Review Article

Ligand Based Drug Targeting System and Their Application

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ABSTRACT

Targeted drug delivery system has a great advances in a research technology. Ligand receptor interaction help to achieve new technique and new receptor interaction to the drug molecule. Specific ligand targeting has a great advances in a technological science and methodology. The disease like rheumatoid arthritis and hepatocellular carcinoma gives the total application for ligand gated system of drug delivery. The various method and technique will help to achieve the recent advances in a ligand gated system of medicine. Basically, targeted drug delivery is to help the drug molecule to succeed in ideally to the specified web site. The inherent advantage of this method ends up in administration of needed drug with its reduced dose and reduced its facet impact this inherent advantage of targeted drug delivery system is underneath high thought of analysis and development in clinical and pharmaceutical fields as backbone of medical specialty too. Various drug carrier which may be employed in this advanced delivery system are soluble polymers, biodegradable microsphere polymers (synthetic and natural), neutrophils, fibroblasts, artificial cells, lipoproteins, liposomes, micelles and immune micelle. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue.

Keywords: Targeted drug delivery system, Active targeting, Passive targeting, Hepatocellular carcinoma, Rheumatoid arthritis.

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INTRODUCTION

The biological effect of drug in a patient depends upon pharmacological properties of the drug these effects arises due to the interaction between drug and receptor at the site of action of the drug. However, the efficacy of these drug targeted interaction stands undetermined unless the drug is delivered to its site of action at such a concentration and rate that cause minimum side effect and maximum therapeutic effects. Targeted drug delivery aims to achieve the same.

The Ultimate goal of targeted drug delivery is to increase control of drug dosing at specific physiological sites such as cells, tissue or organs thereby reducing unwanted side effect at non target sites. A great majority of these drug delivery system are based on passive targeting for greater control of targeting, drug delivery system must be rendered smarter by incorporating unique ligand that are specifically recognized by target disease cells there by converting passive into ligand targeting drug delivery system. The primary reason for developing drug targeting is to decrease toxicity by reducing the site side effect that are prevalent in traditional forms of drug therapy.

TARGETED DRUG DELIVERY SYSTEM

Targeted drug delivery is also known to be as smart drug delivery system there are two methods which involve active targeting and passive targeting. The good delivery system is supposed to transport drug on its target site. An ideal drug which is known to be as cross blood brain barrier. Recently Nano medicine has the great impact on the drug delivery system. and also has the more application on nanotechnology, nanoparticles are very small in size, Nano drug delivery can allow for the delivery of drugs with poor solubility in water and also has impact to aid in avoiding the first pass metabolism of liver. Nanotechnology derived drug delivery can cause, the drug to remain in blood circulation for a long time, so that leads to lesser fluctuations in plasma levels and therefore, less side effects.

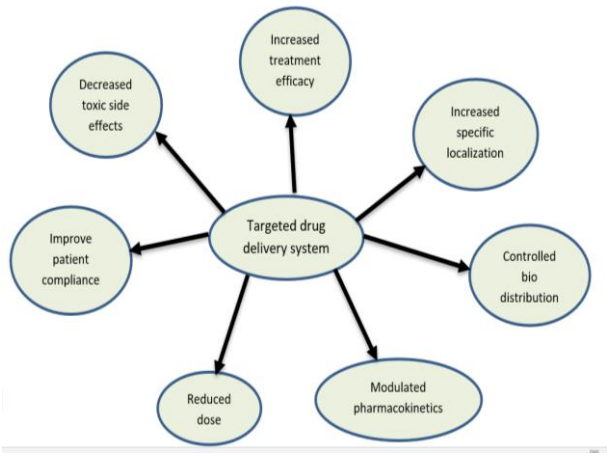

Figure 1: Drug Targeted System

They can be including polymer-drug conjugates and Nano particulate systems such as liposomes, quantum dots, dendrites, etc. There are several other renovation strategies which include, the therapeutic agents are coupled with "targeting ligands" that possess the ability to recognize antigens associated with tumors. [1]

ADVANTAGES OF TARGETED DRUG DELIVERY

Rational for targeted drug delivery system

- ❖ Active
- ❖ Passive

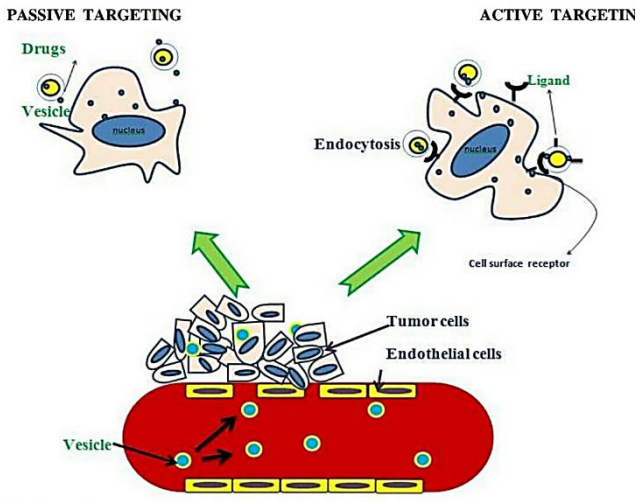

Figure 2: Rationales for drug targeted system

Passive targeting

This is based on the insertion of drug at areas around the site of interest, such as in case of tumor tissue. This all condition is called Enhanced Permeability Retention (EPR) effect. This type of targeting occurs in all types of drug delivery systems carriers. Passive targeting is actually a rare targeting because it cannot really described as a form of selective targeting. Although the EPR effect applies for nanoparticle administered, the majority (95%) of these nanoparticles tend to accumulate in organs other than those of interest such as liver, lungs and spleen. Thus, it causes the distribution of drug by blood circulation. Examples of these the use of anti-malarial drugs being targeted for the treatment of microbial infections such as leishmaniasis, candidiasis and brucellosis. [3]

Active targeting

The ligand receptor interaction occurs only after blood circulation or *extravasation*. Although the use of ligand-receptor interactions, the type of active targeting describes the drug targeting interactions. However, interactions between a ligand and a receptor are possible only when they two are in close phase propinquity, (i.e. less than about 0.5mm). The currently available drug delivery systems are able to reach the target by the virtue of blood circulation and extravasation.[3]

Ligand receptor-based interaction

Ligand is a general term that characterized as molecule that specifically interacts with the receptor of another molecule on the surface of cell, tissue or organ.

Ligand represent a diverse class of molecule that can be exploited for targeted drug delivery because the ligand receptor complex is the result of a specific molecular interaction that requires structural complementary.

Receptor used in ligand based drug targeting

1. Antigen
2. Cadharin
3. Selectins
4. Integrins
5. Vitamin
6. Transferin
7. Hormone

1. Antigens

The use of tumor-associated antigens for the targeting of antibodies has been the most widely exploited form of anticancer targeting drug delivery. The basis for this is that certain antigens usually are expressed in lesser degree in normal tissues than in tumor tissues. Several such antigens have been identified. For example, the carcinogenicity antigen, prevalent in gastrointestinal (GI), lung, and breast tumors, was the first to be identified, and it has been used extensively as a target.[5]

2. Cadherin

Cadherin are a group of glycoproteins that facilitate Ca2+-dependent cell-cell adhesive interaction when cadherin function is disrupted, the release of a tumor cell can result. It was shown that the aggressive metastasis of undifferentiated epithelial carcinoma cells that had lost cell-cell adhesion could be stopped by transfection with E-cadherin cDNA. Therefore, it was suggested that E-cadherin suppresses metastasis, which was further supported by more recent studies that showed the loss of adhesion of human gastric, prostatic, and lung cancer cells was due to the gene mutation of a protein associated with the proper function of cadherin. [6]

3. Selectins

Selectins are another type of cell adhesion molecule that is responsible for carbohydrate binding. Selectins mediate cell adhesion by recognizing specific carbohydrate ligands arranged on the surfaces of cells. In addition, it has been suggested that cell-cell adhesion may not be a result of only a single selectin-carbohydrate ligand binding but rather the cumulative effect of multiple interactions of many sugar moieties, the so called polyvalency or cluster effect. Two examples of this phenomenon were demonstrated by the binding affinity and selectivity of the tetrasaccharide glycolipids sialyl Lewis X (sLex) and sialyl-

LewisA (sLea), which play important roles in inflammation, reperfusion, and metastases.[7]

4. Integrins

The integrin family has been identified as excellent candidates for the development of target specific cancer therapies. Integrins are heterodimeric glycoproteins that consist of α and β subunits, which combine to form the various types of integrins. Currently, 18 α sub-units, 8 β subunits, and approximately different integrins have been identified. [8]

5. Vitamins

Vitamins are essential for normal cellular function and growth. In pathological conditions, these vitamins also play crucial roles. As such, cell surface receptors for vitamins have been considered as drug targets because vitamins generally are internalized into the cell by receptor mediated endocytosis. Such vitamins as folic acid, riboflavin, biotin and vitamin B6 all have been evaluated as potential ligands for targeted delivery of therapeutic agents to specific cells.[9]

6. Transferrin

Transferrin is a glycoprotein responsible for transporting iron into cells. Iron binds to transferrin and enters the cell through a highly specific receptor-mediated endocytosis via the transferrin receptor. The transferrin receptor is expressed on the surfaces of cells in both proliferating and non-proliferating normal tissue, but it is highly up regulated in tumor cells, as evident by reduced transferrin levels in patients with cancer The use of transferrin to target the transferrin receptor has been investigated for targeted drug delivery.[10]

7. Hormone

The presence of hormone receptors in hormone-sensitive cancers presents potential applications of hormone targeted drug delivery of traditional drugs. This approach is potentially applicable to ovarian, endometrial, and breast cancers because the onset of tumor growth in each of these tissues is companied by an increase in hormone receptors.[11]

APPLICATION OF LIGAND BASED DRUG TARGETING SYSTEM

1. Hepatocellular carcinoma

●Introduction:

Hepatocellular carcinoma (HCC) is the most common primary liver cancer having high morbidity and mortality in world. The conventional chemotherapy (medicine) has low desired response due to multi drug resistance, fast clearance rate, nonspecific delivery, severe side effects, and low drug concentration in cancer cells, and so on.

Nanoparticle-mediated targeted drug delivery system will has more modern advances through increased porosity and retention impact and active targeting as a unique approach of medicine for HCC in recent years. The active targeting is influenced by ligands on the delivery system, that acknowledge with and interiorize into hepatocellular carcinoma cells with high specificity and potency for additional advances. This all focuses on the recent advances on targeted delivery systems for HCC and additionally summarizes the ligands that may enhance the capability of active targeting, to produce some insight into future analysis in Nano medicine for HCC.[12]

●Ligand-based active targeting

As described in Figure, the NTDDS could disperse in tumor mass through feeding arteries and then could accumulate into tumor interstitial fluid through fenestration (opening in the wall of structure) by EPR effect. More significantly, the precise NP–cell surface interactions play a vital role in facilitating acquisition of NPs into targeting growth cells. The receptor mediate endocytosis, Associate in nursing approach of active targeting, is one among the foremost common ways for HCC to additional improve the targeting property. Fortunately, some proteins and molecules are overexpressed on the surface of hepatoma cells or intra tumoural angiogenesis compared to normal cells, thus their ligands, including (poly) saccharides, vitamins, antibodies, peptides, aptamers, transferrin(Tf), other small molecules, growth factors, and so on, were utilized to decorate drug delivery system in order to enhance the recognition between NPs and tumor cells. Subsequently, the NTDDS was internalized into cells by receptor-mediated endocytosis triggered by the ligands on the surface of NPs, and then therapeutics in NTDDS was released into cytoplasm in order to kill the tumor cells. [13]

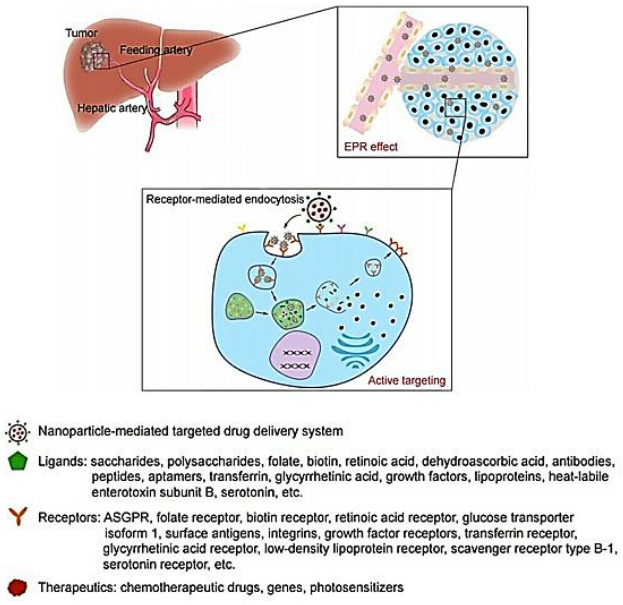

Figure 3: Ligand based targeting

Folate:-

Folate or folic acid (FA), referred to as water-soluble vitamin B9, vitamin M, and vitamin Bc, is required by-

Vitamin-based active targeting:-

Vitamins square measure a series of organic compounds and important nutrients that each one living cells need for his or her survival. Rapid proliferation of neoplasm cells, above all, requires certain vitamins in excess such as folate, biotin, retinoic acid (RA), and de-hydro ascorbic acid (DHAA) to sustain their rapid growth. Compared to the conventional cells, the receptors involved in the uptake of the vitamins are thus up regulated on tumor cell surface. Consequently, these vitamin receptors serve as beneficial target substrates for tumor-targeted drug delivery.[14] Eukaryotic cells for facilitating the transfer of one-carbon units from donor molecules into vital biosynthetic pathways such as methionine, purine, and pyrimidine biosynthesis as various coenzymes, animal cells need to capture exogenous folates to sustain life thanks to lacking key enzymes of the synthesis pathway themselves. The receptor-mediated endocytosis is that the main mechanism of the cellular acquisition through vitamin Bc receptors (FRs) with a high affinity. Down regulation of anti-apoptotic genes enhanced the Natural product triptolide has been proved to be highly effective against many tumor cells including cholangiocarcinoma, pancreatic cancer, HCC, and so on. However, the clinical applications are restricted by poor solubility and extreme aspect effects. Hence, Ling et al synthesized smart pH-sensitive Nano formulated triptolide (Nf-Trip) coated with folate as a targeted therapeutic strategy for HCC cellular uptake of Nf-Trip dramatically diminished, suggesting that folate is an excellent hepatoma cell-specific ligand that effectively facilitate the endocytosis of Nf-Trip.

Showed that an oversized quantity of specific accumulation of the Nf-Trip was detected within the liver tumor tissue. Moreover, the Nf-Trip reduced tumor burden and improved survival while not general toxicity.

Although FA-functionalized drug delivery loaded with small molecular drugs such as DOX and docetaxel could induce tumor cell apoptosis, hepatoma cells may advance several mechanisms to resist apoptosis. Sensitivity of hepatoma cells to chemotherapeutic agents by RNA interference technology.

●Biotin:-

Also known as vitamin H, vitamin B7, or coenzyme R, is one of the water-soluble B complex vitamin families and is a growth promotor at the cellular level. It is reported that the biotin receptors are over expressed more than the FRs in various cancer cells such as leukemia, colon, mastocytoma, lung, renal, and breast cancer cells. A study demonstrated that modification drug delivery with biotin is an effective pattern to enhance cell specificity against the cancer cells over expressed with biotin receptors on the cell surfaces and to accelerate the acquisition of the drug delivery into the targeted cancer cells through receptor-mediated endocytosis. To verify the potential price of B for targeted liver neoplasms. They designed biotin modified erythrocytes loaded with MTX by combining with N-hydroxy succinimide ester of biotin. In vivo study showed that the MTX level of liver administrated with biotinylated erythrocytes was increased fold compared with free MTX and 1.8-fold compared with non-biotinylated erythrocytes at 1h once injection into rats, indicating that this drug system can be place viscose blood vessel catheters for loco regional treatment of liver neoplasms. [15]

●Other ligands for HCC:-

- Glycyrrhetinic acid (GA)
- Epigallocatechin Gallate (EGCG)
- Low-density lipoprotein (LDL) particle
- Hematoporphyrin (HP)
- Recombinant high-density lipoprotein (rHDL) particle
- Heat-labile enterotoxin subunit B (LTB)
- Serotonin (5-HT)
- Somatostatin (SST)

2. Targeting ligand by using antibody receptor

It projected a standard style of a functionalized protocell during which a neoplasm targeting moiety, like an amide or recombinant human protein single chain variable fragment (scFv), is conjugated to a super molecule bilayer close a oxide primarily based nanocarrier core containing a protected therapeutic wares. The functionalized protocell area unit typically tailored to a specific cancer subtype and treatment regime by exchanging the tumor-targeting moiety and/or therapeutic wares or utilized together to form distinctive, the ranostic agents. Other examples of targeting peptides include tumor-targeting peptides derived from luteinizing hormone/chorionic gonadotropin conjugated to membrane-disrupting lytic peptides to effectively inhibit human breast and prostate xenograft tumor growth and metastases .In addition to peptides or antibodies, aptamers, short, single stranded ribonucleic acid or deoxyribonucleic acid oligonucleotides, are developed for targeted cancer medical aid to treat a range of tumors in clinical trials by delivering intercalated chemotherapeutics or conjugated on to nano carriers containing therapeutic cargos. [16]

3. Therapeutic Application of Ligand-Targeted Nanoparticles

The pteroylmonoglutamic acid|B complex| vitamin B complex| vitamin B|B vitamin |B} receptor could be a documented neoplasm marker that binds vitamin B complex and vitamin B complex drug conjugates with a high affinity and carries these certain molecules into the cells via receptor-mediated endocytosis.

It has been checked the incidence of vitamin B complex receptor expression in caput and neck primary and malignant neoplasm tissues and compared them with traditional tissues like the bone marrow.

Folate receptor expression was found in fifty three of those neoplasm samples whereas traditional bone marrow cells failed to show any vitamin B complex receptor expression.

Recently, generated a new folate receptor targeted nano-particle formulation of paclitaxel using heparin as a carrier [heparin-folate-Taxol (paclitaxel), HFT] and tested it using nudemouse animal models. This novel ternary nanoparticle HFT showed more potent activity against the growth of tumor xenografts of human KB and paclitaxel-resistant KB derivatives than did binary heparin-Taxol or free drug

Transferrin, a serum glycoprotein, works as a transporter to deliver iron through the blood and into cells by binding to the transferrin receptor and subsequently being internalized via receptor-mediated endocytosis.

Because the transferring receptor is over expressed in neoplasm tissues compared with traditional tissues, it has been investigated as a target for tumor specific drug delivery.

Transferrin conjugated paclitaxel-loaded [poly(lactic-co-glycolic acid) polymer] nanoparticles displayed larger restrictive effects on cell growth than free paclitaxel in MCF-7 and MCF-7/Adr cells.

Transferrin was also conjugated to liposomes to increase the transfection efficacy of p53, resulting in the sensitization of the transfected cancer cells/xenografts to ionizing radiation. [16]

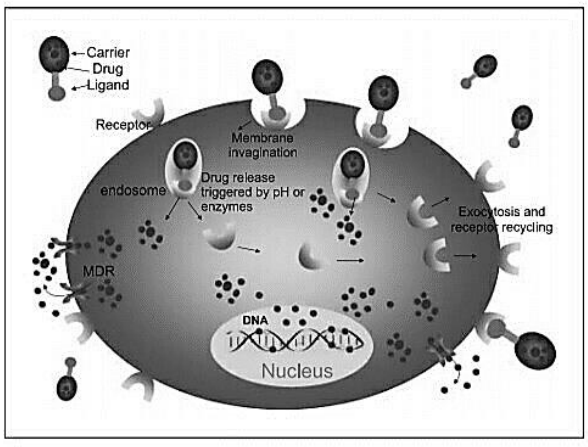

Figure 4: Nanoparticle system

INTERNALIZATION OF NANOPARTICLE VIA RECEPTOR MEDIATED ENDOCYTOSIS

Rheumatoid Arthritis

Arthritis may be defined as inflammation of the joints causing pain, swelling and stiffness. The broad category of arthritis includes diseases that can be classified as inflammatory, metabolic, degenerative or infectious. These conditions affect joints and the surrounding tissues, as well as the connective tissue of the skin, bones, and muscles. RA is the most common form of chronic inflammatory arthritis, characterized by inflammation of the joints, resulting in synovial hyperplasia by infiltration of activated immune cells further leading to cartilage and bone destruction. [17]

Carrier systems

Polymer drug conjugates:

Polymer backbone are used for attachment of therapeutics, solublizer and targeting moiety.

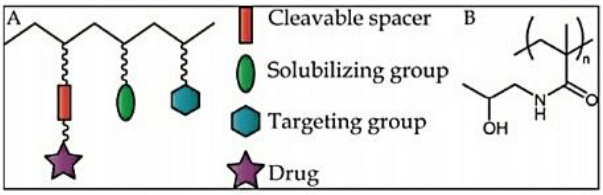

Figure 5: Ringsdorf's model of polymer-drug conjugate

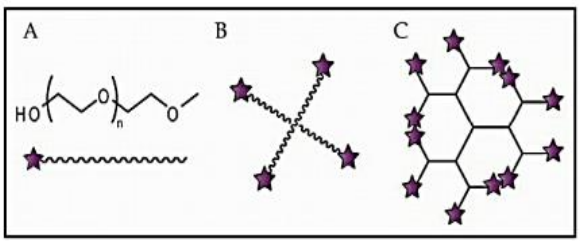

Figure 6: Various polymer articutectures

Nano particulate carrier system

Liposome's, micelles, metallic nanoparticle and polymeric nanoparticle constitute the most commonly used nanocarrier system for drug delivery system.

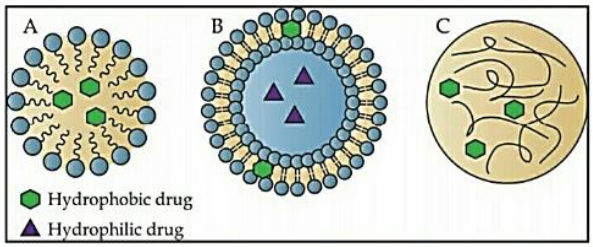

Figure 7: Various nanoparticulate carrier systems

Therapeutic release from carrier system

Cellular uptake of therapeutic loaded carrier systems typically proceeds by fluid phase endocytosis, adsorptive endocytosis, or receptor-mediated endocytosis. An ideal carrier system will only respond to environmental features unique to the diseased tissue, such as elevated levels of a specific enzyme. Stimuli responsive drug delivery systems that are currently in development for the treatment of rheumatoid arthritis. [18]

Polymer-drug conjugates for rheumatoid arthritis treatment

Several polymer-drug conjugates are developed to enhance the therapeutic effectivity of each standard DMARDs and biologics.

A number of these compounds were only recently applied to rheumatoid arthritis after originally being developed for cancer. For example, methotrexate. [18]

Liposomal carrier systems for rheumatoid arthritis treatment

Technecium labelled liposomes accumulated within the synovial tissue of rheumatoid arthritis patients upon intravenous administration A similar phenomenon was observed for phosphatidylcholine and cholesterol-based liposomes given to arthritic rats and encapsulation of clondronate, an antiinflammatory therapeutic that reduces bone resorption, resulted in a halt in disease progression and a reversal in inflammation. [18]

Ex. prednisolone, methotrexate

Micelle carrier systems for rheumatoid arthritis treatment

Camptothecin, originally developed as an anti-cancer drug, has recently been proposed as a new method of controlling pannus formation and reducing cartilage degradation. To circumvent problems with solubility and stability, micelles prepared from PEG-phospholipids were used for drug encapsulation. The camptothecin micelles proved to be more effective than free camptothecin at abrogating inflammation when administered to arthritic mice.

Cyclosporine A is indicated for several different conditions; therefore, micelle-based methods for improving the solubility of this DMARD have been more thoroughly researched. [18]

Nanopartical carrier system for rheumatoid artheratis

Ex Betamethasone

Indomethacin

Multifunctional carrier mediated system

A single platform can be used for the release of multiple therapeutics in a controlled fashion or for both therapeutic release and diagnostic imaging. [18]

Gene therapy

Gives the nature of RA gene therapy, nucleic acids are introduced to a cell to either turn off select gene or upregulate therapeutic gene is an alternative treatment strategy.[18]

TOOL LIKE RECEPTOR

An increasing body of information supports the role of the innate system within the pathologic process of atrophic arthritis (RA).

Toll-like receptors (TLRs) are expressed by cells within the RA joint and a variety of endogenous TLR ligands are present within the inflamed joints of patients with RA. [17]

When exposed to an immunogenic stimulus, such as a microbial pathogen, the initiation of the inflammatory and immune response is mediated by Toll-like receptors (TLRs) which result in the activation of cells of the innate immune system including monocytes, macrophages and dendritic cells. [17]

A number of studies have identified the presence of potential endogenous TLR ligands in the synovial tissue of patients with RA, including fibrinogen, HSP 60 and 70, and EDA fibronectin. [17]

Overview of the role of TLRs in RA:

Endogenous TLR ligands are expressed and released as a result of the **inflammation in early RA and may contribute to persistent, destructive disease. In shared epitope positive individuals, the initial insult may be** the result of immune complexes containing anticyclic citrullinated peptides. The pathogenic immune complexes providing the initial danger signal, together with the released endogenous TLR ligands, such as gp96, may result in a self-perpetuating inflammatory process, driven by the persistent expression of macrophage-related cytokines such as TNFα and IL-6. Non-apoptotic Fas FasL signaling may lower the threshold for the activation of synovial macrophages, and possibly synovial fibroblasts, sensitizing them to activation by the endogenous TLR ligands, there by promoting the development of chronic, persistent disease. The release of low levels IFNγ may further sensitize the synovial macrophages to activation by endogenous TLR ligands. Thus, the local environment of the RA joint may provide the milieu for the perfect storm of chronic inflammation. [17]

DRUGS USED IN RA

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have been used to reduce pain in the early stage of RA because of their anti-inflammatory effect, thereby maintaining the articular function. The mechanism of NSAIDs includes blockade of cyclooxygenases, COX-1 and COX-2, which generate prostaglandins (PGs)that play a key role in inducing pain and inflammation. Despite their pain-relieving effect, NSAIDs do not alter the disease progress and articular damage. Hence, NSAIDs are mostly used as an additive drug with other antirheumatic drugs such as DMARDs. The side effects of NSAIDs include gastrointestinal disturbance and renal malfunction. NSAIDs are also known to increase cardiovascular risk due to their activity on blood pressure. Therefore, NSAIDs are generally used at a low dose with careful monitoring of patients' conditions. [18]

Glucocorticoids

Glucocorticoids such as dexamethasone and prednisolone can be highly effective in treating joint inflammation and

may be used as first-line drugs due to their strong anti-inflammatory and immunoregulatory activity. However, their systemic applications are restricted because repeated or long-term use causes a high incidence of severe side effects such as insulin resistance, skin thinning, osteoporosis, hyper-tension, obesity and inhibition of wound repair; nevertheless, approximately 44% to 75% of RA patients still use glucocorticoids. Numerous studies have suggested that low dose glucocorticoids may have disease-modifying effects in RA. For example, low-dose prednisolone when used in combination with other anti-rheumatoid drugs such as methotrexate, significantly reduced the progression of RA. [18]

Disease-modifying antirheumatic drugs (DMARDs)

The term DMARDs was first used in the late 1980sto refer to agents that were believed to have specific antirheumatic activities. Since clinical outcomes of DMARD treatment become apparent 1 to 6 months after the first use, they have also been referred to as 'slowly acting antirheumatic drugs'. Unlike NSAIDs and glucocorticoids, DMARDs alter the course of RA progression, reducing or pre- venting joint destruction. However, DMARDs do not have direct effects on pain relief and anti-inflammatory effects, thus they are frequently used with NSAIDS or glucocorticoids in an early stage of RA. It is difficult to predict whether or not DMARDs will be effective in a given patient, but approximately two-thirds of patients show positive clinical outcomes with DMARDs and the other one-third require other treatments. Several DMARD agents are currently avail-able. The most commonly used DMARD is methotrexate, which has been considered the first-line antirheumatic agent for the past 20 years because of its relatively rapid onset of action, high efficacy and low toxicity, as well as the ease of administration and relatively low cost. The mechanism of antirheumatic effects of methotrexate is still not clear, but it has an antimetabolic activity via inhibition of purine synthesis. Recently, extracellular adenosine release has been suggested as a major mechanism of antirheumatic effects of methotrexate. Other DMARDs include hydroxychloroquine, sulfasalazine, leflunomide and gold salts, which are commonly used methotrexate native to or in combination with methotrexate.[19-21]

CONCLUSION

Targeted drug delivery is currently developing quick. thanks to its potential to deliver medicine at specific sites. This causes injection of a lower amount of dose as well as a significant decrease in side-effects that were more pronounced earlier because of the inefficacy of any drug

Delivery system to deliver medicine at the precise website of action. The application of nanotechnology in drug delivery has particularly enhanced the delivery of drugs. There are numerous nanoparticles that have been approved for clinical use and, although they are still in their development stages, they hold the key to the future of drug-targeting. Several other approaches have also been developed with similar results.

They all define the brilliant way forward for targeted drug delivery. Although the advent of biologics markedly increased the number of available treatment options, numerous rheumatoid arthritis patients still use, either alone or in combination, NSAIDs, GCs, and conventional DMARDs. All of these compounds are associated with severe negative side effects resultant from non-specific organ toxicity. In some cases, the side effects necessitate the cessation of a treatment option that may be effectively altering the course of the disease. The application of drug delivery strategies, as outlined herein, promises to improve patient outcome by reducing the likelihood of an adverse reaction to NSAIDs, GCs, and biologic and conventional DMARDs. These same strategies may be extended in the future to facilitate diagnostic imaging and gene therapy, thereby further increasing the possibility of successfully controlling the progression of the disease in all people that suffer from rheumatoid arthritis.

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