The foreign body response to biodegradable polymers orchestrated by macrophages and the influence of anti-inflammatory drugs on this process

Lize J.T. Michorius S3337006

Biomedical Technology

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Supervisor: T.G. van Kooten, Department of Biomedical Engineering

Summary
At various stages of the foreign body reaction, macrophages control the proliferative response by secreting chemokines, cytokines and growth factors. Despite the fact that macrophages are thought to be primarily engaged in unwanted breakdown and biomaterial rejection, it is now known that they are required for correct integration of non-degradable biomaterials and destruction of degradable biomaterials such as biodegradable polymers. The aim of this thesis was to give insight into the foreign body response orchestrated by macrophages to the implantation of biomaterials. Furthermore, nonsteroidal and steroidal anti-inflammatory drugs were discussed in terms of how they can affect macrophages in their response to biodegradable polymers.
The capacity of macrophages to modify their phenotypes (gene and protein signatures) is referred to as macrophage plasticity. Two macrophage phenotypes are defined essentially, which are proinflammatory M1 macrophages and anti-inflammatory M2 macrophages. It was found that biodegradable materials, such as biodegradable polymers, require an early M1 macrophage presence and late M2 macrophage dominance is preferred. All together NSAIDs and steroids seem to have an inhibiting effect on prostaglandin synthesis and therefore on inflammatory cytokine production. NSAIDs and steroids seem to tackle various inflammatory cytokines or precursors, such as IL-6, NO and IFN-γ, which are all associated with M1 macrophage polarization or secretion. Administration of NSAIDs or steroids could help in the shift of M1 macrophage to M2 macrophage dominance by suppressing the inflammatory cytokines so that M2 associated cytokines can take over.

Introduction
Over the last decade, the surgical implantation of materials and technologies has risen dramatically. With the increasing use of biomaterials and the rapid growth of the elderly population, this trend is anticipated to continue. The foreign body response, an immunologic reaction characterized by persistent inflammation, foreign body giant cell development, and fibrotic capsule development, is one key factor that restricts the potential of implanted materials and devices.(1)

Most biomaterials, for instance sensors and implants, are recognized as ‘foreign’ by the host and the results can be compared to reflex responses of the host's immune system, which is called the ‘foreign body response’ or FBR. Many modern devices fail to deliver on their promises because they encounter fierce opposition from the host, which perceives them as foreign and hence a possible threat.(2)

The role of the function of macrophages in the foreign body response to biomaterials is quickly shifting. Despite the fact that macrophages are thought to be primarily engaged in unwanted breakdown and biomaterial rejection, it is now known that they are required for correct integration of non-degradable biomaterials and destruction of placeholder, degradable biomaterials such as biodegradable polymers.(3)

Macrophages have a number of important roles in the host defense system, including phagocytosis (the removal of dead cells, debris and pathogens), shaping the inflammatory response and modulating adaptive immunity. (5)(4)(6) Macrophages recognize a wide range of stimuli as part of their immune surveillance duty, ranging from various antigens, apoptotic or necrotic cells to several mediators secreted by other immune cells. Macrophages are activated in response to the stimuli they detect, allowing them to attack infections, perform immunomodulatory functions, and preserve tissue integrity.(7) Macrophages are found in almost every tissue. They vary from circulating peripheral-blood mononuclear cells (PBMCs), which move into tissue in steady state or in reaction to inflammation.(8)

Macrophages are very important cells during the foreign body reaction and the reason why the focus of this thesis will be on the response of macrophages to biomaterials. At various stages of the foreign

body reaction, macrophages control the proliferative response by secreting chemokines, cytokines and growth factors.(1) The aim of this thesis is to give insight into the foreign body response orchestrated by macrophages to the implantation of biomaterials. Furthermore, anti-inflammatory drugs will be discussed in terms of how they can affect macrophages in their response to biodegradable polymers.

Macrophage phenotypes

The capacity of macrophages to modify their phenotypes (gene and protein signatures) is referred to as macrophage plasticity. The phenotypes of macrophages are heterogeneous in vivo.(6) Essentially two macrophage phenotypes are defined. The two phenotypes are the proinflammatory M1 type macrophages that can quickly kill infections and serve as the first defence mechanism of the host, whereas anti-inflammatory M2 type macrophages repair and remodel tissue on a regular basis.(9)

M1 macrophages

T-helper(Th) 1 signaling, such as lipopolysaccharide (LPS) and interferon gamma (IFN-γ), is primarily responsible for the induction of macrophages towards M1. They are pro-inflammatory, expressing high quantities of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1b, IL-6 and monocyte chemoattractant protein-1 (MCP-1). M1 macrophages also express genes related to oxidative stress, such as nitric oxide species (NOS). Th1 cytokines boost macrophages' capacity to destroy pathogens both intracellularly and extracellularly.(10)(11)
M1 macrophages produce surface molecules that make them effector cells, mediating resistance to several different types of infections. M1 macrophages are crucial in the first inflammatory phases of the FBR to biomaterials. Also inflammatory disorders such as rheumatoid arthritis, atherosclerosis, and inflammatory bowel disease are mediated by M1 macrophages.(9)(12) (13)

M2 macrophages

Th2 stimuli, like IL-4, IL-13 and transforming growth factor beta (TGF-β), activate M2 macrophages. Th2 responses are linked to anti-inflammatory responses, parasitic infections, wound healing, tissue remodeling, and tumor growth.(11) Other genes that encode arginase-1, Mrc1(CD206), Ym1, and IL-10, an anti-inflammatory cytokine, are significantly expressed in M2 macrophages.(11)(11)
M2 macrophages promote the wound healing response throughout the resolution stages of the FBR, which typically, but not necessarily results in fibrous capsule formation and failure of implanted devices and scaffolds.(12)(9)(13) The Th1 cytokines IL-2 and IFN-y have the net impact of enhancing cell-mediated responses, whereas the Th2 cytokine IL-4 has the net impact of suppressing cell-mediated responses and hence increasing host immune resistance.(10)

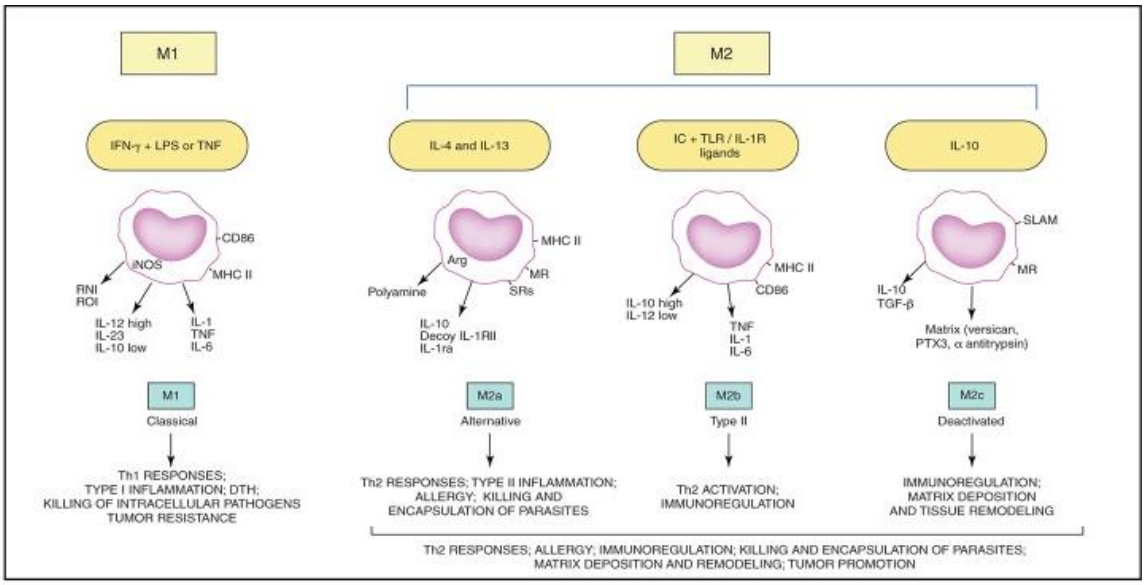

Figure 1: The activation and functions of M1 and M2 macrophages. M1 is activated by certain cytokines including interferon-gamma (IFN-γ) and tumor necrosis factor (TNF). M1 macrophages activate Th1 responses. M2 macrophages are divided in M2a, M2b and M2c macrophages and are activated by cytokines such as interleukin(IL)-4, IL-13 and IL-10.(14)

Biomaterials

In the last decade, the utilization of implanted materials and devices has skyrocketed. Newer technologies like dermal matrices and soft-tissue fillers, in addition to proven devices like as pacemakers, tissue expanders, stents, hernia mesh implants and intraocular lenses, indicate that biomaterials will continue to play an important role in modern medicine. A population of elderly, longer life expectancy, and greater uses for biomaterial technology are likely to drive the popularity of biomaterials that is already present. The word 'biomaterial' has evolved from its original meaning of 'nonviable material utilized in a medical device' to its present, larger meaning of 'any manufactured substance that interacts with a living system to control human medicine'.(1)

One of the fundamental requirements for a successful biomaterial is that it should be accepted by the body, caught in the term biocompatibility. Biocompatibility corresponds to a biomaterial's ability to achieve its therapeutic function without evoking any unwanted impact on the host. Biocompatibility is a quality of a material and its implantation niche.(2)

Biodegradable polymers

In the 1980s, biodegradable polymers were first introduced. Biodegradable polymers are made from both synthetic and natural polymers. Natural polymers are formed from renewable resources in huge numbers, whereas synthetic polymers are made from nonrenewable petroleum resources.(15)

Many biodegradable polymers degrade first in the extracellular matrix (ECM) through nonenzymatic hydrolysis and then continues enzymatically in the macrophages after phagocytosis.(16)

Poly L-lactic acid or PLLA is a typical biodegradable polymer that has been clinically applied for instance as material of bone plates and screws. The low-molecular compound is hydrolyzed into lactic acid oligomers in the body. PLLA has a high mechanical strength and a slow rate of biodegradation (more than a year), which makes it suitable for bone plates and screws. The biocompatibility of PLLA has been researched a lot. (17)

Under certain conditions, polymers with hydrolysable backbones are vulnerable to biodegradation. Polyamides and polyurethanes are examples of polymers that have been created with these characteristics and are also enzymatically degraded.(15)

The chemical stability of polyurethanes in vivo seems to also be influenced by mineralization (especially calcification) and oxidation, besides enzymatic hydrolysis. Many biomedical implant devices made of polyurethanes have been used in the clinical environment over the last decades, for instance for controlled drug release carriers and for cardiovascular implants.(18)

The potential of polyamides as materials with enhanced biodegradability has been widely studied. These polyamides are actually nylons with two methoxy side groups. They have similar thermal and mechanical characteristics as typical unsubstituted nylons but have a far higher affinity for water.(19)

Another polymer that has been used for same applications as polyurethane is poly(trimethylene carbonate) or pTMC.(20) pTMC is a biocompatible high molecular weight polymer. The difference with the other mentioned polymers is that pTMC is rather stable toward hydrolysis. The degradation of pTMC seems to happen through surface erosion.(21) It has been proven by Bat et al. that the products secreted by macrophages play an important role in the in vivo degradation of pTMC.(22)

Foreign body response to biomaterials

Before macrophages come into play in the foreign body response other defense mechanisms of the host take place.(23) The earliest inflammatory reaction is initiated when vascularized connective tissue is harmed. This is true regardless of where the biomaterial is placed in the body.(2) Blood/material interactions occur early in the implantation process, with the adsorption of proteins on the biomaterial surface and the formation of a thrombus on and surrounding the biomaterial.(23) Blood clot formation is a quick but complex process and involves the activation of coagulation systems, the fibrinolytic system, the kinin generating system, platelets and the complement system. The complement system consists of many proteins that are triggered in the presence of foreign substances or pathogens, causing inflammatory and immune cells to be released at the site of implantation.(2)(23)

TGF-β, platelet-derived growth factor, chemokine ligand 4, leukotriene, and interleukin-1 are all released by the provisional matrix, which aids macrophage recruitment. When macrophages are activated, they produce more chemotactic molecules that attract and excite more macrophages at the implant site, culminating in a powerful inflammatory signaling loop.(1)
Proinflammatory M1 macrophages are the first to act on the surface of biomaterials. M1 macrophages emit inflammatory mediators such as oxygen free radicals and reactive oxygen species, as well as degradative enzymes and acids.(2) Many cytokines located in areas of inflammation or infection activate phagocytosis.(24) M1 macrophages cling to the biomaterial and try to phagocytose it. However, a huge mass such as an implant, is too huge for them to digest or phagocytose.(2)

Mast cells and basophils release IL-4 early after tissue injury, stimulating the generation of M2 macrophages that aid wound repair by producing extracellular matrix molecules. These macrophages create very small levels of pro-inflammatory cytokines and generate radicals inefficiently. Low quantities of IL-12 and IL-23 but substantial amounts of anti-inflammatory cytokine IL-10 are expressed by M2 macrophages.(25) Cytokine expression profiles of macrophages and other immune cells at biomaterial implant sites have been studied by Brodbeck et al.. They were able to conclude through enzyme linked immunosorbent assay (ELISA) that IL-1α, IL-1β, TNF-α, and IL-10 were present at the biomaterial surface.(26)

Macrophages fusing to produce foreign body giant cells (FBGCs) at the tissue-implant interface can be an intrinsic part of the foreign body response. When macrophages come upon an implanted item that is too big to be phagocytosed, they are termed to have "frustrated phagocytosis" and merge into FBGCs in an attempt to remove it. FBGCs have the ability to secrete reactive oxygen species and

other chemical agents, which might lead to oxidative damage and device failure. FBGCs, like M2 macrophages, can produce inflammatory cytokines like TGF-β, which cause fibroblasts to build a coating of collagen and eventually a fibrous capsule surrounding the biomaterial.(1)

Macrophage phenotypes with synthetic scaffold implantation were studied by Sussman et al.. It was found that the percentage of M1 macrophages within the pores and on the outside surface of the implant was enhanced (separate from the foreign body capsule). M2 macrophages, on the other hand, were detected within the fibrotic capsule, suggesting that adherence to surfaces and pore walls plays a role in M2 down-regulation.(27)

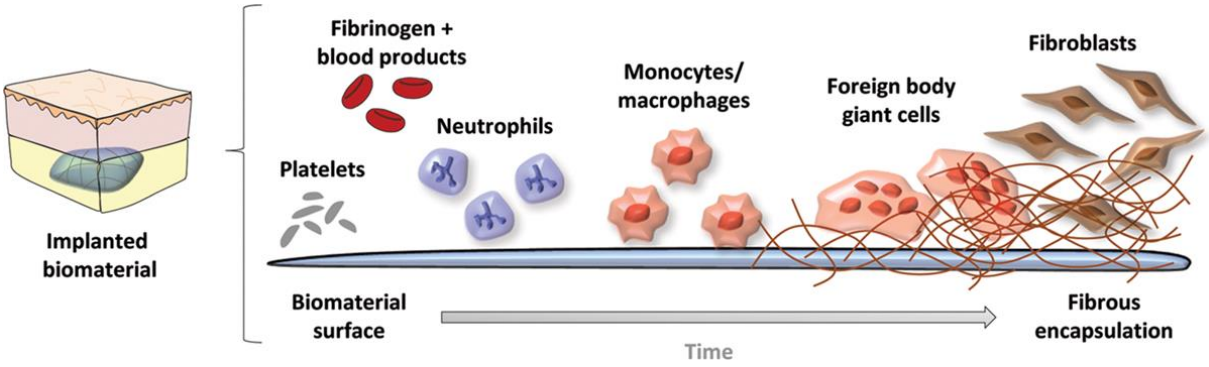

Figure 2: A schematic diagram of the foreign body reaction. A provisional matrix is formed when thrombotic agents and other blood proteins adsorb to the surface of implanted biomaterials. Neutrophils and macrophages are drawn to the implantation site by platelets and other agents in the matrix. Macrophages fuse at the tissue/implant interface to create foreign body giant cells. Continuous inflammatory signaling stimulates fibroblasts to generate collagen at the biomaterial site, which results in the development of a fibrous capsule around the biomaterial implant.(1)

Table 1. Immune cells and cytokines that are involved in the Foreign Body Response.

Molecule	Response
Chemotactic factors	
Fibrinogen	Directs phagocytes to the site of injury and guides formation of phagocytic layer surrounding implant
IL-3, IL-14	Released from mast cells; direct macrophages to the site of injury
TGF-β, PDGF, CXCL4, LTBE, IL-1	Released from thrombolytic agents within the provisional matrix; direct macrophages to implant surface
Cellular adhesion	
Mac-1 (CD11b/CD18)	Macrophage integrin involved in cellular adhesion on implant surface
Fibrinogen, fibronectin, IgG, iC3b, RGD sequences	Protein ligands to integrin receptors involved in cellular adhesion on implant surface
Macrophage polarization	
IFN- γ, TNF-α, lipopolysaccharide	Exposure induces M1 macrophage polarization
ROS, IL-1β, IL-6, and TNF-α	Secreted by polarized M1 macrophages
IL-4, IL-10, IL-13, immune complexes, and glucocorticoid hormones	Exposure induces M2 macrophage polarization
IL-10, TGF-β, and low levels of IL-12	Secreted by polarized M2 macrophages
Macrophage fusion	
IL-4, IL-13	Up-regulate mannose receptors on fusing macrophages
Vitronectin	Adhesion substrate for IL-4–induced FBGC formation
STAT6	Transduces signals of IL-4 to induce FBGC formation
E-cadherin, DC-STAMP	Induced by IL-4 in STAT6-dependent manner, essential for cell fusion
DAP12, Rac1, CCL2/MCP-1	Required for macrophage fusion
Fibrotic encapsulation	
TGF-β1	Secreted by macrophages and FBGCs to induce collagen deposition by fibroblasts
MMP-2, MMP-9	Secreted by macrophages and FBGCs; involved in extracellular matrix remodeling
Fibronectin	Involved in formation of fibrotic capsule

IL, Interleuking; TGF, transforming growth factor; IFN, interferon; TNF, tumor necrosis factor; ROS, reactive oxygen species. Other abbreviations do not have to be taken into account(1)

Macrophages are being seen as the main effector cells in a FBR and thus findings ways to affect macrophages could be interesting to reduce the foreign body response to biomaterials.

The importance of the different cells and cytokines is starting to become clear (see Table 1). Although more research is needed, the function of different cells and mediators has been recognized, making this a highly intriguing and vital topic to investigate, as it contributes to the knowledge of the human body's processes in response to implanted foreign objects.(28)

The FBR is regulated by linked inflammatory/immune processes that are present throughout the medical device's in vivo lifespan. Finding ways to intercept the FBR and direct tissue response to a more positive result would lead to longer lasting in vivo applications of biomaterials.(28)

What macrophage phenotype is preferred with biodegradable materials?

The high heterogeneity of macrophage capabilities, as well as the immune response to biomaterials, raises the question of which macrophage type is preferred following biomaterial implantation.(3) In regenerative research and biomaterial science, there is a widespread trend to value the beneficial impacts of pro-healing M2 macrophages while dismissing the inflammatory M1 macrophages. This observation may not be correct in its most extreme interpretation, and the desired macrophage type may instead be determined by the biomaterial's intended role and destiny at the implantation site. (3) Successful tissue integration of implanted materials is expected to need both M1 and M2 responses.(1)

Degradable biomaterials, such as biodegradable polymers, are commonly used as placeholders and scaffolds to allow host tissue to grow into and fill a specific area. Degradable scaffolds are designed to be destroyed and phagocytosed, a function that M1 macrophages are principally responsible for. By forcing all resident or migratory macrophages in the lesion to adopt the M2 phenotype, the biomaterial's existence in the tissue can be extended. Reduced degradation and an increase in M2 may also have a pro-fibrotic and scarring impact, which is typically undesirable.(3) Poor tissue remodeling and fibrous capsule formation due to extended M1 type immune response and no M2 response was found in studies where nondegradable materials were tested.(30)

For instance, in a study by Brown et al. they examined the role of M1 and M2 macrophages in a tissue remodeling process. Brown et al. implanted 14 different biological surgical meshes in rats and observed the macrophage response. Their findings were that early macrophage presence and higher ratios of M2:M1 macrophages showed more positive tissue remodeling results.(31)

Thus, degradable biomaterials require early M1 presence and late M2 dominance.

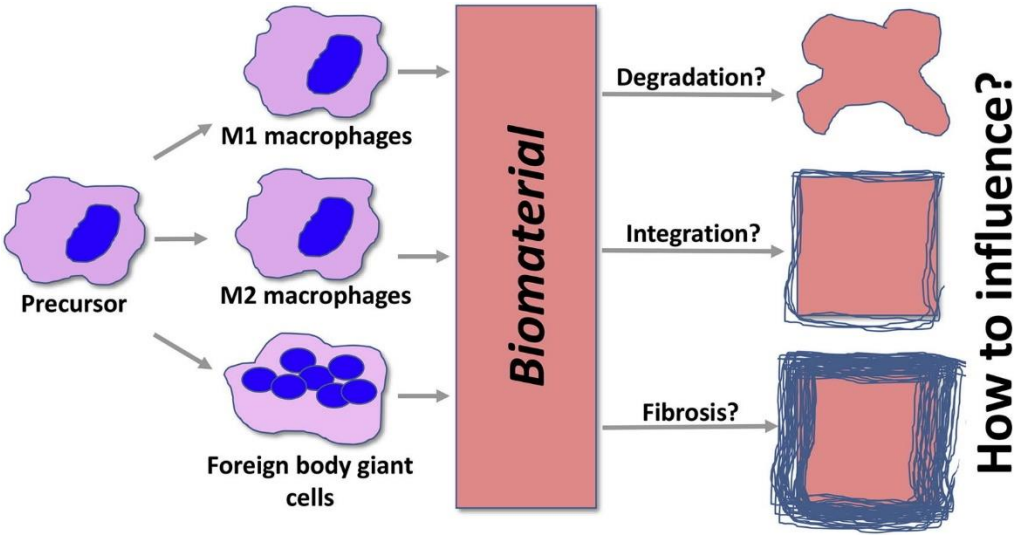

Figure 3: A schematic approach to the Foreign body reaction and the different types of macrophages.(3)

Anti-inflammatory drugs and prostaglandin synthesis

Anti-inflammatory drugs

Non-steroidal anti-inflammatory medications (NSAIDs) and (glucocortico)steroids are the two primary types of anti-inflammatory medications used in clinical practice today.(32) Both NSAIDs and steroids attack inflammation through inhibition of prostaglandin and indirectly cytokine release, however at different sites (see Figure 4). It has been proven by Mokarram et al. that application of biologically active chemicals like growth factors and cytokines can be used to alter macrophage phenotypes and use this in application of biomaterials.(33) Thus, NSAIDs and steroids could maybe be used in attacking cytokine release and could alter macrophage phenotypes to elicit favourable outcomes of biomaterials in for instance tissue remodeling.

Prostaglandins

Prostaglandins are known mediators of inflammation and regulate multiple functions of different immune cells.(34) Prostaglandins are a group of lipid mediators also known as eicosanoids. Arachidonic acid(AA), an essential fatty acid, is used to make prostaglandins. AA is delivered to prostaglandin H synthase, better known as cyclooxygenase or COX, after it is mobilized from cell membrane phospholipids by phospholipase A_2 (PLA_2).(35) COX produces two isoform enzymes called cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).(34)
COX-3, a third enzyme that represents a splicing variation of COX-1, was recently found. COX-1 is present in all tissues while COX-2 can be produced by certain physiological and proinflammatory stimuli, such as IL-1 and TNF-α. COX catalyses the conversion of arachidonic acid to PGH_2, which serves as a precursor for many prostaglandin synthases.(35) One of the prostaglandins that is synthesized by COX is PGE_2, which is being produced a lot at sites of infection.(36)(37) The amount of PGE_2 synthesis is regulated by local expression of COX-2 which causes an inflammatory process, but

can be influenced by other factors, such as the amount of AA that is available. All cell types in the body can synthesize PGE_2, however epithelia, fibroblasts and inflammatory cells such as macrophages are the main producers of PGE_2 during an immune response.(34) Prostaglandins attach to certain G protein-coupled receptors on cell surfaces to carry out their physiological activities.(38)

Prostaglandin inhibition by anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs

As we stated earlier, NSAIDs and steroids attack prostaglandin synthesis at different sites. NSAIDs work by reducing COX activity of prostaglandin H synthase, which reduces the synthesis of prostaglandins, thromboxanes, and other modulators of pain and inflammation.(39)(40) Different NSAIDs are either COX-1 selective (e.g. flurbiprofen or ketoprofen), COX-2 selective (e.g. nimesulide or SC-58125) or nonselective (e.g. indomethacin).(41) Many COX-2 selective NSAIDs are preferred because inhibition of COX-1 by NSAIDs has been linked to gastrointestinal ulcer formation.(42)

Steroids

Glucocorticosteroids (GCs) are also commonly used to treat inflammatory and immunological problems. GCs inhibit phospholipase-dependent arachidonic acid (AA) release, and therefore the synthesis of prostaglandins, which is an important mechanism for the anti-inflammatory effects of GCs. Alveolar macrophages have the ability to generate considerable amounts of AA metabolites, which can trigger and maintain inflammatory reactions in the lungs. The effects of GCs on alveolar macrophages were evaluated in a study of Peters-Golden et al.. Their results showed that the response of macrophages to GC is receptor-mediated and the inhibition of AA release by these drugs is dependent on the formation of lipomodulin. Lipomodulin is a phospholipase-inhibitory protein.(43) The phospholipase A2-mediated release of AA from cell membranes is impaired by GCs and therefore GCs reduce PGE_2 synthesis.(34)

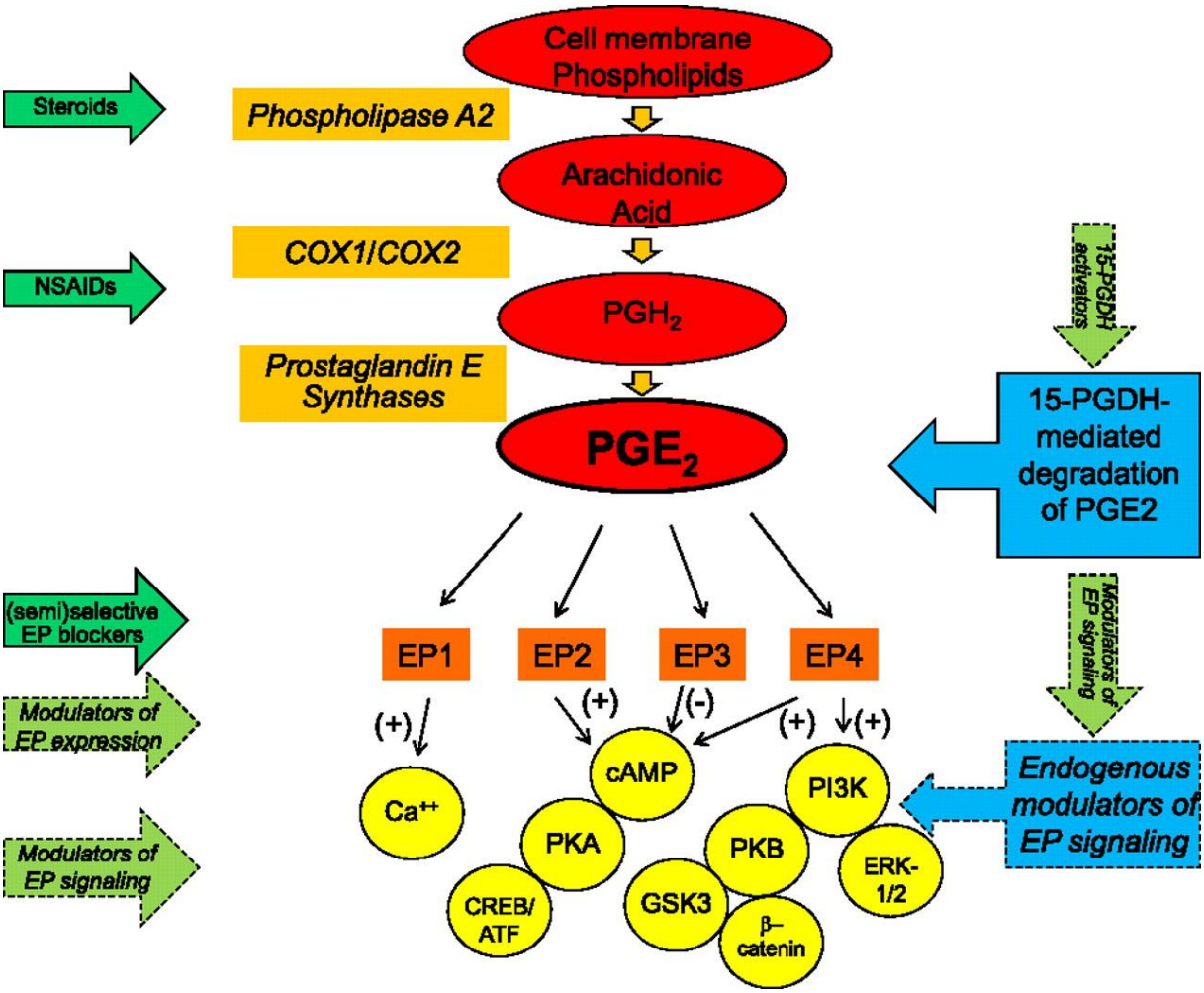

Figure 4: PGE_2 (prostaglandin E_2) production, degradation, and responses. The (glucocorticoid-sensitive) release of arichidonic acid (AA) from cell membranes kicks off PGE_2 production. Cyclooxygenase(COX)-1 and COX-2 convert AA to PGH_2 (prostaglandin H_2), which is then transformed to physiologically active PGE_2 by PGE synthases (prostaglandin E synthases) (process that can be inhibited by NSAIDS or nonsteroid anti-inflammatory medications). Inhibitory medicines are shown by dark green arrows, whereas possible targets for future medicines are indicated by light green arrows. (+) is for activating; (-) is for inhibiting. Other abbreviations do not have to be taken into account.(34)

Prostaglandin effects on cytokine release

As earlier stated with biodegradable materials, such as biodegradable polymers, an early M1 macrophage presence and late M2 macrophage dominance is preferred. Using certain drugs to push macrophages towards M1 or M2 phenotype could be useful in biomaterial applications. We will now discuss the influence of NSAIDs on the prostaglandins-mediated cytokine release and their probable ability to stop M1 macrophage activation and promote M2 macrophages.

Chae et al. studied the effects of PGE_2 on the production of proinflammatory cytokines. Findings were that PGE_2 enhanced production of IL-6 and nitric oxide (NO) but decreased TNF-α by macrophages and altered IFN-γ and IL-6 by splenocytes and thymocytes from pristane-induced lupus mice compared to controls. Chae et al. also introduced an NSAID that is Indomethacin (Indo) and found that Indo inhibited production of IL-6 by macrophages, while enhanced TNF-α production.(44)

Inhibition of M1 macrophage activation

Interferon gamma

Tanaka et al. found that NSAID indomethacin suppressed IFN-γ production.(45) IFN-γ is a cytokine which is related to M1 macrophage polarization. Suppression of IFN-γ would thus suggest no further activation of M1 macrophages.

Tumor necrosis factor alfa
Chae et al. found that levels of inflammatory cytokine TNF-α were decreased by PGE_2. Which would suggest an inflammatory effect of NSAIDs.

However thromboxane A2 (TXA2), another eicosanoid produced with COX-1, seems to have an enhancing effect on TNF-α. Penglis et al. discovered that PGE_2 inhibits TNF-α and IL-1β production whereas TXA_2 enhances it. (46) The increasing effect of TXA_2 on TNF-α would balance out the inhibiting effect of PGE_2 on TNF-α, and would also even out the inflammatory response in total. COX-2 selective inhibitors suppress monocyte PGE_2 synthesis to a much greater extent than TXA_2 synthesis.(46) However, TXA_2 is synthesized with COX-1, so COX-2 selective NSAIDs, such as indomethacin, would have no effect on the production of TXA_2.
For instance, aspirin and meloxicam that inhibit COX-1, were found to lower the synthesis of TNF-α in a study of Joussen et al.(47) Steroids such as dexamethasone and budesonide were found to decrease TNF-α production in rat alveolar macrophages. In macrophages from tracheobronchial fluid from newborn babies, similar effects were seen.(48)

Decreased release of M1 macrophage linked cytokines/chemokines
Interleukin-6
That PGE_2 enhances the synthesis of IL-6 was also reported in a study by Portanova et al.. They found that PGE_2 is an important regulator of IL-6 production in vivo and therefore NSAIDs inhibit certain inflammatory responses by decreased PGE_2 synthesis. (49)

The stimulation of IL-6 synthesis and augmentation of polymorphonuclear (PMN) cell degranulation have been identified as mechanisms of PGE_2-mediated tissue inflammation. These pathways work together to create an inflammatory environment that encourages pathogenic Th17 T cells to differentiate. As a result, one mechanism by which NSAIDs have anti-inflammatory effect is by suppressing PGE_2 and activating the IL-6/PMN/Th-17 downstream.(50) Li et al. found that steroids (dexamethasone and budesonide) also decreased IL-6 levels in rat alveolar macrophages.(48)

Nitric Oxide
Chae et al. found that PGE_2 enhanced NO production.(44) NO is thought to cause vasodilation in the cardiovascular system and is also involved in immunological responses by cytokine-activated macrophages, which produce large levels of NO. The cause of inflammatory illnesses of the joint, gut, and lungs is linked to NO. As a result, NO inhibitors offer a significant advancement in the treatment of inflammatory illnesses.(51) PGE_2 has an enhancing effect on NO production and thus evokes an inflammatory response of the host.(49) This is thus another anti-inflammatory effect of NSAIDs.

Also by-products of the synthesis of PGE_2 are superoxide and hydroxyl free radicals. Effectiveness of NSAIDs could be because of the decrease of compounds with a strong oxidizing activity.(52) Reactive oxygen species have been found to reduce phagocytosis in certain cases, for instance in a study of Goes et al. it was found that certain reactive oxygen species reduced phagocytosis of myelin by macrophages.(53)

Nuclear Factor kappa beta
Joussen et al. also found that high-doses of aspirin and meloxicam suppressed the expression of nuclear factor-κβ through COX-2 inhibition.(47) In a different study it was also found that COX-2 is quickly released in areas of acute inflammation, releasing proinflammatory prostaglandins that activate NF-κβ and inflammatory cytokines.(47)(54)

There is also evidence that steroids directly (not via PG synthesis) inhibit transcription factors, such as activator protein-l (AP-l) and NF-κB. NF-κB regulates many of the genes that code for inflammatory cytokines, including TNF-α, IL-I, IL-6 and NOS.(55)

Interleukin 10

However, surprising from the study of Chae et al. PGE_2 also seemed to enhance the production of anti-inflammatory cytokine IL-10. (44) This was confirmed in a study by Cheon et al. where they found that PGE_2 altered IL-10 signaling and function, which would mean that NSAIDs or steroids would averse this effect.(56) This would suggest an inflammatory response of the host when NSAIDs or steroids are administered.

Conclusion

All together NSAIDs and steroids seem to have an inhibiting effect on PGE_2 synthesis and therefore on inflammatory cytokine production. But the question remains if these drugs are suitable for administration with biomaterial implantation in the body.

As we discussed earlier with biodegradable materials, such as biodegradable polymers, an early M1 macrophage presence and late M2 macrophage dominance is preferred.

NSAIDs and steroids seem to tackle various inflammatory cytokines or precursors, such as IL-6, NO and IFN-γ, which are all associated with M1 macrophage polarization or secretion (Table 1). Administration of NSAIDs or steroids could help in the shift of M1 macrophage to M2 macrophage dominance by suppressing the inflammatory cytokines so that M2 associated cytokines can take over. However, for a good integration of a biomaterial there is still an early M1 macrophage presence needed. So the drugs should be released after the M1 macrophages are present. Solutions for this problem could probably be biodegradable polymer scaffolds that for instance also function as a drug eluting scaffold. Such that straight after presence of M1 macrophages, the drugs are administered and the effects of M1 macrophages are reduced.

What needs to be taken into account however is that NSAIDs and steroids had an increasing effect on the production of anti-inflammatory cytokine IL-10. IL-10 exposure induces macrophages into a M2 phenotype (Table 1). This could mean that NSAIDs and steroids could interfere with the shift of macrophages to M2 phenotype and thus not promote a sufficient tissue integration of the biomaterial. However, there are other cytokines which can promote M2 macrophages, such as IL-4, where NSAIDs and steroids do not seem to have an effect on.

If NSAIDs and steroids really are suitable for administration during biomaterial implantation in vivo still can not be fully declared, however it has promising effects on macrophages in vitro.

References

1. Major MR, Wong VW, Nelson ER, Longaker MT, Gurtner GC. The Foreign Body Response: At the Interface of Surgery and Bioengineering. Plast Reconstr Surg. 2015;135(5):1489–98.

2. Chandorkar Y, Ravikumar K, Basu B. The Foreign Body Response Demystified. ACS Biomater Sci Eng. 2019;5(1):19–44.

3. Klopfleisch R. Macrophage reaction against biomaterials in the mouse model – Phenotypes, functions and markers. Acta Biomater [Internet]. 2016;43:3–13. Available from: http://dx.doi.org/10.1016/j.actbio.2016.07.003

4. Wu MY, Lu JH. Autophagy and Macrophage Functions: Inflammatory Response and Phagocytosis. Cells. 2019;9(1):1–25.

5. Weissleder R, Nahrendorf M, Pittet MJ. Imaging macrophages with nanoparticles. Nat Mater. 2014;13(2):125–38.

6. van de Garde MDB, Martinez FO, Melgert BN, Hylkema MN, Jonkers RE, Hamann J. Chronic Exposure to Glucocorticoids Shapes Gene Expression and Modulates Innate and Adaptive Activation Pathways in Macrophages with Distinct Changes in Leukocyte Attraction. J Immunol. 2014;192(3):1196–208.

7. Röszer T. Understanding the Mysterious M2 Macrophage through Activation Markers and Effector Mechanisms. Mediators Inflamm. 2020;2015:16–8.

8. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol [Internet]. 2008;8(12):958–69. Available from: http://dx.doi.org/10.1038/nri2448

9. Mills CD, Ley K. M1 and M2 macrophages: The chicken and the egg of immunity. J Innate Immun. 2014;6(6):716–26.

10. Gemell E, Marshall I, Seymour J. Cytokines and prostaglandins in immune homeostasisand tissue destruction in periodontal disease. Periodontology. 2000;14(296):112–43.

11. Fujisaka S, Usui I, Nawaz A, Takikawa A, Kado T, Igarashi Y, et al. M2 macrophages in metabolism. Diabetol Int. 2016;7(4):342–51.

12. Gustafson HH, Holt-Casper D, Grainger DW, Ghandehari H. Nanoparticle uptake: The phagocyte problem. Nano Today. 2015;10(4):487–510.

13. Bygd HC, Forsmark KD, Bratlie KM. The significance of macrophage phenotype in cancer and biomaterials. Clin Transl Med. 2014;3(1):1–13.

14. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: Time for reassessment. F1000Prime Rep. 2014;6:1–13.

15. Vroman I, Tighzert L. Biodegradable polymers. Materials (Basel). 2009;2(2):307–44.

16. Pişkin E. Review Biodegradable Polymers as Biomaterials. J Biomater Sci Polym Ed. 1995;6(9):775–95.

17. Asawa Y, Sakamoto T, Komura M, Watanabe M, Nishizawa S, Takazawa Y, et al. Early stage foreign body reaction against biodegradable polymer scaffolds affects tissue regeneration during the autologous transplantation of tissue-engineered cartilage in the canine model. Cell Transplant. 2012;21(7):1431–42.

18. Santerre JP, Labow RS, Adams GA. Enzyme–biomaterial interactions: Effect of biosystems on degradation of polyurethanes. J Biomed Mater Res. 1993;27(1):97–109.

19. Regaño C, Martínez de Ilarduya A, Iribarren JI, Muñoz-Guerra S. Poly(ester amide)s Derived from L -Tartaric Acid and Amino Alcohols. II. Aregic Polymers. J Polym Sci - Part A. 2000;38(15):2687–96.

20. Li X, Chen H, Xie S, Wang N, Wu S, Duan Y, et al. Fabrication of photo-crosslinkable poly (Trimethylene carbonate)/polycaprolactone nanofibrous scaffolds for tendon regeneration. Int J Nanomedicine. 2020;15:6373–83.

21. Bat E, Plantinga JA, Harmsen MC, Van Luyn MJA, Feijen J, Grijpma DW. In vivo behavior of trimethylene carbonate and ε-caprolactone-based (co)polymer networks: Degradation and tissue response. J Biomed Mater Res - Part A. 2010;95(3 A):940–9.

22. Bat E, van Kooten TG, Feijen J, Grijpma DW. Macrophage-mediated erosion of gamma irradiated poly(trimethylene carbonate) films. Biomaterials [Internet]. 2009;30(22):3652–61. Available from: http://dx.doi.org/10.1016/j.biomaterials.2009.03.033

23. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol. 2008;20(2):86–100.

24. Brown EJ. Phagocytosis. BioEssays. 1994;17(2):109–17.

25. Sheikh Z, Brooks PJ, Barzilay O, Fine N, Glogauer M. Macrophages, foreign body giant cells and their response to implantable biomaterials. Materials (Basel). 2015;8(9):5671–701.

26. Brodbeck WG, Voskerician G, Ziats NP, Nakayama Y, Matsuda T, Anderson JM. In vivo leukocyte cytokine mRNA responses to biomaterials are dependent on surface chemistry. J Biomed Mater Res - Part A. 2003;64(2):320–9.

27. Sussman EM, Halpin MC, Muster J, Moon RT, Ratner BD. Porous implants modulate healing and induce shifts in local macrophage polarization in the foreign body reaction. Ann Biomed Eng. 2014;42(7):1508–16.

28. Trindade R, Albrektsson T, Tengvall P, Wennerberg A. Foreign Body Reaction to Biomaterials: On Mechanisms for Buildup and Breakdown of Osseointegration. Clin Implant Dent Relat Res. 2016;18(1):192–203.

29. de Carvalho FO, Felipe FA, de Melo Costa ACS, Teixeira LGB, Silva ÉR, Nunes PS, et al. Inflammatory Mediators and Oxidative Stress in Animals Subjected to Smoke Inhalation: A Systematic Review. Lung. 2016;194(4):487–99.

30. Brown BN, Sicari BM, Badylak SF. Rethinking regenerative medicine: A macrophage-centered approach. Front Immunol. 2014;5(NOV):1–11.

31. Brown BN, Londono R, Tottey S, Zhang L, Kukla KA, Wolf MT, et al. Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials. Acta Biomater [Internet]. 2012;8(3):978–87. Available from: http://dx.doi.org/10.1016/j.actbio.2011.11.031

32. Liu J, Tang J, Zuo Y, Yu Y, Luo P, Yao X. Stauntoside B inhibits macrophage activation by inhibiting NF-kB and ERK MAPK signalling. Pharmacol Res [Internet]. 2016;111:303–15. Available from: http://dx.doi.org/10.1016/j.phrs.2016.06.022

33. Mokarram N, Merchant A, Mukhatyar V, Patel G, Bellamkonda R V. Effect of modulating macrophage phenotype on peripheral nerve repair. Biomaterials [Internet]. 2012;33(34):8793–801. Available from: http://dx.doi.org/10.1016/j.biomaterials.2012.08.050

34. Kalinski P, Alerts E. Regulation of Immune Responses by Prostaglandin E 2. J Immunol. 2012;

35. Scholz H. Prostaglandins. Am J Physiol. 2003;285:512–4.

36. Serezani CH, Chung J, Ballinger MN, Moore BB, Aronoff DM, Peters-golden M. Prostaglandin E 2 Suppresses Bacterial Killing in Alveolar Macrophages by Inhibiting NADPH Oxidase. :17–9.

37. Jae YC. Immunomodulatory effect of nonsteroidal anti-inflammatory drugs (NSAIDs) at the clinically available doses. Arch Pharm Res. 2007;30(1):64–74.

38. Wang D, Dubois RN. Pro-inflammatory prostaglandins and progression of colorectal cancer. Cancer Lett. 2008;267:197–203.

39. Raffa R, Gudin J, Nalamachu S, Pergolizzi JJ. "Selective" COX-1 or COX-2 NSAIDs : time to change a misleading measure. J Clin Pharm Ther. 2014;39:455–6.

40. Goodwin JS. Immunologic Effects of Nonsteroidal Anti-Inflammatory Drugs. Am J Med [Internet]. 1984;77(4):7–15. Available from: http://dx.doi.org/10.1016/S0002-9343(84)80086-8

41. Wallace JL, Chapman K, Mcknight W. Limited anti-inflammatory efficacy of cyclo-oxygenase-2 inhibition in carrageenan-airpouch inflammation. Br J Pharmacol. 1999;1(126):1200–4.

42. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J med. 1998;413–21.

43. Peters-Golden M, Bathon J, Flores R, Hirata F, Newcombe DS. Glucocorticoid Inhibition of Zymosan-lnduced Arachidonic Acid Release by Rat Alveolar Macrophages. Am J Respir Crit Care Med. 1984;803–9.

44. Chae BS, Shin TY, Kim DK, Eun JS, Leem JY, Yang JH. Prostaglandin E 2 -Mediated Dysregulation of Proinflammatory Cytokine Production in Pristane-Induced Lupus Mice. Arch Pharm Res. 2008;31(4):503–10.

45. Tanaka S, Barbour SE, Best AM, Schenkein HA, Tew JG. Prostaglandin E 2 -Mediated Regulation of Immunoglobulin G2 via Interferon Gamma . J Periodontol. 2003;74(6):771–9.

46. Penglis PS, James MJ, Cleland LG, Unit R, Hospital RA. Cyclooxygenase inhibitors: any reservations? Intern Med J. 2001;31:37–41.

47. Joussen A, Poulaki V, Mitsiades N, Kirchhof B, Koizumi K, Döhmen S, et al. Nonsteroidal anti-inflammatory drugs prevent early diabetic retinopathy via TNF alfa; suppression. FASEB J. 2002;

48. Li YH, Brauner A, Jonsson B, Van Der Ploeg I, Söder O, Holst M, et al. Inhibition of macrophage proinflammatory cytokine expression by steroids and recombinant IL-10. Biol Neonate. 2001;80(2):124–32.

49. Portanova JP, Zhang Y, Anderson GD, Hauser SD, Masferrer JL, Seibert K, et al. Selective Neutralization o f Prostaglandin E 2 Blocks Inflammation , Hyperalgesia, and Interleukin 6 Production In Vivo. J Exp Med. 1996;184:883–91.

50. Pennock ND, Martinson HA, Guo Q, Betts CB, Jindal S, Tsujikawa T, et al. Ibuprofen supports macrophage differentiation , T cell recruitment , and tumor suppression in a model of postpartum breast cancer. J Immunother Cancer. 2018;6(98):1–23.

51. Sharma J, Al-Omran A. Role of nitric oxide in inflammatory diseases. Inflammopharmacology. 2007;6.

52. Garella S, Matarese R. Renal Effects of Prostaglandins and Clinical Adverse Effects of Nonsteroidal Anti-Inflammatory Agents. Medicine (Baltimore). 1984;63(3):165–80.

53. Van der Goes A, Brouwer J, Hoekstra K, Roos D. Reactive oxygen species are required for the phagocytosis of myelin by macrophages. J Neuroimmunol. 1998;92:67–75.

54. Sperling RL. Side Effects of NSAIDs A Seven-Step NSAIDs Teaching Plan. Med Rev 101. 2001;19(11):687–9.

55. Schleimer RP. How Do Steroids Work ? Am J Respir Crit Care Med. 1987;(1):3–5.

56. Cheon H, Rho YH, Choi SJ, Lee YH, Song GG, Sohn J, et al. Prostaglandin E 2 Augments IL-10 Signaling and Function . J Immunol. 2006;177(2):1092–100.