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Delivery strategies to target therapies to inflammatory tissue

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Background: Inflammation plays a key role in many chronic disease processes as well as an acute role in injury and wound healing. Various cell types are recruited from the bloodstream to the inflamed site through adhesion molecules, cytokines, chemokines and others. *Objectives*: This review examines many drug-targeting strategies that make use of these molecules or signaling pathways, and seeks to describe certain commonalities irrespective of the disease process or agent to be delivered. *Methods*: A survey of the literature, primarily within the last year, was performed. Search words included 'drug targeting' and 'inflammation' and of those, the scope was refined to include those studies that specifically sought to modify or ameliorate an aspect of the inflammatory process in the treatment of a disease. *Results/conclusion*: Inflammation plays a key role in many diseases, and many similar targets (such as adhesion molecules) are the focus of the treatment of those diseases.

Keywords: adhesion molecules, chemokines, cytokines, inflammation, liposomes, monoclonal antibodies, nanoparticles

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1. Introduction

Inflammation plays a key role in many disease processes, including vascular disease, rheumatoid arthritis and osteoarthritis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, cancer, and autoimmune diseases, among others. Acute inflammation involves initial responses to harmful stimuli, whereas chronic inflammation leads to an accumulation of cells including leukocytes, monocytes, and macrophages that perpetuate the process and contribute simultaneously to tissue destruction and attempts to repair (including fibrosis and angiogenesis).

Recruitment of leukocytes from the bloodstream to the site of injury or disease is receptor mediated. In inflammation, cellular adhesion molecules (CAMs) expressed on the vascular endothelial cell surface attract leukocytes. CAMs are glycoproteins which have cytoplasmic, transmembrane and extracellular domains [1]. Cytokines increase the expression of CAMs and increase the binding of leukocytes through integrins [1]. Chemokines stimulate adhered leukocytes to move between endothelial cells and pass through the basement membranes of tissue. These can then bind to extracellular matrix proteins. Although these are often viewed as discrete steps, it has been suggested that the inflammatory process should be viewed as a rapid cascade with synergistic, overlapping interactions [2].

The receptors involved in this cascade provide potential targets for drug delivery. For example, CAMs are expressed by nearly every cell type [3], and are characterized by strong ligand binding. They participate in cell to cell and cell to extracellular matrix interactions and in some cases also signaling, migration, motility, gene transcription and differentiation [4,5]. CAMs expressed by the endothelium include the immunoglobulin superfamily CAMs (IgSF CAMs)

Table 1. Some common adhesion molecules and potential applications for targeted delivery.

Molecule/receptor	Location	Role in inflammation	Examples for which molecule could be used for targeting
P selectin	Contained in granules in endothelial cells and platelets; activated by histamine and thrombin	Plays an early role in the recruitment of leukocytes, since it is present 'on demand'	Atherosclerosis [36], cancer [51]
E selectin	Expressed on endothelial cells activated by cytokines IL-1 and TNF	Recruitment of leukocytes; relatively low binding affinity causes 'rolling'	Renal disease [35]
L selectin	Expressed on surface of leukocytes	'Homing receptor' which binds to endothelial cells and allows entry of leukocytes into lymphoid tissue	None currently found
ICAM-1	Present in macrophages, lymphocytes and endothelial cells; expression is upregulated by cytokines	Leukocyte binding and transmigration	Vascular disease [33], lung disease [45]
VCAM-1	Expressed by endothelium after stimulation of cytokines	Promotes the adhesion of lymphocytes, monocytes, eosinophils, and basophils. Also mediates signal transduction between leukocyte and endothelial cell	Appears to promote monocyte recruitment in atherosclerosis [25], cell adhesion in melanoma
CD44	Cell surface glycoprotein, hyaluronic acid receptor	Cell/cell interactions, adhesion and migration	Vascular inflammation [38], and arthritis [39]

ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule.

intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and platelet–endothelial cell adhesion molecule-1 (PECAM-1); integrins (cell surface receptors that interact with cellular matrix); and selectins (responsible for the 'rolling' action of leukocytes in contact with the endothelium [3]. Since endothelial CAMs are at the forefront of inflammatory cell recruitment, they have been widely studied as potential therapeutic targets (for example, [6,7]). Other strategies involve targeting of the monocytes, neutrophils or macrophages, for example, by use of arginine–glycine–aspartate (RGD) liposomes [8]. A summary of some of the adhesion molecules involved in the inflammatory process, their function and examples of their use in targeting disease appear in **Table 1**. Some of the studies involving adhesion molecules also form one focus of the discussion below.

Once the adhesion molecules bind with monocytes, macrophages, lymphocytes or platelets, those bound elements become activated themselves, and release proinflammatory cytokines, membrane receptors, and a myriad of enzymes, including interleukins, TNF-α and interferon-α. The expression of inflammatory proteins creates a positive feedback loop by further inciting uptake of inflammatory cells, promoting aggregation of oxidized low density lipoprotein on the endothelial surface and thus causing injury to the endothelium, and excreting further inflammatory mediators [9]. Some drug targeting strategies under investigation involve the use, manipulation or disruption of the cytokines and chemokines involved in the signaling and recruitment of inflammatory cells, as well as the inflammatory cells themselves as carriers or mediators. For example, a recent review focuses on one of the cytokines, IL-18, as a target for inflammatory and autoimmune diseases. Blockade of IL-18 in animal models prevents disease processes and preserves tissue function in the study of autoimmune diseases [10]. Dinesen *et al.* [11] describe the use of a polyethylene glycol (PEG)-ylated Fab′ fragment of an antibody for TNF-α for drug targeting in Crohn's disease. TNF-α is a proinflammatory cytokine present in the intestinal mucosa, and blocking this cytokine may suppress T-cell differentiation or inflammation. Chono and Morimoto [12] studied the uptake of dexamethasone-loaded liposomes by macrophages and foam cells, which *in vitro* inhibit cholesterol ester accumulation and may represent a possible targeted therapy for atherosclerosis. In an *in vitro* model of inflammatory processes, both the presence of cancer cells and use of histamine to increase endothelial cell layer permeability was shown to increase the migration of liposomes across an endothelial monolayer [13]. Thus, the inflammatory process itself can be taken advantage of to enable drug delivery.

Angiogenesis involves growth factors such as fibroblast growth factor and VEGF. Upregulation of VEGF in particular appears to play a role in vascular injury.

Angiogenesis is a complicated issue, since its inhibition is often desirable in the treatment of cancer, whereas its stimulation may be a treatment strategy for myocardial infarction. In the context of chronic inflammation, however, delivery to sites of angiogenesis is being explored as a therapeutic strategy [14].

A recent review of anti-inflammatory agents for COPD discusses some of the current drugs used to treat systemic inflammation, including statins, ACE inhibitors, angiontensin II type 1 receptor blockers, glycosaminoglycans such as hyaluronan, and PPAR agonists [15]. Although in the treatment of inflammation there is clearly benefit from a systemic approach, drug targeting is important because some of the most potent anti-inflammatory agents, such as glucocorticoids, have significant and far-ranging side effects, including adrenal suppression, hyperglycemia, CNS effects, and effects on the bone and skin. Further, although there are systemic manifestations of inflammation, there is often a focal nature of the disease or injury, specific to certain organs or sites.

Below, some of the recent studies on targeted drug delivery are discussed. The vehicles often include self emulsions, vesicular systems and other nanoparticles; and while some do not use a specific targeting strategy, many are targeted directly at one of the components of inflammation, regardless of the pathology or injury that they are designed to treat. Implantable systems involving hydrogels are also being studied. For example, efforts are being made to reduce inflammation following wounds and surgical interventions, and to improve biocompatibility of implantable devices. Choi and Shin [16] describe the release of NSAIDS from percutaneous gels. Patil *et al.* [17] describe a system of poly(lactic-co-glycolic acid) microspheres embedded in hydrogels for the delivery of VEGF and dexamethasone, which they propose to coat implantable devices to reduce inflammatory response. Yeo *et al.* [18] describe the use of a hyaluronan gel to deliver drugs to prevent peritoneal adhesions following surgery or injury. This is intriguing because hyaluronan (also called hyaluronic acid) is a major component of extracellular matrix (ECM) and is involved in cell proliferation and migration. Thus, hyaluronic acid is itself involved in tissue repair and healing. It also participates in a number of cell surface receptor interactions, notably with CD44. CD44 is a family of adhesion molecules, of which there are at least 10 standard isoforms and 10 variant isoforms, and the most populous is the CD44s isoform. The variation among the forms is found in the ECM domain of the structure and accounts for the variation in function [4]. One isoform is highly expressed in the smooth muscle cells of the intima and media of injured arteries [19]. Others are expressed on the endothelium, suggesting regulatory function of growth factors [20]. Several isoforms are all expressed on macrophages and are all highly regulated by the cytokines [21]. CD44 and hyaluronic acid were shown to mediate leukocyte endothelial cell adhesion, previously thought to be the sole domain of the selectin family [22]. The interactions of CD44 and hyaluronic acid have been implicated in cancer, autoimmune diseases, and inflammatory processes [23]. Its potential as a target in vascular disease is discussed below.

2. Inflammation and vascular disease

Atherosclerosis has been described as a 'chronic inflammatory disease of the arterial system' [24]. Atherosclerosis begins with insult or injury to the endothelium, provoking an inflammatory immune response [25]. Endothelial cell dysfunction continues as the disease progresses [26]. It is the expression of adhesion molecules and the influx of leukocytes that perpetuate the disease. VCAM-1 has been shown to play a major role, binding to monocytes and T lymphocytes [27]. A monocyte crossing the endothelium and entering the tunica intima becomes a tissue macrophage, which then takes up lipids and lipoproteins and further transforms into a foam cell [28]. The build up of foam cells is a characteristic of atherosclerotic plaques. The foam cells produce proinflammatory cytokines which further provoke immune response and promote reactive oxygen species [19]. Eventually the foam cells accumulate in the center of the plaque, die, and form a necrotic core. Death of the foam cells is attributed to either apoptosis or the toxic effects of oxidized lipoprotein uptake [29]. The products of the inflammatory cells within the plaques disrupt the stability of the fibrous cap covering the plaque. Macrophages and smooth muscle cells release proteases, such as collagenase and elastase, which break down the structural proteins collagen and elastin [30,31]. The degradation of elastin also disrupts the ability of cells to move though the plaque [19].

Reviews cover the myriad applications pursued in targeting pharmaceuticals to cardiovascular disease [32,33]. Atherosclerotic lesions, circulating blood cells and elements, and endothelial cells have all been addressed as therapeutic targets. Detection of CAMs expressed on the endothelial surface can be achieved using antibody-directed ultrasound contrast agents [34]. Atherosclerotic plaques can also be targeted using activated bound leukocytes through contrast agent antigen receptors [35]. The potential to direct therapy through imaging and simultaneously control drug delivery and release could address several challenges of inflammatory pathologies as greater understanding of the complex chemical and molecular interactions of inflammatory processes drive plaque buildup, instability and vessel restenosis.

Much work has been done with liposomes in the context of cardiovascular disease [36]. *In vitro* and *in vivo* studies of liposomes and immuno-liposomes as drug carriers to many antigens (ECM components such as collagen, laminin and fibronectin) were addressed. Among the topics reviewed was the targeting of vessel wall injury. Detection of disrupted endothelium has been achieved through targeting of expressed antigens providing a 'signal'. The liposomal antibody–antigen binding mimicked nature: cell binding studies showed a

dissociation constant (that describes the affinity between ligand and protein) on the order of 10^{-9} M, a value similar to physiological antigen to free antibody binding constants [36].

Binding to expressed antigens in the endothelium *in vivo* was shown by targeting ACE and adhesion molecules (ICAM-1 and PECAM-1). Vascular accumulation, endothelial uptake, and increased antioxidant protection were all shown by immuno-targeted liposomes to these molecules [37]. Anti-ICAM-1 targeted immunoliposomes of 100 – 300 nm diameters showed specificity of uptake compared with nonspecific antibodies or large vesicle targeting [38]. Immuno-liposomes targeted to E-selectin have also been shown to bind to glomerular endothelium, and are useful in the delivery of dexamethasone to treat glomerulonephritis, an inflammatory renal disease [39].

Adhesion molecule P-selectin is also expressed on activated endothelial cells and platelets. Targeting P-selectin demonstrated therapeutic efficacy in an atherosclerotic mouse model which was cross bred with a P-selectin null mouse model. Reduction in plaque formation and proliferation of leukocytes was observed. However, the presence of soluble P-selectin in the bloodstream complicates the strategy [40].

Interruption of the inflammatory process has been studied using CD44 blocked by the IgG antibody IM7 [41]. Expression of CD44 and its variants was augmented when exposed to proinflammatory cytokines within human atheroma, implicating its involvement in the pathogenesis of arterial diseases [21]. Hyaluronic acid was shown, in a low molecular weight form, to stimulate VCAM-1 and proliferation of smooth muscle cells, whereas high molecular weight forms of hyaluronic acid inhibit smooth muscle cell proliferation [42]. Atherosclerotic prone ApoE-deficient mice bred with CD44-null mice showed a 50 – 70% reduction in aortic lesions compared with CD44 heterozygous and wild type mice [42]. These results suggest that CD44 promotes atherosclerosis by both mediating inflammatory cell recruitment to atherosclerotic lesions and by altering smooth muscle function [42]. Because of its role in inflammatory processes involved in different disease states, Hood *et al.* [43] have targeted CD44 by conjugating IM7 with non-ionic surfactant vesicles in both inflamed synoviocytes and endothelial cells.

In the setting of cardiovascular disease, not only have chronic inflammatory processes been targeted in the context of atherosclerosis, but shorter term applications have also been explored. For example, to combat restenosis following coronary angioplasty, liposomes have been conjugated with peptide sequences created to target glycoprotein IIb – IIIa receptors on activated platelets [44]. Platelet aggregation and deposition is implicated in the pathogenesis of restenosis through deposition of growth factors and inflammatory mediators. To increase circulation time the vesicle surfaces were modified with an oligodextran polymer, analogous to the use of polyethylene glycol (PEG) groups to elude the reticuloendothelial system (RES) [36].

Positively charged untargeted liposomes were observed to accumulate in experimentally produced myocardial tissues as early as the 1970s; further studies confirmed the propensity for liposomes to accumulate in depolarized myocytes and in ischemic tissues in general [36]. These findings provided the groundwork for liposome passive targeting to ischemic tissue and infarcted heart tissue. Active targeting of antimyosin conjugated immunoliposomes to myocardial tissue was studied *in vivo* and showed good accumulation in the ischemic myocardial tissue. This effect is limited in traditional liposomes when access is restricted because of lack of blood supply and vesicles are eliminated by the RES before accumulation occurs. As with other traditional liposomes, surface alterations by the incorporation of PEG groups along with antibodies provided targeting and prolonged circulation time showed greater penetration [36].

3. Inflammation and lung disease

In the treatment of lung disease, aerosols have been developed to efficiently target drug delivery in the lungs [45], as have antibody-mediated delivery to antigens in the lungs [46], and immuno-liposomes directed to the pulmonary endothelium [37,38,47,48]. Some of the targets for the latter studies include ICAM-1 and PECAM-1. Immuno-liposomes targeted to ICAM-1 were shown to bind to and be internalized by epithelial cells *in vitro*, demonstrating the potential to deliver anti-inflammatory drugs to sites of increased ICAM expression [49]. The mechanisms and techniques of successful targeted and untargeted accumulation of drug delivery vesicles in the pulmonary endothelium are also relevant to developing other vascular inflammation strategies. Barnes [50] provides an in-depth review of research into COPD therapy, including both adhesion molecule and chemokine/cytokine-directed therapy, as well as the disruption of other signaling mechanisms. Very recently, Gaggar *et al.* [51] have shown that the targeting of an ECM-derived neutrophil chemoattractant, proline-glycine-proline, using selective antiproteases, may hold promise in the treatment of inflammatory lung diseases such as cystic fibrosis.

4. Inflammation and arthritis

When one thinks of inflammation, autoimmune diseases such as arthritis immediately come to mind. Recently, an NSAID designed to treat osteoarthritis and other acute pain conditions, a COX-2 inhibitor designed to affect prostacyclin synthesis, was shown to increase adverse cardiovascular events. This not only points out the inter-relationship between inflammation and cardiovascular disease but also suggests the need for more precise targeting strategies. Foged *et al.* [52] have recently tested the targeting of stealth

liposomes to synovial lining in the context of rheumatoid arthritis (RA), delivering short interfering (siRNA) to reduce cytokine expression [52]. Lu *et al.* [53] have studied the use of gelatin microspheres containing flubiprofen (a derivative of phenylalkanoic acid) in an RA model. There are also examples of active targeting. Chandrasekar *et al.* [54] studied an animal model of RA and showed reduced side effects and increased targeting efficiency using folate–polyethylene glycol conjugates of anionic dendrimer loaded with indometacin. Tsai *et al.* [55] have studied the use of gold nanoparticles in a rat model. In synovial fluid, these bound to VEGF, which is an angiogenic factor, and as a result inflammation was reduced. In the study by Hood *et al.* [43], the anti-CD44 conjugated niosomes were shown to bind with high selectivity and specificity to synovial lining cells.

5. Inflammation and other chronic diseases

Naturally, there is much work in progress for targeted therapies to cancer, and some of these focus on the inflammatory component of the disease. For example, a review by Ludwig *et al.* [56] describes the potential use of P-selectin as a therapeutic target for metastatic cancer. Taking their lead from strategies targeting sites of angiogenesis in cancer treatment, Trachsel *et al.* [14] showed that the antibody L19, which targets the extra domain B of fibronectin, a marker of angiogenesis, localizes to sites of chronic inflammation. In a recent review, Van Eldik *et al.* [57] discussed strategies of targeting the upregulation of cytokines in brain disorders, especially Alzheimer's disease. In the context of inflammatory bowel disease, microspheres loaded with low molecular weight heparin (LMWH), administered orally, were shown to be as efficient as rectally delivered and superior to percutaneously delivered LMWH in a mouse model of colitis [58]. Dinesen *et al.* [11] described the specific targeting of TNF-α using an antibody fragment in the treatment of Crohn's disease, citing lower immunogenicity and a subcutaneous route of administration as potential advantages over existing treatments. In an animal model of endotoxin-induced uveitis (EIU) [59], liposomes, without specific targeting, were internalized by inflammatory cells including polymorphonuclear leukocytes and macrophages. Adibkia *et al.* [60] studied piroxicam nanoparticles in EIU in rabbits.

There are doubtless other examples of disease-specific targeting which, in fact, seek to manipulate or take advantage of the inflammatory component of the disease. In summary, these may take advantage of receptors expressed in the presence of inflammation, signals from cytokines or chemokines involved in the process, or through manipulation of the inflammatory cells (such as macrophages) themselves.

6. Conclusions: pitfalls and challenges

A survey of recent research into therapeutic targets and into biomarkers associated with various disease processes, including the inflammatory components of the disease, reveals that similar adhesion molecules and biomarkers are being studied. This raises questions about the specificity of using some of these molecules as targets. Furthermore, some adhesion molecules such as P-selectin have soluble forms, which may confound the targeting strategy [40].

Also, there is still uncertainty regarding the use of certain nanoparticles for delivery vehicles. A recent study reveals that, depending on size and composition, nanoparticles may actually induce inflammation in human aortic endothelial cells [61].

7. Expert opinion

The charge to prepare an article on the subject of targeting inflammation proved to be a daunting challenge. Drug targeting strategies under development involve not only acute inflammation, for applications such as wound healing and for the improved biocompatibility of implanted devices, but also chronic inflammation which is a key component in many disease processes.

However, certain strategies emerged that were similar even for different disease processes; for example, the targeting of adhesion molecules expressed by inflamed cells. Indeed, certain adhesion molecules have been targeted with the goal of treating very different disease processes. An attractive feature in the use of adhesion molecules is that this strategy may actually work in two ways – not only does it provide the ability to deliver the therapeutic agent right to the site where the inflammatory process is active but by binding a drug delivery particle to a receptor such as an adhesion molecule, this could help to block a step in the inflammatory process itself. However, different molecules may be expressed at different times in the process – some occurring earlier rather than later – and some may bind more strongly than others, and so the best choice may require careful consideration of the biologic events of the process. Also, since some adhesion molecules are expressed by different cell types, and some have soluble forms that can enter the bloodstream, there are potential complications regarding how site specific some schemes may be.

A second scheme that emerged through review of recent literature regarding the targeting of inflammation was to essentially take advantage of the inflammation process itself. For example, the use of liposomes which are taken up by macrophages and then transported to the diseased sites through the signaling provided by cytokines and chemokines. Ultimately, then, the inflammatory cell itself becomes the drug delivery agent. This method is being studied for targeting atherosclerotic plaque, for example. This does not involve manipulating or disruption of a link in the chain, as does binding to an adhesion molecule, but rather takes advantage of the existing biologic pathway to ensure delivery from the bloodstream to the desired site. It would seem that this approach has the potential to be very site specific and

selective, assuming that the delivered agent remains active while being transported.

Challenges still remain to achieve optimal targeting. For instance, the use of antibody fragments or other peptides rather than complete monoclonal antibodies is favored by some because of the potential for immune response to whole antibodies. Furthermore, different methods of attachment of antibodies (or other structures) to the particle have been proposed. Depending on the number of binding sites and how far they present above the particle surface, the binding affinities will likely be affected. In addition, as mentioned above, the appropriate target molecule will be dependent on application and requires a good understanding of the inflammatory process.

Nonetheless, there are myriad applications currently under investigation that involve the inflammatory component of disease processes. A portion of the discussion in this paper is related to cardiovascular disease. This discussion provides a road map for the use of traditional drug delivery vehicles, such as liposomes or other nanoparticles, to be introduced into the bloodstream and recruited by inflamed cells. This discussion highlights some of the key players involved in the recruitment of inflammatory cells to subjacent tissue sites, and other studies will be summarized that involve use of similar techniques for delivery to other disease conditions. Variants of some of the adhesion molecules expressed by the endothelium are also expressed by other cell types, such as the synovial lining, and efforts are under way to introduce drug delivery particles through the synovial fluid to treat arthritis. Self-emulsifying agents are also under development for inhalation for treatment of inflammation in lung disease. In this article we will not compare the advantages and disadvantages of the use of a particular particle or route of entry, but rather establish some of the common features involved in targeting the inflammatory process or delivery of anti-inflammatory agents as part of the proposed treatment of many disease processes. Successful targeting schemes should not only be selective for the diseased/inflamed tissue, thus delivering powerful agents very locally, but also block the key processes in the inflammatory cascade, especially by suppressing the activities of the inflammatory cells. This would represent a 'dual pronged' approach to the treatment of inflammation.

Declaration of interest

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