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Review article

The inflammasome in host response to biomaterials: Bridging inflammation and tissue regeneration

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ABSTRACT

The development of new biomaterials to be used in tissue engineering applications is creating new solutions for a range of healthcare problems. The trend in biomaterials research has shifted from biocompatible "immune-evasive" biomaterials to "immune-interactive" materials that modulate the inflammatory response supporting implant integration as well as improving healing and tissue regeneration.

Inflammasomes are large intracellular multiprotein complexes that are key players in host defence during innate immune responses and assemble after recognition of pathogens or danger signals. The process of biomaterial implantation causes injury to tissues that will consequently release danger signals that could be sensed by the inflammasome. There are increasing evidences that the inflammasome has a role in several inflammatory processes, from pathogen clearance to chronic inflammation or tissue repair. Thus, modulation of the inflammasome activity appears as an important target in the development of effective approaches in regenerative medicine.

In this review, we discuss the main points of the current understanding on the host response to implanted biomaterials and how the paradigm of "immune-evasive" biomaterials has shifted over the last years; the significance of the inflammasome in the inflammatory response to biomaterials; and the growing idea that the immune system is of key importance in an effective tissue repair and regeneration.

Statement of significance

We herein discuss the main points of the current understanding on the host response to implanted biomaterials and how the paradigm of "immune-evasive" biomaterials has shifted to "immune-interactive" over the last years; the significance of the inflammasome in the inflammatory response to biomaterials; and the growing idea that the immune system is of key importance in an effective tissue repair and regeneration, supporting the emerging concept of Regenerative Immunology. The inflammasome is a recent and central concept in immunology research. Since the beginning of this century the inflammasome is viewed as key platform of the innate immune response. We believe that, successful modulation of the inflammasome activity will become a milestone in the fields of tissue engineering and regenerative medicine.

Abbreviations: ARLs, AIM2-like receptors; ASC, apoptosis-associated speck like protein containing a caspase recruitment domain; ATP, adenosine triphosphate; CARD, caspase activation and recruitment domain; CLRs, C-type lectin receptors; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; ECM, extracellular matrix; FBGCs, foreign body giant cells; FGF-2, basic fibroblast growth factor; HMGB1, high mobility group protein B1; HSP, heat shock proteins; IFN-γ, interferon-gamma; IL, interleukin; KO, knockout; LLRs, leucine-rich-repeat; MCP-1, monocyte chemotactic protein; MIP-1β, macrophage inflammatory protein; NATCH, nucleotide binding domain; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3; NLRs, NOD-like receptors; PAMPs, pathogen-associated molecular patterns; PMNs, polymorphonuclear leukocytes; PRRs, pattern recognition receptors; PYD, pyrin domain; RLRs, RIG-I-like receptors; ROS, reactive oxygen species; SPMs, specialized pro-resolving mediators; TLRs, toll-like receptors; TNF-α, tumour necrosis factor-α; WT, wild-type.

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Contents

1. Introduction

The inflammatory response to implanted biomaterials has been deeply investigated over the last years. James Anderson has provided us several landmark papers concerning the biological responses to biomaterials [1-3]. Over the last years, we have perceived a change in the concept of an ideal biomaterial. Instead of being a passive material design to diminish host responses, biomaterials are now developed to trigger desired immunological responses and therefore enable its integration and subsequent tissue repair [4].

The aim of regenerative medicine is to recover tissues and organs moving them to its functional state. Recent therapies are currently focusing on immunomodulation, instead of traditional approaches that have used biomaterials, stem cells and growth factors either alone or in combination. The use of immunomodulation strategies has created the need of biomaterials with further and precise functions as the capacity to modulate the host immune response [5].

Inflammasomes are intracellular multiprotein complexes with a key role in innate immune responses. Inflammasomes assemble after cellular exposure to danger signals released following tissue injury, orchestrating innate immune responses through activation of caspase-1 and the subsequent production of pro-inflammatory cytokines [6]. Activation of the inflammasome can both run a precise course, leading to the resolution of inflammation and subsequent tissue healing, or be continued, causing chronic disease or fibrosis [7]. Thus, inflammasomes are regulators of the type of inflammatory response and also of tissue repair [8,9].

Recognizing the signalling that is produced by inflammasomes could be useful to retract fibrosis and to improve healing. Therefore, modulation of inflammasome activity is an important target to develop effective strategies for biomaterial integration which is considered a rather important challenge in biomedical research and clinical medicine.

2. The inflammatory responses to biomaterials

2.1. The classical perspective

The inflammatory response can be defined as an acute response to tissue injury directed at limiting damage to the body, and it is started through the detection of signals of acute damage or changes of the steady state [10]. The process of biomaterial implantation results in damage to tissues or organs of the host. This injury together with changes in the homeostatic mechanisms will lead to an inflammatory response to the implanted biomaterial [2,4].

A series of events are initiated upon the implantation process, beginning with an acute inflammatory response that in some circumstances may lead to a chronic inflammatory response, a foreign-body reaction, and the deposition of a collagenous fibrous capsule around the implant. The efficacy of biomedical devices can be affected by the extent and duration of the inflammatory process, having a direct impact on biomaterial stability and compatibility [2,3].

The tissue response to biomaterials is commonly described as a sequence of events that are started by the biomaterial implantation procedure, additionally to its presence [2,3]. We will briefly review these responses starting with (i) blood-material interactions; (ii) release of danger signals by injured cells; (iii) acute inflammation; (iv) chronic inflammation; (v) foreign body reaction.

(i) *Blood-material interactions:* The inflammatory response is always initiated due to injury caused in connective tissue. Shortly after injury, changes in vascular flow and permeability occur, followed by the exudation of fluid, proteins and blood cells from the vascular system into the affected tissues [11]. Almost immediately proteins adsorb to the biomaterial surface [12,13]. This layer of adsorbed proteins (type of proteins, concentration and conformation upon adsorption) will define the initiation of the coagulation cascade, complement system, platelets and immune cells leading to the formation of a transitional fibrin matrix at the implant site (Fig. 1A) [14].

(ii) *Release of danger signals by injured cells:* Following tissue injury, danger signals the "alarmins" are promptly released by cells undergoing necrosis. Alarmins are the endogenous equivalent of pathogen-associated molecular patterns (PAMPs) including for example heat shock proteins, ATP and uric acid. Alarmins are capable of recruit and activate different immune cells such as macrophages and dendritic cells (DCs), being recognized trough pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), scavenger receptors and purinergic receptors [15-17], and thus promoting inflammation [18,19]. As a consequence of biomaterial implantation, alarmins will be released by injured cells at the implant site due to the surgical procedure (Fig. 1A) [20].

(iii) *Acute inflammation:* This step of the inflammatory response is of relative short duration and is mainly characterized by the rapid recruitment of polymorphonuclear leukocytes

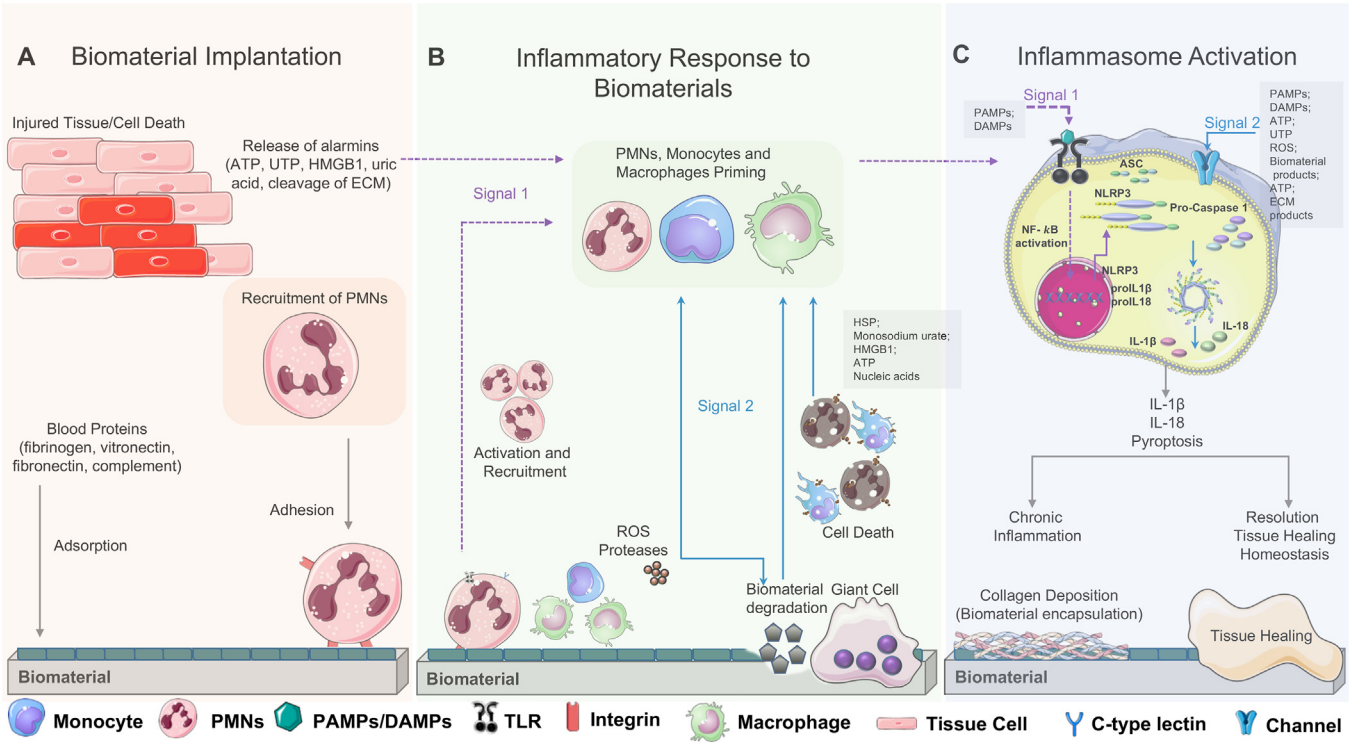

Fig. 1. The inflammasome in the immune response to an implanted biomaterial. (A) Biomaterial implantation: The process of implantation of a biomaterial causes injury to cells. Danger signals released from injured cells (such as alarmins, HMGB1, ATP and UTP) results in the recruitment and activation of polymorphonuclear leukocytes (PMNs), monocytes and resident macrophages, via pattern recognition receptor (PRRs) engagement. Well-known damage associated molecular patterns (DAMPs) include ATP, nucleic acids, HSP, monosodium urate, HMGB1 and inflammatory cytokines. The adsorption of blood proteins to material surface will further recruit immune cells. (B) Acute inflammatory response to biomaterials: Immune cells secrete proteolytic enzymes and reactive oxygen species (ROS) that will degrade the biomaterial surface and ECM components. Endogenous danger signals are usually released from stressed or necrotic cells and also damaged ECM during acute inflammation. (C) Inflammasome activation: Activation of NLRP3 inflammasome, composed of NLRP3, ASC, and pro-caspase-1, is regulated by two-step signals: The first signal (signal 1) can be danger signals released from injured tissues and immune cells that will enhance the expression of inflammasome components and target proteins via activation of NF-κB. The second "activation" signal (signal 2) promotes the assembly of inflammasome components, that involves three major mechanisms, including generation of ROS, lysosomal damage (phagocytosis of biomaterial degradation products), and the potassium efflux. Inflammasome assembly leads to caspase-1 activation that in turn cleaves the pro-forms of cytokines IL-1β and IL-18 as well as gasdermin D that induce the pyroptotic inflammatory cell death. The perpetuation of the inflammatory cascade culminates either in resolution of inflammation, return to homeostasis and tissue healing or in chronic inflammation and biomaterial encapsulation.

(PMNs) to the implant site through the release of chemoattractants by activated platelets and endothelial cells. The PMNs will then initiate a phagocytic response together with the secretion of proteolytic enzymes and reactive oxygen species (ROS). Due to size disparity, phagocytosis will most likely not occur and the destructive agents released by these cells may corrode the material surface (Fig. 1B). Several chemokines such as monocyte chemotactic protein (MCP-1) and macrophage inflammatory protein (MIP-1β), that are chemoattractants and activators of monocytes, macrophages, immature DCs and lymphocytes, will be secreted by activated PMNs. Commonly, PMNs will disappear from the implant site in the first two days after biomaterial implantation, [4,19,21,22].

(iv) *Chronic inflammation:* When the inflammatory stimuli persist, a chronic inflammation will progress, being the macrophage one of the central cell type of this phase of the inflammatory response. Macrophages release a great number of biological active inflammatory mediators such as tumour necrosis factor-α (TNF-α), interleukin (IL)-8, IL-1β, MCP-1 and MIP-1β among others (Fig. 1C). Macrophages are considered as having a fundamental role in wound healing and tissue repair since they exhibit extraordinary plasticity and in response to environmental cues can change their physiology, inducing distinct cell populations with different functions. This has originated the division of macrophages into two major extreme phenotypes (M1 and M2). The classically activated, pro-inflammatory, cytotoxic macrophage phenotype, labelled as M1, promotes pathogen killing and is related with classic signs of active inflammation, mostly with chronic inflammation. The alternatively activated, anti-inflammatory macrophage phenotype, labelled as M2, supports immunoregulation tissue repair and remodelling [23-27].

(v) *Foreign body reaction:* Since macrophages can only phagocytose particles up to 5 μm, when the particle size is larger they will fuse and form foreign body giant cells (FBGCs) (Fig. 1B). It is described in the literature that after fusing in FBGCs, macrophages show a decrease in the phagocytic activity together with an enhanced degradative capacity due to the release of reactive species, thus creating a highly degradative environment at the biomaterial surface [4,28,29]. Macrophages and FBGCs can be found at the implanted biomaterial surface for the lifetime of the implant. There is a fibrous encapsulation around the biomaterial due to fibroblast recruiting factors secreted by FBGCs resulting in its activation and collagen deposition. This fibrous capsule will impair the implant function because it will be isolated from the local tissue environment [3,30,31].

2.2. Resolution of inflammation

Inflammation is a crucial step in an efficient host defence. It is a response to pathogen invasion and also to tissue injury. However,

to re-establish tissue homeostasis it is necessary to resolve the inflammatory response, in order to prevent increased tissue injury and to minimize the development of chronic inflammation, therefore enabling tissue repair and regeneration [32–34].

The resolution of inflammation and the recovery of homeostasis was for many years considered to be a passive process. It was thought that local inflammatory stimuli would just fade or "burn out" with time, allowing tissues to drain, repair and return to normal function. It is today accepted that resolution of inflammation is an active process that is highly regulated. Specialized immunoresolvents have been recently described as having a fundamental role, together with anti-inflammatory cytokines as IL-10, in the termination of inflammation triggering pathways that signal the termination of the acute phase of the inflammatory response. These mediators include a group of endogenous molecules: resolvins, lipoxins, protectins and maresins, collectively coined as specialized pro-resolving mediators (SPMs) [35–37].

In the initial phase of inflammation, lipid mediators such as eicosanoids including prostaglandins and leukotrienes, synthesized from membrane-released arachidonic acid of activated cells, have a central role as local mediators in the advance of an inflammatory condition, inducing an effective chemotactic response of leukocytes whose activation is associated to the local release of pro-inflammatory cytokines. A high increase in the production of inflammatory mediators such as prostaglandins and leukotrienes is associated with an advance from acute to chronic inflammation. In a second phase, an active shift in the type of mediators leads to the production of immunoresolvents initiating the resolution of inflammation. Transcellular metabolism of arachidonic acid by lipoxygenase/lipoxygenase interaction pathways gives rise to SPMs [38,39]. These endogenous lipid pro-resolution mediators are generated through complex pathways being the (i) lipoxins derived from endogenous fatty acids (arachidonic acid), while (ii) resolvins, (iii) protectins and (iv) maresins are derived from dietary fatty acids, specifically ω-3 fatty-acids [40].

(i) *Lipoxins* (lipoxygenase interaction products) are considered to be effective stop signals for PMNs, limiting their recruitment to sites of inflammation through the reduction of vascular permeability and stimulating the return to homeostasis; they also induce nonphlogistic recruitment of macrophages that are required for wound healing and for the uptake of apoptotic PMNs [41-43].
(ii) *Resolvins* (resolution-phase interaction products) induce several functions in the resolution of inflammation such as the regulation of cytokines and reactive oxygen species; the prevention of PMNs infiltration; the increase phagocytosis of apoptotic PMNs that will clear the lesion and lower the magnitude of the response and thus promote tissue regeneration [41,44].
(iii) *Protectins* (the term was introduced due to the general anti-inflammatory and protective actions) reduce PMNs recruitment and reinforce the clearance of apoptotic PMNs by macrophages [45].
(iv) *Maresins* (macrophage mediators in resolving inflammation) were described as being produced by macrophages that have homeostatic functions, these mediators also support the removal of apoptotic PMNs by macrophages contributing to the re-establishing of tissue homeostasis [46,47].

General evidences of resolution are the general decrease of pro-inflammatory cytokines, phagocytosis of apoptotic PMNs and clearance of the inflammatory debris. SPMs stimulate re-epithelialization, wound healing, and tissue regeneration reducing the pro-inflammatory chemical mediators. Chronic inflammation and fibrosis will occur if inflammatory resolution fails [48].

2.3. The new trend in biomaterial development

For many years, it was accepted that the key for long term durability and function of an implanted biomaterial was its ability to elicit a minimal inflammatory response, since it was considered to be an adverse reaction. Within the last years, this paradigm of the host-biomaterial response has been intensely refined [49]. During several decades biomaterial engineering was dedicated on the development of passive biomaterials to minimize the host response, but it has now been understood that allowing specific biological responses is beneficial for both biomaterial integration and performance [50]. In view of this, biomaterials development has change from "immune-evasive" to "immune-interactive" biomaterials to allow the modulation of the inflammatory response improving healing and regeneration [51].

It has now became clear that the immune system is fundamental in orchestrating and defining the nature of the repair response [33,52], and that without injury and ensuing inflammation regeneration or repair does not occur [53]. The coordination between inflammation and its resolution is required for successful tissue repair and regeneration [34]. Nowadays, there is growing evidence that the immune response supports repair and provides local tissue protection [54]. The link amongst repair and immune response is complex and both positive and negative roles are described. The result of the tissue healing process can change from incomplete healing and repair that may cause scarring or fibrosis, to complete restoration of the tissue functions being this significantly affected by the immune response [33].

John Hunter, a famous Scottish surgeon, in 1794, wrote that "inflammation in itself is not to be considered as a disease, but as a salutary operation consequent to some violence or some disease" [55]. Hunter's rational is rather interesting taking in consideration the recent findings of inflammation being crucial in tissue repair and regeneration.

An impressive number of immune mediators cooperate in every step of the tissue healing process. For example, the macrophage response is crucial for an effective tissue remodelling following biomaterial implantation, since macrophages are rather important in the process of tissue healing [56], and if macrophage infiltration is prevented, healing is severely impaired [29]. Therefore, modulating the immune system response, namely specific immune cell types, is a valid strategy to support tissue regeneration [57].

Recovery of tissue integrity and return to homeostasis following injury is a central property of all organisms and the immune system is of key importance in defining the quality of the repair process [9,10]. Recently, new and unexpected roles of immune cells have been described in the promotion of a local environment favourable for effective cell replacement and restoration of tissue integrity. Hence, an in-depth knowledge of the mechanisms controlling the inflammatory response and how it is related with the healing process, will be an important milestone in tissue repair [11,12].

The challenge nowadays, is to develop capable biomaterial and delivery systems to regulate tissue healing through immune-mediated mechanisms. The next generation of regenerative approaches may progress from typical "biomaterial-, stem cell-, or growth factor-centric approaches" to an "immune-centric" approach, following the modulation of the immune system as a way of stimulating repair of tissues and organs [57].

2.3.1. Immunomodulatory biomaterials

Traditionally, the immune system has been viewed by biomedical engineers as an enemy to the adequate design of biomaterials, as a coordinator of the host response that decreases the duration and function of implants. However, interest is increasingly growing

on engineering biomaterials to wisely control the immune system by enhancing or suppressing immune reactions [58].

The emergence of tissue engineering and regenerative medicine has motivated the development of novel biomaterials with additional and precise functions, such as the ability to change inflammatory and innate immune response [59].

The conception of biomaterials that are able to modulate the immune system response is a developing field that is evolving together with advances in immunology. There is solid hope on the potential of biomaterials to elicit appropriate immune responses through the modulation of immune cell function, the so called immunomodulatory biomaterials [60].

The use of biomaterials to change immune responses is creating interesting new approaches in different research areas such as cancer immunotherapy, vaccination, establishing tolerance in organ transplantation and treatment of autoimmune disorders [58]. However, in this review we will focus on the repair of damage tissues using immune-mediated strategies that is emerging as an innovative approach. Engineering biomaterials to control the immune system may encourage the development of therapies that stimulate pro-regenerative immune responses, leading to an improved tissue repair [61].

These so-called immunomodulatory biomaterials should ideally influence immune cell function promoting tissue healing and the integration of the implant while supporting its function [62]. Different strategies are used in biomaterial-based immunomodulation such as (i) tuning of the chemical properties of biomaterials; (ii) changing the physical properties of the materials (iii) incorporation of bioactive molecules either anti-inflammatory drugs or pro-resolution mediators or growth factors; (iv) biomaterials based on decellularized extracellular matrix (ECM) and (v) cell therapy methods either by including immune cells or by inducing their recruitment [51].

The studies described in the literature attempting to modulate immune responses are mostly focused on the macrophage, namely in macrophage polarization (Fig. 2). This is because macrophages are highly plastic cells [63,64] that play a decisive role in inflammation and also in the coordination of tissue repair, fibrosis and tissue regeneration [65].

The development of structures that either mimic or use components or decellularized ECM will allow the establishment of a microenvironment favourable for healing and repair [66]. Brown et al. [67] have demonstrated that there is an association between early macrophage response to implanted ECM scaffold materials and the result of tissue remodelling probably associated with M1 vs. M2 macrophage response, being increased ratios of M2:M1 macrophages associated with positive remodelling outcomes (Fig. 2). Franz et al. [56] have investigated different artificial ECM derivatives and suggest that these materials could be used as coatings for biomaterials allowing the modulation of macrophage functions during the healing response, since they were able to *in vitro* impair the polarization of human M1 macrophages.

The delivery of bioactive molecules such as cytokines or pro-resolution mediators has provided rather interesting results. Gower et al. [59] were able to modulate leukocyte infiltration and phenotype after a poly(lactide-co-glycolide) (PLG) scaffold implantation using a gene-therapy approach consisting in the localized delivery of IL-10, decreasing the leukocyte inflammatory response. Spiller et al. [68] designed a scaffold that allowed the sequential delivery of interferon-gamma (IFN-γ) followed by IL-4, in order to promote the transition of M1 to M2 macrophages. Chen et al. [69] have used the same rationale and developed a system of

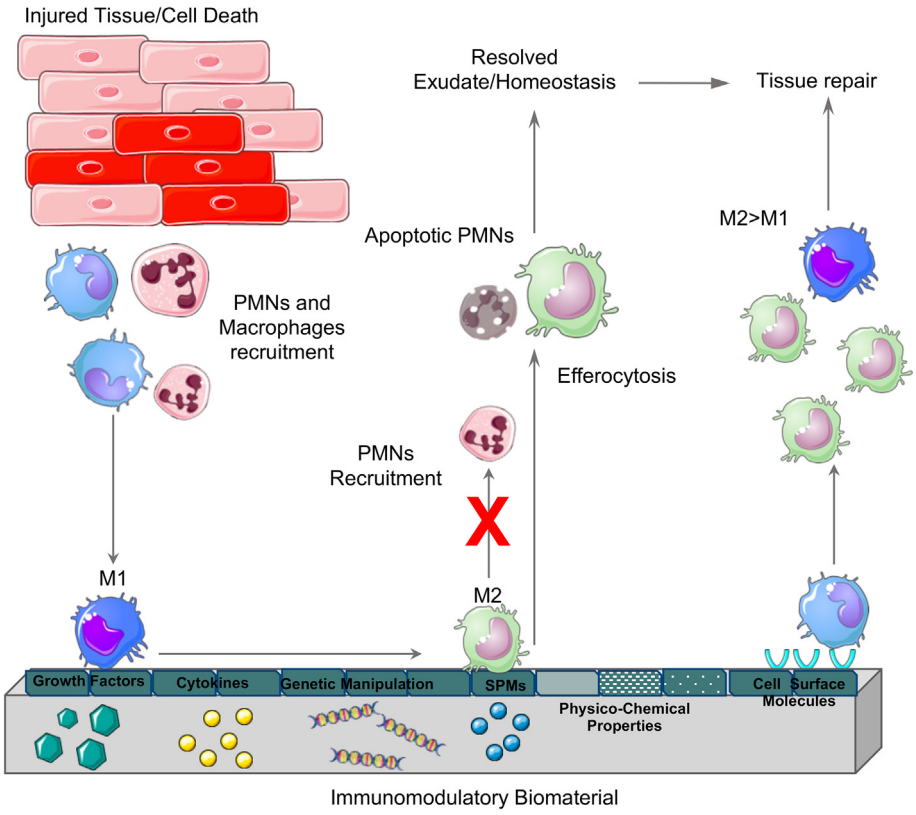

Fig. 2. Modulation of macrophage interaction with biomaterials. Implantation of a biomaterial triggers an acute inflammatory response, resulting in the recruitment of polymorphonuclear leukocytes (PMNs) and macrophages that will initially polarize to M1 pro-inflammatory macrophages. Afterwards, the immunomodulatory biomaterial will release anti-inflammatory agents (such as cytokines or specialized pro-resolving mediators (SPMs)) leading to changes in the macrophage polarization towards a M2 pro-healing phenotype, promoting implant integration and tissue healing.

double hydrogel layers on titania nanotubes (TNT) to achieve a controlled release of IL-4 and IFN-γ. We have developed an immunomodulatory strategy based on the local delivery of SPMs, namely lipoxin A4 and resolvin D1, and we were able to *in vivo* shift the macrophage phenotypic profile towards a M2 reparative response [70,71].

Exploring the physicochemical properties of biomaterials has also led to some promising outcomes. Shayan et al. [72] have used nanopatterned bulk metallic glasses to modulate murine macrophage polarization and concluded that nanopatterned surfaces lead to a more constructive tissue repair with higher vascularization and increased M2 to M1 ratio, when compared to flat surfaces. Wang et al. [73] have produced macroporous electrospun polycaprolactone scaffolds with different fiber size and concluded that macrophages cultured on thicker-fiber scaffolds tended to polarize into M2 phenotype, whereas those cultured on thinner-fiber scaffolds expressed mainly M1 phenotype. Lee et al. [74] have performed a chemical surface modification in a titanium implants using the divalent cations calcium and strontium and were able to up-regulate M2 macrophage phenotype expression. Li et al. [75] have developed titanium implants doped with magnesium with the objective of assessing the macrophage response both *in vitro* and *in vivo* and were able to induce a higher percentage of M2 macrophages and higher concentrations of the anti-inflammatory cytokines IL-4 and IL-10.

The next generation of biomaterials will be developed upon knowledge of the biology of inflammation and healing and will regulate biological responses with precision [50]. It is essential to understand which cells and/or mediators of the immune system can be used to actively stimulate regeneration [5]. Material science has also a great deal to offer to the field of immunology through the design of different biomaterial-based immunomodulatory approaches.

3. The inflammasome

3.1. What is the inflammasome?

As explained before, inflammation is initiated on the recognition of signs of acute damage or disturbances of the steady state and mainly mediated by the production of soluble factors like cytokines. The innate immune system has several PRRs that upon activation induce the production of different pro-inflammatory cytokines. PRRs can be subdivided into two major classes based in their subcellular location: TLRs and C-type lectin receptors (CLRs) are transmembrane proteins; while the RIG-I-like receptors (RLRs) and the NOD-like receptors (NLRs), reside in the intracellular compartments. These receptors recognize and activate in response, for example, to distinct PAMPs and also host-derived signals produced during tissue damage or homeostasis disturbances called damage-associated molecular patterns (DAMPs) [76,77].

The concept of inflammasome was introduced in the beginning of this century by Jörg Tschopp. The term inflammasome was coined to describe an intracellular multiprotein complex that perceives pathogenic microorganisms and sterile stressors, being responsible for the activation of the highly pro-inflammatory cytokines IL-1β and IL-18 [78]. Inflammasome is derived from the word inflammation – to reflect the function of this complex - and the suffix "some" from the Greek "soma" that means body, which is generally used to define several molecular complexes such as liposome or ribosome [6].

The inflammasome complex (Fig. 3) consists of a cytosolic sensor that could be a PRR of the NLRs or AIM2-like receptors (ARLs) families, in some cases includes an adaptor protein called apoptosis-associated speck like protein containing a caspase recruitment domain (ASC), and an effector protein that in the canonical inflammasomes is caspase-1 [79]. ASC is a bipartite molecule that contains both an N-terminal Pyrin domain (PYD) and a C-terminal caspase activation and recruitment domain (CARD), enabling it to bridge the inflammasome sensor with PYD domain (NLRs or ALRs) and the effector pro-caspase-1. Additionally to NLRs and ALRs, other proteins with a PYD domain could also assemble ASC to form inflammasomes, such as the protein Pyrin [80].

Different PRRs have been identified to form inflammasomes, including NLRP1, NLRP3, NLRC4 or AIM2, among others. In some conditions the combined activation of two inflammasomes could contribute to the inflammatory response [81–83]. The assembly of these PRRs in pentameric or heptameric structures oligomerize ASC in filaments and these ASC filaments recruit caspase-1 leading to the formation of the inflammasome. The inflammasome complex oligomerize in response to a varied set of inflammation-inducing stimuli including PAMPs and DAMPs and are appreciated as an important sensing system that allows the host to mount an effective immune response [84]. This response is mediated by the activation of caspase-1 within the inflammasome, a response that induces by one hand the cleavage of pro-IL-1β and pro-IL-18 into their mature biological active forms and a special type of cell death termed pyroptosis upon cleavage of gasdermin D. Pyroptosis is executed by the formation of pores in the plasma membrane by the insertion of the resulting N-terminus fragment of gasdermin D and the leakage of intracellular content including mature IL-1β and IL-18 cytokines (Fig. 4).

The NLRP3 inflammasome (previously known as cryopyrin or NALP3) is presently the most fully characterized inflammasome

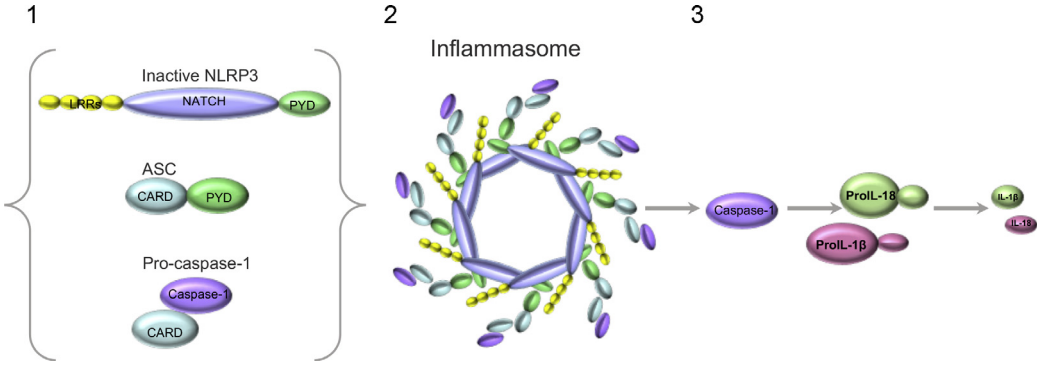

Fig. 3. NLRP3 Inflammasome assembly. (1) NLRP3 recruits procaspase-1 through ASC to form the inflammasome. (2) Within the inflammasome, procaspase-1 undergoes autocatalytic processing, resulting in active caspase-1 which in turn cleaves the pro-IL-1β and pro-IL-18 into the mature and active form (3). NLR: nucleotide-binding domain, leucine-rich repeat containing; PYD: pyrin domain; LRR: leucine-rich repeat; NATCH: nucleotide-binding domain; ASC: apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD). . Adapted from [128]

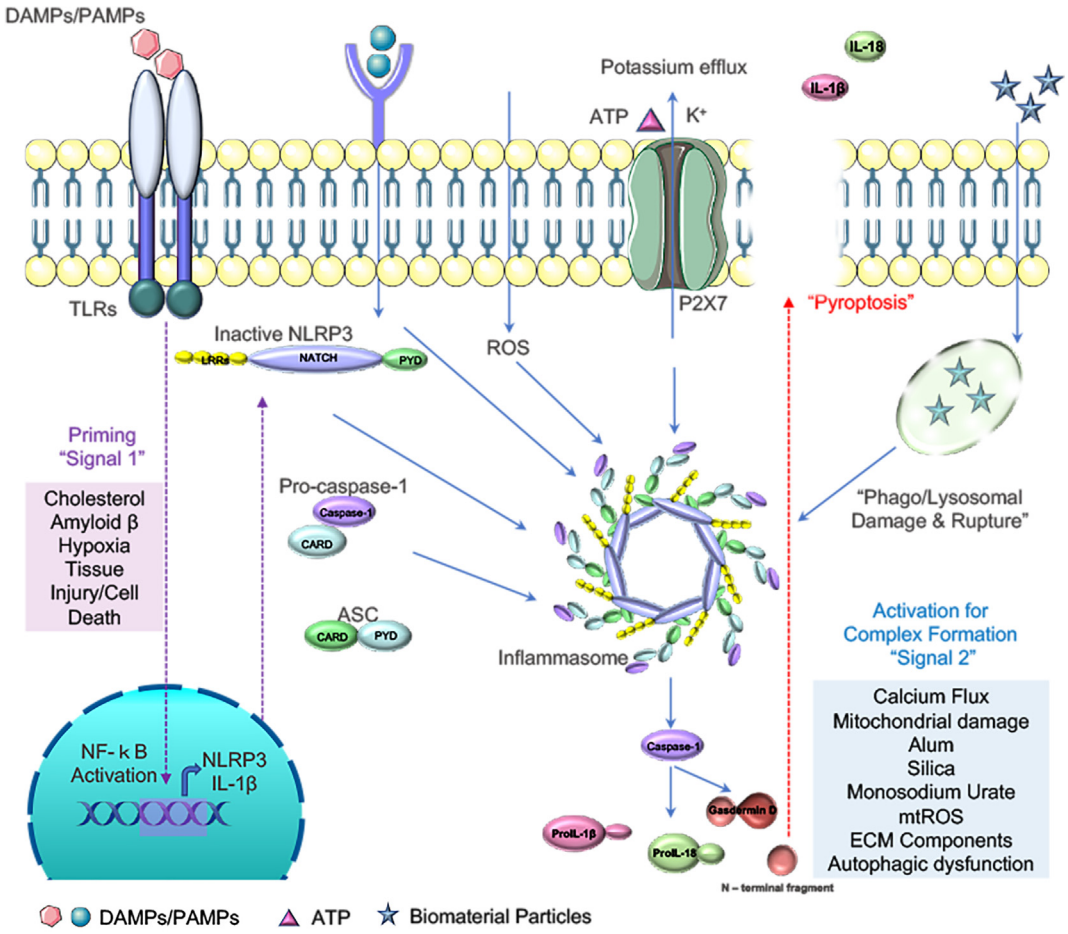

Fig. 4. Inflammasome activation. The exposure to pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs), leads to Toll-like receptors (TLRs) stimulation causing NF-κB activation. NF-κB will then promote the transcription of NLRP3, proIL-1β, and proIL-18 that remain inactive in the cytoplasm. This signal ("Signal 1") is a priming event. For NLRP3 inflammasome activation a second signal is required ("Signal 2") leading to the oligomerization of inactive NLRP3, apoptosis-associated speck-like protein (ASC), and procaspase-1. This protein complex will then convert procaspase-1 to caspase-1, which leads to the production and secretion of the mature IL-1β and IL-18. Different mediators have been described as the second step of inflammasome activation: Extracellular ATP can induce K+/potassium efflux through a purinergic P2X7-dependent pore; PAMPs and DAMPs trigger the generation of ROS; Phagocytosed environmental irritants or biomaterials (nanoparticles or biomaterial degradation products) may lead to lysosomal rupture and release of their contents. All the above described factors induce NLRP3 inflammasome assembly and activation.

and consists of the NLRP3 scaffold, the ASC adaptor protein and caspase-1, together with the accessory protein NEK7 that maintain NLRP3 oligomer in active state [85,86]. The NLRP3 inflammasome is primarily expressed in monocytes, macrophages, granulocytes, dendritic cells, and also in epithelial cells and osteoblast, being its expression in myeloid cells highly inducible [87]. This inflammasome is initially primed in response to diverse signals (Fig. 4, priming "signal 1"), including *de novo* translation driven by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and post-transcriptional modifications, including phosphorylation, dephosphorylation, deubiquitination, nitrosylation and ribosylation [88]. Upon NLRP3 priming, diverse endogenous host-derived activators (such as extracellular ATP, uric acid crystals or hyaluronan), environmental-derived molecules (such as asbestos and silica particles) and several PAMPs are recognized by myeloid cells and induces the oligomerization of NLRP3 [77,89,90]. This second activator signal (Fig. 4, activation for complex formation "signal 2") is transduced by various mechanisms such as ROS production or lysosomal damage, being a key common step the intracellular potassium efflux [87,91,92]. Therefore, the NLRP3 inflammasome recognise an optimal intracellular milieu [93].

Furthermore, different mutations in NLRP3 results in a protein conformation with increase ability to oligomerize and induce spontaneous activation of the NLRP3 inflammasome in the absence or with a low threshold of activators. These mutations lead to autoinflammatory syndromes in humans known as Cryopyrin-associated periodic syndromes (CAPS), characterized by recurrent inflammatory flares [94].

3.2. The importance of the inflammasome in the innate immune response

Our knowledge on the molecular mechanisms underlying the different functions of the innate immune system has significantly advanced in the past decade, in particular the activity of the inflammasome in leading innate immune responses, being now considered a central platform for a correct innate immune response [89], and recognized as one of the cornerstones of the intracellular surveillance system [95].

The innate immune system is capable to distinguish non-pathogenic or commensals from pathogenic microbes, but the mechanisms behind this feature is still unknown. Matzinger and colleagues [96], to explain these unanswered questions of the "self-from-nonself model", proposed a different hypothesis, *"the danger hypothesis*". This model suggests that an efficient immune response will be triggered through an antigen presentation in the context of a danger signal and not only by the foreignness of the antigen. Interestingly, an increasing number of studies disclose

an important function of the inflammasome in the sensing of a controversial signal: danger [6]. The discovery that the NLRP3 inflammasome can be activated by host-derived molecules supports the idea that the innate immune system senses endogenous indicators of cellular danger or stress [89], as in the sterile immune response to allografts [97].

In addition, the effective activity of the inflammasome in guiding innate immune responses is clearly revealed by some heritable and acquired diseases in which the dysregulation of the NLRP3 inflammasome activity due to mutations that affect its structure is observed, and also by the success with which many of these diseases can be treated using IL-1β receptors or an antagonist [89,94].

3.3. The inflammasome in the inflammatory response to biomaterials

Different host-derived molecules that are revealing of tissue injury will activate the NLRP3 inflammasome; these molecules include extracellular ATP, HMGB1, different types of crystals, as uric acid or cholesterol and hyaluronan [89,98]. The implantation process of a biomaterial causes injury to the cells and will consequently release danger signals that could activate the NLRP3 inflammasome (Fig. 1).

The activation of inflammasomes by implanted biomaterials is still poorly understood and requires a more in-depth investigation. There are already studies in the literature exploring the activation of inflammasomes by gold nanoshells [99], silver nanoparticles [100] and chitin/chitosan [101] based in the quantification of IL-1β production as a measure of inflammasome activation. Malik et al. [102] have performed a more detailed study and demonstrated the involvement of the inflammasome in interactions between cells and biomaterials and in the progress of the foreign body response using NLRP3, ASC, NLRC4 and caspase-1 deficient mice. They have observed that microspheres of poly(methyl metacrylate) (PMMA) can stimulate the NLRP3 inflammasome and cause the formation of an inflammatory exudate that depends on the inflammasome components NLRP3, ASC and caspase-1, and lead to the formation of active caspase-1 and secretion of IL-1β. Reisetter et al. [103] have demonstrated with *in vitro* studies using macrophages that exposure to carbon black nanoparticles lead to inflammasome activation assessed by the cleavage of caspase-1 to its active form and subsequent IL-1β release. Lunov et al. [104] have shown *in vitro* that amino-functionalized polystyrene nanoparticles (PS-NH_2), but not carboxyl- (PS-COOH) or non-functionalized particles, trigger NLRP3 inflammasome assembly and downstream release of pro-inflammatory IL-1β by human macrophages. Gómes et al. [105] have investigated *in vitro* the activation of the NLRP3 inflammasome by silica nanoparticles (SiNPs) and reported that SiNPs lead to the production of pro-inflammatory cytokines with the participation of NLRP3 inflammasome components. Caicedo et al. [106] studied the role of shape and size of Cobalt-Chromium-Molybdenum (CoCrMo) alloy particles on human macrophage phagocytosis and inflammasome activation and found that larger and irregular particles induce higher macrophage IL-1β production due to inflammasome activation.

The NLRP3 inflammasome has been implicated in the biological response to wear debris resulting from joint replacements (Fig. 5). The normal usage of joint replacements inevitably results in the generation of wear debris and the biological response to these particles is complex and often drives the process towards periprosthetic tissue destruction and implant loosening. Wear debris act as danger signals in tissues around loose implants and are recognized as such or after phagocytosis by several PPRs. This will induce the activation of the NLRP3 inflammasome pathway leading to the activation of the proinflammatory cytokine precursors pro-IL-1β and pro-IL-18 by caspase-1, these proinflammatory mediators present in the joint fluid will lead to the recruitment, differentiation and maturation of osteoclasts precursors and thus, bone resorption will predominate over osteogenesis at the bone-implant interface eventually leading to the loosening of the implant [106–109]. Burton et al. [110] investigated both *in vitro* and *in vivo* the contribution of the NLRP3 inflammasome in *peri*-implant osteolysis using perturbations of caspase-1 and inflammasome components. They recognize the NLRP3 inflammasome as an important mediator of wear-induced osteolysis and as a potential beneficial target for the treatment of periprosthetic osteolysis.

Continued investigation into how biomaterials activate the inflammasome is therefore of great interest [111]. Biomaterial recognition by inflammasomes [100,101,112] comprises key pathways, that can be targeted to improve biomaterial-tissue integration and subsequent tissue repair [102].

3.4. The inflammasome as a bridge between inflammation and regeneration

The immune system is of primary importance in orchestrating a correct repair process [33,34], and since inflammasomes are involved in the innate immune response, it is expected that they have a key role in tissue repair/regeneration. The activation of the inflammasome and thus of caspase-1 has surprising consequences: it not only induces the inflammatory response through the activation and secretion of proinflammatory cytokines, but it also has an important role in the regulation of the extracellular levels of specific proteins, such as basic fibroblast growth factor (FGF-2), that are clearly involved in the processes of tissue repair and cytoprotection [113].

There are already some evidences described in the literature on the role of inflammasomes in tissue repair/regeneration. Recent studies using a murine skin wound repair model have interestingly establish a clear bridge between inflammation and tissue repair through the NLRP3 pathway. Weinheimer-Haus et al. [114] used a murine wound repair model in mice deficient in NLRP-3 and caspase-1 and observed that these animals exhibited a reduced inflammatory response at day 5 following wounding with reduced levels of the pro-inflammatory cytokines IL-1β and TNF-α together with reduced neutrophil and macrophage accumulation when compared to wild-type (WT) animals. It was also observed in the Knockout (KO) mice a delay in wound healing when compared with WT mice. To assess whether loss of IL-1β in wounds of NLRP-3 KO mice was responsible for the defects observed in wound healing the authors performed a rescue experiment in NLRP-3 KO mice treating the wounds with recombinant IL-1β and concluded that treatment IL-1β exhibited a trend of accelerated re-epithelialization. Taken together, these findings indicate that the NLRP3 inflammasome contributes to the early inflammatory phase following skin wounding and is important for efficient healing. Ito et al. [115] used WT and NALP3-KO and ASC-KO mice, and the overall conclusion of the study was that wound repair in mice was significantly impaired in NALP3 and ASC-KO mice when compared to the WT. The authors concluded that the genetic deficiency of NALP3 decreased the expression of pro-inflammatory cytokines together with a reduced inflammatory response at the skin wound site, resulting in impairment of wound repair, being similar results obtained using an inhibitor of NALP3. In addition, this study revealed that topical treatment with adenosine triphosphate (ATP), which is a ligand of NALP3, up-regulated the expression of pro-inflammatory cytokines at the wound site and accelerated wound healing in the WT mice. The authors demonstrated that the NALP3 pathway activation is involved in wound repair via upregulation of the inflammatory response, and the topical use of ATP promoted skin wound closure through the upregulation of the inflammatory response in the early wound-healing stage.

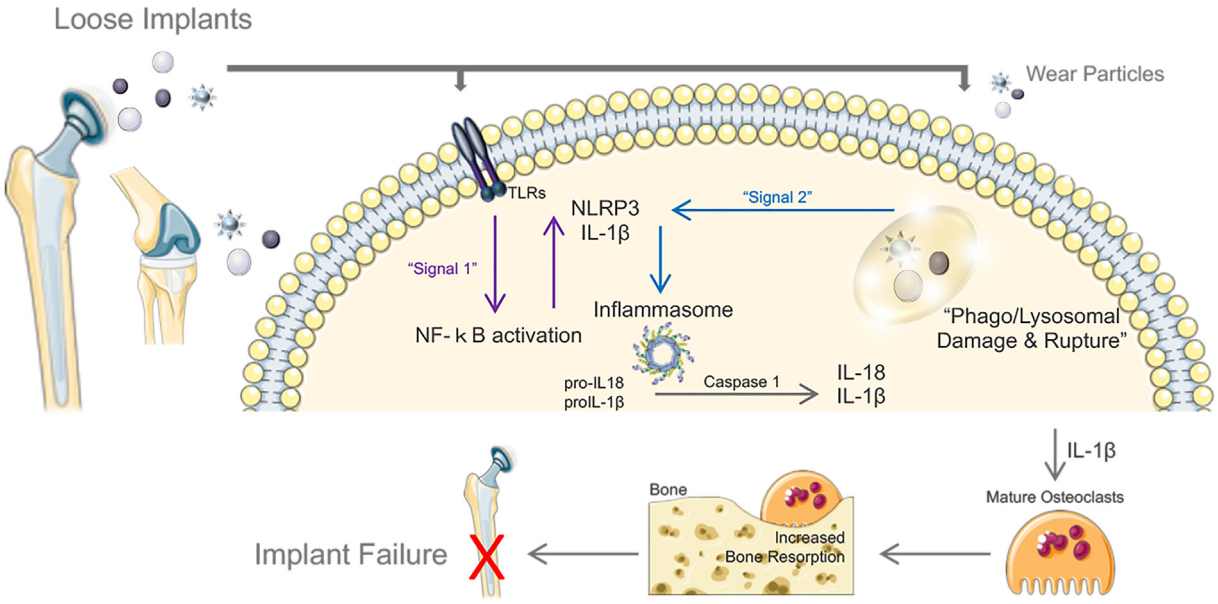

Fig. 5. Wear particles released from loose implants lead to inflammasome activation. Wear particles are recognized as such or after phagocytosis (lysosomal rupture), by PRRs including TLRs and NLRs leading to the assembly of NLRP3 inflammasome. Once assembled the NLRP3 inflammasome cleaves pro-IL-1β into the active IL-1β. Secreted IL-1β can promote the maturation of osteoclasts into bone-resorbing cells increasing bone resorption and consequently impairing implant function.

A very interesting study of liver regeneration using NLRP3-KO mice revealed that deficiency of NLRP3 signalling impairs liver regeneration. The activation of inflammasomes in the liver was induced after 70% partial hepatectomy. The liver-to-body weight ratio was significantly decreased in NALP3-KO mice when compared to WT mice after partial hepatectomy, and the expression of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) was decreased in the remnant liver of NALP3-KO mice compared to WT mice. In addition, treatment with ATP increased the liver-to-body weight ratio in WT mice. These results indicate that NALP3 signalling is required for the induction of an inflammatory response and the improvement of liver regeneration after partial hepatectomy [116].

Taken together, these results directly link inflammation to protective and regenerative processes being the inflammasome now considered as an attractive target to control tissue regeneration [117]. Thus, the understanding of the signalling that is elicited by inflammasome can be employed to improve healing [7].

There is extensive interest in the discovery of effective approaches that selectively inhibit the NLRP3 inflammasome pathway because this inflammasome is involved in a wide range of important processes from inflammation to tissue repair [118-122]. Therefore, modulation of NLRP3 activity is an important target to develop effective strategies for biomaterial integration which represents a rather important challenge in the biomedical research and clinical medicine [123,124].

4. Concluding remarks and future perspectives

Recently, research effort is being placed in the development of state-of-the-art tissue engineering procedures and biomedical implants directed to the improvement or even restoration of the function of diseased tissues or organs. However, the adverse immune reactions to biomaterials that often interfere with healing are one of the main challenges to clinical success. The outcome of tissue engineering therapies and medical implants can be significantly ameliorated through biomaterial-based immunomodulation strategies [51,125].

The engineering of biomaterials that not only fulfil all the needed requirements of the past but that can also modulate the immune system, both innate and adaptive responses, is now a major goal of several studies. The use of biomaterials that stimulate the establishment of a pro-regenerative microenvironment at the implantation site is clearly an emerging field of research. In this context, biomaterials are considered as key modulators of the immune response and thus can have important effects in tissue regeneration and repair. It is our view that immunomodulatory biomaterials can have a profound impact on patient care if success in modulating wound healing and tissue regeneration is achieved [126].

Discoveries emerging from investigating inflammasome biology promise insights into key pathways regulating immunity, inflammation and homeostasis. Therefore, successful modulation of the inflammasome activity may become a milestone in bioengineering. Given the evidence that NLRP3 inflammasome is involved in a series of processes from inflammation to tissue repair, there is extensive interest in the discovery of effective approaches that selectively inhibit the NLRP3 inflammasome pathway [84,127].

There is still poor information on the role of the inflammasome in the biological response to large scale biomaterials because up to now studies regarding inflammasome activation were mostly performed using nano- or micro-particles. Clearly, a good number of tissue engineering approaches involve the implantation of macroscopic scaffolds or devices, thus further research into how these materials activate the inflammasome is of great interest.

Additional studies in this area will be a significant step for developing effective and novel strategies in regenerative medicine. The utmost advanced solutions will rise from a close collaboration between scientist of different areas of research as tissue engineering, regenerative medicine, materials science and immunology. The regenerative immunology is an emerging and rather promising field of research.

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