Recent Advances in Antiinflammatory Material Design

Eloïse Lebaudy, Sylvie Fournel, Philippe Lavalle, Nihal Engin Vrana,*
and Varvara Gribova*

Implants and prostheses are widely used to replace damaged tissues or to treat various diseases. However, besides the risk of bacterial or fungal infection, an inflammatory response usually occurs. Here, recent progress in the field of anti-inflammatory biomaterials is described. Different materials and approaches are used to decrease the inflammatory response, including hydrogels, nanoparticles, implant surface coating by polymers, and a variety of systems for anti-inflammatory drug delivery. Complex multifunctional systems dealing with inflammation, microbial infection, bone regeneration, or angiogenesis are also described. New promising stimuli-responsive systems, such as pH- and temperature-responsive materials, are also being developed that would enable an "intelligent" antiinflammatory response when the inflammation occurs. Together, different approaches hold promise for creation of novel multifunctional smart materials allowing better implant integration and tissue regeneration.

1. Introduction

Implants and prostheses are very common nowadays and serve to replace damaged tissues or to treat various diseases. Dental implants, as well as bone and cartilage repairing implants, are widely used. Some conditions like spinal stenosis[1] or hernias also require usage of implants. For instance, groin hernia

repair concerns more than 20 million patients annually, and mesh implant is recommended as the first choice to solve the problem.[2] Implants may also be used for aesthetic purposes: this is the case of breast or jaw implants.

Different types of materials, such as metals, polymers, or ceramics, are used to design implants and prostheses. Material's choice is crucial and will be guided by the final application. For example, prostheses for bone replacements, besides being nontoxic and chemically inert, also need to have mechanical properties as close as possible to the bone.[3] Polymers are also widely used for implants because their physical and chemical properties can be controlled in many ways, making them appropriate for different applications.[4] Besides such physicochemical considerations, another important aspect is the immune response induced by a given material upon its implantation into the body.

1.1. Inflammatory Response to Biomaterials

Biocompatibility is an important notion related to biomaterials, which describes material's ability to interact with living matter while avoiding undesirable effects such as injury, toxicity, or rejection by the host's immune system.[5] The new biomaterial design has to include biocompatibility specifications, in addition to functionality for the treatment of diseases.[6]

However, achieving good biocompatibility *in vivo* is not an easy deal. Besides the risk of bacterial or fungal infection, an inflammatory response always occurs.[7] In its acute phase, the inflammatory response recruits immune cells to the diseased site, resulting in the elimination of the pathogens or the damaged tissue. In its resolution phase, inflammation is helpful for the healing and the tissue regeneration. However, a severe acute or strong chronic inflammation can lead to foreign body response (FBR) and collateral tissue damage.[8]

That is why, nowadays, biomaterials researchers are developing new systems to decrease the inflammatory response to the implanted materials.[9] A diversity of materials in different forms (coatings, hydrogels, nanoparticles etc.) has been produced for this purpose. Of note, interaction between different materials and the biological environment seems to be the key to create new systems that enable the management of the inflammatory response and lead to a decreased risk of chronic inflammation.

The mechanism of the inflammatory response in the presence of an implant, named FBR, has been described by Anderson[10]

E. Lebaudy, Dr. P. Lavalle, Dr. V. Gribova
Institut National de la Santé et de la Recherche Médicale
INSERM Unité 1121 Biomaterials and Bioengineering
11 rue Humann, Strasbourg Cedex 67085, France
E-mail: varvara.gribova@inserm.fr
E. Lebaudy, Dr. P. Lavalle, Dr. V. Gribova
Faculté de Chirurgie Dentaire
Université de Strasbourg
Strasbourg 67000 France
Prof. S. Fournel
Université de Strasbourg
CNRS
3Bio team
Laboratoire de Conception et Application de Molécules Bioactives
UMR 7199
Faculté de Pharmacie
74 route du Rhin, Illkirch Cedex 67401, France
Dr. P. Lavalle, Dr. N. E. Vrana
SPARTHA Medical
14B Rue de la Canardiere, Strasbourg 67100, France
E-mail: evrana@sparthamedical.eu

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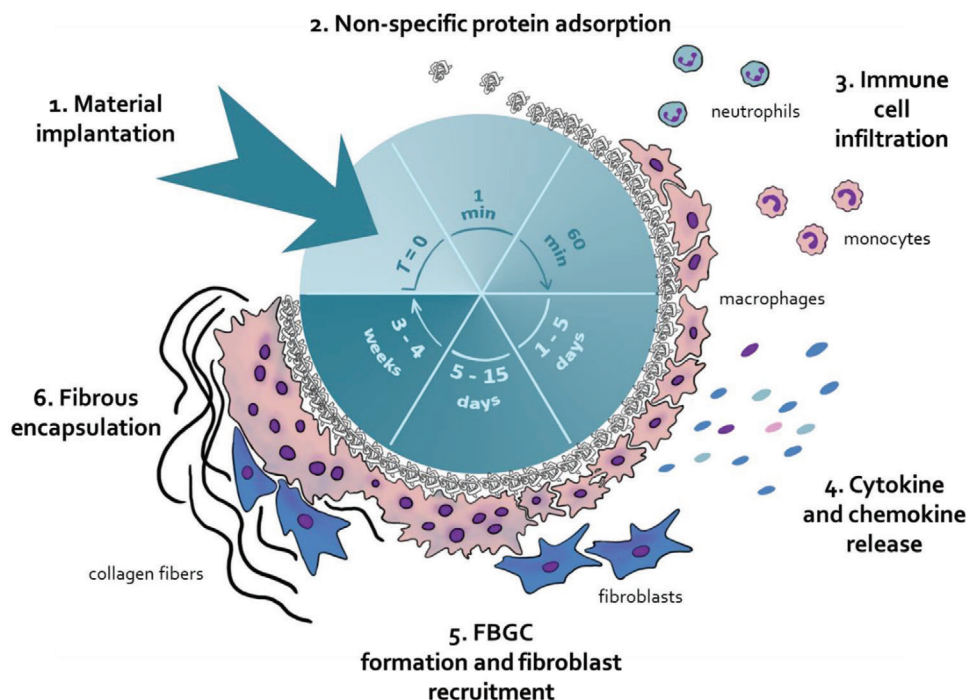**MATERIALS**
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Figure 1. Inflammatory response of the body following the implantation of inert biomaterial. First of all, a layer of proteins adsorbs on the biomaterial surface. Then, different cells such as platelets and macrophages adhere and release cytokines and chemokines, and form foreign body giant cells (FBGC). Finally, nonfunctional fibrous tissue encapsulates the implant because of an excessive number of fibroblasts that have been recruited during the proinflammatory reaction. Adapted with permission.[11] Copyright 2015, Elsevier.

and, later, by Sridharan et al. (**Figure 1**).[11] After implantation, blood proteins are adsorbed to the biomaterial surface, forming a provisional matrix around the biomaterial. This provisional matrix is rich in growth factors, cytokines, and chemo-attractants capable of recruiting cells of the innate immune system, like neutrophils, macrophages, and monocytes, to the injury site. The recruited cells produce various inflammatory mediators (proinflammatory cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), chemo-attractive cytokine like interleukin-8 (IL-8), chemokines, eicosanoids, histamine etc.) that results in acute inflammation. During this step, neutrophils and macrophages "clean" implantation site by eliminating all foreign bodies including solid waste (such as damaged cell debris) and infectious microorganisms. The innate immune response can be prolonged by an adaptive immune response that could result in T and B cell activation and, for example, antibody production.

At the end of the acute inflammation, there are two possible outcomes: if the inflammation is resolved by the activities of the adhered cells, a local homeostasis is achieved, and the implant integrates with the surrounding tissues. Among the cells known to contribute to the resolution of the inflammation, the most studied cells are the M2 macrophages. However, some reports have shown that neutrophils are also involved in this resolution.[12] However, if the inflammation is not resolved and becomes chronic, the adhered cells continue to create a proinflammatory environment which results in the formation of granuloma. A granuloma is a focal aggregate of immune cells, essentially macrophages that forms in response to a persistent

inflammatory stimulus. Finally, due to the excessive recruitment of fibroblasts and their unorganized extracellular matrix (ECM) secretion, the encapsulation of the implant by a nonfunctional fibrous tissue would be the end result.

One of the major cell types recruited to implants is monocytes, which then differentiate to macrophages. It is well established that immune microenvironment could modulate the immune response and especially the macrophage fate.[11] Indeed, presence of proinflammatory factors results in the differentiation of macrophages into phenotype M1 (**Figure 2**). This macrophages polarization leads to the secretion of proinflammatory cytokines like IL-1, IL-6, and TNF-α[13] and thus to a high inflammatory response. On the contrary, in presence of anti-inflammatory factors like IL-4 or IL-13, the macrophages are differentiated into M2 phenotype. This polarization leads to the secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor β1 (TGFβ1),[14] which contribute to the integration of biomaterials. This is the reason a lot of researchers tend to create biomaterials that orient the polarization of macrophages into M2 phenotype. For more details on M1/M2 macrophage polarization, readers are invited to consult more specialized reviews.[15]

1.2. Evaluation of Inflammatory Response to Biomaterials

In vitro evaluation of the anti-inflammatory or pro-inflammatory properties of a material is usually conducted by culturing them with macrophages (primary or cell lines) that can be activated
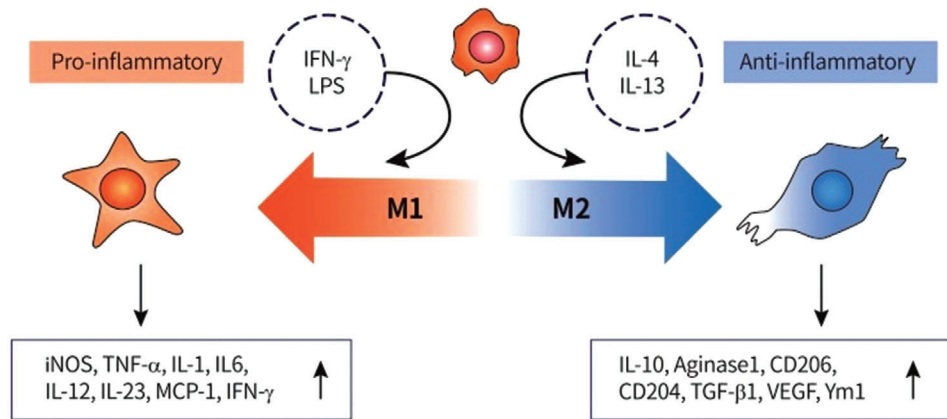
Figure 2. Polarization of macrophages into M1 and M2 phenotypes. LPS and Interferon-γ stimulate macrophages into M1 polarization (inflammation) whereas interleukin-4 and 13 lead to M2 polarization (immune regulation and tissue remodeling). IFN: interferon, LPS: lipopolysaccharide, IL: interleukin, iNOS: inducible nitric oxide synthase, TNF: tumor necrosis factor, MCP: monocyte chemoattractant protein, CD: cluster of differentiation, Ym1: chitinase-like 3, TGF: transforming growth factor, VEGF: vascular endothelial growth factor. Adapted with permission under the terms of the Creative Commons Attribution License.[14b] Copyright 2019, Medical Biological Science and Engineering.
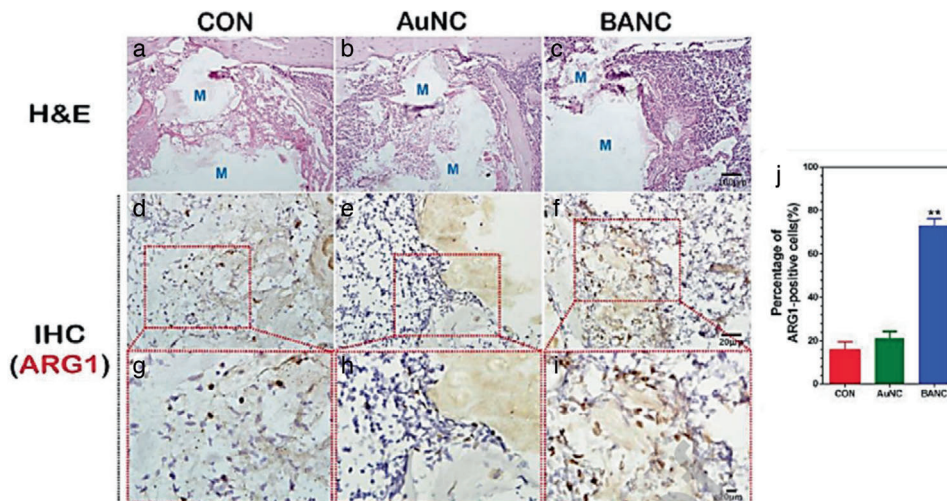

Figure 3. Effect of the biomimetic nanocapsule (BANC) on macrophage polarization in vivo. a–c) The pictures present histological staining images including hematoxylin & eosin (H&E) staining and d–i) immunohistochemical (IHC) staining of arginase 1 (ARG1). j) The graph presents the quantification of ARG1-positive cells of IHC staining. CON: control, AuNC: gold nanocage. Adapted with permission.[21] Copyright 2020, Elsevier.

by chemical compounds such as endotoxin lipopolysaccharide (LPS) to mimic inflammation.[16] Then, the inflammatory activity is evaluated by analyzing the amount of pro-inflammatory markers such as nitric oxide (NO) or cytokines. NO is released by activated macrophages that can be easily measured in cell culture supernatant by colorimetry using the Griess reagent.[17] The level of other pro-inflammatory markers such as TNF-α, cycloxygenase-2 (COX-2), inducible NO synthase (iNOS), and IL-6, or anti-inflammatory IL-10, can be evaluated by ELISA and Western blotting techniques.[16,18]

One of the widely used applications of anti-inflammatory biomaterials is wound healing. To evaluate the contribution of such materials *in vitro*, scratch assay using epithelial cells (e.g., kidney epithelial cells such as Vero cells) is used, and re-epithelization is being followed.[18a]

In vivo, anti-inflammatory activity is evaluated in animal inflammation models. For instance, to screen for new drugs, researchers use mouse paw edema test.[19] After induction of the inflammation by carrageenan, swelling of the paw is measured, and the antiinflammatory effect is presented as the decrease in the paw volume. Another model is arachidonic acid-induced mouse ear edema, which is measured using a thickness gauge. After the sacrifice, fragments of ears are weighted, allowing to quantify edema.[20]

In the case of the implants for tissue regeneration purposes, immunohistological staining of the implant-surrounding tissues can be performed to evaluate the level of the inflammation, e.g. by staining arginase 1 (ARG1)[21] (**Figure 3**). Otherwise, the levels of inflammatory cytokines, i.e., IL-1β, IL-6, and TNF-α, in the surrounding tissues can be determined.[22]

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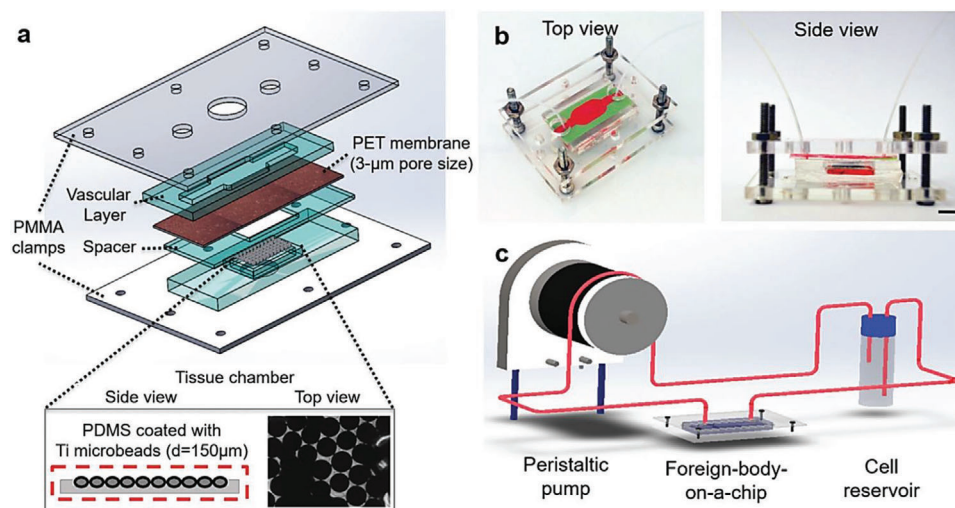**MATERIALS**
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Figure 4. Design of the FBROC (FBR-on-a-chip) device. a) In the bioreactor, endothelialized porous membrane is sandwiched in between a vascular channel and a tissue chamber. b) Top- and side-views of the bioreactor. c) Diagram showing the operation of the device. Adapted with permission.[24] Copyright 2019, Wiley-VCH GmbH.
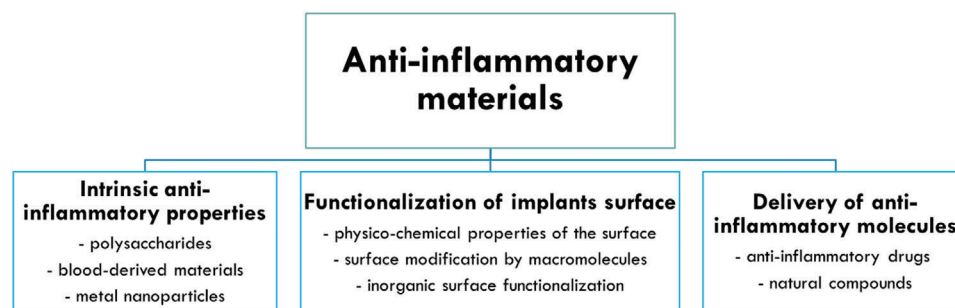

Figure 5. Anti-inflammatory biomaterial design. Different types of materials and numerous compounds, embedded or grafted, can be used to achieve antiinflammatory properties.

Ex vivo models such as porcine gingiva are used in some studies to evaluate anti-inflammatory effect.[23] Additional tools for FBR evaluation such as microfluidic platform were also reported: for instance, Sharifi et al. developed FBR-on-a-chip (FBROC) to model the immune cell response to implants (**Figure 4**). The platform provides a model of the native implant microenvironment and provides a strategy to assess the FBR on various implants, in an individual and physiologically relevant manner.[24]

1.3. Anti-inflammatory Biomaterial Design

In this review, we discuss the most recent advances in the field of anti-inflammatory biomaterial design. A great diversity of compounds, embedded or grafted, as well as complex architectures are used to achieve maximal anti-inflammatory properties. We will describe simple systems based on biomaterials possessing intrinsic anti-inflammatory properties, anti-inflammatory surface coatings, and delivery of anti-inflammatory agents by biomaterials (**Figure 5**). Finally, we will present more complex architectures elaborated for optimal anti-inflammatory response, stimuli-responsive anti-inflammatory activity, and multifunctionality. Such multifunctional materials are needed

in many medical device-related fields in order to simultaneously address the problems of biocompatibility, microbial infections, inflammatory response, and tissue regeneration.

2. Materials Presenting Intrinsic Anti-inflammatory Properties

Some materials possess intrinsic anti-inflammatory properties and can be used to avoid FBR. Below, we will describe natural anti-inflammatory materials made of polysaccharides, as well as blood-derived materials. The advantage of such materials is their high biocompatibility and multifunctionality. Besides natural organic materials, inorganic materials like gold and zinc, which are often used as nanoparticles, also present immunomodulatory properties.

2.1. Polysaccharides

Hyaluronic acid (HA) is a polyanionic polysaccharide that is naturally present in the ECM of vertebrate tissues (hyaline cartilage, synovial fluid, and vitreous humor of the eye), and

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composed of a repeating disaccharide unit of (1,4)-glucuronic acid-β(1,3)-N-acetylglucosamine (GlcNAc).[25] HA is biocompatible and used for multiple biomedical applications: osteoarthritis treatment, dermal injections, eye surgery, and wound regeneration.[26] It possesses antifouling properties which reduce bacterial adhesion,[27] but also anti-inflammatory properties which suppress pro-inflammatory cytokines such as TNF-α, IL-1, IL-6.[28] Its anti-inflammatory properties could be related to the interactions between HA and CD44, a glycoprotein involved in cell adhesion and migration. Those interactions can regulate the cytokines production and moderate the inflammatory response.[28,29] Because of these properties, HA is an efficient agent for treatment of multiple skin and joint inflammatory diseases.[30] Recently, intra-articular injections of HA have been approved for treating degenerative knee arthritis.[31]

However, HA can also act as a promoter of inflammation, making its role in the inflammation multifaceted. It was shown that while high molecular weight HA demonstrates anti-inflammatory and immunosuppressive properties, low molecular weight HA can act as a potent pro-inflammatory molecule.[32] For instance, study by Chen et al. suggested that high molecular weight HA may be beneficial for treatment of periodontal inflammation and oral wounds. It was also shown that high molecular weight HA inhibits *Porphyromonas gingivalis*-induced inflammatory cytokine secretion in gingival fibroblast cells, while promoting their migration.[33]

Another widely used polysaccharide exerting anti-inflammatory action is chitosan, a polycationic polysaccharide consisting of linear chains of predominantly β-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-D-glucose (also named N-acetyl-D-glucosamine) residues. It is biocompatible and presents antimicrobial properties, as already described in many reviews.[34] Similar to the case of HA, the chitosan molecular can affect its antiinflammatory activities. In a recent study, it was shown that larger molecular weight (>29.2 kDa) chitosans are mostly anti-inflammatory whereas smaller molecular weight (≤29.2 kDa) chitosans are proinflammatory.[35]

Chitosan-based materials can be modified to achieve multifunctionality. For example, Huber et al. described anti-inflammatory and antioxidant properties of phenolic-O-carboxymethyl chitosan (CMCS) hydrogels.[36] Hydrogels made of phenolic-CMCS demonstrated antioxidant and anti-inflammatory properties in vitro and in vivo, in a rat inflammation model.[37]

In another study, chitosan scaffolds were functionalized with BMP-2 mimetic peptide sequence to add osteoinductive activity.[18c] Results showed that bioactivated scaffolds were able to inhibit secretion of inflammatory mediators such as IL-1β, promote anti-inflammatory markers production (IL-10), and reduce oxidative stress metabolites.

The reasons chitosan shows anti-inflammatory properties seem to be related to inhibiting MAP kinase signaling, which leads to a decrease in cytokine production.[38]

Besides HA and chitosan, other molecules like polysaccharide from *Schizophyllum commune*[17] and neutral polysaccharide extracted from maca roots[39] have shown anti-inflammatory activity in solution. These natural polymers are promising for the elaboration of new anti-inflammatory biomaterials.

2.2. Blood-Derived Materials

Several molecules derived from the blood were shown to have anti-inflammatory properties, including, fibrin, which is a major factor in thrombosis, wound healing, and several other biological functions and pathological conditions.[40] It is used as a hydrogel in biomedical applications and as a scaffold in tissue engineering.[41]

In the field of anti-inflammatory materials, Tanaka et al. showed that fibrin hydrogels have a strong promoting effect on the recruitment of anti-inflammatory M2 macrophages.[18b] In their study, the secretion of proinflammatory cytokine TNF-α decreased and the secretion of an anti-inflammatory cytokine IL-10 increased in mouse bone marrow-derived macrophages.

Platelets are non-nucleated blood components that are the primary cells regulating hemostasis and thrombosis, but also active participants in the inflammatory response.[42] Platelet rich plasma (PRP), which consists of a high concentration of platelets, contains various cytokines and growth factors which accelerate healing process and promote for instance cartilage repair.[43]

In a study by Renn et al.,[16] different fractions containing platelets or platelet-derived products (platelet-poor-plasma, platelet lysate with cell debris or cell-free, platelet gel releasate and solvent/detergent-treated platelet lysate) were used to assess their antiinflammatory activity.[16] The results showed that all plasma and platelet fractions exerted an inhibitory effect on macrophage-induced inflammation. Thus, both plasma and platelet proteomes seem to contribute to the induction of an anti-inflammatory phenotype.

However, the fractions were only tested in solution, so development of novel platelet-based materials for biomedical applications is required. As an example of such materials, leukocyte-platelet rich fibrin (L-PRF) has been developed. It is a solid 3D fibrin membrane enriched with platelets and growth factors, which is a popular adjunct in surgeries.[44]

2.3. Metal Nanoparticles

Nanoparticles are nowadays widely used for a wide range of applications in the biomaterial field, like dental implants,[45] cancer treatments[46] or regenerative medicine.[47] A lot of studies are made in order to develop new nanoparticles with anti-inflammatory properties.[48]

The interaction of metal nanoparticles with tissues is very complex. Metal nanoparticles can interact with the proteins in blood plasma, which form a protein corona around them.[48a] Protein layer composition depends on the physical properties of the nanoparticles, such as their size and their surface roughness. This protein corona enters in contact with inflammatory molecules, and the "soft" layer composed of serum proteins seems to activate M2 macrophages, which are directly linked to the anti-inflammatory response. In addition to this phenomenon, the nanometric size of the particles seems to improve their penetration inside epithelial and inflammatory cells.[49] Moreover, the interaction of nanoparticles with cells is improved as their reactivity is higher, due to their high surface/volume ratio. Those properties are very interesting for the formulation of materials for drug release, as it will be explained further. However,

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when nanoparticles enter in contact with the cells, FBR may also occur.[50] Thus, proper nanoparticle design is required to achieve anti-inflammatory properties and avoid the FBR.

Gold nanoparticles have interesting applications because of their high stability and biocompatibility.[51] Gold nanoparticles also have anti-inflammatory properties, and their interaction with biological environment has been widely studied in order to improve their immunomodulatory properties and to extend their applications.[52] Moreover, the synthesis of gold nanoparticles is quite easy. In most of cases, a gold salt (chloroauric acid) is reduced by a reducer, for instance citrate.[53] de Carvalho et al. used glycerol as reducer for the synthesis of gold nanoparticles, that been delivered by the oral route in rat liver injury model, and their effect on the secretion of two pro-inflammatory signals: TNF-α and Il-1β, has been studied.[54] The results showed a decrease of those markers, which demonstrate the anti-inflammatory properties of gold nanoparticles *in vivo*.

Zinc nanoparticles are also studied for the development of anti-inflammatory materials. Agarwal et al. investigated anti-inflammatory potential of zinc oxide (ZnO) nanoparticles on LPS-activated murine macrophage RAW 264.7 cells.[55] The results showed that ZnO nanoparticles blocked the production and the release of proinflammatory factors.

Meanwhile, researchers tend nowadays to synthetize nanoparticles in a "green" way. "Green chemistry" is being developed, as the environment is at the heart of many discussions. Natural reagents such as leaves or fruit extracts can be used to synthetize nanoparticles.[56] This can also be a good strategy to decrease the use of anti-inflammatory drugs. By capping silver nanoparticles with molecules such as belladonna, Das et al. proposed a system with a higher in vitro anti-inflammatory response than diclofenac, a powerful anti-inflammatory drug.[57] This type of synthesis and the use of natural reagents allow to increase the biocompatibility of nanomaterials while controlling their size and the shape.

Thus, metallic nanoparticles are a very promising tool for the delivery of an anti-inflammatory activity, as they are small enough to go through biological membrane. Moreover, those nanomaterials are able to block different pro-inflammatory markers, such as TNF-α and IL-1β, which is an effective way to prevent chronic inflammation.

3. Anti-inflammatory Functionalization of Implants Surface

The implantation of a material leads to a high inflammatory response from the host. For this reason, new coatings allowing to decrease the inflammatory reaction are urgently needed. Different solutions are being proposed, including, modification of physico-chemical properties of the surface, surface functionalization with covalently grafted molecules, or surface coating with metals.

3.1. Changing the Physico-Chemical Properties of the Surface

In order to modify the physico-chemical properties, different surface treatments can be applied. Those techniques allow improving the anti-inflammatory properties of an implant by changing its roughness, surface chemistry, and porosity.

3.1.1. Roughness and Surface Chemistry

Many implants, such as bone or teeth implants, are made of titanium. The biocompatibility of this metal, but also its nontoxicity and resistivity to corrosion, are a great asset for the fabrication of implants.[58] Some results showed that the roughness of the titanium surface has an important impact on the inflammatory response.[59] It has been demonstrated that macrophages cultured on rough surfaces increased the production of anti-inflammatory cytokines, while on smooth surfaces, they produced pro-inflammatory markers. Moreover, it seems that the hydrophobicity of the surface has an impact on the macrophages too, with a better anti-inflammatory activity when the rough surface is hydrophilic.[60] In a study by Zhang et al., it was shown that the chemical and physical properties of titanium surfaces have a great impact on the polarization of macrophages into M1 or M2 phenotypes.[61] They produced disks of titanium with different roughness and compared the macrophage adhesion and polarization on these samples. They observed that the ratio of macrophages polarized into M2 phenotypes increased only in narrow range of roughness (Ra between 0.51 and 1.36 μm). In another study, Abaricia et al. compared rough and smooth titanium surfaces with hydrophilic-rough surfaces effects on the secretion of pro and anti-inflammatory cytokines as well as neutrophil recruitment during inflammatory response.[59a] The results demonstrated a decrease of secreted pro-inflammatory cytokines for hydrophilic-rough surfaces compared to the smooth and rough surfaces. Moreover, the secretion of anti-inflammatory cytokines was more important when the surface was hydrophilic and rough. Thus, it seems that improving the host anti-inflammatory response is directly linked to the hydrophobicity and roughness of the implant's surface and the better anti-inflammatory properties obtained for hydrophilic and rough surfaces.

The surface treatment that is commonly used in order to improve the roughness and the hydrophilicity of the titanium surface is a sandblast/acid etching.[62] This processing can be followed by an oxidation state in order to increase the hydrophilicity of the surface. An acid etching surface treatment seems to be efficient for microbeads microporous titanium implants.[63] The new structure obtained after this process seems to limit adhesion of macrophages onto the biomaterial, decreasing the inflammatory reaction and improving the integration of the implant.

Surface chemistry also influences the inflammatory response by modulating the macrophages phenotype.[61] For example, Hotchkiss et al. compared the anti-inflammatory activity of two surfaces: one made with pure titanium and the other with a titanium zirconium alloy.[62b] Titanium zirconium alloy increased the expression of M2 phenotypes compared to pure titanium. Although the roughness of the implant surface is the same, a difference of nanostructure density can be observed, which can explain the difference in the inflammatory response (higher polarization of macrophages into M2 phenotype as the density decreases). It can also be due to the difference in chemical composition. Thus, the manufacturing process of titanium for biomedical devices has to be carefully considered.

Synthetic polymers like polyethylene, polystyrene, polyetheretherketone, poly(methyl methacrylate), etc. are also widely used for bone implants, for instance in knee and

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hip prostheses, because of their high biocompatibility, flexibility, and resistance to degradation .[64] Therefore, many researchers study the effect of polymer-based implants on the inflammatory response. Again, surface properties were found to have a great importance for modulating the macrophage polarization. In a study by Rostam et al., an etching surface treatment on polystyrene sample using O_2 plasma in order to oxidize the surface and make it hydrophilic was performed.[65] The untreated and the treated surface had similar roughness. The results showed that the hydrophobic surface presented a higher anti-inflammatory response, as the cells produced more IL-10 than in contact with the hydrophilic polystyrene. These results conflicted with the results found for the titanium rough material. In these studies,[59a,60] the highest anti-inflammatory response has been found for rough hydrophilic titanium surface. Thus, surface roughness is necessary to improve the macrophage polarization into M2 and can drastically change the inflammatory response whatever the chemistry of the surface is.[11] However, the nature of the material used for the implant (metal or polymeric) influences macrophage's reaction with the surface: in case of titanium, better anti-inflammatory activity was observed when the surface was hydrophilic,[59a,60] while for polymer-based materials, hydrophobic surface presented a higher anti-inflammatory response.[65]

3.1.2. Porosity

The impact of pore's size of material on the macrophages' polarization has also been shown. Indeed, different studies have been made on porous materials and their role in the inflammatory response. In 2013, Sussman et al.[66] compared three implants made of poly(methyl methacrylate) with different porosities. They studied the FBR, the macrophage types, and how the material is vascularized after few days. They observed a healing improvement and an increase in vascularization as the material is porous. The made the hypothesis that it is due to macrophages polarization turning into M2 type.

More recently, other studies presented how important it is to control the porosity and to have an optimal size of pores. Wei et al.[67] worked on 3D porous poly(etheretherketone) (PEEK). The porous structure is given by a step of sulfonation. The macrophage polarization in contact with sulfonated PEEK is then compared to the polarization when the material is nonporous. The results presented that the number of anti-inflammatory cytokines increased as the material is porous, which indicate a change in the inflammatory response. Moreover, it seemed that the porous PEEK enabled to decrease the FBR and promoted the tissue repair. The same conclusions have been drawn by Yin et al.[68] They compared chitosan/collagen scaffolds with controlled pore sizes thanks to a freeze-drying method. They showed that materials with greater pores encourage transitions from M1 to M2 macrophages polarization. Moreover, large pores expressed more M2-related genes, and so a larger secretion of anti-inflammatory cytokines. Thus, the control of material porosity, at the surface or in bulk, seems to be an interesting way to control the foreign body reaction and the inflammatory response.

Those different studies, summarized in **Table 1**, showed the importance of controlling the implant surface properties, which is a direct factor modulating the inflammatory response by the host. Thus, scientists have tended in recent years to modify the surface, for example with macromolecules.

3.2. Surface Modification by Macromolecules

The implant surface can be functionalized with different molecules that provide antiinflammatory activity. For instance, macromolecules such as polymers and peptides can be grafted in order to change the surface properties. The molecules can be adsorbed on the surface or attached via covalent bonds.

In the field of hernia repair, Bredikhin et al. conducted in vivo studies of polypropylene hernia meshes coated with vitamin E (α-tocopherol).[69] The results showed reduced foreign body reaction and suggest that vitamin E can be a potential coating to decrease post-surgical inflammation.

Glycosaminoglycans are a part of the extracellular matrix, and some of them (heparin, hyaluronic acid, etc.) promote anti-inflammatory activity by preventing the adhesion of proteins and cells onto the implanted material.[70] Multilayers made of either hyaluronic acid or heparin in combination with chitosan were studied by Alkhoury et al.[71] The results showed that hyaluronic acid or heparin-containing multilayers decreased the inflammatory response by reducing formation of multinucleated giant cells and IL-1β release. The same group has also covalently immobilized hyaluronan and heparin via NH_2-modified surfaces using EDC/NHS, and the resulting system has also shown anti-inflammatory properties.[72]

Hyaluronic acid, chondroitin sulfate, and heparin were used to covalently functionalize the surface of an implant.[73] This functionalization could be obtained through a first functionalization of the implant surface with aminosilane that produced an amino-terminated surface. The glycosaminoglycans were finally immobilized onto the surface thanks to those amine groups. The final surface was more hydrophilic, and macrophage adhesion was greatly reduced with this. The secretion of pro-inflammatory cytokines decreased with the glycosaminoglycans at the surface of the implant, thus decreasing the inflammatory activity.

Zwitterionic polymers such as poly(sulfobetaine methacrylate) with antifouling properties can be deposited by dip-coating, which is a widely used method for the deposition of polymers.[74] Combined with polydopamine, the zwitterionic polymer improved anti-inflammatory response by the host. Polydopamine can thus be used for the improvement of coating stability, but also the immobilization of molecules on the surface, thanks to its adhesive properties.[75] Peptides, nanoparticles and anti-inflammatory drugs can be grafted to the polydopamine-modified surfaces to add different functionalities, including anti-inflammatory properties.[76] For instance, IL-4/polydopamine-coated titanium alloy implants modulated M2 macrophage polarization and improved the in vivo implant integration.[77] In addition to polydopamine, dopamine has been used for the attachment of molecules to the polymers, e.g. for immobilization of the hyaluronic acid, providing anti-biofouling properties.[78] Dopamine is a neurotransmitter that also enables to functionalize polymers with different molecules with anti-inflammatory activity such as dexamethasone (DEX).[79]

Another promising candidate for anti-inflammatory materials fabrication is keratin, that is contained in keratinous materials

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Table 1. Changing the physico-chemical properties of the surface.

Type of material on the surface	Studied parameters	Outcomes on the inflammatory response	References
Ti	Roughness	• Roughness of the implant's surface has an important role on the macrophage polarization • Production of antiinflammatory cytokines increased as the surface roughness increased • For a narrow range of roughness, the ratio of macrophages polarized into M2 phenotype increased	Hotchkiss et al. 2016[59b] Abaricia et al. 2020[59a] Zhang et al. 2019[61]
Ti	Hydrophobicity + roughness	• Higher antiinflammatory activity for rough-hydrophilic surfaces • Hydrophobicity has an impact on the macrophage polarization into M1 or M2 phenotypes • Increase of the secretion of antiinflammatory cytokines when the rough surface is hydrophilic • Ti surface which is rough and hydrophilic leaded to a higher secretion of antiinflammatory markers than smooth or rough Ti surfaces	Hotchkiss et al. 2019[60] Abaricia et al. 2020[59a]
Ti and TiZr	Chemical composition	• Difference in nanostructure density (Ti nanostructure denser than TiZr) • Higher polarization of macrophages into M2 phenotypes as the density decreased • The chemical composition had an impact on the inflammatory response	Hotchkiss et al. 2017[62b]
Polystyrene	Hydrophobicity	• Hydrophobic polystyrene surface presented a higher antiinflammatory response • Higher production of antiinflammatory cytokines for the hydrophobic surface	Rostam et al. 2016[65]
Poly(methyl methacrylate)	Porosity	• Increase in the vascularization of the implant as the material is porous • Hypothesis: macrophages polarization turns into M2 type	Sussman et al. 2014[66]
Poly(etheretherketone)	Porosity	• Porous structure is given by a step of sulfonation • Secretion of antiinflammatory cytokines increased as the material is porous	Wei et al. 2019[67]
Chitosan/collagen scaffolds	Porosity	• Transition from M1 to M2 macrophages increased with the pores' size • The secretion of antiinflammatory cytokines is stimulated by the increase of the size of pores	Yin et al. 2020[68]

such as wool, feathers and hooves.[80] Keratin hydrogels were shown to promote wound healing.[81] Interestingly, the wound-healing properties of feather keratin were similar to those of human, in addition to being.[82] Thus, keratin is a cheap material that owns intrinsic anti-inflammatory properties, making it a strong candidate for implant functionalization.[83] For instance, Fearing et al. studied the effect of keratin coating on macrophages polarization.[84] They showed that macrophages in contact with keratin turned to M2 phenotype, leading to an anti-inflammatory response. This study confirmed that keratin has an impact on the macrophages' polarization.

Thus, macromolecular coatings are efficient for functionalization of the implant surfaces and to confer anti-inflammatory host response. In addition, polymer coatings can also be used for loading of anti-inflammatory molecules.[85] The release of anti-inflammatory molecules by coatings will be detailed further.

3.3. Inorganic Surface Functionalization

Other types of coatings can be used for implants surface modification, such as functionalization by inorganic molecules.

Magnesium can be deposited onto titanium by a micro arc oxidation.[86] First of all, titanium surface is grounded with abrasive paper and then oxidized in electrolytes. In the electrolytes, magnesium chloride hexahydrate is added and a voltage is applied. Porous titanium oxide is thus created, and magnesium is incorporated into the surface. The effect of magnesium ions on inflammatory markers was studied without changing the roughness or the wettability of the surface between samples and the results inferred that ions tend to switch macrophages from M1 to M2 phenotypes. Thus, magnesium ions incorporated into a coating are promising for the anti-inflammatory surface treatment.

Coupling magnesium with zinc in organic milieu, making a hybrid coating, was described by Shen at al.[87] This coating was deposited after the etching of the titanium surface. The results showed that magnesium coupled with zinc enabled to increase the anti-inflammatory properties.[88] The same conclusions was made for magnesium coupled with titanium.[86]

Cerium and cerium oxide coatings are studied too. It is possible to deposit cerium by a plasma spraying technique. Shao et al.[89] showed, by changing the composition of gas in the deposition chamber, that the valence of the cerium deposited onto the titanium substrate has an influence on the anti-inflammatory response. Indeed, it seems that a higher Ce^{4+}/Ce^{3+} ratio
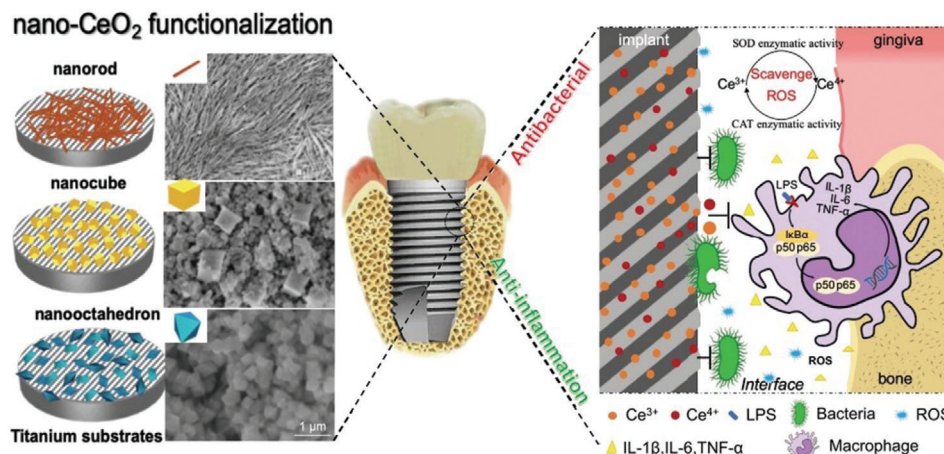
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Figure 6. Scheme represents the modification of the implant's surface thanks to nano-CeO$_2$ (rod-CeO$_2$, cube-CeO$_2$, and octa-CeO$_2$) in order to provide antibacterial and antiinflammatory properties. Nano-CeO$_2$ is positively charged, and the bacterial cell surface is negatively charged. Thus, electrostatic attraction between both is possible, which could induce the antibacterial effects. Moreover, nano-CeO$_2$, because of interaction through thiol groups, avoids the activation of bacterial cell surface protein. This leads to the decrease of the cell membrane permeability. Then, nano-CeO$_2$ has both CAT and SOD activities. Ce^{4+} could react with H$_2$O and O$_2$ with OH$^-$ participation while Ce^{4+} could be reduced to Ce^{3+}. Both activities promote anti-inflammatory activity. SOD: superoxide dismutase; CAT: catalase. Adapted with permission.[90] Copyright 2019, Elsevier.

suppresses M1 macrophages polarization, responsible for the pro-inflammatory reaction.

Furthermore, the nanostructure of the deposited material seems to have an effect on the inflammatory response. Li et al.[90] deposited nanostructured cerium oxide by spin coating onto pure titanium substrate. Different nanostructures of cerium oxide (nanocube, nanooctahedron and nanorod) were first fabricated. TNF-α, IL-6, and IL-1β production decreased around the implant when nano-CeO$_2$ is added to the surface. The largest decrease was obtained when the nano-octahedron cerium oxide was deposited demonstrating that this structure presented the highest anti-inflammatory response (**Figure 6**).

Silane can be grafted to the surface of titanium implant by the hydroxyl functions thanks to sol-gel process. Such silane-functionalized titanium enabled to increase the ratio of M2 macrophages.[91] Moreover, silane can own amino groups that can be reactive for the addition of other molecules.[92] Thus, glycosaminoglycans could be grafted to amino-terminated surfaces to improve the anti-inflammatory properties, as it has been described previously.[73]

4. Delivery of Anti-inflammatory Molecules by Biomaterials

Besides using biomaterials which have intrinsic anti-inflammatory properties as such or as a coating on implants/prostheses surface, plenty of biomaterials are used for anti-inflammatory drug delivery. Depending on the application, anti-inflammatory molecules are delivered by coatings, hydrogels, scaffolds, nanoparticles, and metal complexes. Some biomaterials can be used as both thin coatings and thicker hydrogels/scaffolds, which is the case of keratin[93] and gelatin.[94]

Among the drugs used to fight inflammation, three major groups can be listed. First one is nonsteroidal anti-inflammatory drugs such as ketoprofen, diclofenac sodium, aceclofenac, indomethacin, piroxicam, and celecoxib. The second group is based

on corticosteroid drugs: dexamethasone, betamethasone, and prednisolone. And finally, a variety of natural compounds can be used: curcumin, honey, aloe vera, quercetin, glycyrrhizic acid, copaiba oil, nerolidol, cynaroside, and fucoidan.

In this part, we will describe new systems and materials for delivery of such anti-inflammatory molecules.

4.1. Films and Membranes

Layer-by-layer (LbL) films represent a class of versatile surface coatings that can be designed and used for a variety of biomedical applications[95] including drug delivery.[96] However, little was done in terms of anti-inflammatory LbL films development.

In a study by Ozcelik et al.,[97] an original multifunctional coating was developed. It was based on polyarginine (PAR) and HA polyelectrolyte multilayer film loaded with antimicrobial peptide catestatin. The system demonstrated antimicrobial and immunomodulatory properties. Multilayer film of poly-L-lysine and HA were also used as a system for release of IL-4 to stimulate the differentiation of primary human monocytes into M2 prohealing macrophage phenotypes.[98] Park et al. described LbL nanofilms composed of carboxymethylcellulose and chitosan loaded with antimicrobial and anti-inflammatory agents, levofloxacin and prednisolone 21-acetate, respectively.[85]

We already described keratin hydrogels,[81] as well as keratin coatings,[83,84] exerting anti-inflammatory properties. However, keratin can also be used for delivery of anti-inflammatory drugs. Thus, keratin/hydrotalcyte hybrid films could release diclofenac and support fibroblast growth, suggesting their potential use for wound healing.[93]

Another films for diclofenac delivery were made from hydroxypropylmethyl cellulose (HPMC).[23] In this study, mucoadhesive HPMC thin films contain chlorhexidine or diclofenac sodium and lidocaine hydrochloride or betamethasone dipropionate (**Figure 7**). These films designed for the treatment of periodontal

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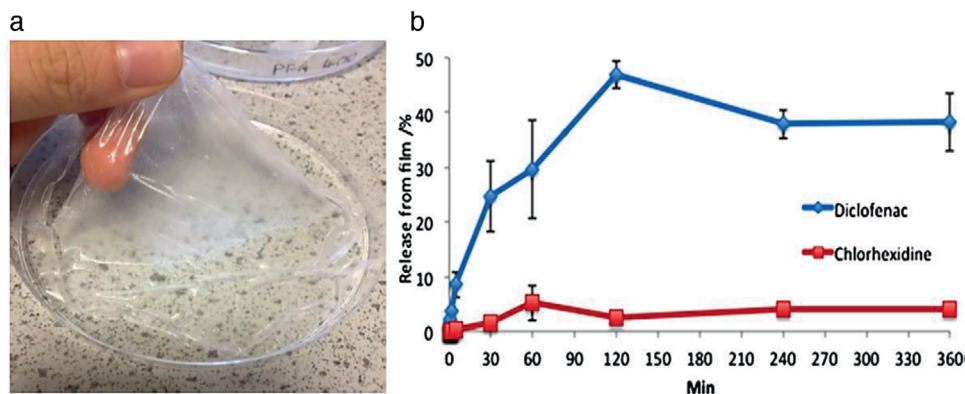HEALTHCARE
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Figure 7. Mucoadhesive thin films for drug release. a) Photo of a translucent, polymer-based drug-loaded mucoadhesive thin film. The average thickness of such a film is ≈100 μm. b) Drugs release profile in percentage for chlorhexidine and diclofenac from a thin film containing 25 mg chlorhexidine and 10 mg diclofenac. 50% of diclofenac is released from the film in 120 min and then the release reaches the plateau phase. Adapted with permission.[23] Copyright 2020, Elsevier.

diseases, demonstrated antibacterial and anti-inflammatory activity in vitro and ex vivo.

Natural anti-inflammatory components can also be used. For instance, Sarkar et al. described honey incorporated into electrospun nanofiber membranes for wound regeneration.[18a] The membranes demonstrated antioxidant, antibacterial and antiinflammatory activity in vitro.

Other types of coatings can be produced with anti-inflammatory drug release. Some of them are based on hydrogels or microgels and can be loaded with peptides that promote anti-inflammatory activity thanks to electrostatic interactions.[99] In another study, Ryabov et al. described thin films based on gelatin/tyraminated hyaluronic acid loaded with cytokines (IL-4/IL-10/TGF-β1). The films induced stable M2-like macrophage polarization, decreased secretion of pro-inflammatory and increased secretion of anti-inflammatory cytokines.[100]

4.2. Hydrogels and Scaffolds

Hydrogels are a class of materials that is widely used for anti-inflammatory drug delivery. Compared to thin coatings, hydrogels can absorb higher quantities of anti-inflammatory molecules. In addition, hydrogels composition and properties can be tuned in order to achieve maximal anti-inflammatory functionality.

Hydrogels made of natural compounds (hyaluronic acid, chitosan, alginate, gelatin, and silk) are often used for anti-inflammatory drug delivery. Hydrogels are mostly used externally as wound dressings,[101] for surgical trauma healing[102] or for treatment of skin inflammation.[19] However some of them are used as coating of medical devices,[94] or as carriers for pancreatic islet delivery.[103]

Scaffolds are 3D materials that are often used for tissue regeneration, being able to support cell adhesion and growth.[104]

4.2.1. Wound Healing

Bacterial cellulose (BC) is a material that has been described as wound dressing and drug delivery system in many studies.[105]

Recently, scale up production of BC hydrogels loaded with anti-inflammatory drug diclofenac was described.[106] In addition, the team investigated spray loading of diclofenac for reduction in loading time. These results are very promising for BC use as anti-inflammatory wound dressing at large scale.

Gelatin loaded with anti-inflammatory agents is another material allowing large scale production of biomaterials. In a study by Gritsch et al., crosslinked gelatin hydrogels were used as carriers for controlled release of heparin. Heparin is an anticoagulant, anti-inflammatory and growth factor binding agent. The results showed that heparin-loaded hydrogels were less adhesive for platelets, making them an interesting option for anti-inflammatory skin dressings.[94]

Plant-derived compounds are also very popular in anti-inflammatory hydrogel formulations. For wound healing applications, calcium-alginate plasticized with PEG-methyl ether methacrylate and blended with the freeze-dried gel of *Aloe vera* and leave extracts of *Moringa oleifera* showed great potential.[107] Alginate hydrogel formulations carrying cynaroside showed anti-inflammatory activities in mouse model. Cynaroside (CYN) is a derivative of luteiolin from *Bidens tripartite*, and is used in traditional medicine as an antiseptic and anti-inflammatory agent, as well as diaphoretic and diuretic. The researchers demonstrated that CYN inhibited inflammatory mediators release, and histopathology showed a reduction in paw skin and ear tissue inflammation.[19]

HA and chitosan are also commonly used as drug delivery vehicles. Polyphenol-incorporated HA-based hydrogel exhibited high tissue adhesiveness both in wet and dry conditions and displayed insignificant in vivo host tissue responses.[101] Anti-inflammatory catecholic chitosan hydrogel was also used for filling the tumor-resected cavity. The results showed wet-adhesion ability and anti-inflammatory properties.[102]

Lucca et al. described the formulation of hydrogel containing copaiba oil, which is used as a popular anti-inflammatory medicine in the Amazonian forest region. Carbopol and hydroxyethyl cellulose hydrogels presented good stability, and anti-inflammatory effect was observed in *in vivo* mouse edema model.[20]
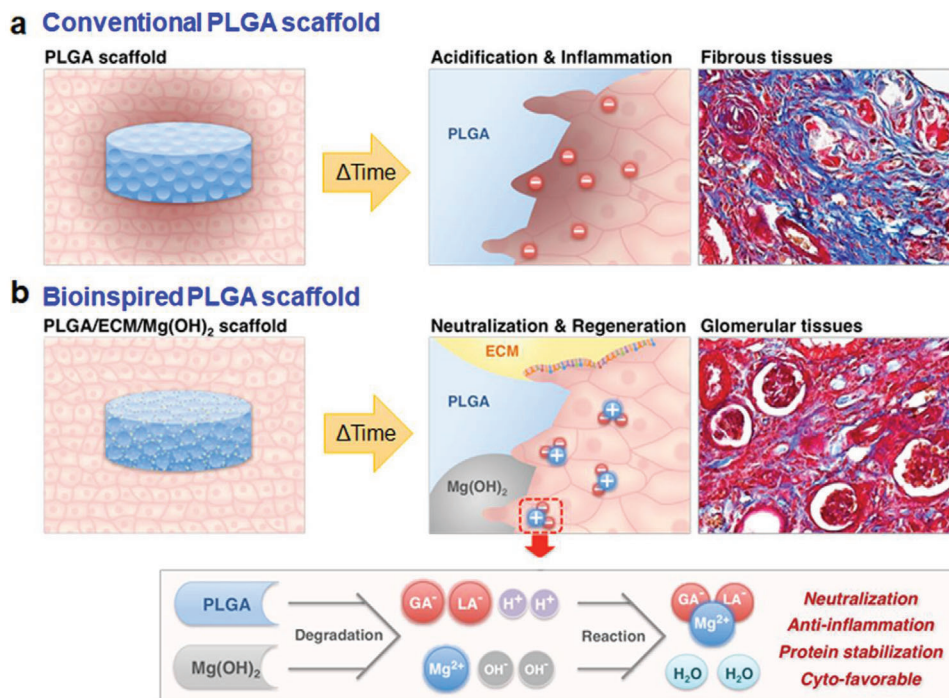
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Figure 8. Bioinspired scaffold for renal tissue regeneration, its biological and chemical mechanism. a) Conventional PLGA scaffold causes inflammation and fibrosis due to the acidic microenvironment formed during the degradation process. b) A bioinspired scaffold neutralizes the acidic microenvironment, inhibits the inflammatory response and has a good cytocompatibility. Adapted with permission.[109] Copyright 2019, American Chemical Society.

4.2.2. Tissue Engineering and Regenerative Medicine

Biomaterials are essential components in the field of tissue regeneration. However, despite usually good biocompatibility of the used materials, they are still able to promote inflammatory response which can compromise their functionality.

For instance, pancreatic islet transplantation is one of the potential approaches for the treatment of type 1 diabetes, affecting millions of people worldwide. However, the survival of pancreatic islets in the host's body is not always good.[108] That's why different techniques for the improvement of islets viability are being developed. One of the approaches consists in using biomaterials allowing to decrease the inflammatory response. Thus, immunomodulatory injectable silk hydrogels were used for delivery of islets. IL-4 and dexamethasone-loaded silk hydrogels promoted anti-inflammatory M2 macrophages polarization.[103a] In another study, DEX was locally released fro m macroporous polydimethylsiloxane scaffold. This system promoted anti-inflammatory M2 macrophages and accelerated islet transplant engraftment.[103b]

Anti-inflammatory scaffolds are also required for regeneration of other tissues. Scaffold made of poly(lactide-*co*-glycolide) (PLGA), magnesium hydroxide ($Mg(OH)_2$), and decellularized renal extracellular matrix neutralized the acidic microenvironment formed by degradation products of PLGA in renal tissue regeneration, thus inhibiting material-induced inflammatory reactions (**Figure 8**).[109]

In another study, osteogenic and anti-inflammatory activities were enhanced by using 3D poly(ʟ-lactide)/chitosan micro/nano fibrous scaffolds functionalized with quercetin–polydopamine.[110] Also in the field of bone tissue engineering,

Lee et al.[111] developed 3D polycaprolactone (PCL) scaffolds via a layer-by-layer process using a 3D printing technique. Coating with tannic acid (TA) was followed by BMP-2 immobilization on PCL or TA-coated PCL (TA/PCL) scaffolds to yield BMP-2/PCL or BMP-2/TA/PCL scaffolds. The results showed that BMP-2/TA/PCL scaffold significantly suppressed expression of pro-inflammatory cytokines while enhancing the osteogenic differentiation of cells. This study is a good example of multifunctional materials.

4.3. Nanoparticles and Inclusion Complexes

4.3.1. Nanoparticles

Macromolecules were studied to form nanoparticles for the loading and delivery of anti-inflammatory molecules. Different techniques can be used to synthetize nanoparticles based on polymers and peptides. For instance, ionotropic gelation is one of the major techniques assumed for the synthesis of polymers nanoparticles.[112] Others techniques based on solvent evaporation were also developed.[113]

Materials based on polyelectrolytes are nowadays highly studied. Those materials combine a polyanion with a polycation that interact thanks to electrostatic interactions.[114] Moreover, the loading of drugs into a polyelectrolyte is quite easy.[112b]

Chitosan is a widely used polycation in medical field.[115] Actually, chitosan is biocompatible, has intrinsic anti-inflammatory, and can also encapsulate molecules with anti-inflammatory properties.[112a] It is thus possible to load this polysaccharide

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with a drug, for instance minocycline, to enhance the anti-inflammatory response.[112b,116] Those nanosystems are very interesting because the dose of drugs needed to promote an anti-inflammatory activity is lower than the one needed when the drug is free in solution.[117]

Chitosan can be complexed with polyanion molecules, like dermatan sulfate, in order to improve the loading of drugs and their release.[112c] Blachman et al.[112c] proposed to bind dermatan sulfate, a polyanion, to an anti-inflammatory tripeptide loaded chitosan in order to mediate the response and to release the drug. Moreover, those polyelectrolytes nanoparticles present different interesting biological properties such as antioxidant activity and endothelial cell binding.[114] Other polymers, in most of the case, natural ones, can also be complexed with chitosan to obtain a biomaterial with interesting biological properties thanks to the release of drugs. For example, polymers, such as poly-γ-glutamic acid or hydroxypropyl cellulose, were added to chitosan in order to improve the assimilation of the biomaterial.[118] Teixeira et al.[118a] studied chitosan/poly-γ-glutamic nanoparticles with an incorporation of diclofenac. This system showed the reduction of pro-inflammatory mediators such as IL-6 and IL-8. Moreover, the polyelectrolyte nanoparticles could be used for other therapies which suggest the loading of other drugs or molecules. Yokota et al.[118b] proposed another polyanion, the hydroxypropyl cellulose with the loading of different drugs (indomethacin, ketoprofen, and piroxicam). They concluded that the introduction of drugs into polymer nanoparticles enables to increase the drug penetration and retention *in vitro* as a small size of particles leads to a higher anti-inflammatory activity, compared to a bulk-drug system.

The size of materials seems to be important for the efficiency of the drug delivery and so for the anti-inflammatory activity. Different systems decrease the inflammatory response because of the release of drugs next to the inflammation area, as the size of nanoparticles is small. This is the case for polylactide and poly(lactic-*co*-glycolic acid), that have been studied for the loading of anti-inflammatory drugs such as diclofenac or dexamethasone.[113,119] Copolymers such as poly(vinylimidazole)/methacrylic derivatives of ibuprofen (IBU) can also be considered. Interestingly, pH sensitivity of polymers can be used in order to control the drug release. Indeed, those kinds of polymers have amphiphilic properties, which means that they can form micelles and release rapidly the loaded molecules.[120] Kang et al.[121] studied the amphiphilic properties of poly(ethylene glycol). It appears that hydrophobic molecules are preferentially released in acidic environment. This is due to the change of hydrophilicity properties of the amphiphilic polymers with the pH. The hydrophobic drug will be loaded, at neutral pH, into the hydrophobic core of the polymer. However, if the pH decreases and become acidic, the protonation of the protanable groups, (here the amine groups) of the polymer cause the transition from hydrophobic to hydrophilic which completely dissociate micelles and so release the anti-inflammatory drugs. This kind of system enables to control the release of drugs and so the delivery of the anti-inflammatory activity will occur when the body is injured, inflammation being associated with the lowering of tissue pH.[122]

The use of polymer nanoparticles for the encapsulation of drugs can also be applied for drugs with high volatility and low solubility. Barros Silva Soares de Souza et al.[123] used poly ϵ-caprolactone to nanoencapsulate nerolidol, a sesquiterpene with high anti-inflammatory properties but low solubility. The study demonstrates that encapsulating the nerolidol into the polymers improved its anti-inflammatory effect on arthritis in mice.

Natural polymers and proteins are commonly used as nanoparticle's scaffolds. Crivelli et al.[124] suggested the use of silk fibroin for the synthesis of nanoparticles to deliver celecoxib and curcumin. The drugs loaded into silk fibroin nanoparticles systems show smaller cytotoxicity than free drugs. Thus, those protein nanoparticles enable to deliver an anti-inflammatory activity while keeping cells alive.

Finally, another interest of loading drugs into polymer nano or microcapsules is that the anti-inflammatory activity is prolonged over time.[125] The loading into nanoparticles increases the stability of drugs in aqueous media. This allows to sustain the release of the drug for at least one month, which could not only allow to diminish the drug dose, but also be an interesting way for the treatment of chronic inflammations.

Porous particles could serve for encapsulation of different drugs with anti-inflammatory properties. Metal–organic frameworks are a new hybrid materials family, based on coordinated complexes of molecules, with interesting properties for anti-inflammatory drug loading such as high porosity and crystallinity.[126] However, the toxicity of those materials remains high because of the presence of organic linkers that are not biocompatible.[127] Abuçafy et al.[127] synthetized a new metal–organic framework with cyclodextrin as organic linker in order to improve the biocompatibility of those coordinated particles. Then, impregnation method was used for the loading of drugs with anti-inflammatory properties into the porous system. A very fast release of the drug occurs thanks to the porous structure. Other drugs and systems based on nanoparticles that are biocompatible and anti-inflammatory were proposed in the last years.[126,128] For instance, Neisi et al.[126] used polypyrrole as organic linkers to create a copper metallic–organic framework biomaterial with good in vitro and *in vivo* biocompatibility. Moreover, the loading of curcumin into the pores delivered an anti-inflammatory activity.

4.3.2. Inclusion Complexes

Inclusion compounds might be a way for the delivery of antiinflammatory molecules. Those systems are composed of two compounds: a host molecule and a guest molecule.[129]

The guest molecule is included in the cavity of the host molecule. Solid state cyclodextrin and hydroxypropyl cyclodextrin can be used as a host molecule for different drugs or anti-inflammatory molecules, like citral or naringenin.[130] Indeed, cyclodextrins are based on cyclic glucose that can have a hydrophilic exterior surface but a hydrophobic interior conical cavity, and so hydrophobic drugs can be loaded into the hydrophobic part of the molecule.[131] The goal of the formation of this kind of system for the delivery of drugs is, as for nanoparticles, to improve the therapeutic properties of the anti-inflammatory molecules and increase their bioavailability. The reason why inclusion complexes are able to increase the bioavailability of drugs is that cyclodextrins made them more soluble and less
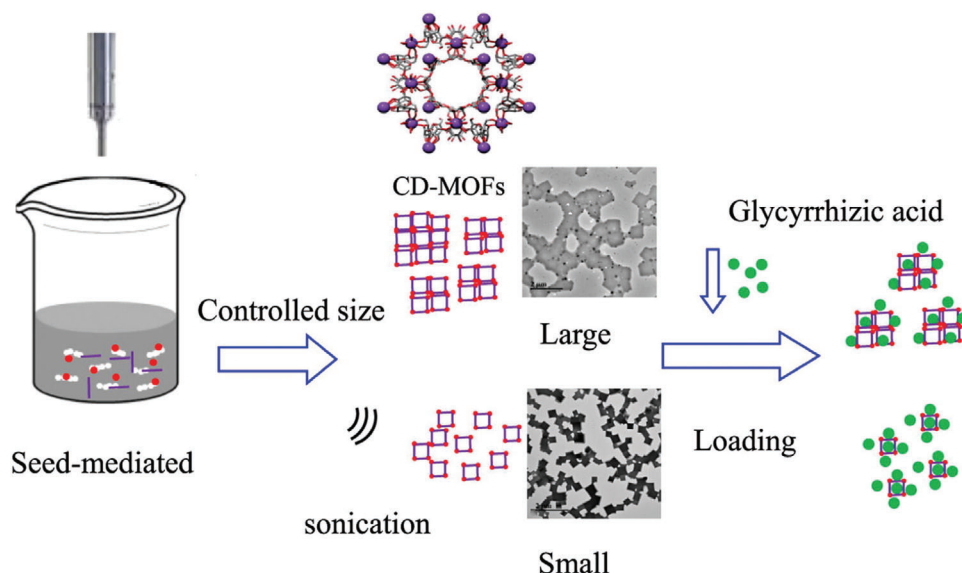
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Figure 9. Schematic illustration of the development of nanoscale bioactive delivery system using sonication. Seeds with controlled size are first of all mixed with CD-MOFs. Sonication can be used in order to avoid the formation of aggregates. Then, glycyrrhizic acid, a natural triterpene glycoside with antibacterial and antiinflammatory properties, is added to the CD-MOFs seeds. When sonication is used during the first mixing, the glycyrrhizic acid loading is more efficient than without the sonication, thanks to the lack of aggregates. CD-MOFs: γ-cyclodextrin metal–organic frameworks. Adapted with permission.[128] Copyright 2019, Elsevier.

volatile in the biological milieu.[132] Thus, the physicochemical properties of drugs are changed when loaded into cyclodextrin.

For example, Campos et al.[130a] loaded citral into cyclodextrin. They found that the complex had positive effect on the properties of citral. Indeed, the production of TNF-α was smaller when the cells were in contact with the complex than with the free drug, for the same dose. This finding was also demonstrated by Lima et al.[133] In their study, they loaded morin, a flavonoid with anti-inflammatory properties, into hydroxypropyl cyclodextrin thanks to a freeze-drying method, and evaluated its bioavailability and anti-inflammatory activity. The results showed that the availability of complexed morin was more than four times than free morin. As a consequence, the morin's dose that enabled to decrease TNF-α production was lowered, and thus they were able to decrease the dose of drugs delivered to the organism without changing their effectiveness.

Another technique, called solvent change precipitation, was also used for the loading of drugs into inclusion complexes.[130b] Gratieri et al.[130b] tested this method for the inclusion of naringenin into cyclodextrin. This method is based on the precipitation of naringenin when an aqueous solution of cyclodextrin is rapidly poured into a naringenin acetone solution. This technique resulted in a high stability and dissolution performance of the naringenin in the inclusion complex. Moreover, the *in vitro* and *in vivo* anti-inflammatory were improved when the drug was loaded into the cyclodextrin, in comparison with free naringenin.

Another way to benefit from the interesting structure of cyclodextrins is to combine them with metal in a metallic–organic framework. Qiu et al.[128] synthetized a cyclodextrin metal–organic framework (CD-MOF), with short-chain starch as seeds, using sonication to obtain small size and promote aggregates. Then, glycyrrhizic acid can be loaded into the system as it is presented in **Figure 9**. The encapsulation of drugs was possible

thanks to interaction between the glycyrrhizic acid and the cyclodextrin metal–organic framework. Moreover, the CD-MOF increased not only the solubility of the drug but also its loading efficiency. The system seemed to be nontoxic which could lead to interesting drug delivery systems.

5. Anti-inflammatory Architectures Based on Molecular Complexes: Toward Multifunctionality

As a distinct class of materials, we will present here complex anti-inflammatory material architectures, including, stimuli-responsive, multifunctional, as well as complex multicomponent materials (**Table 2**).

Complex architectures can be used to facilitate the embedding of a hydrophobic/hydrophilic drug and control its release profile. In a study by Hardy et al.,[134] compact polyelectrolyte complexes (CoPECs) were obtained by ultracentrifugation of a polyanion/polycation complexes suspension. Noncytotoxic β-cyclodextrin-functionalized chitosan was used as a polycation and alginate as a polyanion. Due to the presence of cyclodextrins, hydrophobic drugs such as piroxicam could be loaded and released. In vitro LPS-stimulated murine macrophages model was used to assess the anti-inflammatory properties of the system, and it was shown that CoPECs inhibited LPS-induced TNF-α and NO production and moderated the differentiation of LPS-activated macrophages.

Alginate hydrogel microgranules (Alg-Ms) carrying a hydrophobic agent octadecyltrichlorosilane were used in another study to allow the prolonged release of small hydrophilic drug sodium benzoate (SB), which is a highly water-soluble antimicrobial and anti-inflammatory compound.[135]

In the study by Nyström et al.,[99] microgels loaded with antimicrobial and anti-inflammatory peptide were used as

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Table 2. Complex antiinflammatory, multifunctional, and stimuli-responsive architectures.

Material's architecture	Basic components	Loaded/grafted molecules	Effects	References
Compact polyelectrolyte complexes	• β-cyclodextrin-functionalized chitosan • Alginate	Piroxicam	• Antiinflammatory	Hardy et al. 2018[134]
Microgranules	• Alginate • Octadecyltrichlorosilane	Sodium benzoate	• Antimicrobial • Antiinflammatory	Wang and Newby 2020[135]
Microgels as surface coatings	• Poly(ethyl acrylate-co-methacrylic acid) grafted with human heparin cofactor II-derived peptide KYE28 and its PEGylated version		• Antifouling • Antibacterial • Antiinflammatory effects	Nystrom et al. 2018[99]
Nanospheres	• Chitosan • Gelatin	Dexamethasone	• Antiinflammatory • Osteogenic	Qi et al. 2018[136]
Nanocapsule	• Gold nanocage • Macrophage cell membranes	Resolvin D1	• Antiinflammatory • Osteogenic	Yin et al. 2020[21]
Hydrogel	• Hyaluronic acid • Dextran • β-cyclodextrin (β-CD)	• Resveratrol • VEGF-encoding plasmid DNA	• Antiinflammatory • Angiogenic	Wang et al. 2019[137]
Bi-functional silk was created by co-expressing the human basic fibroblast growth factor (FGF2) and transforming growth factor-β1 (TGF-β1) genes in silkworm			• Antiinflammatory • Cell proliferation	Wang et al. 2019[138]
Nanocarrier	• Cerium • Chitosan • ZM241385	Pilocarpine	• Antioxidant • Antiinflammatory	Luo et al. 2020[139]
Nanoparticles	• Gold • Poly(catechin)	Amfenac	• Antiinflammatory • Good tolerability in vivo	Li et al. 2019[140]
Injectable biodegradable thermogels	• Amine-terminated polyamidoamine dendrimers • Gelatin • Poly(N-isopropylacrylamide)	• Pilocarpine • Ascorbic acid	• Anti-inflammatory • Proregenerative	Nguyen et al. 2019[141]
Scaffold + pH-sensitive LbL films	• Poly(lactic acid) • Hydroxyapatite • Star-PDMAEMA • PAMAM-COOH	Indomethacin	• Antiinflammatory	Wu et al. 2015[22]
Thermosensitive micellar hydrogel	• Poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone)-poly(ethylene glycol)-poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone) (PECT)	• Ibuprofen • Basic fibroblast growth factor (bFGF)	• Antiinflammatory • Cell adhesive • Cell proliferation	Chen et al. 2019[142]
pH and temperature responsive hydrogels	• Carboxymethyl starch • Poly(2-dimethylaminoethyl methacrylate)	Ibuprofen	• Antiinflammatory • Osteogenic	Nita et al. 2020[143]

surface coatings. The researchers covalently immobilized poly(ethyl acrylate-co-methacrylic acid) microgels loaded with human heparin cofactor II-derived peptide KYE28 (KYEITTI-HNLFRKLTHRLFRRNFGYTLR), as well as its poly(ethylene glycol)-conjugated (PEGylated) version, KYE28PEG. Microgel-modified surfaces demonstrated antifouling properties, contact killing and release-killing of bacteria in vitro. In addition, KYE28- and KYE28PEG-loaded microgels showed anti-inflammatory effects on human monocytes stimulated with LPS by suppressing expression of pro-inflammatory cytokines.

Another coating for the delivery of anti-inflammatory molecules was prepared by Qi et al.[136] They developed chitosan/gelatin nanospheres composite coating loaded with DEX. The coating showed a two-stage release that suppressed inflammation (initial release) and promoted osteogenic differentiation (sustained release period). Such bone regeneration-promoting coatings can be potentially used for surface modification of metallic orthopedic implants.

Also in the bone repair area, a complex system was fabricated by Yin et al.[21] They constructed biomimetic anti-inflammatory nanocapsules (BANC) coated with macrophage cell membranes carrying cytokine receptors, enveloping gold nanocages and loaded with resolvin D1, whose controlled-release could be triggered under near-infrared laser irradiation (**Figure 10**). Femoral bone defect in vivo studies showed that BANC composite boron-containing glass scaffolds prevented inflammatory response, promoted M2 polarization, and thus improved bone tissue repair.

In another study, Wu et al.[22] prepared poly(lactic acid)/hydroxyapatite (PLA/HA) composite as an implantable material. It was then coated with multifunctional pH-sensitive LbL films loaded with an anti-inflammatory drug indomethacin (**Figure 11**). They showed that such multifunctional coating decreased the local inflammation for at least 8 weeks in vivo.

For even greater multifunctionality, a triple-functional polyetheretherketone (PEEK) surface with enhanced bacteriostatic, anti-inflammatory and osseointegrative properties for
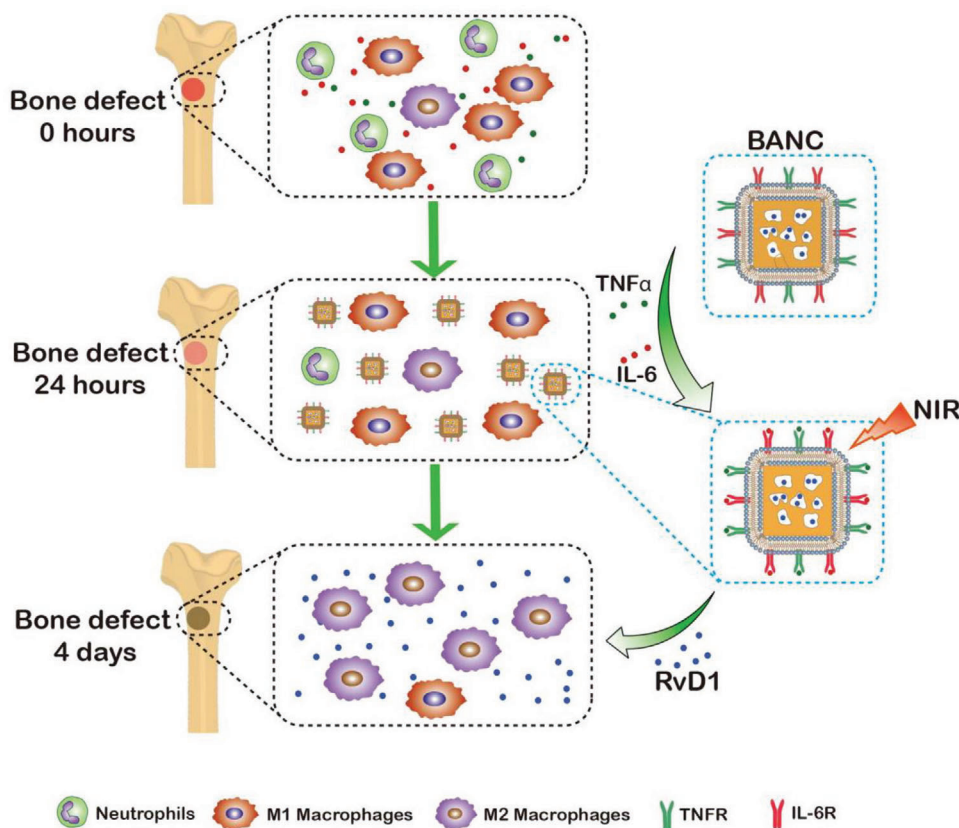
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Figure 10. Schematic illustration of the role of biomimetic antiinflammatory nanocapsule (BANC) for the progress of bone tissue repair. Cytokines receptors are localized on the surface, promoting the neutralization of proinflammatory cytokines and decrease of the proinflammation reaction. Then, BANC could promote M2 macrophages polarization and inhibit the M1 polarization thanks to the controlled release of Resolvin D1 (RvD1) under near infrared (NIR) irradiation. Finally, the bone tissue for femoral bone defects is better repaired thanks to BANC. Adapted with permission.[21] Copyright 2020, Elsevier.

implant application was developed by Xu et al.[79] In this study, bioinert PEEK was modified by DEX and minocycline-loaded liposomes (DEX/Mino liposomes), which were bonded by a mussel-inspired polydopamine coating. This material has a great potential as an orthopedic/dental implant material for clinical application.

Few articles deal with growth factor delivery to tune inflammation. Wang et al. developed anti-inflammatory hydrogel loaded with vascular endothelial growth factor (VEGF)-encoding plasmid DNA for burn wound healing.[137] The system was designed to deal with excessive inflammation and reduced angiogenesis, that are two major obstacles in burn wound healing and skin regeneration. Researchers designed a complex hydrogel based on chemically modified HA, dextran, and β-cyclodextrin integrating resveratrol , and VEGF plasmid. The system inhibited inflammation response, promoted microvascular formation and thus improved burn wound healing.

In another field of application, Luo et al. described a complex system for delivery of ophthalmic drugs.[139] They developed a nanocarrier platform made of chitosan and ZM241385 functionalized onto surfaces of hollow ceria nanoparticles (hCe NPs) for delivery of pilocarpine, a drug for the treatment of glaucoma. The nanocarriers demonstrated in vitro and in vivo antioxidant and anti-inflammatory properties. In an earlier study, they used poly(catechin) capped-gold nanoparticles (Au@Poly-CH NPs) carrying a nonsteroidal anti-inflammatory drug amfenac.[140] Their results showed that Au@Poly-CH NPs acted against inflammation. In addition, in vivo biocompatibility assays demonstrated good tolerability of AF/Au@Poly-CH NPs.

Finally, the group also developed injectable biodegradable thermogels for therapy of glaucoma.[141] Intracameral injection of thermogels co-loaded with pilocarpine and ascorbic acid demonstrated anti-inflammatory and proregenerative activities.

Also in the field of thermoresponsive systems, Chen et al.[142] described encapsulation of IBU and basic fibroblast growth factor (bFGF) in a thermosensitive micellar hydrogel for early local treatment of peri-implantitis. The hydrogel showed anti-inflammatory properties and was favorable for the proliferation and adhesion of human gingival fibroblasts.

Stimuli-responsive drug delivery system was also developed by Nita et al.,[143] who prepared semi-interpenetrating polymer network hydrogels of carboxymethyl starch and poly(2-dimethylaminoethyl methacrylate) loaded with ibuprofen. The hydrogels demonstrated pH and temperature responsiveness. Such hydrogels can be potentially used as drug delivery systems or transdermal patches.

Besides traditional approaches to design the materials, gene manipulation is another way to modify the materials properties.
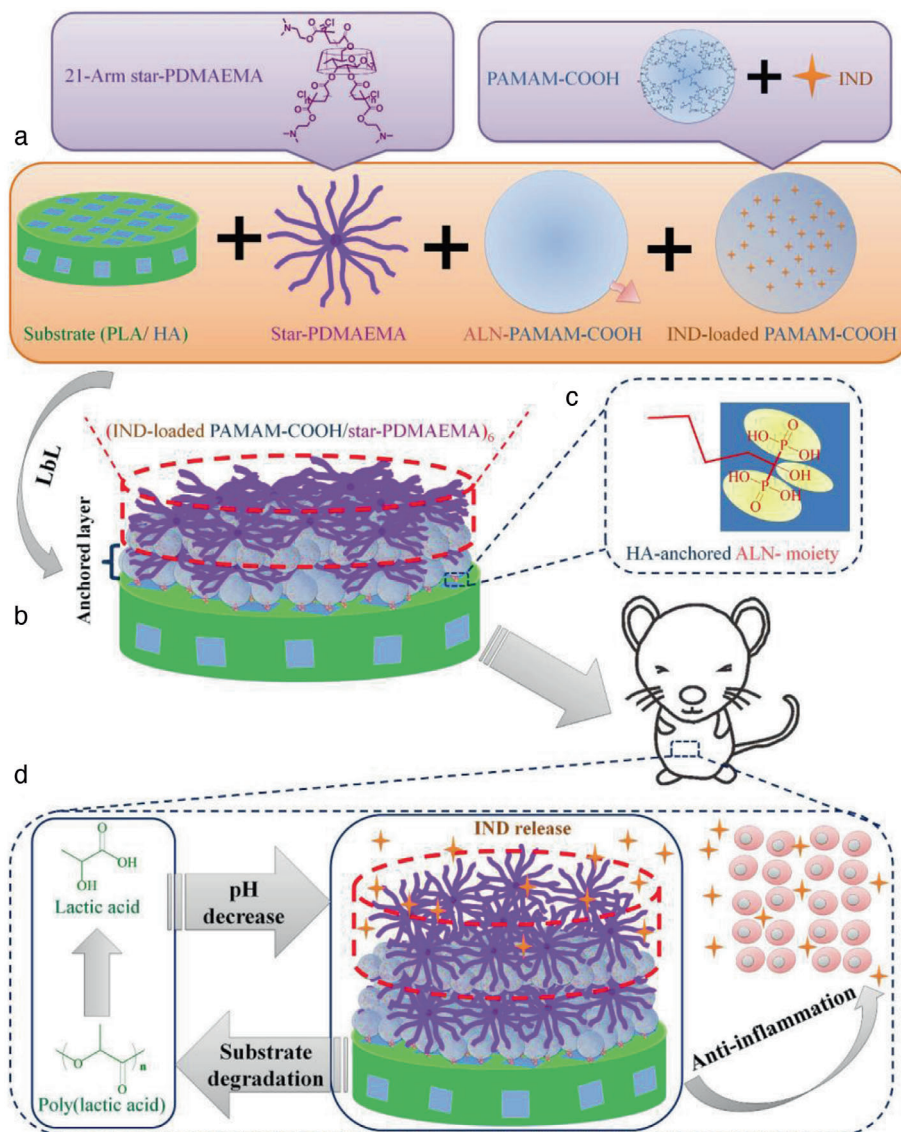
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Figure 11. New multifunctional and degradation-sensitive coating for implant materials. a) Biodegradable substrate of implant material (PLA/HA) and building blocks of the LbL coating (star-PDMAEMA, ALN-PAMAM-COOH and IND-loaded PAMAM-COOH). b) Coating-AP/S in the form of ALN-PAMAM-COOH/star-PDMAEMA+ (IND-loaded PAMAM-COOH/star-PDMAEMA). c) ALN moiety providing substrate anchorage property; d) final complex architecture which releases the antiinflammatory drug upon degradation. Adapted with permission under the terms of the Creative Commons License.[22] Copyright 2015, the Authors. Published by Springer Nature.

Recently, genetically engineered silk material designed by Wang et al.[138] improved cell proliferation and anti-inflammatory activity. This novel bi-functional silk was created by co-expressing the human basic fibroblast growth factor (FGF2) and TGF-β1 genes in silkworm. The material significantly reduced LPS-induced inflammation, promoting interesting properties for production of silk sutures, hydrogels, films, as well as 3D scaffolds for wound healing and tissue regeneration.

6. Conclusions and Perspectives

In this review, we described recent progress done in the field of anti-inflammatory biomaterials. Many different approaches are being used to decrease the inflammatory response by the host, including hydrogels, nanoparticles, implant surface coating by polymers, and a variety of systems for anti-inflammatory drug delivery. However, the requirements are different depending on the application, hence all the different systems may find applications. For instance, surface modifications are useful for solid implants, while hydrogel systems and porous scaffolds are suitable for wound healing or tissue engineering applications.

Anti-inflammatory effect of the systems is often evaluated in vitro using macrophages, via monitoring pro and anti-inflammatory cytokines secretion that reflect macrophage polarization into M1 or M2 type, respectively. Primary macrophages or cell lines are being used for such tests. Other studies include

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in vivo tests using animal models of inflammation, and only few studies use ex vivo systems.

In this review, we described three major groups of anti-inflammatory materials: materials possessing intrinsic anti-inflammatory properties, materials used for implants coatings and materials for anti-inflammatory drug delivery, which is the largest group. Anti-inflammatory properties of the developed materials are often combined with antimicrobial functionalization, because implant-associated infection is another reason leading to the implant failure. We also described complex multifunctional systems dealing with inflammation and, for instance, bone regeneration and angiogenesis. New stimuli-responsive systems are being developed, such as pH- and temperature-responsive materials. Such systems are very promising, as they would enable an "intelligent" anti-inflammatory response, i.e., when the inflammation occurs. Genetic engineering of natural materials is also being developed.

Mechanisms of anti-inflammatory activity of different materials start to be elucidated, as it is the case for chitosan, for instance. However, there is much work to do to dissect these mechanisms for each newly developed material.

We believe that together, different approaches will lead to creation of novel multifunctional smart materials, for better implant integration and tissue regeneration.

Conflict of Interest

N.E.V. and P.L. are stockholders of SPARTHA Medical.

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Eloïse Lebaudy obtained her Engineering Diploma in materials chemistry from the European School of Chemistry, Polymers and Materials of Strasbourg (France) in 2020. In autumn, she will start a Ph.D. program at Inserm U1121 Biomaterials and Bioengineering under direction of Dr. Philippe Lavalle. Her work will consist of developing of smart hydrogels with antibacterial properties.

Varvara Gribova obtained a Master's in cellular biology, development, and stem cells from the University of Pierre and Marie Curie in Paris. She obtained her Ph.D. from the Grenoble Institute of Technology in 2013, where she worked on layer-by-layer films for muscle tissue engineering applications in Prof. Catherine Picart's team. She is currently a postdoctoral researcher at Inserm U1121 Biomaterials and Bioengineering and works under direction of Dr. Philippe Lavalle. Her project consists of the elaboration of novel antibacterial and antiinflammatory hydrogels as well as their cytotoxicity and genotoxicity evaluation.