Inflammation-Responsive Polymers

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7.1 INTRODUCTION

Controlled inflammatory response (i.e., acute inflammation) is a natural defense mechanism aimed to eliminate injurious pathogens from the organism while, at the same time, triggering tissue repair ([Kamaly et al., 2013](#)). However, in its chronic uncontrolled form, inflammation may cause serious tissue damage and degenerative diseases like inflammatory bowel diseases (IBD), atherosclerosis, or neurodegenerative disease among others ([Joshi-Barr et al., 2014](#); [Ulbrich and Lamprecht, 2010](#)). There is also clear evidence that the inflammation microenvironment plays a key role in tumor formation and progression ([Zhao et al., 2017](#)).

Nevertheless, currently available drugs for the treatment of inflammation-related diseases (e.g., nonsteroidal antiinflammatory drugs [NSAIDs] and glucocorticoids) present high hydrophobicity and hence low bioavailability ([Wu et al., 2011](#)). This makes necessary the systemic administration of high doses that lead to significant cardiovascular ([McGettigan and Henry, 2011](#)), renal ([Harirforoosh and Jamali, 2009](#); [Whelton and Hamilton, 1991](#)), and gastrointestinal (GI) ([Laine, 2006](#)) side effects, which altogether highlights the importance of developing new inflammation-responsive or inflammation-targeted therapeutics that precisely control the drug release. In the last decades, researchers have described several systems based on inorganic compounds, liposomes, dendrimers, polymers, or composite systems ([Howard et al., 2014](#)).

In particular, this chapter will focus on **inflammation-sensitive synthetic polymers** that can be defined as macromolecules that undergo physical or chemical changes in response to specific features of the inflammatory microenvironment. Therefore to set the basis of the design of these polymeric systems, it is necessary to identify the biomarkers of inflammation and to establish the main differences with healthy tissue.

One of the hallmarks of inflamed tissue is the increased permeability of the blood vessels (Shaji and Lal, 2013). This, like in the case of cancer, allows **passive targeting** of high molecular-weight (≥ 40 kDa), long-circulating macromolecules to sites of inflammation, a phenomenon first observed by Matsumura and Maeda in 1986 (Matsumura and Maeda, 1986). In the case of inflamed tissue, retention occurs due to inflammatory cell sequestration as opposed to retarded lymphatic drainage in solid tumors. This is the reason why this effect is known as extravasation through leaky vasculature and the subsequent inflammatory cell-mediated sequestration (ELVIS) in contrast to the enhanced permeation and retention (EPR) effect in tumors (d'Arcy and Tirelli, 2014).

Furthermore, during the inflammatory processes the number of leukocytes in the bloodstream substantially increases. Most of these white blood cells are recruited to the site of inflammation and have the capacity to extravasate from blood vessels to the diseased tissue. Based on this and on the phagocytic capacity of some of these cells (e.g., macrophages), a novel strategy to target inflammation sites, known as **cell-mediated targeting**, is gaining importance (Dong et al., 2017).

Nevertheless, **direct targeting** to inflamed areas is also possible due to the upregulation of a number of cell surface receptors that occurs upon inflammatory activation. The most studied ones are cell adhesion molecules (CAMs) such as selectins, immunoglobulin gene superfamily (IgSF), and integrins; and those receptors overexpressed in the surface of activated macrophages including mannose receptor (MR) (Coco et al., 2013), folate receptor (FR), or scavenger receptor (SR), and CD44 (d'Arcy and Tirelli, 2014), among others.

Other characteristic features of pathologically inflamed tissue that may be considered when designing inflammation-responsive polymers are: (i) **reduced pH** (~ 6.4) with respect to healthy tissue (~ 7.4) (Shaji and Lal, 2013) due either to the bacterial metabolites in the case of infection-associated inflammatory processes or to the hypoxic conditions that induce a shift toward anaerobic glycolysis and lactate formation (Li et al., 2017); (ii) **high oxidative stress**, with reactive oxygen species (ROS) levels 10- to 1000-fold higher than in normal human plasma (Xu et al., 2016); and (iii) **overexpressed inflammatory and matrix-remodeling enzymes** like MMPs (particularly MMP-2 and MMP-9), ureases, cathepsins, elastases, or phospholipases A2 (PLA2s) (d'Arcy and Tirelli, 2014).

Furthermore, heat is one of the five cardinal signs of inflammation (i.e., pain, redness, swelling, loss of function, and heat) (Chandrasoma, 2013) and, therefore, temperature-responsive polymers seem to be interesting for targeting sites of inflammation. However, this strategy may only work for inflammation occurring on the skin's surface where temperature usually varies between 33.5°C and 36.9°C (Bierman, 1936), and the inflammation-related extravasation of a large amount of blood at body core temperature leads to an increase of the normal temperature. This phenomenon cannot be extrapolated to internally occurring inflammatory processes where tissue is already at physiological temperature (Chandrasoma, 2013).

It is demonstrated that inflammation is a hallmark of tumor development and progression (Diakos et al., 2014). In fact, most of the aforementioned inflammation markers are shared with cancer characteristics like increased vessel permeability (Howard et al., 2014), increased oxidative stress (Reuter et al., 2010), lower pH (Kato et al., 2013), and overexpression of certain proteins (e.g., MMPs and cytokines) (Landskron et al., 2014; Kessenbrock et al., 2010). Due to all these similarities, almost any polymer-based structure that undergoes changes in inflammatory conditions will behave similarly in cancer areas (Sun et al., 2013).

pH-responsive polymers have been widely explored to obtain inflammation-responsive systems; the most explored approaches are (i) polymeric prodrugs based on a hydrophilic polymer and a hydrophobic drug linked by acid-labile hydrazone bonds (Li et al., 2017; Liu et al., 2010), and (ii) polymeric systems based on groups that undergo accelerated hydrolysis under acidic conditions (e.g., esters, amides, ketal, acetal, or orthoesters) (Lee et al., 2015; Yuan et al., 2014; Coco et al., 2013; Yang et al., 2008). Moreover, in recent years, pH-labile bonds and hydrazone linkage have primarily been studied as a way to overcome the so-called poly(ethylene glycol) (PEG) dilemma. PEGylation of molecules or carriers increases their circulation time and enhances the EPR effect, however PEGylation also avoids recognition by cell surface receptors and internalization of the carriers. pH-sensitive hydrazone linkage has been used to trigger dePEGylation of PEGylated molecules of carriers at the inflammation or cancer site to favor these processes.

An overaccumulation of ROS is also considered a biomarker of inflammation, therefore other types of inflammation-responsive polymers are those containing bonds that lyse in the presence of these ROS. One of the pioneered inflammation-responsive polymeric drug delivery systems described were biodegradable hydrogels of cross-linked hyaluronic acid (HA), which specifically degrades in the presence of hydroxyl radicals (Nobuhiko et al., 1992). Since then, different architectures based on HA have been used with this aim (Nobuhiko et al., 1993; Bijukumar et al., 2016). More recently, other redox-responsive polymers have also been exploited

for targeting inflammatory areas or for treating inflammation-related diseases reducing local oxidative stress. Some examples include copolymers containing polysulfide hydrophobic blocks (Fu et al., 2014; Rehor et al., 2005; Yi et al., 2016), thioketal-based polymers (Wilson et al., 2010; Martin et al., 2014; Knipe et al., 2016), polyoxolates (Yoo et al., 2013; Kim et al., 2011), or boron-based polymeric systems (Jager et al., 2016). Other interesting redox-sensitive polymer structures that are still uninvestigated for inflammation treatment have been exploited in the frame of cancer therapies such as diselenides (Sun et al., 2013).

A more recent approach involves polymers that can be degraded by inflammatory enzymes. These polymers present enzyme-labile bonds that are cleaved at inflammation site and may release an active compound at a rate and location depending on the extent of overexpression of the specific enzyme (d'Arcy and Tirelli, 2014). This strategy has been used mainly in the frame of cancer therapies and specifically using MMP-2 (Ke et al., 2016; Zhu et al., 2014). Moreover, enzyme-cleavable linkages' potential to overcome PEG dilemma in cancer has been investigated in the last few years with interesting results in vitro (Ke et al., 2016). Regarding inflammation-responsiveness, there are also some examples of polymeric systems containing neutrophil elastase (Aimetti et al., 2009), urease (Xu et al., 2013), or MMP-9-labile (Steinhagen et al., 2014) structures. Polymeric structures that allow imaging overexpressed enzymes in sites of inflammation like COX-2 have also been reported for the early clinical detection of inflammation-related diseases (Seo et al., 2016).

Currently, dual-responsive polymeric systems combining two of these strategies are also being designed for treatment of inflammation-related diseases (Kwon et al., 2013; Daniel et al., 2016; Mahmoud et al., 2011). An example of dual-responsive polymers described in the bibliography is a polythioether ketal that structurally contains a thioether moiety acting as a solubility switch when it becomes oxidized to a sulfone, as well as a ketal group that undergoes accelerated hydrolysis at acidic conditions (Mahmoud et al., 2011).

Inflammation-responsive polymers described in the bibliography include: (a) linear polymeric prodrugs that incorporate the bioactive molecule in their backbone (Kwon et al., 2013; Mahmoud et al., 2011); (b) linear homopolymers or copolymers and amphiphilic block copolymers that form micro- and nanoparticles (Naeem et al., 2014; Lee et al., 2015; Li et al., 2017; Nobuhiko et al., 1993; Rehor et al., 2005; Yoo et al., 2013); (c) dendrimers (Huang et al., 2016); (d) hydrogels (Nobuhiko et al., 1992; Ito et al., 2007), (e) bioactive films (Xu et al., 2013; Steinhagen et al., 2014; Wu et al., 2015), or (f) scaffolds (Martin et al., 2014; Yuan et al., 2014).

These inflammation-sensitive polymeric systems have been designed for different applications such as drug delivery systems (Mountziaris et al., 2011; Zhang et al., 2015b; Lee et al., 2015; Li et al., 2017; Nobuhiko et al., 1993;

Bijukumar et al., 2016) for the treatment of inflammation-related diseases such as atherosclerosis, ischemia, rheumatoid arthritis, coronary artery disease, IBD, or, the most studied one, cancer. Moreover, bioactive films based on these kinds of polymers have been used as implant coatings to reduce the so-called foreign body reaction to implanted biomaterials (Kim et al., 2011; Wu et al., 2015; Mercanzini et al., 2010). Finally, they have also been used for imaging purposes for the early diagnosis of inflammation-related diseases (Seo et al., 2016; Rossin et al., 2008).

7.2 INFLAMMATORY MICROENVIRONMENT

The design of inflammation-responsive polymer structures requires an extensive study on the microenvironment of the inflamed areas. Thus the main hallmarks of inflammation will be described emphasizing the differences between inflamed and healthy tissues.

7.2.1 Inflammatory Vasculature and Passive Targeting

Endothelial cells lining healthy vasculature serve as a dynamic barrier between blood and normal tissue. It allows the extravasation of solutes and small molecules while restricting the passage of large molecules or cells (Claesson-Welsh, 2015). However, in certain pathologies including inflammation and cancer, the newly formed vasculature presents structural abnormalities like thinner and fenestrated walls (d'Arcy and Tirelli, 2014). More specifically, these blood vessels are characterized by a higher number of proliferating endothelial cells, deficit of pericytes, or aberrant basement membrane leading to increased permeability (Shaji and Lal, 2013).

In 1986, Matsumura and Maeda (1986) observed for the first time that this increased permeability allows passive accumulation of high molecular weight molecules (>40 kDa; i.e., molecular weight cutoff for glomerular filtration) in murine solid tumors. Nowadays, this mechanism is known as an EPR effect and consists of the preferential accumulation in tumor beds of long-circulating large molecules through leaky vasculature (Fang et al., 2011), although this phenomenon has not only been seen in tumors but also in inflammation-related diseases. In 1971, Kushner and Somerville observed a similar phenomenon with proteins in arthritic joints. The proteins' concentration in the synovial fluid of the diseased joint depended on the protein molecular weight and the degree of inflammation (Kushner and Somerville, 1971). Three decades later, Wang et al. (2004) demonstrated the extravasation of plasma albumin into arthritic synovium by intravenously injecting a strong albumin-binding dye in a rat model of adjuvant-induced arthritis. And then, in 2007, was the first report of an

FIG. 7.1 Representation of the differences and common points between ELVIS and EPR effects.

analogous passive accumulation mechanism of dexamethasone-based polymeric prodrugs administered systemically in an adjuvant-induced arthritis rat model (Wang et al., 2007).

However, there exist some significant differences between EPR effect in cancer and ELVIS effect in inflammatory diseases (Fig. 7.1). In 2010, Quan et al. (2010) attributed the observed passive accumulation into inflamed tissue to the enhanced vascular permeability in arthritic joints and the internalization of a dexamethasone-containing polymeric prodrug by synovial cells. Therefore in inflamed tissue, the retention occurs due to the inflammatory cells' sequestration of the molecule (d'Arcy and Tirelli, 2014). In contrast, molecules are retained in the interstitial space of tumors because of the reduced lymphatic drainage (Kobayashi et al., 2014). To distinguish between both phenomena, the acronym ELVIS (extravasation through leaky vasculature and the subsequent inflammatory cell-mediated sequestration) is currently used to refer to the effect observed in inflamed tissue (d'Arcy and Tirelli, 2014).

In the last decade, the ELVIS effect has been exploited for passive targeting of polymeric systems into inflammation sites with the aim of increasing the efficacy of drugs (e.g., glucocorticoids and NSAIDs) and reducing their toxicity by minimizing the dose. For that purpose, there are a wide variety of polymeric systems based on NSAIDs and glucocorticoids described in the literature. However, to date, most of the in vivo biodistribution studies demonstrating the ELVIS effect involve glucocorticoids (Wang et al., 2007; Ishihara et al., 2009; Liu et al., 2010; Ren et al., 2014; Knudsen et al., 2015; Yuan et al., 2012) and only a reduced number use polymeric vehicles based on NSAIDs (Clond et al., 2013).

Although there are some reports of microparticulated carriers (Yang et al., 2008), the main polymeric vehicles studied are drug-polymer conjugates (Liu et al., 2010; Quan et al., 2010) and nanoparticles (Lee et al., 2015; Purdue et al., 2013; Zhao et al., 2017) because passive targeting is enhanced using carrier diameters between 100 and 150 nm.

7.2.2 Inflammatory Cells and Leukocyte-Mediated Targeting

During an inflammatory process, there is a significant increase in the number of leukocytes (white blood cells [WBCs]) in circulation (Dong et al., 2017). These cells are recruited into disease sites, and some of them (i.e., neutrophils, macrophages, and monocytes) also perform phagocytic functions. When polymeric nanotherapeutics are administered systemically, they are cleared from circulation by WBCs resident in reticuloendothelial system (RES) organs but also by those migrated to the site of inflammation (Shaji and Lal, 2013). Therefore the capacity of these cells to extravasate into inflamed tissue and their phagocytic function makes them perfect candidates for the targeted transport of nanotherapeutics to inflammation sites for the treatments of inflammation-related diseases (Anselmo et al., 2015).

Recent studies demonstrated the feasibility of the leukocyte-mediated targeting approach (Anselmo and Mitragotri, 2014; Batrakova et al., 2011). The two main strategies explored up to date are (1) nanoparticles attached to the surface of leukocytes or (2) nanoparticles internalized by leukocytes. Regarding the first strategy, it is important to design the polymeric system in such a way that it does not affect the leukocyte-binding functions (Dong et al., 2017). Moreover, nanoparticles can be targeted to leukocytes in vivo or in vitro, followed in the last case by an administration of the nanoparticle-leukocyte complex to animals (Dong et al., 2017). In particular, this approach has been used with nanoparticulated systems for the treatment of inflammation-related diseases of the central nervous system (CNS) (Tong et al., 2016; Batrakova et al., 2007), the skin and lungs (Anselmo et al., 2015), or cardiovascular tissue (Lee, 2014). However, there are only a few examples in the bibliography involving polymeric nanocarriers (Anselmo and Mitragotri, 2014; Batrakova et al., 2007) meaning that it is barely explored, but it is an emerging and interesting field of research.

7.2.3 Overexpressed Cell-Surface Receptors and Active Targeting

Some cell-surface receptors are upregulated in inflammatory cells, and hence active targeting to inflammation sites may be achieved by functionalization of polymeric carriers with specific receptor ligands (d'Arcy and

Tirelli, 2014). This active targeting may translate into an enhanced selective accumulation of drugs in the lesion sites by affinity ligand-receptor interactions, increasing their efficiency and reducing adverse effects.

In particular, CAMs (i.e., selectins, immunoglobulin gene superfamily (IgSF), and integrins) are cell surface transmembrane receptors involved in binding with other cells or with ECM that are essential for the regulation of an immune response and extravasation of inflammatory cells into inflamed areas (d'Arcy and Tirelli, 2014). They have been demonstrated to be upregulated in several inflammation-related diseases like ischemic stroke (Supanc et al., 2011), atherosclerosis (Gargiulo et al., 2016), cancer (Paschos et al., 2009), periodontal disease (Crawford and Watanabe, 1994), and inflammatory diseases of the skin, kidneys, GI tract, brain, and liver, among others (Paschos et al., 2009; Frijns and Kappelle, 2002; Molitoris and Marrs, 1999; Barker, 1995).

The selectins are a family of three calcium-dependent transmembrane glycoproteins, including endothelial-selectin (i.e., E-selectin or ELAM-1), markedly overexpressed in an endothelial cell surface when they are activated by proinflammatory factors (e.g., TNF- α [tumor necrosis factor alpha] or interleukin-1 [IL-1]) (Jubeli et al., 2012); platelet-selectin (P-selectin), expressed in platelets as well as in endothelial cells; and leukocyte-selectin (L-selectin), which mediates the interaction between leukocytes and endothelium during the inflammatory processes (Newman et al., 2009).

Besides, the most important members of the IgSF for inflammation targeting are intercellular adhesion molecule-1 (ICAM-1 or CD54) and vascular cell adhesion molecule-1 (VCAM-1 or CD106). In particular, VCAM-1 expression has been confirmed to increase on endothelium of atherosclerosis models or in models of colonic inflammation (Charoenphol et al., 2011; Deosarkar et al., 2008). In case of ICAM-1, overexpression has also been observed in all subtypes of atherosclerotic lesions (Helbing et al., 2010) and in inflammation-related disorders of the CNS (Wong and Dorovini-Zis, 1992).

Regarding the integrin family, one common target in antiinflammatory therapies is the $\alpha_v\beta_3$ integrin, which is a heterodimeric surface receptor expressed by endothelial cells and macrophages associated with neovascularization (Shaji and Lal, 2013). It facilitates adhesion and migration of cells of the immune system during inflammatory processes and has been extensively studied in models of inflammatory diseases (Koning et al., 2006; Wilder, 2002). Moreover, the VCAM-1-binding $\alpha_4\beta_1$ integrin has also been targeted in other inflammation-related diseases like IBD (Singh et al., 2016).

Receptors overexpressed on the surface of activated macrophages, including the folate receptor (FR), the mannose receptor (MR), and the scavenger receptor (SR) have also been exploited as targets in inflammation

(d'Arcy and Tirelli, 2014; Shaji and Lal, 2013). Activated macrophages are present in several diseases like rheumatoid arthritis, atherosclerosis, lupus, inflammatory osteoarthritis, diabetes, or ischemia reperfusion injury (Shaji and Lal, 2013). Therefore these receptors may allow a macrophage-targeted treatment of almost any inflammatory disease. Most of the studies in the literature in previous years target FR, MR, and SR for treatment or imaging of arthritic joints, atherosclerotic plaques, and cancer (Benchaala et al., 2014; Yang et al., 2017b).

Furthermore, CD44, a cell-adhesion molecule exposed on leukocytes and parenchymal cells surface, and its ligand (i.e., hyaluronan [HA]) have been implicated in several inflammatory diseases (Tamura et al., 2016; Beldman et al., 2017). In fact, several HA-based therapeutics has been designed to selectively target CD44 for the noninvasive detection of atherosclerotic plaques (Beldman et al., 2017) and for the treatment of other inflammation-related disorders (Tamura et al., 2016).

Moreover, tissue-specific features can be targeted to achieve an efficient drug delivery or to visualize inflamed tissue. For example, the brain demands high amounts of glucose as its main energy source. This singularity can be exploited to target glycosylated antiinflammatory prodrugs to those areas. The idea is to bind these glycosylated drugs to glucose transporter 1 (GLU1) in such a way that they may overcome the blood-brain barrier (BBB) (Fan et al., 2011).

These are only some examples of the most studied upregulated surface receptors in polymer-based antiinflammation therapies. However, for each specific disease and inflammatory cell, there are different overexpressed receptors that can be used for active targeting, but this is out of the scope of this work. In this chapter, we will focus on the smart polymeric systems actively targeted to sites of inflammation by means of these receptors.

7.2.4 Acidosis

Local extracellular acidification has been demonstrated at sites of ischemia and inflammation. The pH in inflamed areas is about 6.4, one point lower than pH values in healthy tissue (d'Arcy and Tirelli, 2014).

Hypoxia is one of the characteristic features of inflamed tissue. This lack of oxygen may cause the change from aerobic to anaerobic metabolism to sustain the organism's energy requirements. The switch between the oxygen-dependent mitochondrial respiration to the oxygen-independent glycolysis transduces into an increased lactic acid production and, hence, into acidosis (Li et al., 2017). Moreover, in the case of infection-associated inflammation, bacterial metabolites like D-lactate may also contribute to acidification of interstitial spaces (d'Arcy and Tirelli, 2014).

Regardless of the cause, the acidic environment observed in inflammation-related diseases has been widely studied as a potential

trigger for controlled drug delivery in disease sites using different strategies. In particular, pH-sensitive polymeric vehicles such as nanoparticles (Li et al., 2017; Aldayel et al., 2016), microparticles (Mountziaris et al., 2011, 2012), nanogels (Knipe et al., 2016), hydrogels (Ito et al., 2007), dendrimers (Huang et al., 2016), polymer-drug conjugates (Liu et al., 2010), scaffolds (Yuan et al., 2014), and bioactive coatings (Wu et al., 2015) have been extensively studied.

7.2.5 Reactive Oxygen Species

ROS, like superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$), or peroxynitrite ($ONOO^-$) are produced from several endogenous sources. However, the major site of ROS production in most mammalian cells is the mitochondria mainly through oxidation-reduction reactions occurring in the electron transport chain during aerobic respiration (Xu et al., 2016). At physiological moderate tissue levels, these free radicals play key roles in cell-signaling pathways, which are critical to preserve and control cellular functions like growth, migration, proliferation, and survival (Chatterjee, 2016). However, high levels of ROS can cause damage to several biomolecules including DNA, proteins, and lipids (Zhang et al., 2015a). To avoid oxidative damage, it is necessary to maintain a balance between generation, transformation, and elimination of ROS to preserve normal metabolic activity (Xu et al., 2016).

During acute inflammatory response, ROS accumulation facilitates clearance of tissue-invasive pathogens. Nevertheless, when inflammation becomes chronic, ROS are produced for prolonged periods promoting oxidative stress (Chatterjee, 2016), which is a classical and ubiquitous marker of inflammatory pathologies such as atherosclerosis (Mugge, 1998), neurodegeneration (Uttara et al., 2009), IBDs (Bhattacharyya et al., 2014), rheumatoid arthritis (Mateen et al., 2016), and cancer (Sullivan and Chandel, 2014), among others.

For example, the average H_2O_2 level in normal human plasma is $3\mu M$, whereas activated macrophages produce from 10- to 1000-fold higher local H_2O_2 concentration (Joshi-Barr et al., 2014). In particular, in the brain, extracellular H_2O_2 concentration can reach values of $100\mu M$ during ischemia and reperfusion (Hyslop et al., 1995). In these areas, oxidative stress causes modification of neuronal proteins and structural components leading to neuroinflammation and loss of cognitive function in Alzheimer's disease, Parkinson disease, or Multiple Sclerosis (Uttara et al., 2009). Besides, ROS overproduction may cause disruption of the GI tract barrier leading to increased gut permeability and contributing to inflammation in a variety of GI diseases (Bhattacharyya et al., 2014). In inflammatory lung disease, respiratory lining cells experience 20-fold higher H_2O_2 levels than in healthy tissue (Kostikas et al., 2003).

This redox microenvironment defines the difference between healthy and inflamed tissue and, hence, can be exploited as marker of inflammation-related diseases for detection, diagnosis, and therapy. In particular, different ROS-responsive polymers including polymer-drug conjugates that self-assemble into nanoparticles (Clond et al., 2013; Wilson et al., 2010; Jager et al., 2016), microparticles (Nobuhiko et al., 1993), cross-linked hydrogels (Nobuhiko et al., 1992; Ito et al., 2007), bioactive coating (Kim et al., 2011), and scaffolds (Martin et al., 2014) have been widely investigated in the last decades because of their potential as drug delivery systems to sites of inflammation (Wilson et al., 2010; Bijukumar et al., 2016) or as tools for the early diagnosis and monitorization of inflammatory-related diseases (Sowers et al., 2014; Seo et al., 2016).

7.2.6 Overexpressed Inflammatory and Matrix-Remodeling Enzymes

Among the main targets of antiinflammatory therapies are all cyclooxygenase isoforms (COX-1 and COX-2) (Ricciotti and FitzGerald, 2011; Cho et al., 2015). They are important biological mediators of inflammation that catalyze the conversion of phospholipids into arachidonic acid and then to eicosanoids, a class of inflammatory mediators that includes prostaglandins (d'Arcy and Tirelli, 2014). In particular, COX-2 is considered to be upregulated in inflamed tissue (d'Arcy and Tirelli, 2014; Uddin et al., 2016), and therefore it is considered an important target for the treatment of inflammation disease as well as for an early diagnosis of inflammation-related diseases including cancer (Uddin et al., 2016).

Moreover, the dynamic state of ECM in inflammation sites is well known. Its constant remodeling facilitates leukocyte infiltration and angiogenic processes, and implies the overexpression of certain inflammation-related matrix-remodeling enzymes (e.g., MMPs, cathepsins, or elastases) (d'Arcy and Tirelli, 2014). In addition, during infection-associated inflammatory processes, bacteria produce some specific enzymes like urease or azoreductase that possess proinflammatory capacity (Uberti et al., 2013).

In the last few years, different polymers containing enzyme-cleavable structures including bioactive coatings (Steinhagen et al., 2014), membranes for wound dressing (Xu et al., 2013), hydrogels (Aimetti et al., 2009; Zhang et al., 2015b), dual-sensitive nanoparticles (Naeem et al., 2014; Daniel et al., 2016), and microencapsulated nanogels (Knipe et al., 2016) have been developed as novel potential drug delivery systems for inflammation-related diseases. However, this strategy has been much widely studied within the scope of cancer therapies (Zhu et al., 2014; Ke et al., 2016).

7.3 KEY TYPES AND PROPERTIES OF INFLAMMATION-RESPONSIVE POLYMERS

7.3.1 Passively Targeted Polymers

There are two critical design factors that should be taken into account for a successful passive targeting of polymeric systems to sites of inflammation. First, the polymeric system circulation time should be maximized to favor accumulation in the disease site. For this purpose, the polymeric structures should have a molecular weight higher than 40 KDa, which corresponds to the glomerular filtration limit. In addition, highly hydrophilic polymers like PEG, the most widely used, can be incorporated in the outermost layer to stealth the system, avoiding opsonization, a protein adsorption process that facilitates carrier elimination through the RES (Banik et al., 2016).

Second, it should be taken into account that the lymphatic drainage in inflamed tissues is preserved and, hence, sequestration and uptake of the polymer-drug complex by inflammatory cells plays a key role in retention (d'Arcy and Tirelli, 2014). Then, either the drug is linked to the polymer by a rapidly cleavable acid/ROS/enzyme-labile bond in such a way that the release occurs almost immediately after being exposed to the inflammatory microenvironment, or the polymeric system should be designed to promote endocytosis by inflammatory cells.

The easy internalization can be achieved either through direct ligand-receptor interactions (i.e., active targeting) or by tailoring the size, shape, and surface of polymeric carriers. Regarding shape, it has been demonstrated that spherical systems are easier to internalize than nonspherical ones. Besides, it has been reported that nanoparticles smaller than 100 nm in diameter are prone to clearance by lymphatic vessels in the skin (Cheng et al., 2015), and therefore to avoid lymphatic drainage and favor retention, polymeric nanosystem should be larger than 100 nm. Moreover, He et al. (2010) have concluded that a combination of high-surface charge and large nanoparticles (diameter = 200–500 nm) is the most effective way for an optimum uptake by macrophages. However, nonphagocytic cells internalize only those systems smaller than 150 nm in diameter. Finally, a positive surface charge also favors endocytosis as it opposes the charge of the cell membrane phospholipids (Banik et al., 2016).

ELVIS has been demonstrated in several inflammation-sensitive polymer-drug conjugates. Since its first description in 2007 (Wang et al., 2007), the selective retention of pH-sensitive HPMA-dexamethasone prodrugs (P-Dex, Fig. 7.2) in inflamed areas has been supported by various in vivo biodistribution studies. For example, Quan et al. (2010) observed local retention of P-Dex in the synovial cavity of rats with adjuvant-induced arthritis. The same effect was reported by Yuan et al. (2012) in

FIG. 7.2 *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-dexamethasone conjugate. Hydrazone bond in red.

lupus-prone female (NZB×NZW)F1 mice with accumulation in the inflamed kidneys; by [Knudsen et al. \(2015\)](#) in the inflamed temporomandibular joint of juvenile rats; or by [Quan et al. \(2016\)](#) in the diseased joint on a collagen-induced arthritis mouse model. Moreover, a study in dextran sulfate sodium-induced mice ulcerative colitis ([Ren et al., 2015](#)) found that the glucocorticoid-based prodrug passively targeted the inflamed colon, and retention was achieved thanks to epithelial cells and local inflammatory infiltrates. The same prodrug was also tested for prevention of wear particle-induced osteolysis and the loss of fixation in a murine prosthesis failure model ([Ren et al., 2014](#)), and it demonstrated reduced systemic toxicity thanks to the selective local retention. The therapeutic efficacy of this P-Dex conjugate relies not only on the selective accumulation via ELVIS effect into inflamed tissue but also on the controlled drug release achieved by the cleavage of the **hydrazone bond** (in red, [Fig. 7.2](#)) at low pH conditions ([Wang et al., 2007](#)).

Besides, [Liu et al. \(2010\)](#) designed a PEG-Dexamethasone polymer-drug conjugate for the treatment of rheumatoid arthritis based on the same passive targeting and **hydrazone bond** linkage strategy. They confirmed via in vivo imaging the accumulation of the conjugates in the joints and the enhanced therapeutic effect with respect to the free drug.

The passive targeting of inflammation-responsive nanomedicines to inflamed tissues based on enhanced permeability has also been demonstrated in vivo. In 2013, [Clond et al. \(2013\)](#) showed accumulation of an ibuprofen/tocopherol-based nanoprodrug in traumatic brain injury in mice using confocal and bioluminescence imaging. In this case, the drug

delivery was also pH-dependent; it occurred through the accelerated hydrolysis of esters bonds between ibuprofen and a derivative of PEG.

Aldayel et al. (2016) confirmed an increased biodistribution of small interfering RNA (siRNA) in inflamed areas of a mouse model of lipopolysaccharide-induced chronic inflammation when it was encapsulated by acid-sensitive sheddable PEGylated poly(lactic-co-glycolic acid) (PLGA) nanoparticles incorporating hydrazone bonds. The same pH-responsive strategy was used to increase the retention of PEG-prednisolone nanocarriers in a mouse model (Li et al., 2017). The authors demonstrated that the PEG external layer increases the nanoparticles' circulation time and, in consequence, the concentration of the drug in plasma and arthritic joints was also increased. Once the nanomicelles encountered the acidic environment in inflamed joints, the acid-labile bonds were cleaved and prednisolone was selectively released locally.

All these *in vivo* models have shown the enhanced therapeutic effect and the reduced systemic toxicity of the polymeric prodrug and nanomedicines with respect to the free drug.

7.3.2 Cell-Mediated Targeted Polymers

The literature about leukocyte-mediated targeting to sites of inflammation involving smart polymeric structures is limited. Besides, the reduced number of reported studies employ the *in vitro* strategy to form the polymer-cell conjugate. Furthermore, all of them involve pH-responsive nano-sized systems that could be either nanoparticles (Batrakova et al., 2007; Brynskikh et al., 2010; Haney et al., 2011) or polyelectrolyte multilayers with dimensions in the nanoscale (Anselmo et al., 2015).

In 2007, Elena and coworkers (Batrakova et al., 2007) described a pH-responsive nanocarrier based on a cationic block copolymer, poly(ethyleneimine)-poly(ethylene glycol) (PEI-*b*-PEG), that encapsulated catalase (an anionic ROS-scavenging enzyme) by ionic interactions. The PEI-*b*-PEG-based nanocarriers were stable in a pH range between 7.4 and 11. Out of this range, like the low pH encountered in inflamed tissues, either the catalase or the copolymer becomes discharged and nanoparticles destabilize delivering the cargo. In an *in vitro* study, they demonstrated that the particles were rapidly taken up by bone marrow-derived macrophage (BMM), and in an *in vivo* mouse model of Parkinson disease, they confirmed the accumulation of BMM containing the particles into neuroinflammatory sites. Moreover, in contrast with the free enzyme, the encapsulated catalase retained its catalytic activity, and it is delivered in a controlled manner to the inflammation site.

Similar monocyte-mediated targeting strategies using the same pH-responsive polymer (PEI-*b*-PEG) were described in 2010 and 2011 for

the treatment of other inflammation-related neurodegenerative diseases (Brynskikh et al., 2010; Haney et al., 2011).

More recently, in 2015, Anselmo et al. (Anselmo et al., 2015) described a novel strategy in which monocytes are used as carriers, but the polymeric particles (i.e., cellular backpacks [BPs]) are attached to their surface instead of being phagocytosed. These BPs were based on polyelectrolyte multilayers of pH-sensitive polymers (i.e., poly(methylacrylic acid) (PMAA), poly(vinylpyrrolidone) (PVP), and poly(allylamine hydrochloride) (PAH)). The first layer of PMAA and PVP dissolved when exposed to a pH below 6.5 (i.e., the acidic pH of inflammation microenvironment) due to the ionization of the acid, whereas the other layers remained unaltered. Besides, the last PAH layer was chemically modified (PAH-biotin₄) to selectively attach to circulating monocytes. The successful targeting to inflamed tissue of the monocyte-BP complex was demonstrated in *in vitro* and *in vivo* mouse models of skin and lungs.

Nevertheless, this strategy requires a careful design of the polymeric system to avoid cell internalization and prolong cell-surface exposure. As demonstrated that rounded shapes facilitate cell internalization of nanocarriers, spherical NPs are more suitable for the approach involving endocytosis whereas nonspherical ones are preferred for the leukocytes' surface attachment. For instance, in the previous example, Anselmo et al. designed the BPs with a size, disk-like shape, and flexibility *in vivo* that prevented them from undergoing phagocytosis.

These studies are clear examples of the potential of monocytes and macrophages as targeted carriers of smart nanotherapeutics for an improved treatment of inflammation-related diseases. However, it is a barely unexplored research field that will raise increased interest in the next several years.

7.3.3 Active Targeting

Active targeting of polymeric inflammation-responsive carriers to inflammation sites is a relatively novel strategy. In the last decade, pH, ROS, and enzyme-sensitive polymeric systems have been reported to effectively target sites of inflammation using an active receptor-ligand approach (Table 7.1).

The most widely studied structures are those undergoing changes in response to variations in pH. The simplest strategy is based on the **accelerated hydrolysis** of ester bonds under acidic conditions found in inflammation microenvironments. In 2014, Shin et al. (2014) described a hyaluronic acid-methotrexate conjugate (HA-MTX) based on an ester linkage between the polymer and the drug that was effectively internalized by active macrophages via the specific binding of HA and the overexpressed surface receptor CD44. In an *in vivo* mouse model of collagen-induced

TABLE 7.1 Receptor-Ligand Pairs Used to Target Inflammation

Receptor	Ligand	Reference
Folate	Folate	Yang et al. (2016)
Scavenger	Dextran sulfate	Yang et al. (2017b)
Mannose	Mannose	Yu et al. (2013) and O'Mary et al. (2017)
CD44	Hyaluronic acid	Tamura et al. (2016) and Homma et al. (2010)
ICAM-1	Major ligand-binding domain (I domain) of Integrin $\alpha_L\beta_2$	Kang et al. (2013)
E-selectin	Thioaptamer	Ma et al. (2016)

arthritis, they showed that the actively targeted HA-MTX conjugate was selectively accumulated into the diseased joint, and it showed a superior therapeutic effect with respect to the free drug. Based on the same drug delivery approach involving an ester bond, [Yang et al. \(2016\)](#) reported a folate-modified dextran-MTX conjugate that self-assembles into spherical micelles that target the folate receptor overexpressed in activated macrophages. In an in vivo mouse model of collagen-induced arthritis, they demonstrated that the folate-modified carrier presents superior cellular uptake, an improved biodistribution at the disease site, and a stronger remission of the symptoms with respect to the nonmodified ones. A year later ([Yang et al., 2017b](#)), they modified the system to target the overexpressed scavenger receptors instead of the folate receptor. To do so, they developed a dextran sulfate (DS)-MTX drug conjugate that selectively targets active macrophages thanks to the specific recognition of DS to SR. This system exhibited enhanced accumulation and retention in the synovial cavity of a collagen-induced arthritis mouse model as well as the improved treatment of the inflammatory process by inhibiting the expression of proinflammatory cytokines (i.e., TNF- α IL1- β and IL-6).

However, although they have been widely studied, there are some significant challenges with ester prodrugs, including the stability of the ester bond when the drugs are administered systemically, owing to the presence of ubiquitous esterases in blood, as well as the difficult prediction of prodrugs pharmacokinetics in humans, due to important differences in the activity of specific esterases in preclinical species ([Rautio et al., 2008](#)).

Besides, **polyelectrolytes** such as poly(ethylenimine) (PEI), a cationic polymer widely used for gene transfection, were used for gene therapy in the scope of inflammation. In 2013, [Kang et al. \(2013\)](#) described a nanoparticulated system formed by the electrostatic interaction between PEI and a mixture of genetic material and a polyanionic peptide containing the ligand-binding domain of integrin $\alpha_L\beta_2$ that targeted intercellular adhesion molecule-1 (ICAM-1), an overexpressed surface receptor in inflammation.

A similar strategy was used to treat atherosclerosis in male apolipoprotein E-deficient mice (Ma et al., 2016). In this case, the miRNA was encapsulated in PEG-PEI nanoparticles loaded into the nanopores of a micrometer-sized silicon microparticle. The microparticle itself was covalently linked to a thioaptamer (ESTA), a specific ligand of E-selectin, an overexpressed integrin in inflammatory processes. Moreover, in 2013, Yu et al. (2013) designed mannosylated pH-responsive polymeric micelles with potential to be used for siRNA delivery at inflamed areas by targeting the overexpressed mannose receptor in the surface of activated macrophages. The system was based on a triblock copolymer, poly(BMA-co-PAA-co-DMAEMA)-*b*-poly(DMAEMA)-*b*-poly(AzEMA) (i.e., butyl methacrylate (BMA), 2-propylacrylic acid (PAA), 2-dimethylaminoethyl methacrylate (DMAEMA), and 2-azidoethyl methacrylate (AzEMA)), and it formed stable nanoparticles at physiological pH, but at pH lower or equal to 6.2 (endosomal pH), the pH-dependent block (i.e., BMA-co-PAA-co-DMAEMA) became highly protonated, which led to micelle destabilization, disruption of the endosomal membrane, and delivery of the genetic content.

Another approach relaying on pH-responsive polymers targeting the mannose receptor involves the acid-cleavable **hydrazone bond**. In 2017, O'Mary et al. (2017) showed the higher retention and enhanced therapeutic effect of hydrazone-based sheddable PEGylated mannose-modified nanoparticles containing bethamethasone-21-acetate, a synthetic glucocorticoid, in comparison with the free drug in an in vivo mouse model of chronic inflammation. At the acidic pH in an inflammatory microenvironment, the hydrazone bond was cleaved and the external shell of PEG was delivered in such a way that mannose is available for the interaction with mannose receptors in the surface of activated macrophages favoring retention.

Regarding enzyme-responsive polymeric systems, it is worth mentioning the HA-MTX conjugate (DK226) that was first described in 2010 (Fig. 7.3) (Homma et al., 2010). This polymer-drug conjugate incorporated HA on its structure to target CD44-overexpressed surface receptor in activated macrophages and a peptide linker (Phe-Phe) that can be cleaved by cathepsins, remodeling enzymes overexpressed in inflammatory microenvironments (Tamura et al., 2016). The superior biodistribution and efficacy of this system for the treatment of arthritis has been recently probed in two in vivo antigen-induced arthritis rat models (Tamura et al., 2016; Homma et al., 2010).

Another example of enzyme-responsive polymeric systems was the glucosyl thiamine disulfide naproxen prodrug described in 2011 (Fan et al., 2011). The high demand of glucose as the main source of energy of the brain makes it possible for this glycosylated prodrug to overcome the BBB by binding to the glucose transporter 1 (GLU₁). Once in the inflamed brain tissue, the thiamine disulfide moiety may be reduced by the

FIG. 7.3 Schematic representations of the chemical structure of the Hyaluronic acid-Methotrexate (HA-MTX) conjugate (DK226). Reproduced with permission of Tamura, T., Higuchi, Y., Kitamura, H., Murao, N., Saitoh, R., Morikawa, T., et al., 2016. Novel hyaluronic acid-methotrexate conjugate suppresses joint inflammation in the rat knee: efficacy and safety evaluation in two rat arthritis models. *Arthritis Res. Ther.* 18, doi:10.1186/s13075-016-0971-8. <https://creativecommons.org/licenses/by/4.0/legalcode>.

abundant disulfide reductase and immediately undergo a cyclization facilitating naproxen retention and delivery in the brain. In vivo biodistribution studies have demonstrated a significant increase in the levels of naproxen in mice brains using this approach.

7.3.4 pH-Responsive Polymers

There is an extensive literature about inflammation-responsive polymers that rely on the acidic pH encountered in the inflammatory microenvironment for the release of their cargo, and they are mainly based on acid-cleavable structures or linkers.

The polymeric structures that undergo accelerated hydrolysis when in an acidic microenvironment used in inflammation-responsive systems are summarized in Table 7.2. However, there exist other acid-labile structures that have not been reported with inflammation-responsive purposes like imines or polyamides among others. The most widely studied are ester-containing polymeric systems because of their simplicity and, in particular, PLGA, which has already been approved by the FDA for certain applications and is widely used as a biodegradable polymer. PLGA microparticles have been recently reported as efficient drug delivery vehicles for celecoxib, an antiinflammatory drug, on an in vivo acetic acid-induced colitis rat model (Bazan et al., 2016). Moreover, PLGA nanoparticles containing budesonide have been demonstrated to enhance the drug therapeutic effect in in vivo models of colitis (Ali et al., 2016). However, the byproducts that result from the degradation of this polymer are not innocuous and even may cause an additional inflammatory process.

TABLE 7.2 pH-Responsive Structures Used on the Design of Inflammation-Responsive Polymers

Name	Structure	Reference
Anhydride ester		Bazan et al. (2016) and Chandorkar et al. (2014)
Acetal		Chen et al. (2016) and Tang et al. (2017)
Ketal		Somasuntharam et al. (2013) and Yang et al. (2017a)
Hydrazone		Yuan et al. (2012), Ren et al. (2014, 2015), Knudsen et al. (2015), and Quan et al. (2016)
Ortho ester		Cheng et al. (2012)
Boronate ester		Song et al. (2013)

Some alternatives that may overcome PLGA drawbacks can be found in recent literature like polyanhydride-esters, which have demonstrated to be good candidates for controlled drug delivery at inflamed areas enhancing therapeutic outcomes in in vitro (Chandorkar et al., 2014) and in vivo studies (Harten et al., 2005). Another example are the nanoparticles based on poly(tetrahydropyran-2-yl methacrylate) (poly(THPMA)) designed by Lee et al. in 2015. They demonstrated the in vitro-controlled release under acidic conditions of an antagonist of the P2X₇ receptor, which plays a key role in inflammation (Lee et al., 2015).

Polyacetals have also attracted high interest as they present great pH sensitivity and nonacidic metabolites. In 2016, Chen et al. (2016) described microparticulated systems based on acetylated dextran biopolymers as potential drug delivery systems in inflammation and tumor sites responding to acidic pH. The same year, Huang et al. reported a simple synthesis of pH-labile polyacetal dendrimers functionalized with PEG to obtain an amphiphilic polymeric system that form micelles and nanofibers in aqueous

media. The drug delivery vehicle degrades at low pH values found in inflamed or tumor tissues, making it a potential candidate for controlled drug delivery at diseased sites (Huang et al., 2016). More interestingly, in 2017, Tang et al. designed a siRNA-delivery nanoparticulated system by chemically cross-linking it with multiarmed PEG via acetal linkers. They demonstrated that the system allowed a controlled delivery of TNF- α siRNA into macrophages in vitro and, when presenting mannose targeting moieties accumulated in mice liver in vivo, protected the mice from inflammation-induced liver injury (Tang et al., 2017).

The **ketal group** has also gained some attention in the last decade presenting accelerated hydrolysis at low pH and biocompatible byproducts. In 2008, Yang et al. (2008) described polyketal copolymers as “a new acid-sensitive delivery vehicle for treating acute inflammatory diseases” based on an in vivo study demonstrating that polyketal-based microparticles encapsulating an antiinflammatory drug (i.e., imatinib) significantly improve the efficacy of the drug in treating acute liver failure (Fig. 7.4). In 2010, this system was compared to PLGA in a model of lung fibrosis. Results showed that it presents no alveolar or airway inflammation when compared to the small inflammatory response generated when using PLGA microparticles (Fiore et al., 2010). The same year, polyketal microparticles loaded with superoxide dismutase (SOD), an endogenous superoxide scavenger, were tested in vivo in a rat model of ischemia/reperfusion (IR) injury. The system allowed a sustained, controlled release of SOD leading to increased cardiomyocyte survival following injury and ultimately preserving cardiac function (Seshadri et al., 2010). In 2013, Somasuntharam et al. (2013) tested the polyketal-based microparticulated system for siRNA-controlled delivery both in vitro and in vivo in mice model of myocardial infarction. They demonstrated the microparticles’ internalization by macrophages as well as the knockdown of the specific gene and protein levels in vitro and restoration of cardiac function in vivo. And finally, in 2017, another in vivo study in mice models of myocardial infarction demonstrated the feasibility of using this polyketal-based system for the delivery of genetic material, miRNAs in this case, into infarcted areas improving therapeutic outcomes (Yang et al., 2017a).

FIG. 7.4 Chemical structure of the polyketal copolymer.

Recently, **ortho ester** linkage-based polymers have also been proposed as potential pH-responsive vehicles for targeted drug delivery to inflamed areas (Cheng et al., 2012). More interestingly, these systems incorporating **boronate esters** also show oxidation-accelerated hydrolysis as good candidates for inflammation responsiveness and specific cargo delivery. Song et al. (2013) demonstrated that the phenylboronic ester oxidation rate was faster than the ortho ester hydrolysis rate at neutral pH, and that an increased concentration of H_2O_2 accelerated these processes.

The **hydrazone bond** has also attracted much attention in inflammation-targeting applications as it presents a degradation rate 10 times faster at pH 5.5 than at pH 7.4. Already in 2007, Ito et al. described an HA-dexamethasone-based hydrogel cross-linked through hydrazone bonds that allowed a controlled delivery of the drug within 5 days and reduced inflammatory response in primary mouse macrophages in vitro (Wang et al., 2007). The same year, the already mentioned P-Dex copolymer conjugate was first described as a promising drug delivery system for selective targeting of dexamethasone to inflamed joints. They demonstrated in vitro the high level of drug release at pH 5, 37°C, thanks to the degradation of the hydrazone linkage between the polymer and the drug. Since then, this hydrazone-containing polymer-drug conjugate has demonstrated, in several in vivo models of inflammation, its improved therapeutic effects when compared to the free drug (Yuan et al., 2012; Ren et al., 2014, 2015; Knudsen et al., 2015; Quan et al., 2016).

Moreover, recently, the hydrazone bond has been used to overcome the so-called *PEG dilemma*. PEGylation increases circulation time of nanoparticulated systems favoring passive accumulation in inflammation or cancer sites by ELVIS or EPR effect, respectively. However, PEGylation also prevents internalization by inflammatory cells. To overcome this problem, novel inflammation-dependent dePEGylation strategies have been described. The most popular one is the conjugation of PEG via an acid-labile hydrazone linkage. This approach was employed by Aldayel et al. (2016) who designed acid-sensitive sheddable PEGylated PLGA nanoparticles encapsulating TNF- α siRNA and compared them with PLGA nanoparticles prepared with an acid-sensitive emulsifying agent. DePEGylation-based strategy showed an in vivo increased biodistribution of the genetic cargo in an inflamed mouse foot and a reduction of the inflammatory process at the disease area. Only 1 year later, Li et al. (2017) exploited this strategy to increase the retention of PEG-prednisolone nanocarriers in a mouse model of collagen-induce arthritis. The system showed better anti-inflammatory effects than the free drug.

Other acid-cleavable structures have been tested in other acidic pH environments like in cancer or in hybrid polymer-lipid structures like Schiff bases (imines, oximes, hydroazones), citraconic/dimethyl maleic, or simply β -carboxylic amides or β -thioether esters (d'Arcy and Tirelli, 2014).

However, to date, these polymeric structures have not been exploited for inflammation targeting or treatment.

Furthermore, although they are out of the scope of this review, which is focused on synthetic polymers, pH-responsive natural polymers containing ionizable moieties on their structure have also been exploited with inflammation-targeting purposes. The most commonly used is chitosan, because it swells at acidic pH, presents intrinsic antiinflammatory capacity, and presents mucoadhesive properties, which makes it a good candidate for the treatment of inflammatory diseases of the GI track (Rajitha et al., 2016). In the last 2 years, there are several examples of chitosan and chitosan-alginate nano- or microparticles that have demonstrated their high potential as drug and RNA delivery systems to inflamed tissues in vitro and in in vivo models of rheumatoid arthritis (Kumar et al., 2017), ulcerative colitis (Wang et al., 2016), diabetic wounds (Karri et al., 2016), or ophthalmic inflammation (Asasutjarit et al., 2015). Other polymeric structures based on polyelectrolyte natural polymers used in the field of inflammation are alginate aerogels (Gaudio et al., 2013) or agarose hydrogels (Ninan et al., 2016).

7.3.5 Redox-Responsive Polymers

Redox-sensitive polymers (Table 7.3) have also been studied as inflammation-responsive polymers.

In this sense, **sulfur-based polymers** present important advantages like the abrupt change in polarity that occurs when sulfur (II) is oxidized to sulfoxide (IV) or sulfone (IV), which facilitates inflammation-sensitive release and the facile synthesis through episulfide ring-opening polymerization (d'Arcy and Tirelli, 2014). In 2010, Mercanzini et al. (2010)

TABLE 7.3 ROS-Responsive Structures Used on the Design of Inflammation-Responsive Polymers

Name	Structure	Reference
Poly(propylene sulfide)		Mercanzini et al. (2010), Gupta et al. (2012), and Poole et al. (2015)
Poly(oxalate)		Kim et al. (2011) and Lee et al. (2013)
Poly(thioketal)		Wilson et al. (2010) and Martin et al. (2014)

designed a novel nanoparticle-embedded implant coating to reduce the postimplantation foreign body reaction to microfabricated cortical neuroprostheses. The coating was based on a bioresorbable polymer poly(ethylene oxide) (PEO) that degraded soon after implantation exposing the poly(propylene sulfide) (PPS) nanoparticles containing dexamethasone. It was *in vivo* tested on the cortex of rats demonstrating a long-term decrease in the tissue response and increasing the half-life of implants. In 2012, Gupta et al. (2012) reported a new micelle drug delivery system consisting of a diblock amphiphilic copolymer of propylene sulfide (PS) and *N,N*-dimethylacrylamide (DMA); and only few years later, they also described an oxidation-responsive OEGylated poly-L-cysteine homopolypeptide able to self-assemble into spherical micelles in aqueous solution (Fu et al., 2014). Both systems were designed for their applications in the inflammation field, and their feasibility to deliver cargo in the presence of an oxidative environment was demonstrated *in vitro*. More recently, PPS nanoparticulated systems encapsulating curcumin were tested in an *in vivo* diabetic mouse hind limb ischemia model showing an accelerated recovery when compared with the free drug (Poole et al., 2015).

Besides, **polyoxalates** have also attracted much attention because they undergo depolymerization reactions when exposed to hydrogen peroxides. Based on these polymers, Kim et al. (2011) developed in 2011 a *p*-hydroxybenzyl alcohol (HBA)-incorporated polyoxalate that decomposes in the presence of hydroxyl radicals into three known and safe compounds: cyclohexanedimethanol, HBA (a potent antioxidant), and CO₂. The polymeric systems were tested *in vivo* in mice asthma models showing a reduction in pulmonary inflammation. Moreover, the intrinsic antioxidant and antiinflammatory activities of this system were also demonstrated *in vitro* and *in vivo* in a model of hind limb ischemia-reperfusion (Lee et al., 2013).

Furthermore, in 2010, Wilson et al. (2010) described a novel polymer, poly(1,4-phenyleneacetone dimethylene thioketal) (PPADT), containing the **thioketal** moiety that selectively degrades when in the presence of ROS. They encapsulated TNF α -siRNA and demonstrated that, when NPs were delivered orally in a murine model of ulcerative colitis, the mRNA levels in the colon were reduced as well as inflammation symptoms. More recently, Martin and collaborators developed a polythioketal urethane-based biomaterial scaffold that specifically degraded as a function of ROS concentration. They demonstrated the superior rate of tissue in-growth and cell-mediated scaffold biodegradation in comparison to analogous poly(ester urethane) scaffolds for their application in tissue engineering and wound dressing (Martin et al., 2014).

Other redox-sensitive structures than have already been used in cancer therapy that may find application in the inflammation field are boronate, selenide, or telluride-based polymers (Xu et al., 2016).

7.3.6 Enzyme-Responsive Polymers

The bibliography regarding enzyme-responsive polymers for their application in inflammation-related disorders is limited and mainly recent ([Table 7.4](#)).

Polymeric systems exploiting overexpressed ECM-remodeling enzymes (i.e., cathepsins, neutrophil elastase and MMP2 or MMP9) are the most studied ones. In 2010, [Homma et al. \(2010\)](#) optimized the peptide, the linker and the molecular weight of a HA-MTX conjugate in which the drug and the polymer were linked by a cathepsin-cleavable peptide. They concluded that the conjugate with the Phe-Phe peptide chain and the ethylenediamine linker was the best drug candidate for the treatment of osteoarthritis. The in vivo superior efficacy of this prodrug in comparison with the free drug was probed in 2016 in a collagen-induced arthritis rat knee model ([Tamura et al., 2016](#)).

In 2009, [Aimetti et al. \(2009\)](#) developed a novel enzyme-responsive hydrogel drug delivery system with the potential to treat local inflammation. The human neutrophil elastase (HNE)-sensitive peptide linkers (Ala-Ala-Pro-Val) were incorporated within PEG hydrogel by photopolymerization. They described the drug delivery platform and demonstrate its degradability in the presence of HNE in vitro.

More recently, MMP-2 and MMP-9-cleavable linkers have been used for the design of inflammation-responsive systems. In particular, in 2014, [Steinhagen et al. \(2014\)](#) reported a novel polymeric film functionalized with the antiinflammatory chemokine stromal cell-derived factor 1 α (SDF-1 α) via MMP-9-cleavable peptidic linker (Cys-Gly-Pro-Leu-Ser-Leu-Arg-Ser-Ahx-Glu-Lys-Ahx-Pra-NH₂) that demonstrated to have potential for biomedical applications by improving wound healing and tissue regeneration after surgery.

TABLE 7.4 Enzyme-Responsive Structures Used on the Design of Inflammation-Responsive Polymers

Enzyme	Cleavable structure	References
Cathepsin	Phe-Phe	Homma et al. (2010) and Tamura et al. (2016)
Human neutrophil elastase (HNE)	Ala-Ala-Pro-Val	Aimetti et al. (2009)
MMPs	Cys-Gly-Pro-Leu-Ser-Leu-Arg-Ser-Ahx-Glu-Lys-Ahx-Pra-NH ₂ (MMP-9)	Steinhagen et al. (2014)
Urease	Urea linkage	Xu et al. (2013)
Azoreductase	Azo group	Jilani et al. (2013)

Besides, polymer backbones cleavable by specific enzymes generated by bacteria during infection-associated inflammatory processes have also been described (Xu et al., 2013). A good example is the asymmetric polyurethane (PU) membrane based on a sulfanilamide (antibiotic)-conjugated PU designed for wound dressing. The urea linkages are cleaved by ureases generated by bacteria delivering the antibiotic, enhancing the efficacy and minimizing side effects (Xu et al., 2013). Another bacteria-generated enzyme that may be used with this purpose is the azoreductase, but, to date, the introduction of azo moieties has only been employed in the design of prodrugs (Jilani et al., 2013) and on a dual responsive system that will be described later.

7.3.7 Dual-Responsive Polymers

Some polymeric structures reported in the literature present a more complex inflammation responsiveness as they combine sensitivity to two or more inflammatory microenvironment features at the same time. Examples of the three possible combinations can be found as pH/ROS responsiveness, enzyme/ROS responsiveness, and enzyme/pH responsiveness.

In a very recent study, Daniel et al. (2016) reported a dual-responsive nanoparticulated system capable of releasing the cargo in response to both ROS and MMPs (Fig. 7.5). A MMP-12 substrate (i.e., GPLGLAGGERDG) constituted the hydrophilic block of the amphiphilic polymeric system whereas the hydrophobic segment was based on a MMP inhibitor covalently linked through a ROS-sensitive bond, specifically an aryl boronic ester. When exposed to MMPs in the inflammatory microenvironment, the hydrophilic block is cleaved and destabilization of the micelle occurs exposing the hydrophobic block. Then the aryl boronic ester bond suffers a nucleophilic attack by H_2O_2 leading to the release of the MMP inhibitor. However, this system was just tested *in vitro*, and it is necessary to perform further studies to demonstrate its efficacy *in vivo*.

Enzyme/pH-responsiveness has also been investigated mainly for the treatment of IBD. In 2014, Naeem et al. (2014) reported a colonic-specific nanoparticulated drug delivery system based on a polymeric mixture of enzyme-sensitive azo-polyurethane and the pH-sensitive Eudragit S100 (a commercial form of PLGA) encapsulating coumarin-6 as a model drug. Both pH and enzyme-sensitivity were demonstrated *in vitro*. They also demonstrated the selective distribution of the nanoparticles in the inflamed colon through an *in vivo* localization study in rat GI tract.

Knipe et al. (2016) designed a complex polymeric carrier for oral delivery of TNF- α siRNA. pH-responsive polycationic 2-(diethylamino)ethyl methacrylate (DEAEMA)-based nanogels (size ~ 100 nm) were encapsulated on a poly(methacrylic acid-*co*-*N*-vinyl-2-pyrrolidone) [P(MAA-*co*-NVP)] microgel cross-linked via trypsin-degradable peptide linkers.

FIG. 7.5 Monomer, polymer, and nanoparticle structures. (A) PS peptide substrate, (B) PSC peptide substrate control, (C) PD1 prodrug-1, and (D) PD1C prodrug-1 control. (E) Micellar structure with cores composed of the hydrophobic PD1 or PD1C, and shells composed of PS or PSC. Reproduced from Daniel, K. B., Callmann, C. E., Gianneschi, N. C., Cohen, S. M., 2016. Dual-responsive nanoparticles release cargo upon exposure to matrix metalloproteinase and reactive oxygen species. *Chem. Commun.* 52, 2126–2128 with permission of The Royal Society of Chemistry.

The microgel provided protection to the nanogels under extreme acidic environment in the stomach (pH 2–4), but when in the intestine (pH 6–7.5), it swelled favoring enzymatic degradation and nanogel delivery. This system was tested *in vitro*, which showed a significant reduction of secreted TNF- α level in murine macrophages.

pH and ROS-sensitivity have also been combined in polymeric structures to prepare inflammation-responsive drug delivery systems. In 2013, [Kwon et al. \(2013\)](#) developed the so-called poly(vanillin oxalate), a novel inflammation-responsive antioxidant polymeric prodrug containing vanillin, a potent antioxidant and antiinflammatory agent. The polymer

self-assembles into nanoparticles in aqueous media, and it was based on H_2O_2 -reacting peroxalate ester bonds and bioactive vanillin linked via acid-cleavable acetal linkages. The system exhibited potent antioxidant and antiinflammatory activity both in vitro and in vivo on a mouse model of acetaminophen-induced liver injury demonstrating its great potential for the treatment of ROS-associated inflammatory diseases. Another well-known antioxidant and antiinflammatory agent, curcumin, was encapsulated on *N*-palmitoyl chitosan nanoparticles (NPCS) bearing a hydrophobic Cy3 moiety together with a ROS-responsive poly-(1,4-phenyleneactone dimethylene thioketal) (PPADT) (Pu et al., 2014). Chitosan-based polyelectrolyte swelled at the acidic pH encountered in the inflamed tissue, and the hydrophobic PPADT degrades into hydrophilic fragments in response to ROS, altogether contributing to the instability of the system leading to the curcumin release. The feasibility of this system for the treatment of arthritis was demonstrated in vitro and in an in vivo mouse model with lipopolysaccharide (LPS)-induced ankle inflammation as it was able to reduce the oxidative stress in inflamed tissue.

7.4 CURRENT AND FUTURE TRENDS

To date, in vitro and in vivo studies have demonstrated the great potential of pH, ROS, enzyme, or dual-responsive polymeric systems for the treatment of inflammation-related diseases including diabetes, cardiovascular diseases, pulmonary diseases, neurodegenerative diseases, IBD, cancer, skin diseases, ocular diseases, and arthritis, among others. In fact, they have been shown to be effective not only in controlled drug delivery but also in gene therapy facilitating the release of genetic material (i.e., miRNAs or siRNAs) at the site of inflammation. These systems have also exhibited interesting outcomes in the field of implant coatings contributing to the reduction of the foreign body reaction to biomaterials that is the main cause of premature implant failure. They have even shown potential as scaffolds for tissue engineering and wound dressing applications.

Nevertheless, new trends have emerged in the last few years including (i) cell-mediated targeting, which has demonstrated high efficiency on targeting inflammation sites, and (ii) the proposed solution to the PEG dilemma consisting on the shedding of PEG external shell in response to environmental specific stimuli. Due to the fact that, based on the ELVIS effect, to achieve retention in inflamed tissue internalization within inflammatory cells is crucial, these two approaches are considered highly promising and should be exploited in future research.

Finally, there are still unexplored pH, ROS, and enzyme-responsive structures that may be subjects of further studies. In fact, due to the tight

link between cancer and inflammation, most of the strategies used for cancer treatment may find promising applications in the inflammation field.

7.5 CONCLUSIONS

To conclude, and based on the recent literature mentioned in this chapter, in the last decade, polymeric systems undergoing changes in response to specific features of the inflammatory microenvironment have demonstrated great potential to significantly improve the treatment of most inflammation-associated diseases. The low bioavailability of inflammatory drugs due to their hydrophobicity and the fact that most of these diseases, like cardiovascular, cancer, or neurodegenerative diseases, present high-mortality rates, highlight the importance of further development of these systems.

pH, ROS, enzyme, and dual-responsive polymers have arisen as potent and relatively simple tools to achieve superior outcomes in inflammation therapies. However, the importance of an intelligent design strategy is still a challenge. In fact, the bibliography has undoubtedly probed that, to achieve the highest efficiency and minimization of adverse effects of these disease treatments, the inflammatory microenvironment should be deeply studied and understood.

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