We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Biodegradation of Medical Purpose Polymeric Materials and Their Impact on Biocompatibility

Elisa Tamariz and Ariadna Rios-Ramírez

Additional information is available at the end of the chapter

1. Introduction

The use of polymeric materials in medical devices and pharmaceutical applications has been extended in the last decades. Biodegradable implantable polymers for tissue engineering and drug release have the advantage to avoid a permanent and chronic immune response, and to avoid removal surgery; moreover the versatility of polymeric materials aloud the design of specific biodegradable characteristics to control drug release, to develop resorbable devices, and to improve cell integration.

Biodegradation is a term used to describe the process of break down a material by nature; however in the case of medical purpose biomaterials, biodegradation is focus in the biological processes inside the body that cause a gradual breakdown of the material.

Biomaterials degradation is a very important aspect to consider when they are used for medical purpose, since their ability to function for a certain application depends on the length of time that it is necessary to keep them in the body.

Polymers biodegradation process and rate within an organism is related to the polymer characteristics and the place in the body where will be exposed. This chapter intended to offer an overview of the mechanisms that influences the biodegradation of polymeric materials used for medical purposes, with special emphasis in the immunological mechanisms that modulates biodegradation rates and biocompatibility, and in the features that implies their use in the central nervous system (CNS). It will be also focused in the importance of modulate the biodegradation for some biomedical application, and how the on purpose control of biodegradation could be a relevant aspect to design biomaterials with a more interactive and efficient role in medicine.

2. Polymeric material for biomedical applications

The use of polymers in biomedical applications is now widely accepted and they are termed with the generic name of polymeric biomaterials. A biomaterial can be defined by their function as a material in contact with living tissue, used to the treatment of disease or injury, and to improve human health by restoring the function of tissue and organs in the body [1]. The 1982 Consensus Development Conference Statement of the National Institute of Health (NIH) defines a biomaterial as any substance (other than drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments or replaces any tissue, organ or function in the body [2]. Polymeric biomaterials in medicine include surgical sutures, drug delivery vectors, orthopedic devices and implants, and scaffolds for tissue engineering.

After decades of research many polymeric biomaterials have been developed from synthetic or natural origin. All the polymeric biomaterials have to be evaluated in terms of their biocompatibility, mechanical properties and biodegradation to determine if they are suitable for specific medical applications.

Biocompatibility refers to several characteristics of the biomaterial which leads to the acceptance of the material in the body, such as being non toxic, non carcinogenic, non allergenic, non immunogenic. The materials for in vivo use have to be exposed to hemocompatibility, citotoxicity, mutagenicity, and pyrogenicity test [1].

Mechanical properties like elastic modulus, compression modulus, fatigue, and viscoelasticity are important characteristics to determined their use in the body, for example for bone implants and prosthesis; however micrometric or nanometric characterization is also important in the case of biomaterials for tissue replacement and cell scaffolds, since micro and nano-characteristics are important to manipulate cell proliferation, differentiation, and function to mimic the tissue to be replaced [3].

Biodegradation refers to the rate of breakdown mediated by biological activity, and is an important property for biomaterials used as non permanent scaffolds, implants, drug delivery vectors, and sutures [1].

The most commercial and earliest developed polymers for biomedical applications were the synthetic polymers developed from linear aliphatic polyesters. Synthetic polymers are made by linking small molecules (mers) through primary covalent binding in the main molecular chain backbone, and have a close resemble with natural occurring tissue components like proteins, polysaccharides and deoxyribonucleic acids. Besides synthetic polymers, natural occurring polymers are also used as biomaterials. Many of the natural polymers are synthesized by condensation reactions and the condensing molecule is always the water [4]. Natural polymers and their chemical and mechanical properties specifically provide functions to each of them in the organisms, for example collagen in the dermis, fibrin in the clot, chitin in the exoskeleton of insects and crustaceans [5, 6].

Either synthetic and natural polymers, or bonds among both has been studied and used as materials for medical application; below we shortly describe some examples of the main

natural and synthetic polymers and some of their proposed uses in medicine, particularly in the nervous system.

2.1. Natural polymers

Natural polymers are used in clinical applications such as dermal fillers, lubricants, wound sealants and surgical sponges. Other naturally derived polymers have readily available functional groups which facilitate chemical modification.

Agarose is a polysaccharide of D-galactose and 3,6- anhydro-L-galactopyranose derived from the cell walls of red algae. Agarose is biologically inert and is attractive for drug delivery because it has soft, tissue-like mechanical properties, and can form porous gels at low temperatures. Agarose is heated to solubilize the powder in aqueous solutions and then gels through hydrogen bonding upon cooling [7]. Agarose decrease potential immune rejection when inserted into the brain, for example, Brain-derived neurotrophic factor (BDNF) delivered in this way was found to reduce the reactivity of the astrocytes and the production of chondroitin sulfate proteoglycans (CSPGs), and to enhance the number of regenerating fibers that entered the hydrogel into the injured spinal cord in rats [7, 8].

Fibrin is a promising material because of its natural role in wound healing and its current application as a tissue sealant. Obtained from pooled human plasma, fibrin presents an advantage since it could be an autologous source avoiding risk of immune rejection. The most used gel is the fibrin glue and consist of fibrinogen and thrombin enzymatically crosslinked; however it has also used in conjugation with other polymers such as hyaluronic acid [1, 9]. This polymer has the advantage to be injected and polymerized in situ and has been tested for controlled delivery of Nerve growth factor (NGF), Neurotrophin -3 (NT-3) and BDNF in the CNS [7].

Collagen is the main component of connective tissue and is the most abundant protein in mammals, there are at least 19 different types of collagen, for example type I collagen is a fibril forming collagen and is present in the skin and fibrocartilage, type II collagen is found in articular cartilage[10, 11]. Collagen can be isolated from tissue like skin, bone or tendon. Collagen gels alone are quite weak, and are often crosslinked to improve durability. While many applications use unmodified collagen, chemical crosslinkers can be used to inhibit in vivo absorption in applications which require slow degrading constructs, such as drug delivery [7, 12]. Although collagen is abundant in many tissues, is not the main component in the CNS extracellular matrix, therefore some concern is present about their use as CNS cells scaffolds [12], however their use for stably releasing of growth factors like ciliary neurotrophic factor (CNTF), has shown to improve the survival, growth and proliferation of neural stem/progenitor cells (NSPCs) [1].

Alginate is a linear block copolymer of D-mannuronic acid (M) and L-guluronic acid (G) residues. Commercially available, alginate is extracted from brown seaweed algae. Alginate has a high biocompatibility since their hydrophobic nature; however, cannot be enzimatically broken down and has poorly regulated degradation. Partial oxidation of alginate with sodium periodate makes the chains more susceptible to be degraded by hydrolysis [13]. Mammalian

cells cannot adhere to alginate unless it is modified with cellular adhesion molecules like laminin, fibronectin, collagen, and RGD sequences, which allow more specific interactions [9]. Covalently modified gels of alginate containing different ration of RGD peptides have been used to encapsulate cells and to induce their differentiation [14].

Hyaluronic acid (HA) is a glycosamine glycane made of residues of N-acetylglucosamine and D-glucuronic. HA is normally presented at high levels in the extracellular matrix of connective, epithelial and neural tissues, and is known to play roles in cellular processes like cell proliferation, morphogenesis, inflammation, and wound repair. However, HA alone does not gel and is rapidly degraded through the action of the enzyme hyaluronidase into smaller oligosacharides, HA can also be degraded by reactive oxygen species at the site of inflammation [15], and is readily cleared due to its high solubility [1]. HA is fabricated into hydrogels using chemical crosslinkers such as glutaraldehyde or carbodiimide, and has also been widely derivatized to form photocrosslinkable and injectable hydrogels. Its polyanionic and hydrophilic characteristics made it highly biocompatible and suitable for applications with minimal cell invasion [9].

Poly(β-1,4-D-glucosamine) or Chitosan is a natural polymer that can be prepared by de-N-acetylation of chitin from crustacean shells, the degree of chitosan deacetylation affects the charge density of the polysaccharide, more deacetylation increase the positive-charge character of the chitosan chains. It can form gels by covalent crosslinking with aldehydes such as glutaraldehyde or ionic crosslinking by polyanions such as sodium citrate or sodium tripolyphosphate [6]. The limited solubility of chitosan in neutral pH provides a unique opportunity to form nanoparticulate drug/gene delivery platforms, but it is also an obstacle if one intends to apply chitosan as a solution in the physiological condition [5]. Chitosan can be easily conjugated with organic materials as well as biomolecules, a number of studies have reported controlled drug delivery using chitosan nanoparticles that incorporate biologically active ingredients such as DNA, proteins, anticancer drugs, and insulin [16]. Chitosan has been extensively investigated as a potential biomaterial in a variety of applications, including drug carriers, wound-healing agents, and in tissue engineering. Chitosan scaffolds have been used to transplant viable peripheral nerve grafts, neural stem cells, and neural progenitor cells into rat spinal cords, resulting in increased axonal regeneration [17].

Methylcellulose (MC) is a chemically modified cellulose derivative in which there is a partial substitution of OH groups with methoxy moieties forming a non-toxic material. MC is a water-soluble polymer at low temperature with thermo reversible gelation at a particular temperature. Thermoreversible characteristics are related to the association of MC hydrophobic groups, and the gelation temperature can be manipulated by salts or ions [18]. MC is widely accepted as a highly compatible material and has been used in traumatic CNS lesion like a scaffold for tissue regeneration [19].

2.2. Synthetic polymers

Synthetic polymers offer exceptional control over polymer composition, architecture, and physical properties not fully accessible with natural polymers. After many years of research

in this field numerous polymers have developed like polyesters, polyurethanes, polyanhydrides, polyacrylates, polyphosphoesters, and polydiaxanone. One of the first and now most common uses of polymers in medicine is for resorbable sutures, pins and screws. An extensive review of synthetic polymers is out of this chapter and we will only mention some examples and their main characteristics.

2.2.1. Polyesters

Polyglycolide or polyglycolic acid (PGA) is polymerized from glycolic acid and many of the most important polymer for biomedical use are derived from PGA either through copolymerization or modified glicolide monomers. PGA is one of the most successful and commercially available polymers and is widely used as biodegradable biomaterial in surgery [20].

Poly(lactide-co-glycolide) acid (PLGA) is a PGA derived polymer, is a polyesters obtainable by linear polycondensation of hydroxyacids, or by ring opening of the corresponding lactones. It is the most commonly used biomaterial in medicine. This polymeric agent has been implanted into the brain and has shown good biocompatibility and sustainable drug delivery [8]. In normal untreated animals, polymer microspheres implanted into the brain did not produce gross behavioral or neurological symptoms, and it has been approved for the FDA for repair of human peripheral nerves [5]. Various drugs, especially therapeutic proteins like neurotrophic factors have been encapsulated in this type of brain delivery system, however, the in vivo hydrolysis of PLGA produce and acidic environment that result in a transient pH decline that can compromise the proteins action and stability, and consequently the process of encapsulation and release from biodegradable microspheres must be carefully monitored [5, 21].

Polyethylene glycol (PEG)- based polymers are hydrophilic and water-swellable cross-linked polymers with a high level of elasticity, making them ideal candidates for tissue engineering; more importantly, the degradation rate of the implant can be controlled by simply altering the chemistry of the cross-links within the polymer network [9]. PEG has a variety of applications in drug delivery and tissue engineering, their hydrophilic and non ionic characteristics made it relatively resistant to protein adsorption and highly biocompatible. *In vitro*, they can support the survival of PC12 cells, fetal ventral mesencephalic neural cells, and human neural progenitor cells. Furthermore, in culture, neural cells encapsulated into PEG-based hydrogels survive, maintain phenotype, and extend processes indicating that the hydrogels are not themselves cytotoxic [22, 23]. A recent study in primates found that PEG was completely degraded and the neuroimmune response was less than that found in sham penetrated brains [22, 23].

2.2.2. Polyacrylates

Poly(2-hydroxethyl methacrylate) PHEMA, is one of the earliest polymer used as implantable material. Polymerized from 2-hydroxyethyl methacrylate using free radical precipitation, PHEMA forms a hydrogel biologically inert. One of the main concerns about PHEMA is its low biodegradability, their biodegradation however can be manipulated by modifying the porosity by photopatterning [24]. One of the earliest uses of PHEMA was as an artificial cornea, or keratoprosthesis [25]. Methacrylic-acid- and acrylic-acid-based hydrogels have a high

affinity for calcium and other alkaline earth metals, making them more prone to calcification, thereby some calcification episodes has been found after in vivo implantation [9].

Poly(N-isopropylacrylamide) (PNIPAAm) has been widely studied as a temperature responsive drug delivery system. It has the particular ability to undergo a thermally induced phase transition at 32 °C that induces swelling in the polymer network. The phase transition temperature can be tuned via copolymerization of more hydrophilic or hydrophobic co-monomers to achieve desired transitions in relevant *in vivo* environments. At physiological temperatures, PNIPAAm homopolymer gels hold little water and show poor elastic recovery [7, 26].

2.2.3. Poly(ω-hydroxyl acids)

The poly(ω-caprolactone) contains five $(CH)_2$ units in the repeating unit, making the chains much more flexible than PGA, which has one. Therefore, thermal and mechanical properties decreased considerably compared to PGA. However, the rate of biodegradation is slow, making it better suited to slow drug release applications such as one-year implantable contraceptives, biodegradable wound closure staples, etc [27].

2.2.4. Poly(ortho esters)

Poly(ortho esters) (POE) undergo surface degradation, making them ideal as a drug-delivery vehicle. Erosion process is confined predominantly to the surface layers; therefore controlled drug release is possible as well as maintenance of an essentially neutral pH in the interior of the matrix because acidic hydrolysis products diffuse away from the device. The rate of degradation can be controlled by incorporating acidic or basic excipients into the polymer matrix since the orthoester link is less stable in an acid than in a base [27]. The polymer is stable at room temperature when stored under anhydrous conditions. Either solid or injectable materials can be fabricated into different shapes such as wafers, strands, or microspheres that allow drug incorporation by a simple mixing at room temperature and without the use of solvents [28].

2.2.5. Poly(ester-amides)

Poly(ester-amides) (PEAs) combine the high degradability of polyesters with high thermal stability and high modulus and tensil strength of polyamides [29], are non-toxic building blocks and had excellent film forming properties. These polymers were mostly amorphous materials, combine the well-known absorbability and biocompatibility of linear aliphatic polyesters with the high performance and the flexibility of potential chemical reactive sites of amide of polyamides [20]. PEAs can be functionalized to conjugated different drug, peptides or molecules for cells signaling and had been used for microspheres and hydrogels formation [29].

2.2.6. Others

Poly(vinyl alcohol) PVA is prepared from the partial hydrolysis of poly(vinyl acetate). It can be crosslinked into a gel either physically or chemically. In recent studies, PVA was photocured to produce hydrogels as an alternative to chemical crosslinking [9]. PVA is similar to PHEMA in having available pendant alcohol groups that act as attachment sites for biological molecules. In addition to having multiple attachment sites, PVA is also elastic and thus can induce cell orientation or matrix synthesis by enhancing the transmission of mechanical stimuli to seeded cells [30].

3. Biodegradation of polymeric biomaterials

Biodegradation process could be driven by chemical, physical, and biological interactions.

Biodegradation rate within an organism is related to the polymer characteristics and the place in the body where will be exposed. Chemical degradation is influenced by composition and molecular structure, polydispersity, crystallinity, surface area, hydrophilic or hydrophobic characteristics. In general chemical degradation causes the deterioration of the main polymer chains by random cleavage of covalent bounds, depolymerization or crosslinking of linear polymers, interfering with regularly order chain and with cristallinity, decreasing the mechanical properties [1]. Degradation can be by surface degradation or bulk degradation. In the case of bulk degradation, water uptake by hydrophilic polymers is faster than the rate of conversion of polymer into water-soluble materials, bulk degradation causes the collapse of all the material since the degradation process occurs in throughout their volume. Surface degradation appears in hydrophobic polymers, leaving the inner structure intact, these polymers offers a better control of degradation rates [4].

Biodegradation in a biological environment may be defined as a gradual breakdown of a material mediated by a specific biological activity; when materials are exposed to the body fluids may undergo changes in their physicochemical properties as a result of chemical, physical, mechanical, and biological interactions between the material and the surrounding environment. A very important factor in biodegradation is the interaction with the immune system and their specialized cells.

Polymeric materials can be degraded inside the body by at least three general mechanisms, oxidation, hydrolytic, and enzymatic mechanism.

3.1. Hydrolytic mechanism

Hydrolytic degradation of polymers may be defined as the scission of chemical bonds in the polymer backbone by the attack of water to form oligomers and finally monomers. This kind of hydrolysis could not require of specific biological compounds as proteases, although many of the biodegradation process by enzymatic mechanisms mentioned further are hydrolysis reactions.

All biodegradable polymers contain hydrolysable bonds like glycosides, esters, orthoesters, anhydrides, carbonates, amides, urethanes, ureas; while materials with strong covalent bonds in the backbone or non hydrolyzable groups have less biodegradable rates [31].

In the first step of hydrolytic mechanism, water contacts the water-labile bond, by either direct access to the polymer surface or by imbibitions into the polymer matrix followed by bond hydrolysis. Hydrolysis reactions may be catalyzed by acids, bases, or salts. After implantation, the biomaterial absorbs water and swells, and degradation will progress from the exterior of material towards its interior. In general, the first degradation reaction, even after contact with water molecules, is the hydrolytic scission of the polymer chains leadings to a decrease in the molecular weight. While degradation progress, the molecular weight of degradation products is reduced by further hydrolysis which allows them to diffuse from the bulk material to the surface and then to the solution, causing significant weight loss [31]. Rate of hydrolytic degradation is modulated by hydrophilic characteristics of the polymers as mentioned before, therefore materials such as PEG derived hydrogels have a high biodegradation rate [9]. In the case of hydrolysis of aliphatic polyesters such as PLGA, the acid products accelerate biodegradation due to autocatalysis [32].

3.2. Oxidation mechanism

Polymeric biomaterials could be degraded by oxidation when they are exposed to the body fluids and tissues. It is well known that during inflammatory response to foreign materials, inflammatory cells, particularly leukocytes and macrophages are able to produce highly reactive oxygen species such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), and hypochlorous acid (HOCl). The oxidative effect of these species may cause polymer chain scission and contribute to their degradation. For example superoxide could accelerate the degradation of aliphatic polyesters by the cleavage of ester bonds via nucleophilic attack of O_2^- [20, 31]. A resorbable suture of multifilament of poly(α-hydroxyester), commercially available as Vicryl, for example, exhibited many irregular surface cracks after incubation for 7 and 14 days in an aqueous free radical solution prepared from H_2O_2 and $FeSO_4$, while the same suture in control solution did not have surface cracks, suggesting a role of free radicals in the observed degradation [33]. It has also reported that polyurethanes are attacked initially by neutrophils which secretes reactive oxygen species (ROS) and HOCl, one of the most oxidative compounds [34].

3.3. Enzymatic mechanism

Enzymes are biological catalysts; they accelerate reaction rates in living organisms without undergoing themselves any permanent change. Hydrolysis reactions may be catalyzed by enzymes known as hydrolases, which include proteases, esterases, glycosidases, and phosphatases, among others. For example, it has been shown that the degree of biodegradation of polyurethanes, in the presence of cholesterol esterase enzyme, is about 10 times higher than in the presence of buffer alone [35].

Enzymatic surface degradation occurs when enzymes cannot penetrate the interior of the polymer, due to high cross-link density or limited access to cleavage points, forcing the surface or exterior bonds to cleave first. The mode of interaction between the enzymes and the polymeric chains involves typically four steps:

• Diffusion of the enzyme from the bulk solution to the solid surface.

• Adsorption of the enzyme on the substrate, resulting in the formation of the enzyme–substrate complex.

• Catalysis of the hydrolysis reaction

• Diffusion of the soluble degradation products from the solid substrate to the solution [20, 31].

Enzymatic degradation of natural origin polymer is held by the action of specific enzymes, for example degradation of hyaluronic acid in mammals is carried out by the concerted action of three enzymes: hyaluronidase, b-D-glucuronidase, and b-N -acetyl- D hexosaminidase; in the case of chitin derivatives, lysozyme is the enzyme involved in their degradation inside the body [31].

In vivo degradation rates of a polymers could be faster than *in vitro*; the higher *in vivo* degradation rate have been explained by the effects caused by cellular and enzymatic activities found in the body [36]. *In vitro* degradation tests of polymers in simple aging media are normally conducted to predict the performance of such polymers in the clinical situation; however, taking into account the complexity of the body fluids, it is common to find different results when the same materials are studied both *in vitro* and *in vivo,* mainly because of several oxidation y enzymatic factors are absent in *in vitro* used medias.

4. Immune response and biodegradation

Immune system in the living organism is devoted to continuously surveillance the body to detect self and non-self patterns. Immune system has cellular and molecular entities capable to recognize and induce a response to eliminate the potential dangerous entity or non self elements. There are two kinds of responses, innate immunity and adaptive immunity, the former is a non specific and fast first reaction against a pathogen or a foreign body, while the last is a slow, specific response to a first exposure pathogen or foreign body [37]. The two systems of immunity are related, innate immunity system provides information to the adaptive system by inflammatory mediators and cells such as macrophages and dendritic cells, which process the antigens and present them to T cells of the adaptive immune system [38].

The interaction of inflammatory cells with biomaterials surface-adsorbed proteins constitutes the major immune recognition system for biomaterials; therefore, the study of materials surface properties to avoid the absorption of certain class of proteins has been determinant to understand their compatibility and their degradation process [39-41].

Foreign materials exposed to blood or plasma are immediately covered by proteins commonly called opsonins, the most common opsonins are protein forming the complement system, a

group of about 30 proteins that assemble to form a lityc complex and a recognizable system for phagocytic cells [37]. The recognition through specific receptors in the phagocytic cells is determinant to induce phagocytic and inflammatory response. Phagocytosis is one of the main processes undertaken by innate immunity. Different kind of polymorphonuclear leukocytes like neutrophils, and mononuclear leucocytes like monocytes, macrophages, and dendritic cells, engulf the opsonized foreign material. Once inside the cell enzymes and oxidative processes destroy them [37, 42].

The recognition of opsonized material by specific receptors in monocytes like Fc receptors, mannose receptors or complement receptor triggers the rapid induction of proinflamatory cytokines and recruitment of inflammatory cells [42]; while recognition of non opsinized materials by scavenger receptors leads to non inflammatory phagocytic mechanism [43]. The binding of other proteins like fibrin, collagen, albumim, fibronectin and vitronectin present in the blood, plasma and surrounding tissue are also important to mediate an inflammatory process and the recruitment of inflammatory cells [42].

Many biomaterials has to be implanted in the body through chirurgic procedures, the wound healing process after the implantation induce the recruitment of inflammatory cells and an acute inflammatory response, exposing the biomaterials to the immune system.

The first cells present in the injury site are neutrophils, and within a day or two monocytes, macrophages and later lymphocytes arrive to the implantation site forming a chronic inflammatory process (Figure 1).

If the inflammatory process continues and the biomaterial persist, a foreign body reaction can appears, where multinucleated cell, resulted from the fusion of macrophages, invade the implant site and collagen producing cells like fibroblasts arrives to form a fibrotic tissue around the material forming a capsule [44].

In the case of biomaterials directly exposed to the blood, circulating monocytes, platelets, leucocytes and dendritic cells recognize the materials inducing a similar oposinization and inflammatory process, besides, the activation of platelets and blood coagulation system can induce thrombotic occlusion and serious non desired effects in medical devices like artificial valves, hearts or cardiac stents [44, 45].

Neutrophils and macrophages normally phagocyte foreign materials smaller than 10μm like micro and nanoparticles, and degrade them after engulf into the phagolysosomes, a vesicles containing numerous hydrolases within an acidic environment. When biomaterial particles are large, among 10 to 100μm, multinucleated body giant cells can engulf and digest them, however; when biomaterials are larger enough to avoid phagocytosis, frustrated phagocyte response leads to secretion of numerous proteases, toxic oxygen derived metabolites or oxygen radicals contained in phagocytic and phagolysosome degradatory vesicles [46-48]. The amount of enzymes and radicals released depends on the size of the polymer particles, larger particles induce greater amount of enzyme release. The phagocytable form of the biomaterial, particles or powder, can also exert a differential response as compared for example with a less phagocytable material like a film [44]. A recent study however, shows that the induction of pro-
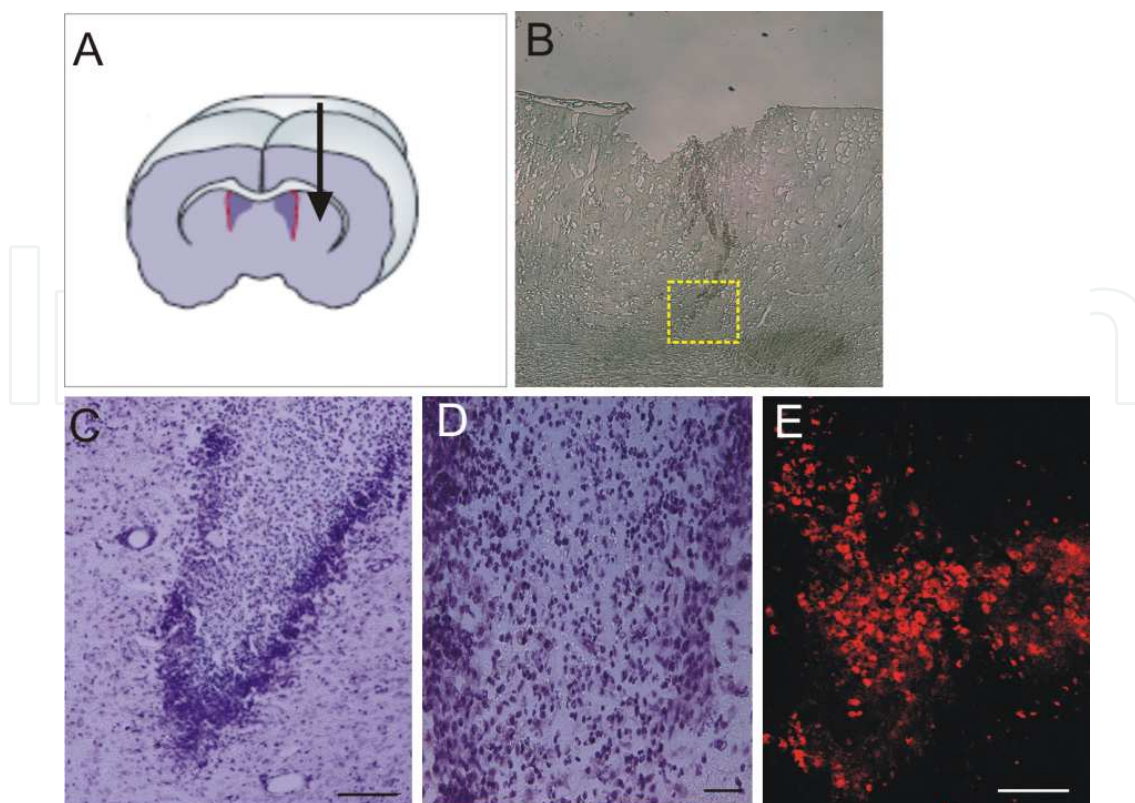
Figure 1. Inflammatory response after 3 days post injection of PEG-Silica gel into rat striatum. (A) Arrow indicates the area of polymer implantation, (B) Phase contrast image of the implanted area, (C) Cresyl Violet staining of the area marked in B, showing cell infiltration at the deepest injection area, (D) Higher magnification showing cell infiltration, (E) Confocal image of a section immunostained to detect activated macrophages at the implanted area. Scales bars: C= 50μm, D and E=100μm.

inflammatory cytokines in macrophages, is held after biomaterials contact with macrophages cell membrane independently of the particles size [49].

Interestingly, fusion of macrophages into giant cells is dependent on the presence of interleukins like IL4, but also of the biomaterials surface properties, for example biomaterials with hydrophilic and anionic surfaces induce the apoptosis or programmed cell dead of macrophages, as compared with hydrophobic and cationic surfaces [50]. The formation of giant cells by macrophages fusion is also modulated by the adsorption of plasma proteins like fibronectin and vitronectin on the materials surface [40, 51].

It is important to mention that there is heterogeneity in the macrophages differentiated from the arrived monocytes into the inflammation site; macrophages known as M1 are the "classical" activated macrophages, stimulated by the TH1 cells or natural killers and microbial products like lipopolysacharides. M1 produce cytotoxic products like reactive nitrogen and oxygen species, and lead to chronic inflammation and formation of foreign body giant cells [52, 53]. M2 macrophages are commonly termed "anti-inflammatory" macrophages. M2 are induced by Interleukine IL4 and IL13 and release high amount of inflammatory suppressors like interleukins IL10, M2 also suppress the nitric oxide release, thereby M2 macrophages are related to immunosuppressive and protective activities like wound healing and fibrosis [53,

54]. Interestingly biomaterials are able to modulate monocytes differentiation to anti-inflamatory, pro regenerative M2 macrophages, or to avoid their differentiation into macrophages, or the fusion of macrophages into multinucleated foreign body giant cells, diminishing the undesirable inflammatory effects and the deleterious biodegradation [52].

Cholesterol esterase has been identified as an enzyme involved in the degradation of polyester(urethane)s and polyether- and polycarbonate-poly(urethane), this enzyme is also used as a marker of monocyte derived macrophages [55]; some materials like degradable polar hydrophobic ionic polyurethane (D-PHI) reduce the expression of esterase activity as compared with cell cultures under polystyrene tissue culture plate, decrease pro-inflammatory interleukins and cytokines like TNFbeta and increase the anti-inflammatory interleukins expression like IL10, suggesting that monocytes can differentiate to an "anti-inflammatory" or M2 phenotypes depending of the biomaterial and therefore influence the regenerative process after wound healing [56].

Enzymes release by activated phagocytes influence the biomaterials degradation by different rates depending upon many characteristic like chemical composition, homogeneity and porosity. Activated macrophages and neutrophils secrete high amount of enzymes like myeloperoxidases, lyzosime and metalloproteinases that contribute to the destruction of invaders and to their migration into the injury or inflammation site; however in the case of chronic inflammatory states enzymes secretion can be deleterious generating an extend and irreversible damage to the tissue [57-59].

As mentioned before surface characteristic of polymeric materials are very important to induce the recruitment, attachment and release of enzymes from neutrophils and macrophages; hydrophilic surfaces induce the interaction with blood containing proteins like fibronectin, fibrin, and albumin, inducing neutrophils adhesion to the proteins and stimulating the degranulation behavior or delivery of primary and secondary granules containing high amounts of enzymes.

For example macrophages cultured on polymers like poly(carbonate-) and poly(ether-) urethanes secrete cholesterol esterase, carboxyl esterase, and serine protease mediating the hydrolytic degradation of the polymers [34].

Hydrolases work under the low pH medium present in the phagolysosme, however when the hydrolases are released outside the cell the extracellular buffer solutions could impair their action; however a highly close interaction of macrophages with the materials forms a tight seal with the substrate, thereby protecting the secreted substances from potential inhibitory environment and therefore a transient and local decrease of pH at the site of phagocytosis improves the hydrolases enzymatic activity [47, 60].

In vitro assays to analyze the hydrolytic degradation of biomaterials are not always very accurate since paradoxically, the *in vitro* rates of degradation could be faster than in vivo rate due to encapsulation of a polymer by fibrotic tissue after a foreign body reaction [36], therefore it is important to perform *in vitro* plus *in vivo* assays in order to characterize the biodegradation rates of polymeric material.

The defense system against pathogens and foreign material includes the release of potent oxidizing agents by activated neutrophils and macrophages. Many of the oxidative products are released to the phagosome after their fusion with the lysosome once the leucocytes has engulf the foreign invader; however, as mentioned before, these potent oxidants could be also released to the extracellular space. After cells activation, oxidant are rapidly formed inside the cells by a process known as oxidative burst that includes an elevated consume of oxygen and the assembly of an enzymatic complex which catalyze the formation of superoxide anion O_2^-. Superoxide anions are further dismutated to hydrogen peroxide H_2O_2, which in the presence of myeloperoxidase generates very potent oxidizing agents like hypochlorous acid and chloroamines. The induction of nitric oxide synthase (iNOS) and the production of reactive nitrogen species and other oxidative species such as hydroxyl radical are also involved in the oxidative mechanisms [61, 62]. In the case of human macrophages however non iNOS induction was detected and therefore some differences as compared with mouse macrophages are reported [62].

Besides their original antibacterial function therefore, the activation of macrophages after contact with materials and the subsequent events like phagocytosis, release of cytokines and foreign body reaction are determinant event in biodegradation of materials. In most of the cases the delivery of high amount of reactive nitrogen and oxygen species and hydrolytic enzymes in response to foreign material, are deleterious to biomaterials but also to the surrounding tissues compromising the compatibility of biomaterials; hence fast biodegradation rates can be beneficial to attenuate undesired inflammatory effects.

4.1. The particular case of the brain

Central nervous system (CNS) is the most highly protected organ in the body; it is located behind the blood-brain barrier (BBB), a specialized structure formed by endothelial cells tightly joint together, a basal membrane, perycytes, microglial cells and astrocytes endfeets forming the glia limitants area [63]. Although the BBB provides an isolated environment for the brain and represent a way to isolate and difficult the crosses of blood molecules and cells, brain is not devoid of immune system monitoring and of interchange of proteins and cells, hence the mentioned characteristics of BBB do not impair but delay the immune response [63].

Other characteristic of CNS immune response are the lack of classical dendritic cells in the parenchyma of the CNS, and non conventional lymphoid drainage which impede the migration and interaction of antigen presenting cell with the naïve memory T cell in the lymphoid nodes; therefore, innate immune response in the brain cannot directly initiate the adaptive immune response [64-66].

Immunological surveillance in the brain is held by several cell types, among them resident microglia is considered the immune cells of the CNS. Microglia is generated independent of the bone-marrow cells in adult organism, and is normally present in the brain in a non activated form; however, although different from tissue resident macrophages, is also suitable of activation and cell shape transformation from a ramified neuronal like morphology into a rounded phagocytic macrophage type, able not only to engulf foreign material but to release inflammatory mediators [67].

Astrocytes are neural derived cells that participate in the homeostasis of the tissue, but after an injury or foreign material presence, activated astrocytes deliver inflammatory mediators that can modify the permeability of BBB allowing the entrance of blood circulating leukocytes. Astrocytes can also phagocyte and form a glial scar or fibrous capsules to isolate the foreign material [65, 66, 68].

Although the presence of conventional dendritic cells in the brain parenchyma has been a controversial issue, recently it has reported the presence of them in the meninges and in the endothelial cell layer that filters liquid from the blood and form the cerebrospinal fluid named the choroid plexus, these cells are able to present antigens to induce adaptive immune response [69].

Perivascular cells are bone-marrow derived cells, monocytes and macrophages, located in the space between blood vessels and glia limitans, and can act as antigen presenting cells. The perivascular cells are the first and early arrival periphery cells entering to the brain parenchyma after an injury of inflammatory process [65, 70].

The particular immunological characteristics of CNS are complemented with the secretion, by astrocytes and microglia, of some cytokines like transforming growth factor beta (TGFβ) which suppress immune reaction, creating a particular immunosuppressive environment in the brain parenchyma that attenuates inflammation and protect the brain from deleterious effects of inflammation in neuronal integrity [71].

Polymeric biomaterials for CNS use are in expansion due to their properties as a drug delivery vectors or as cells and nerves scaffolds. BBB is an impediment for parental drug administration; therefore the use of biodegradable polymer for in situ delivery is an alternative to target the CNS. Biodegradable polymers offers a high advantage to control the temporal and spatial delivery of drugs and cells, besides biodegradable polymers circumvents the need of a second surgery to retire the vector as compared with non degradable devices like mini pumps [5, 72, 73].

Some approaches using biodegradable polymers for neurodegenerative disorders like Parkinson´s disease, Alzheimer and Huntington disease are being studied in different animal models. For example the use of continuous releasing of neurotrophic factors like Glial Derived Neurotrophic Factor (GDNF) in a rat model of Parkinson´s disease has shown to protect neurons from degenerative process [74]. Some other approaches combining the encapsulation of cells and neurotrophic factor releasing microspheres have been recently assayed, obtaining an amelioration of the asymmetric motor activity symptoms [75]. In the case of the treatment of Alzheimer disease (AD), implantation of PLGA microspheres secreting the Neuronal Growth Factor (NGF) promotes the survival of cholinergic neurons in a rodent model that consist in the transaction of septo-hippocampal pathway to induces similar symptoms to AD [76].

The disruption of BBB by injury in *in situ* delivery approaches can induce an immunological reaction that not only implies the particular CNS immune characteristics, but the interaction with periphery immune cells producing an extended inflammatory reaction; therefore, the development of materials for low invasive delivery, like low viscosity injectable hydrogels,

has been one of the approaches [5]. Another recent and in expansion approach is the use of functionalized polymeric micro and nanoparticles capable to cross the BBB, offering an advantage to other invasive procedure; however some immunotoxicologycal non desired aspects has to be considered, like the induction of inflammatory response after phagocytosis by microglia and astrocytes, and the subsequent activation of innate inflammatory processes that could rend to uncontrol and extensive damage to the brain and neurodegeneration [77-80].

Different polymers application requires different biodegradation rates, some drug delivery vectors for example depends in the biodegradation rates to deliver the desired drug concentrations, while in the case of cell scaffolds, the time of polymeric degradation could be longer in order to maintain an appropriate environment for cell survival or for isolate them from immune surveillance.

Delivery of growth factors that improves neuronal regeneration and projection using biodegradable polymer such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA) and poly(e-caprolactone) (PCL) has been extensively studied. These polymers degrade by non enzymatic hydrolytic cleavage of the backbone ester bond to alcohol and carboxylic acid, the latter of which catalyzes further degradation and the biodegradation rate can be controlled by the composition, molecular weight or size of the particles [81, 82]. The blend of polymers at different ratios modifies the biodegradation rates and hence their delivery profiles, for example, PGA derived microspheres with different blend ratio to delivery NGF showed different *in vitro* degradation rates: PLGA 50/50 degrade completely after 84 days of *in vitro* incubation with phosphate buffered saline (PBS) at 37ºC, PLGA 85/15 degrade by 80%, and PCL by less than 30% under the same conditions; this profile of degradation coincides with the accumulative release of proteins, with the greatest accumulative release for PLGA 50/50; although the protein release profile is also influenced by the protein loading and the water soluble products exposed to surrounding medium in *in vitro* assays [81].

Besides biodegradation, it is important to consider the biodegradation products generated, the biodegradation of PGA derived polymers leads to the release of carboxylic acid groups that in vitro can be buffered by PBS; however, after implantation in the brain, acidification of local environment by biodegradation products can induce inflammatory response [81]. Inflammatory response induced by biodegradation products has been also studied by analyzing the microglia and astrocytes response of triblocks of lactic acid-b-PEG-b-lactic acid copolymers with two different degradable rates; it has shown an increase in reactive astrocytes in fast degrading hydrogels as compared with low degrading rate gels. This result could be due to the presence of more lactid acid as a product of degradation and a lactid acidosis in the implanted area of fast degrading gel; however, in the case of activated microglia, there were found a higher amount in slow and non degrade hydrogels [23]. In other report of the same research group, long lasting studies shown less microglia and astrocytes activation when the polymer has completely degraded, indicating that long term inflammatory response decrease with fast degrading polymer [22].

The tissue damage induced by biodegradation products could have severe deleterious effects in the CNS as reported for poly (methylidene malonate 2.1.2) (PMM 2.1.2); implanted microspheres of PMM 2.1.2 in rats striatum did not exert an important inflammatory response 1 or

2 months after implantation, and only a transient and mild characteristic foreign body reaction was observed. After 6 months post implantation however, when more degraded microspheres were present, an important microglia and iNOS positive cells infiltrate where observed in the implanted site together with extensive tissue damage. The extensive brain damage could be due to the inflammatory stimulus exerted by acidic polyanions generated during degradation process of PMM 2.1.2, and by the recruitment of activated macrophages and T cells with the subsequent oxidative and enzyme release that contributes to the damage [83].

A delayed inflammatory response after biodegradation of PEG-Silica nanocomposite gel implanted in the rat striatum was also observed [84]. PEG-Silica nanocomposite is suitable for *in vitro* delivery of proteins involve in the stimulation of dopaminergic neurons, without cell toxicity and no inflammatory response at short term in vivo implantation periods; however after 30 days after implantation an increase in activated macrophages and gliosis could be observed. *In vitro* assays using scattered Raman Spectroscopy after PEG-Silica incubation in simulated body fluid, a solution with ions similar to extracellular body fluids, showed an increase in PEG degradation and no modification of silica particles. PEG reduce protein absorption on the surface of silica particles and therefore reduces their immunogenicity [85]; however after PEG degradation, silica nanoparticles could be exposed to the immune system cells inducing an accumulation of activated macrophages and a glial reaction around the implantation site [84].

Biocompatibility and biodegradation studies of the polymeric materials in the CNS requires hence special considerations, the high vulnerability of neurons to long lasting chronic inflammatory reactions, oxidative environments, and biodegradation products, make the use of biodegradable polymeric material in CNS a challenge to avoid important deleterious effects in this tissue [86, 87]; further, delayed immune response in the brain could rend to late inflammation and therefore long term screening of CNS implanted polymers must be performed.

5. On Designed polymers for control biodegradation rates in biomedical applications

The design of specific characteristic to modulate degradation has many biological applications. The degradation of materials by non enzymatic hydrolysis is hard to regulate and only polymers blends and copolymerization can modulate the biodegradation rates. Other approaches to modulate biodegradation are modifications of chemical properties like crystallinity, hydrophobicity, and of surface characteristics like porosity [31].

The design of biomaterials for tissue engineering like cell scaffolds has to consider the mechanical properties and an appropriate architecture to allow the growth, proliferation or differentiation of cells; the modulation of biodegradation rate also contributes to the gradual incorporation of extracellular matrix (ECM) components and cellular in growth [88]. It the other hand, the design of cell responding delivery vectors for sequential delivery of different growth factors are interesting approaches to exert an specific tissue activity, that could lead to

a more biological control of drug delivery [89]. A more integrative approach hence is proposed to manipulate biodegradation rates by cells interactions.

On designed polymers can modulate the degradation rate by enzymatic and oxidative processes, and a vast numbers of reports can be found in the literature about this topic; in this chapter we would mention some of the relevant strategies of the on purpose biodegradation polymers and their future on biomedical applications.

The design of enzymatic biodegradable polymeric biomaterials has been explored in the last years and is mainly intended to approach to the biological mechanisms that regulate the functions of ECM. ECM is composed for many different types of proteins and has an instructive role for cells; their biochemical and mechanical properties changes during development and regeneration, and is specific for each tissue. Inspired in the structural and biochemical characteristics of ECM, and by their mechanism of degradation during biological process, it has been developed several polymers that mimic their dynamic characteristics. In vivo release of growth factors (GF) is linked to ECM degradation, since usually GF are interacting with ECM components as a way to control their activity, as well as for inducing a site specific action; for example, by protecting them from enzymatic degradation, or by optimizing their biological activity improving their interaction with their receptors [90, 91]. The control of polymer biodegradation by enzymatic cleavage has been suggested for release of drugs and growth factors in sequence and on demand by the cells of the polymer implantation site, or by the cells introduced inside it. Among the most common enzymes used for on design biodegradable polymer are the matrix metalloproteinases (MMP) enzyme family. MMP are zinc-dependent proteins involved in degradation of ECM during several cell activities like migration, proliferation, adhesion, apoptosis and host defense; and involved in different tissue process like immune reaction, wound healing, morphogenesis, tumor progression and angiogenesis [92].

Among the most common MMP used in biodegradable polymer design are elastase, plasmin and collagenase.

The formation of new blood vessels requires of several growth factors like Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), and Transforming Growth Factor (TGF). Blood vessels formation is an important process during wound repair, cell transplantation therapies, and for tissue engineering. Passive delivery of VEGF could lead to a low efficacy because of a rapid clear from the site, and an over or insufficient dosage. Hubbell and co workers pioneered the development of a metalloproteinase (MMP) sensitive PEG hydrogel to deliver VEGF in response to cells, showing that cell demanded release of VEGF supports the endothelial cells growth and the formation of completely remodeled vascularized tissue at the site of the hydrogel implantation [93].

The enhancing of MMP proteolytic degradation of polymeric materials can also improve cell differentiation and function; therefore their use as cell scaffold seems to be a promising approach. Conjugating peptides containing multiple sequences of MMP proteolytic cleavage to poly (ethylene glycol) diacrylate (PEGDA) hydrogels can control degradation rate and the amount of endothelial cells invasion; hydrogels with peptides containing three different proteolytic cleavage sites degraded faster and improved the amount and profundity of vessel

invasion of human umbilical vein endothelial cells and human umbilical artery smooth muscle cells, as compared with hydrogels conjugated to peptides with only one proteolytic cleavage site [94].

The release of proteins combined with controlled biodegradable hydrogels can influence the differentiation of stem cells to specific cell types, for example, using MMP sensitive hyaluronic acid hydrogels containing bone morphogenetic protein (BMP) and mesenchymal stem cells, induce almost a completely coverage of rat calvarian bone defect as compared with MMP insensitive gel, showing the importance of cell responding scaffold to stimulate tissue regeneration [95]. The use of PEG hydrogels linked to MMP-1 or collagenase sensitive peptides has also shown a better differentiation of pre-adypocites cells, enhancing the triglyceride accumulation and the formation of adipose tissue like structures in this hydrogel intended for soft tissue augmentation uses [96].

An important aspect during CNS regeneration is the axonal outgrowth of regenerating neurons. After an injury the formation of glial scar and the presence of inhibitory proteins in the ECM impair the projection of neurons to regenerate the damaged connections. MMP play an important role in neuronal outgrowth during morphogenesis and regeneration by modulating the release of guiding factor or by degrading the inhibitory ECM proteins in the scar [97, 98]. In PEGylated fibrinogen hydrogels for example the presence of MMP3 inhibitor impairs the axon outgrowth of dorsal root ganglion neurons; therefore MMP secretion is an important step in the elongation of neurons inside the biomaterial [99]. The projection of neurons can be improved by tuning the degradation rates of PEG-PLA hydrogels [100].

Improve of degradation by oxidative process is another interesting approach. The design of biomaterials responsive to high oxidative environments can be used to modulate release of drug for immunomodulation in pathological conditions like artheriosclerosis, implant rejection sites or vaccines. For example the design of an ABA block copolymeric amphiphiles with PEG as A block hydrophilic polymer and a B block hydrophobic poly(propylene sulfide)-(PPS), exhibited hydrophobic-to hydrophilic changes when is oxidized in the presence of H_2O_2, a behavior that can be used for controlled release applications like vaccine nanoparticles [101, 102]. In a similar approach an oligo(proline)- crosslinked to a PEG, poly(ε-caprolactone), and poly(carboxyl-ε-caprolactone) terpolymer system to form a polymeric scaffold were synthesized, showing and increased biodegradation rate after expose to H_2O_2, or to activated macrophages [103].

6. Conclusions

Manipulation of biodegradation process is fundamental not only to modulate the duration of a material inside the body but to modulate biocompatibility, drug release, and cell invasion. Mimic the dynamic and remarkably important extracellular environment by biomaterials is another characteristic that could improved their functionality and biocompatibility. The interaction among biomaterials and proteins or cells is relevant for functions like drug delivery or cell proliferation and differentiation, and is one of the ongoing challenge that promise the

development of specific and bio-responsive materials. Design of synthetic polymers that fully integrate the knowledge accumulated from chemistry, material engineering and biological disciplines like cell biology, biochemistry, and biophysics are the last paradigm in biomaterials. In the particular case of biodegradation of polymeric biomaterials, the profound knowledge about the chemical, physical and the biological mechanisms will render a more comprehensive on purpose biomaterials design.

Acknowledgements

Author details

Elisa Tamariz[1] and Ariadna Rios-Ramírez[2]

*Address all correspondence to: etamariz@uv.mx; elisatammx@gmail.com

Biomedical Department, Health Science Institute, Veracruzana University, Veracruz, México

2 Neurobiology Institute, National University of México, Querétaro, México

References

[1] Park, J. B, & Lakes, R. S. Biomaterials An Introduction. New York: Springer; (2007).

[2] NIHClinical applications of biomaterials: NIH Consens Statement; (1982).

[3] Huebsch, N, & Mooney, D. J. Inspiration and application in the evolution of biomaterials. Nature (2009). Nov 26;, 462(7272), 426-432.

[4] Park, J. B, & Lakes, R. S. Polymeric implants materials. In: Park JB, Lakes RS, editors. Biomaterials An Introduction. New York: Springer; (2007). , 173-205.

[5] Straley, K. S, Foo, C. W, & Heilshorn, S. C. Biomaterial design strategies for the treatment of spinal cord injuries. J Neurotrauma (2010). Jan;, 27(1), 1-19.

[6] Hirano, S. Chitin biotechnology applications. Biotechnol Annu Rev (1996). , 2237-258.

[7] Pakulska, M. M, Ballios, B. G, & Shoichet, M. S. Injectable hydrogels for central nervous system therapy. Biomed Mater (2012). Apr;7(2)024101.

[8] Aurand, E. R, Lampe, K. J, & Bjugstad, K. B. Defining and designing polymers and hydrogels for neural tissue engineering. Neurosci Res (2012). Mar;, 72(3), 199-213.

[9] Slaughter, B. V, Khurshid, S. S, Fisher, O. Z, Khademhosseini, A, & Peppas, N. A. Hydrogels in regenerative medicine. Adv Mater (2009). Sep 4;21(32-33)3307-3329.

[10] Harkness, R. D. Biological functions of collagen. Biol Rev Camb Philos Soc (1961). Nov;, 36399-463.

[11] Lee, C. H, Singla, A, & Lee, Y. Biomedical applications of collagen. Int J Pharm (2001). Jun 19;221(1-2)1-22.

[12] Khaing, Z. Z, & Schmidt, C. E. Advances in natural biomaterials for nerve tissue repair. Neurosci Lett (2012). Jun 25;, 519(2), 103-114.

[13] Bouhadir, K. H, Lee, K. Y, Alsberg, E, Damm, K. L, Anderson, K. W, & Mooney, D. J. Degradation of partially oxidized alginate and its potential application for tissue engineering. Biotechnol Prog (2001). Sep-Oct;, 17(5), 945-950.

[14] Rowley, J. A, & Mooney, D. J. Alginate type and RGD density control myoblast phenotype. J Biomed Mater Res (2002). May;, 60(2), 217-223.

[15] Noble, P. W. Hyaluronan and its catabolic products in tissue injury and repair. Matrix Biol (2002). Jan;, 21(1), 25-29.

[16] Bajaj, G, Van Alstine, W. G, & Yeo, Y. Zwitterionic chitosan derivative, a new biocompatible pharmaceutical excipient, prevents endotoxin-mediated cytokine release. PLoS One (2012). e30899.

[17] Nomura, H, Tator, C. H, & Shoichet, M. S. Bioengineered strategies for spinal cord repair. J Neurotrauma (2006). Mar-Apr;23(3-4)496-507.

[18] Bain, M. K, Bhowmick, B, Maity, D, Mondal, D, Mollick, M. M, Rana, D, et al. Synergistic effect of salt mixture on the gelation temperature and morphology of methylcellulose hydrogel. Int J Biol Macromol (2012). Dec;, 51(5), 831-836.

[19] Tate, M. C, Shear, D. A, Hoffman, S. W, & Stein, D. G. LaPlaca MC. Biocompatibility of methylcellulose-based constructs designed for intracerebral gelation following experimental traumatic brain injury. Biomaterials (2001). May;, 22(10), 1113-1123.

[20] Chu, C. editor. Biodegradable Polymeric Biomaterials: An Updated Overview. The Biomedical Engineering Handbook(2000).

[21] Aubert-pouessel, A, Venier-julienne, M. C, Clavreul, A, Sergent, M, Jollivet, C, Montero-menei, C. N, et al. In vitro study of GDNF release from biodegradable PLGA microspheres. J Control Release (2004). Mar 24;, 95(3), 463-475.

[22] Bjugstad, K. B, Lampe, K, Kern, D. S, & Mahoney, M. Biocompatibility of poly(ethylene glycol)-based hydrogels in the brain: an analysis of the glial response across space and time. J Biomed Mater Res A (2010). Oct;, 95(1), 79-91.

[23] Bjugstad, K. B, & Redmond, D. E. Jr., Lampe KJ, Kern DS, Sladek JR, Jr., Mahoney MJ. Biocompatibility of PEG-based hydrogels in primate brain. Cell Transplant (2008). , 17(4), 409-415.

[24] Bryant, S. J, Cuy, J. L, Hauch, K. D, & Ratner, B. D. Photo-patterning of porous hydrogels for tissue engineering. Biomaterials (2007). Jul;, 28(19), 2978-2986.

[25] Chirila, T. V. An overview of the development of artificial corneas with porous skirts and the use of PHEMA for such an application. Biomaterials (2001). Dec;, 22(24), 3311-3317.

[26] Patenaude, M, & Hoare, T. Injectable, mixed natural-synthetic polymer hydrogels with modular properties. Biomacromolecules (2012). Feb 13;, 13(2), 369-378.

[27] Park, J. B, & Lakes, R. S. Tissue Engineering materials and regeneration. In: Park JB, Lakes RS, editors. Biomaterials An Introduction New York: Springer; (2007). , 485-515.

[28] Heller, J, Barr, J, Ng, S. Y, Abdellauoi, K. S, & Gurny, R. Poly(ortho esters): synthesis, characterization, properties and uses. Adv Drug Deliv Rev (2002). Oct 16;, 54(7), 1015-1039.

[29] Rodriguez-galan, A, Franco, L, & Puiggali, J. Biodegradable Poly(ester amide) s: Synthesis and Application. In: Felton GP, editor. Biodegradable Polymers: Processing, Degradation and Application Nova Science Publishers, Inc.; (2011). , 207-272.

[30] Schmedlen, R. H, Masters, K. S, & West, J. L. Photocrosslinkable polyvinyl alcohol hydrogels that can be modified with cell adhesion peptides for use in tissue engineering. Biomaterials (2002). Nov;, 23(22), 4325-4332.

[31] Azevedo, H. S, & Reis, R. L. Undestanding the enzymatic degradation of biodegradable polymers and strategies to control their degradation rate. In: Reis R, San Roman J, editors. biodegradable systems in tissue engineering and regenerative medicine. Boca Ratón Florida: CRC Press; (2004).

[32] Yu, L, Zhang, Z, Zhang, H, & Ding, J. Biodegradability and biocompatibility of thermoreversible hydrogels formed from mixing a sol and a precipitate of block copolymers in water. Biomacromolecules (2010). Aug 9;, 11(8), 2169-2178.

[33] Zhong, S, & Williams, D. Are free radicals involved in biodegradation of polymeric medical devices in situ Advanced Materials (1991).

[34] Santerre, J. P, Woodhouse, K, Laroche, G, & Labow, R. S. Understanding the biodegradation of polyurethanes: from classical implants to tissue engineering materials. Biomaterials (2005). Dec;, 26(35), 7457-7470.

[35] Santerre, J. P, Labow, R. S, Duguay, D. G, Erfle, D, & Adams, G. A. Biodegradation evaluation of polyether and polyester-urethanes with oxidative and hydrolytic enzymes. J Biomed Mater Res (1994). Oct;, 28(10), 1187-1199.

[36] Jiang, H. L, Tang, G. P, Weng, L. H, & Zhu, K. J. In vivo degradation and biocompatibility of a new class of alternate poly(ester-anhydrides) based on aliphatic and aromatic diacids. J Biomater Sci Polym Ed (2001). , 12(12), 1281-1292.

[37] Paul, P. W. editor. Fundamental Immunology. Philadelphia, PA, U. S. A: Lippincott Williams & Wilkins; (2008).

[38] Iwasaki, A, & Medzhitov, R. Regulation of adaptive immunity by the innate immune system. Science (2010). Jan 15;, 327(5963), 291-295.

[39] Jenney, C. R, & Anderson, J. M. Adsorbed serum proteins responsible for surface dependent human macrophage behavior. J Biomed Mater Res (2000). Mar 15;, 49(4), 435-447.

[40] Keselowsky, B. G, Bridges, A. W, Burns, K. L, Tate, C. C, & Babensee, J. E. LaPlaca MC, et al. Role of plasma fibronectin in the foreign body response to biomaterials. Biomaterials (2007). Sep;, 28(25), 3626-3631.

[41] Wilson, C. J, Clegg, R. E, Leavesley, D. I, & Pearcy, M. J. Mediation of biomaterial-cell interactions by adsorbed proteins: a review. Tissue Eng (2005). Jan-Feb;11(1-2)1-18.

[42] Aderem, A, & Underhill, D. M. Mechanisms of phagocytosis in macrophages. Annu Rev Immunol (1999). , 17593-623.

[43] Plourde, N. M, Kortagere, S, Welsh, W, & Moghe, P. V. Structure-activity relations of nanolipoblockers with the atherogenic domain of human macrophage scavenger receptor A. Biomacromolecules (2009). Jun 8;, 10(6), 1381-1391.

[44] Anderson, J. M, Rodriguez, A, & Chang, D. T. Foreign body reaction to biomaterials. Semin Immunol (2008). Apr;, 20(2), 86-100.

[45] Salacinski, H. J, Tiwari, A, Hamilton, G, & Seifalian, A. M. Cellular engineering of vascular bypass grafts: role of chemical coatings for enhancing endothelial cell attachment. Med Biol Eng Comput (2001). Nov;, 39(6), 609-618.

[46] Henson, P. M. The immunologic release of constituents from neutrophil leukocytes. II. Mechanisms of release during phagocytosis, and adherence to nonphagocytosable surfaces. J Immunol (1971). Dec;, 107(6), 1547-1557.

[47] Henson, P. M. Mechanisms of exocytosis in phagocytic inflammatory cells. Parke-Davis Award Lecture. Am J Pathol (1980). Dec;, 101(3), 494-511.

[48] Kou, P. M, & Babensee, J. E. Macrophage and dendritic cell phenotypic diversity in the context of biomaterials. J Biomed Mater Res A (2011). Jan;, 96(1), 239-260.

[49] Malik, A. F, Hoque, R, Ouyang, X, Ghani, A, Hong, E, Khan, K, et al. Inflammasome components Asc and caspase-1 mediate biomaterial-induced inflammation and foreign body response. Proc Natl Acad Sci U S A (2011). Dec 13;, 108(50), 20095-20100.

[50] Brodbeck, W. G, Shive, M. S, Colton, E, Nakayama, Y, Matsuda, T, & Anderson, J. M. Influence of biomaterial surface chemistry on the apoptosis of adherent cells. J Biomed Mater Res (2001). Jun 15;, 55(4), 661-668.

[51] Mcnally, A. K, Jones, J. A, Macewan, S. R, Colton, E, & Anderson, J. M. Vitronectin is a critical protein adhesion substrate for IL-4-induced foreign body giant cell formation. J Biomed Mater Res A (2008). Aug;, 86(2), 535-543.

[52] Bryers, J. D, Giachelli, C. M, & Ratner, B. D. Engineering biomaterials to integrate and heal: the biocompatibility paradigm shifts. Biotechnol Bioeng (2012). Aug;, 109(8), 1898-1911.

[53] Gordon, S. Alternative activation of macrophages. Nat Rev Immunol (2003). Jan;, 3(1), 23-35.

[54] Mosser, D. M, & Edwards, J. P. Exploring the full spectrum of macrophage activation. Nat Rev Immunol (2008). Dec;, 8(12), 958-969.

[55] Labow, R. S, Meek, E, & Santerre, J. P. Synthesis of cholesterol esterase by monocyte-derived macrophages: a potential role in the biodegradation of poly(urethane)s. J Biomater Appl (1999). Jan;, 13(3), 187-205.

[56] Mcbane, J. E, Matheson, L. A, Sharifpoor, S, Santerre, J. P, & Labow, R. S. Effect of polyurethane chemistry and protein coating on monocyte differentiation towards a wound healing phenotype macrophage. Biomaterials (2009). Oct;, 30(29), 5497-5504.

[57] Bretz, U, & Baggiolini, M. Biochemical and morphological characterization of azurophil and specific granules of human neutrophilic polymorphonuclear leukocytes. J Cell Biol (1974). Oct;, 63(1), 251-269.

[58] Swirski, F. K, & Nahrendorf, M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. Science (2013). Jan 11;, 339(6116), 161-166.

[59] Xu, X, & Hakansson, L. Degranulation of primary and secondary granules in adherent human neutrophils. Scand J Immunol (2002). Feb;, 55(2), 178-188.

[60] Heiple, J. M, Wright, S. D, Allen, N. S, & Silverstein, S. C. Macrophages form circular zones of very close apposition to IgG-coated surfaces. Cell Motil Cytoskeleton (1990). , 15(4), 260-270.

[61] Labro, M. T. Interference of antibacterial agents with phagocyte functions: immunomodulation or "immuno-fairy tales"? Clin Microbiol Rev (2000). Oct;, 13(4), 615-650.

[62] Murray, P. J, & Wynn, T. A. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol (2011). Nov;, 11(11), 723-737.

[63] Galea, I, Bechmann, I, & Perry, V. H. What is immune privilege (not)? Trends Immunol (2007). Jan;, 28(1), 12-18.

[64] Weller, R. O, Engelhardt, B, & Phillips, M. J. Lymphocyte targeting of the central nervous system: a review of afferent and efferent CNS-immune pathways. Brain Pathol (1996). Jul;, 6(3), 275-288.

[65] Wraith, D. C, & Nicholson, L. B. The adaptive immune system in diseases of the central nervous system. J Clin Invest (2012). Apr 2;, 122(4), 1172-1179.

[66] Fournier, E, Passirani, C, Montero-menei, C. N, & Benoit, J. P. Biocompatibility of implantable synthetic polymeric drug carriers: focus on brain biocompatibility. Biomaterials (2003). Aug;, 24(19), 3311-3331.

[67] Hanisch, U. K, & Kettenmann, H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci (2007). Nov;, 10(11), 1387-1394.

[68] Ransohoff, R. M, & Brown, M. A. Innate immunity in the central nervous system. J Clin Invest (2012). Apr 2;, 122(4), 1164-1171.

[69] Agostino, D, Gottfried-blackmore, P. M, Anandasabapathy, A, & Bulloch, N. K. Brain dendritic cells: biology and pathology. Acta Neuropathol (2012). Nov;, 124(5), 599-614.

[70] Guillemin, G. J, & Brew, B. J. Microglia, macrophages, perivascular macrophages, and pericytes: a review of function and identification. J Leukoc Biol (2004). Mar;, 75(3), 388-397.

[71] Pratt, B. M, & Mcpherson, J. M. TGF-beta in the central nervous system: potential roles in ischemic injury and neurodegenerative diseases. Cytokine Growth Factor Rev (1997). Dec;, 8(4), 267-292.

[72] Popovic, N, & Brundin, P. Therapeutic potential of controlled drug delivery systems in neurodegenerative diseases. Int J Pharm (2006). May 18;, 314(2), 120-126.

[73] Zhong, Y, & Bellamkonda, R. V. Biomaterials for the central nervous system. J R Soc Interface (2008). Sep 6;, 5(26), 957-975.

[74] Gouhier, C, Chalon, S, Aubert-pouessel, A, Venier-julienne, M. C, Jollivet, C, Benoit, J. P, et al. Protection of dopaminergic nigrostriatal afferents by GDNF delivered by microspheres in a rodent model of Parkinson's disease. Synapse (2002). Jun 1;, 44(3), 124-131.

[75] Delcroix, G. J, Garbayo, E, Sindji, L, Thomas, O, Vanpouille-box, C, Schiller, P. C, et al. The therapeutic potential of human multipotent mesenchymal stromal cells combined with pharmacologically active microcarriers transplanted in hemi-parkinsonian rats. Biomaterials (2011). Feb;, 32(6), 1560-1573.

[76] Pean, J. M, Menei, P, Morel, O, Montero-menei, C. N, & Benoit, J. P. Intraseptal implantation of NGF-releasing microspheres promote the survival of axotomized cholinergic neurons. Biomaterials (2000). Oct;, 21(20), 2097-2101.

[77] Gagliardi, M, Bardi, G, & Bifone, A. Polymeric nanocarriers for controlled and enhanced delivery of therapeutic agents to the CNS. Ther Deliv (2012). Jul;, 3(7), 875-887.

[78] Graber, D. J, Snyder-keller, A, Lawrence, D. A, & Turner, J. N. Neurodegeneration by activated microglia across a nanofiltration membrane. J Biochem Mol Toxicol (2012). Feb;, 26(2), 45-53.

[79] Minami, S. S, Sun, B, Popat, K, Kauppinen, T, Pleiss, M, Zhou, Y, et al. Selective targeting of microglia by quantum dots. J Neuroinflammation (2012).

[80] Sharma, H. S, & Sharma, A. Nanoparticles aggravate heat stress induced cognitive deficits, blood-brain barrier disruption, edema formation and brain pathology. Prog Brain Res (2007). , 162245-273.

[81] Cao, X, & Schoichet, M. S. Delivering neuroactive molecules from biodegradable microspheres for application in central nervous system disorders. Biomaterials (1999). Feb;, 20(4), 329-339.

[82] Porjazoska, A, Goracinova, K, Mladenovska, K, Glavas, M, Simonovska, M, Janjevic, E. I, et al. Poly(lactide-co-glycolide) microparticles as systems for controlled release of proteins-- preparation and characterization. Acta Pharm (2004). Sep;, 54(3), 215-229.

[83] Fournier, E, Passirani, C, Colin, N, Sagodira, S, Menei, P, Benoit, J. P, et al. The brain tissue response to biodegradable poly(methylidene malonate 2.1.2)-based microspheres in the rat. Biomaterials (2006). Oct;, 27(28), 4963-4974.

[84] Tamariz, E, Wan, A. C, Pek, Y. S, Giordano, M, Hernandez-padron, G, Varela-echavarria, A, et al. Delivery of chemotropic proteins and improvement of dopaminergic neuron outgrowth through a thixotropic hybrid nano-gel. J Mater Sci Mater Med (2011). Sep;, 22(9), 2097-2109.

[85] Xu, H, Yan, F, Monson, E. E, & Kopelman, R. Room-temperature preparation and characterization of poly (ethylene glycol)-coated silica nanoparticles for biomedical applications. J Biomed Mater Res A (2003). Sep 15;, 66(4), 870-879.

[86] Leach, J. B, Achyuta, A. K, & Murthy, S. K. Bridging the Divide between Neuroprosthetic Design, Tissue Engineering and Neurobiology. Front Neuroeng (2010).

[87] Mcconnell, G. C, Rees, H. D, Levey, A. I, Gutekunst, C. A, Gross, R. E, & Bellamkonda, R. V. Implanted neural electrodes cause chronic, local inflammation that is correlated with local neurodegeneration. J Neural Eng (2009). Oct;6(5)056003.

[88] Lutolf, M. P. Biomaterials: Spotlight on hydrogels. Nat Mater (2009). Jun;, 8(6), 451-453.

[89] Lee, K, Silva, E. A, & Mooney, D. J. Growth factor delivery-based tissue engineering: general approaches and a review of recent developments. J R Soc Interface (2011). Feb 6;, 8(55), 153-170.

[90] Ramirez, F, & Rifkin, D. B. Cell signaling events: a view from the matrix. Matrix Biol (2003). Apr;, 22(2), 101-107.

[91] Schultz, G. S, & Wysocki, A. Interactions between extracellular matrix and growth factors in wound healing. Wound Repair Regen (2009). Mar-Apr;, 17(2), 153-162.

[92] Vu, T. H, & Werb, Z. Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev (2000). Sep 1;, 14(17), 2123-2133.

[93] Zisch, A. H, Lutolf, M. P, Ehrbar, M, Raeber, G. P, Rizzi, S. C, Davies, N, et al. Cell-demanded release of VEGF from synthetic, biointeractive cell ingrowth matrices for vascularized tissue growth. FASEB J (2003). Dec;, 17(15), 2260-2262.

[94] Sokic, S, & Papavasiliou, G. Controlled proteolytic cleavage site presentation in biomimetic PEGDA hydrogels enhances neovascularization in vitro. Tissue Eng Part A (2012). Dec;18(23-24)2477-2486.

[95] Kim, J, Kim, I. S, Cho, T. H, Kim, H. C, Yoon, S. J, Choi, J, et al. In vivo evaluation of MMP sensitive high-molecular weight HA-based hydrogels for bone tissue engineering. J Biomed Mater Res A (2010). Dec 1;, 95(3), 673-681.

[96] Brandl, F. P, Seitz, A. K, Tessmar, J. K, Blunk, T, & Gopferich, A. M. Enzymatically degradable poly(ethylene glycol) based hydrogels for adipose tissue engineering. Biomaterials (2010). May;, 31(14), 3957-3966.

[97] Bai, G, & Pfaff, S. L. Protease regulation: the Yin and Yang of neural development and disease. Neuron (2011). Oct 6;, 72(1), 9-21.

[98] Zuo, J, Ferguson, T. A, Hernandez, Y. J, Stetler-stevenson, W. G, & Muir, D. Neuronal matrix metalloproteinase-2 degrades and inactivates a neurite-inhibiting chondroitin sulfate proteoglycan. J Neurosci (1998). Jul 15;, 18(14), 5203-5211.

[99] Sarig-nadir, O, & Seliktar, D. The role of matrix metalloproteinases in regulating neuronal and nonneuronal cell invasion into PEGylated fibrinogen hydrogels. Biomaterials (2010). Sep;, 31(25), 6411-6416.

[100] Mahoney, M. J, & Anseth, K. S. Three-dimensional growth and function of neural tissue in degradable polyethylene glycol hydrogels. Biomaterials (2006). Apr;, 27(10), 2265-2274.

[101] Napoli, A, Valentini, M, Tirelli, N, Muller, M, & Hubbell, J. A. Oxidation-responsive polymeric vesicles. Nat Mater (2004). Mar;, 3(3), 183-189.

[102] Thomas, S. N, Van Der Vlies, A. J, Neil, O, Reddy, C. P, Yu, S. T, & Giorgio, S. S. TD, et al. Engineering complement activation on polypropylene sulfide vaccine nanoparticles. Biomaterials (2011). Mar;, 32(8), 2194-2203.

[103] Yu, S. S, Koblin, R. L, Zachman, A. L, Perrien, D. S, Hofmeister, L. H, Giorgio, T. D, et al. Physiologically relevant oxidative degradation of oligo(proline) cross-linked polymeric scaffolds. Biomacromolecules (2011). Dec 12;, 12(12), 4357-4366.