL-1 in the synoviocytes and subsequently induces the synthesis of matrix metalloproteinases (MMPs) in chondrocytes and fibroblasts. These enzymes degrade extracellular components, such as collagens, proteoglycans, and hyaluronic acids, causing the cartilage to lose its movement and pressure protection—leading to joint damage and bone erosion (Burrage *et al.*, 2006). In a preclinical study, the number of synovial inflammation cells in an RA-induced mouse dwindled after receiving TNFα blocker treatment. Furthermore, the treatment also managed to control the level of IL-6 in the mouse serum, though not contrarily. Thus, TNFα blocking is a potential strategy in RA therapy (Matsuno *et al.*, 2002).

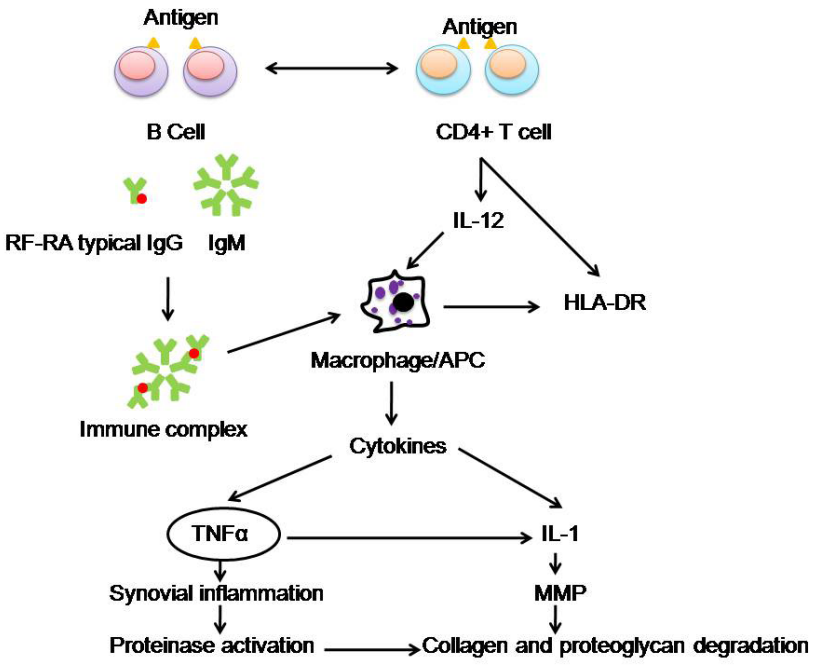

Fig. 1: Pathogenesis of rheumatoid arthritis. TNFα plays an important role in synovial inflammation (Robbins and Kumar, 1995; Toussirot and Wendling, 2004).

TNFα BLOCKERS: BIOLOGICAL DRUG OF CHOICE FOR RHEUMATOID ARTHRITIS

Various types of TNFα blockers have been available on the market worldwide and commonly used in clinical therapy for RA (Table 1). TNFα blocker as a biological drug is recommended for patients with moderate and severe RA when DMARD (disease modifying anti-rheumatoid drugs) like methotrexate is not effective (Singh *et al.*, 2015). TNFα blockers have been developed in two subclasses. The first subclass is an anti-TNFα antibody that neutralizes TNFα, while the second subclass acts as TNFα soluble receptor to prevent TNFα from binding with its cell surface receptor (Salfeld and Kaymakcalan, 1998; Taylor *et al.*, 2009; Moelants, *et al.*, 2013).

Table 1. List of approved TNFα blockers (Krzysztof *et al.*, 2014; Knight, 1993; Kempeni, 2000; Mittal and Raychaudhuri, 2010; Marotte and Cimaz, 2014).

Name	Molecule	Date of approval	Developer	Marketing Authorization Holder
Infliximab (Remicade®)	Murine Fab-human Fc	FDA – 1998 EMA – 1999	Centocor Schering – Plough	Janssen Biologics B.V.
Adalimumab (Humira®)	Human Fab-human Fc	FDA – 2005 EMA – 2003	Abbott	AbbVie Ltd.
Golimumab (Simponi®)	Human Fab- human Fc	FDA – 2009 EMA – 2009	Centocor Schering – Plough	Janssen Biologics B.V.
Etanercept (Enbrel®)	The extracellular domain of human soluble TNFR – human Fc	FDA – 1998 EMA – 2000	Amgen, Wyeth, Takeda	Pfizer Ltd.

Infliximab, which was previously named A2 antibody (cA2), is the pioneer of TNFα blocker approved as a biological drug for RA (Taylor *et al.*, 2009). It is a chimeric anti-TNFα antibody containing murine antigen binding fragment (Fab) and human constant fragment (Fc). In the early days of its development, infliximab had shown a specific affinity to human TNFα. It neither binds to lymphotoxin (TNFb) nor TNFα from other species (except small binding to chimpanzee`s TNFα) (Knight *et al.*, 1993). Infliximab was launched in the market in 1998 with the brand name of Remicade®. The next anti-TNFα antibody, named D2E7 or adalimumab, is also developed as a monoclonal antibody. However, the murine Fab region was substituted with human's, and therefore, claimed to be less immunogenic (Salfeld and Kaymakcalan, 1998; Kempeni, 2000). This antibody is marketed as Humira® and is leading in terms of sales among anti-TNFα antibodies (Lybecker, 2012). The presence of adalimumab is followed by CNTO148 (Golimumab, Simponi®). Both have a similar half-time (14 days), but golimumab is prepared for once per month dosage, whereas adalimumab needs a more frequent administration that is twice per month (Mittal and Raychaudhuri, 2010).

The second subclass of TNFα blocker is represented by etanercept. Unlike infliximab and other anti-TNFα antibodies, etanercept is designed as the fusion of two extracellular domains—human soluble p75 TNF receptor and the Fc of human IgG1 (Marotte and Cimaz, 2014). The development of etanercept was initiated by a study on the fusion of extracellular domains, namely p55 TNF receptor and the Fc of murine IgG1 performed by Peppel and colleagues (Peppel *et al.*, 1991). Etanercept mimics the mechanism of soluble TNF receptor to bind the TNFα prior to interacting with TNFα receptors on the cell surface. Therefore, it only binds to the soluble TNFα, not targeting the receptor bound-TNFα. Up to now, etanercept is the only TNFα blocker in the second subclass and has been marketed since 1998 under the product name of Enbrel® (Krzyztof *et al.*, 2014). TNFα blockers achieved over 15 billion USD in sales in 2014, giving it the title of top-selling RA medicine, with other biological drugs and DMARDs following behind (Chaudari *et al.*, 2016). Apart from the above-mentioned product names of TNFα blocker, Humira®, Enbrel®, and Remicade® have become top-selling biological drugs for years (Lawrence and Lehteenmaki, 2013; Lybecker, 2016).

Even though TNFα blockers have shown lots of advantages in RA therapy, some shortcomings are causing problems. The ones available thus far are only for systemic effects and used via intravenous or subcutaneous injection. This leads to several adverse effects related to the natural immune condition. Long-term use of TNFα blockers has the potential to cause lymphoma, infections, and other diseases related to the immune system (Scheinfeld, 2004; Bongartz *et al.*, 2006).

At the beginning of its discovery, TNFα was found as a necrotic cytokine secreted by macrophages against tumor cells (Carswell *et al.*, 1975). Later on, it was found that TNFα plays pivotal roles in the regulation of cell differentiation, proliferation, and death (Wang and Lin, 2008). In regards to cell death, TNFα stimulates TNFR1 to recruit TNFα receptor-associated death domain (TRADD), Fas-associated death domain (FADD) and Caspase 8 or FADD-like ICE (FLICE) resulting pro-apoptotic and anti-apoptotic proteins that regulate membrane outer mitochondrial permeabilization (MOMP). As a consequence, cytochrome-c is released from mitochondria and activates caspase-3, which leads to apoptosis. Therefore, interference of TNFα's role in cell death triggers uncontrolled cell growth closely associated with cancer (Elmore, 2007; Sethi, 2008; Tait and Green, 2013).

It is reported that TNFα blockers contribute specifically to lymphoma cancers (even though the correlation was weak) instead of the non-lymphoma ones (Scheinfeld, 2004). In another study, it is suggested that there is no significant difference between the lymphoma risk of patients treated with TNFα blockers and those receiving non-biological DMARDs. However, patients who had suffered from lymphoma should avoid TNFα blockers since it could increase the risk of recurrence (Jain and Singh, 2013).

TNFα is an imperative cytokine in suppressing microbial infections (Rahman and McFadden, 2006). Therefore, inhibiting TNFα using an immunosuppressant such as TNFα blocker increases the risk of infection by two-fold in patients with RA (Listing *et al.*, 2013). It is also reported that TNFα blockers induce some instances of bacterial infections: *Mycobacterium tuberculosis,*

Streptococcus pneumoniae and *Listeria monocytogenes*; fungal infections: *Pneumocystis jirrovecii, Aspergillus fumigates, Cryptococcus neoformans* and *Histoplasma capsulatum*; and viral infections: hepatitis B virus (HBV) and hepatitis C virus (HCV) (Ellerin *et al.*, 2003; Murdaca *et al.*, 2015). Nevertheless, infection in patients with RA is not solely caused by TNFα blockers administration. Other causes of infection are the comorbidity of the RA itself, a combination of TNFα blockers with DMARDs or glucocorticoids (GCs), and chronic infection related medical history. In addition, infection susceptibility is higher in elderly patients (Listing *et al.*, 2013). Whereas the risk of serious infection in patients increases upon receiving standard or a higher dose of biological drugs, the risk of serious infection in patients receiving TNFα blockers increases when the dosage is low (Singh *et al.*, 2015).

Based on the above-mentioned issues, targeted delivery of TNFα blockers is then considered. As TNFα is accumulated in inflamed synovial tissue, targeting that very tissue would be an effective strategy which can be applied by conjugating a synovial targeting agent with a TNFα blocker (Garrood and Pitzallis, 2006).

DEVELOPMENTOFSYNOVIUMTARGETINGAGENTS FOR TNFα BLOCKERS

Synovial tissue is a membrane which lines the inner parts of the synovial joint. It houses articular cartilage and joint cavity and filled with synovial fluid (Barland *et al.*, 1962). The membrane is composed of two layers: the intima and subintima layers. Intima layer, which is found in the surface of the tissue, consists of two types of cells, namely the macrophage-like synoviocytes (MLS) or type A synoviocytes and fibroblast-like synoviocytes (FLS) or type B synoviocytes (Figure 2). This layer provides extracellular matrix molecules to regulate the production and clearance of synovial fluid. Subintima layer, the one below intima, is formed by adipocytes, fibroblasts, macrophages, mast cells, elastin, and blood vessels. Subintima layer has components with fibrous, areolar, and adipose morphology (Tiwari, 2010). In patients with RA, synovial tissue has characteristics distinguishable from that of a healthy population. Hence, the characteristics of synovial tissue found in patients with RA are valuable to determine the appropriate RA therapy. In the synovial tissue of patients with RA, the proliferation of intima layer is detected, along with lymphocytes and plasma cells infiltration as well as increased vascularity and fibrosis (Bartok and Firestein, 2010).

To our knowledge, TNFα blockers have not been conjugated or fused with any synovial targeting agents yet. However, a number of studies have been carried out to develop the targeting agents, such as homing peptide for other anti-inflammatory drugs and other biological products for RA therapy (Mi *et al.*, 2003; Yang *et al.*, 2011; Wythe *et al.*, 2013). In addition, the discovery of RA biomarkers might be useful in developing anti-biomarkers which can also be used as targeting agents (Bao *et al.*, 2009).

Synthetic peptides for synovium targeting

Several synthetic homing peptides have been identified and showed specificity to synovium or synovial membrane and to endothelial cells in the synovial membrane. Therefore, they are suggested to be coupled with TNFα blockers for synovium targeting delivery thereof.

Mi *et al.* (2003) successfully screened two synovial homing peptides, HAP-1 (SFHQFARATLAS) and HAP-2 (HIQLSPFSQSWR) from an M13 phage library. Those peptides facilitated internalization of large protein into HIG-82—a synovium cell line, but HAP-1 was more effective than HAP-2.

Yang *et al.* (2011) identified targeting peptides, ADK (CRNADKFPC) and NQR (CLDNQRPKC) which was specific for endothelial cells in the inflamed synovial membranes. The accumulation of those peptides was higher in the inflamed synovial membrane than in other inflamed tissues, like skin or normal tissues.

Wythe *et al.* (2013) synthesized synovium targeting peptide, namely SyETP (CKSTHDRLC) and fused it with an anti-inflammatory cytokine: IL-4. In the study, the fusion of SyETP-IL4 was injected into a human synovial tissue transplanted mouse. The SyETP increased the accumulation of IL-4 in the synovial tissue and prolonged the half-life ($t^1/_2$) of the IL4, making it approximately twice as long compared to free IL-4. The biological activity of the fusion was represented as the level of STAT6 phosphorylation in the synovial tissue that activated by IL-4 (Wythe *et al.*, 2013). Colombo *et al.* (2016) reported a synovial membrane targeting delivery system called MC13, in which a synthetic peptide (CKSTHDRLC) was attached to Fab of adalimumab. The system was effective to neutralize TNFα in an in vitro study, selective at the inflamed synovial membrane and showed no toxic effects in an in vivo study.

Rheumatoid arthritis biomarkers to target the synovium

In addition to targeting peptides design, biomarkers discovery in RA pathogenesis also promotes the development of synovial targeting agent. Expression of podoplanin (PDPN) and CD248 or endosialin have been detected on TGF-1b, TNFα and IL-1b induced synovial fibroblasts or fibroblast-like synoviocytes (FLS), a population of synovial cells responding collectively with extracellular matrix and collagen. Both PDPN and CD248 are found in normal tissue (Croft *et al.*, 2016). PDPN is mainly found in intima layers of the synovial membrane, while the CD248 is found in both intima and subintima layers (Croft *et al.*, 2016; Hardy *et al.*, 2013) **(**Figure 2**)**. The allocation of those proteins is controlled by the FLS themselves without any interferences from other immune cells or stimulus (Lee *et al.*, 2007). In regards to RA pathogenesis, PDPN plays a more important role than CD248 because the intima layers undergo hyperplasia, invade cartilage and bone, and ultimately cause cartilage damage and bone erosion (Ekwall *et al.*, 2011). Therefore, it is suggested that PDPN might be beneficial as RA target therapy. On one hand, an anti-PDPN is considered in PDPN neutralization, but on the other hand, it can be fused with other RA therapy agents, such TNFα blocker, for the sake of a specific delivery.

Visfatin, another RA biomarker, is also demonstrated as a potential therapeutic target. Visfatin or pro-B cell colony-enhancing factor (PBEF) or nicotinamide phosphoribosyl transferase (Nampt) is a 52 kDa protein secreted by adipose, synovial, and cartilage tissue as well as peripheral blood mononuclear cells (Laiguillon *et al.*, 2014) **(**Figure 2**)**. In mouse models and patients with RA, serum and synovial tissue level of visfatin were found to be significantly higher than in normal

population (Busso *et al.*, 2008; Mirfeizi *et al.*, 2014; Lee *et al.*, 2017). It induced secretion of pro-inflammatory cytokines and assumed to be facilitating joint damage via MMP secretion (Bao *et al.*, 2009). Therefore, visfatin is considered as a potential target for RA therapy (Mirfeizi *et al.*, 2014). Similar with PDPN, an anti-visfatin can be used to neutralize the level of visfatin or as a targeting agent to deliver other anti-RA drugs to the synovial tissue, like TNFα blocker. Surprisingly, administration of TNFα blocker, namely infliximab, did not suppress the serum level of visfatin in a clinical study (Gonzalez *et al.*, 2010). The effect of the anti-RA drug on visfatin level in the synovial tissue needs more investigation. Moreover, finding out the capacity of visfatin in the synovial tissue so as to accumulate anti-visfatin or other RA drugs in the local joint still requires more studies (Bao *et al.*, 2009).

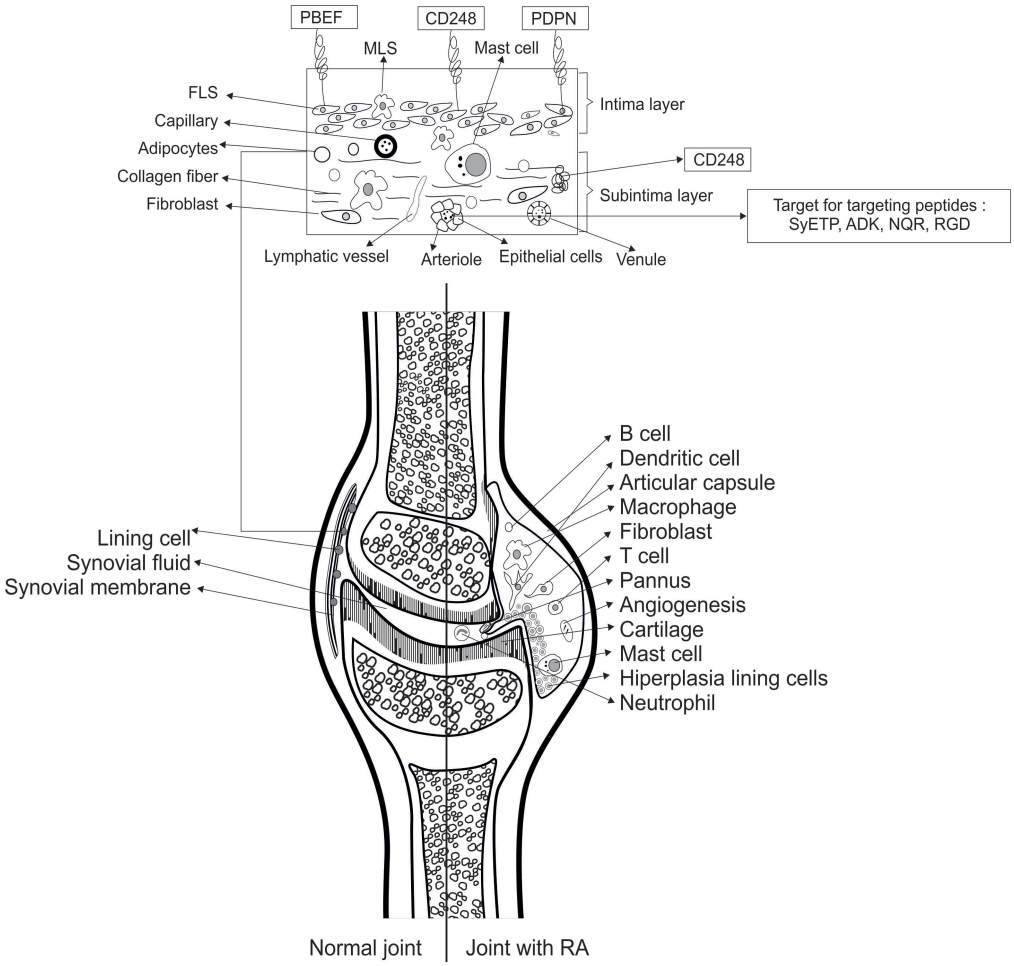

Fig. 2: Structure of normal joint and a joint with rheumatoid arthritis (RA). In the magnified synovial membrane: RA specific biomarkers, such as PBEF and PDPN are found in the fibroblast like-synoviocytes, and CD248 is found both in intima and subintima layer. The synthetic targeting peptides are designed to target epithelial cells in the subintima layer (Brentano *et al.*, 2007; Croft *et al.*, 2016; Hardy *et al.*, 2013; Meier *et al.*, 2012).

Conclusion and future perspective

TNFα blockers are known as strong inhibitors for inflammation diseases, like RA, but they might cause a systematic side effect. The systematic side effect of TNFα blockers can be reduced by specific delivery to a certain target. In regards to the application of TNFα in RA therapy, synovial membrane is considered as a potential target because TNFα and its receptor are highly found therein

From the previous studies, a number of synthetic synovium homing peptides were reported. They were coupled with any compounds to direct them to the synovial membrane. HAP-1 and HAP-2 facilitated internalization of large proteins to the synovial membrane, whereas ADK, NQR, dan SyETP were used as targeting agents to the endothelial cells in the synovial membrane. According to those reports, the synovium homing peptides are suggested to be coupled with TNFα blockers, so they are able to be specifically delivered to the inflamed synovial membrane.

In addition, an anti-RA biomarker, for instance, anti-podoplanin, anti-endosialin, and anti-visfatin are also potential to be coupled with TNFα blockers because they have been known as specific RA biomarkers which are accumulated in the inflamed synovial membrane. However, advanced studies still need to be carried out in order to confirm the effectivity and selectivity of these strategies for specific delivery of TNFα blockers.

As previously mentioned, the more potential a drug, the higher the tendency of side effects occurrence. Nonetheless, to take optimal benefits of the drug, a specific delivery is needed. In this case, TNFα blockers which are the most used and potential drug for RA therapy are suggested to be coupled with the reviewed agents to the obtained specific accumulation of them in the damaged tissue such as a synovial membrane.

CONFLICT OF INTEREST

The authors have no conflict of interest.

LIST OF ABBREVIATION

ACPAs: anticitrullinated peptides antibodies
DMARD: disease-modifying anti-rheumatoid drugs
Fab: antigen binding fragment
FADD: Fas-associated protein with death domain
Fc: constant fragment
FLICE: FADD-like IL-1β-converting enzyme
FLS: fibroblast-like synoviocytes
GCs: glucocorticoids
GTase: beta 1,4-Galactosyltransferase
HBV: hepatitis B virus
HCV: hepatitis C virus
HLA: human leukocyte antigen
Ig: immunoglobulin
IL: interleukin
MLS: macrophage-like synoviocytes
MOMP: membrane outer mitochondria permeabilization
MMP: matrix metalloproteinase
PBEF: pro-B cell colony enhancing factor
RA: rheumatoid arthritis
RANKL: Receptor activator of nuclear factor kappa-B ligand
RF: rheumatoid factor
TACE: TNFα converting enzyme
TNFα: tumor necrosis factor α
TRADD: TNFR1-associated death domain protein

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