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Review article

Immune response differences in degradable and non-degradable alloy implants

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A B S T R A C T

Alloy based implants have made a great impact in the clinic and in preclinical research. Immune responses are one of the major causes of failure of these implants in the clinic. Although the immune responses toward non-degradable alloy implants are well documented, there is a poor understanding of the immune responses against degradable alloy implants. Recently, there have been several reports suggesting that degradable implants may develop substantial immune responses. This phenomenon needs to be further studied in detail to make the case for the degradable implants to be utilized in clinics. Herein, we review these new recent reports suggesting the role of innate and potentially adaptive immune cells in inducing immune responses against degradable implants. First, we discussed immune responses to allergen components of non-degradable implants to give a better overview on differences in the immune response between non-degradable and degradable implants. Furthermore, we also provide potential areas of research that can be undertaken that may shed light on the local and global immune responses that are generated in response to degradable implants.

1. Introduction

Non-degradable alloys have been vastly utilized in clinics and have led to numerous advances in both bone and arterial areas. These implants are intended to completely replace the injured tissue with artificial devices [1]. Surgeries like tooth implants, total hip and knee replacement, and spinal fixation devices have helped millions of people worldwide (Fig. 1) [2]. Common clinical alloy implants are Titanium, Stainless steel, and Cobalt-chromium alloys. These implants have shown excellent efficiency; however, their permanent features often render a need for a second surgical intervention [3]. Also, traditional non-degradable materials do not engage in the regeneration of diseased tissue [1]. In order to limit the need for a second surgery and also enable host tissue replacement, scientists have been developing biodegradable metallic alloys. Some of the degradable implants proposed to the market include Mg-based, Fe-based, and Zn-based alloys [4–7]; these elements are naturally present in the human body and hence can safely degrade. Biodegradable alloys are prepared to disintegrate in the human body after serving their intended purpose, causing no harm to the host [8].

1.1. Main features of degradable alloys and examples of their clinical applications

Several studies have researched the biocompatibility, degradability and mechanical properties of degradable metal implants [9–11]. Although the biodegradability characteristics of these alloys allow them to be ideal for temporary medical implant applications, the corrosion rate and corrosion byproducts of degradable metals may not be compatible. For example, Mg has a high corrosion rate and generates hydrogen gases during degradation, restricting its usage. On the contrary, the corrosion rate of Fe is relatively low, which negatively prolongs the host's exposure to the metal [12]. In addition, degradable metal implants exhibit low mechanical strengths. These obstacles of low mechanical strength and the unsuitable corrosion rate can be potentially resolved by generating appropriate alloys [13,14]. Some of the most common biodegradable alloys that have been generated include ZX50 (MgZn–5Ca-0.25) [15], WZ21 (Mg–2Y–1Zn-0.25Ca-0.15Mn) [15], AZ31 (Mg–3Al–1Zn) [16] and JDBM (Mg-2.1Nd-0.2Zn-0.5Zr) [17]. These implants and their immunological interaction are further discussed in section 3.

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Notably, there are a few degradable implants that have been approved for clinical use. For example, MAGNEZIX CS [18] bioabsorbable compression screw composed of >90% magnesium (MgYREZr) has been approved by the FDA as a breakthrough device. This Mg-based alloy has shown similar results to a standard titanium screw in a chevron osteotomy in terms of patient motion. Additionally, there was no significant elevation in body magnesium levels, no sign of bone erosion and avascular necrosis. Radiographs showed improvements in the hallus valgus angle, the intermetatarsal angle, and the distal metatarsal articular angular in both groups; the healing rate was determined to be 100%. Although the degradation of Mg alloys produces hydrogen gas and could possibly create gas cavities, none of the patients ended up developing palpable gas cavities. This study suggested that the clinical outcomes for both degradable and standard titanium screws were acceptable. Additionally, these in vivo results indicated that the magnesium alloys could have osteoconductive qualities that could help expedite bone healing [18]. Another clinically approved Mg alloy implant is made of Mg–5Ca–1Zn. This implant is named K-MET screw and was designed by U&I corporation for use in South Korea. This product has been tested in clinical studies for hand and wrist fractures and is expected to be fully degraded and replaced by newly formed bone within a year post-implantation. Histological staining confirmed the formation of a calcified matrix and new bone at the implant interface 8 weeks after the operation. Also, normal healing rate, full range of motion, and normal grip power were preserved in all patients [19]. Since degradable alloys continue to be studied for medical applications, it is necessary to investigate whether they can regulate the immune and inflammatory responses or improve implant-host interaction [20]. A discussion of the immune reaction of these biodegradable implants is discussed further in section 3.

1.2. Metal hypersensitivity and immune rejection

One of the main obstacles that has limited the use of metal implants is metal hypersensitivity and metal ion toxicity [21], which is well studied in non-degradable metal implants and needs to be studied further in degradable metal implants. Metal hypersensitivity is an adverse side-effect of metal implants leading to implant failure or loosening [22,23]. Implant debris is the corrosion and the wear products of non-degradable implants and specifically accumulates in neighboring soft tissues, lymph nodes, liver and spleen [23]. These degradation products engage with the body in various forms such as metallic particles or ions, colloidal organometallics, and metal oxides or salts [24] and thus interfere with the body's normal mechanism. Importantly, the implant debris serves as the primary immune trigger [25,26], and an excessive amount of metal particles can cause cell necrosis and lymphocyte reaction [27]. The immune reaction to metal implants engages both the innate and adaptive immune systems [28,29]. Implants are able to activate acute inflammatory responses mainly through phagocyte activation, chemotaxis and protein adhesion to the implant surface [30].

Phagocytes play a crucial role in innate immunity through inhibition of pathogen (non-self) attack by ingesting the invading substances [15,31]. These cells immediately recognize the biomaterial particles as non-self-material and interact with metal alloys [32]. On the other hand, the adaptive immune system reaction to metal implant fragments occurs within weeks and leads to delayed-type hypersensitivity (DTH). DTH is often followed by implant loosening and warrants interventions for long-term implant usage [25,33,34]. In this review, we first discussed the impact of each immune cell type and molecular mechanism associated with implant loosening. In section 3 we compare differences between non-degradable and degradable implants where we cover the impact of implant composition. Notably, the influence of alloying elements and implant composition on the immune cells' interaction with degradable metal implants. Other important factors that influence implant interaction with the body, like implant width, geometry and the gender of the patients are not covered in this review, and the reader is encouraged to read articles referenced here [22,35,36].

2. Immune interaction and gene profile in peri-implant tissues

2.1. The underlying mechanism associated with metal hypersensitivity

Following implantation, the body starts to react with the biomaterial and a cascade of events follow. These events include wound injury, blood-implant interaction, provisional matrix formation, acute inflammation, chronic inflammation, formation of granule tissue, foreign body reaction, and fibrosis [37]. The blood-biomaterial interaction starts when proteins get adsorbed onto the implant's surface, leading to extracellular matrix formation, anda blood clot at the implant site [37]. The adsorbed proteins facilitate the recruitment of leukocytes from blood circulation, followed by acute inflammation [20]. Notably, adsorption of plasma proteins covers the implant surface with a layer of proteins like, fibrinogen, vitronectin, fibronectin and members of complement system proteins and the innate immune response against the biomaterial is initiated. The protein layer binds to the integrin receptor present on innate cells such as neutrophils and macrophages. Also, danger-associated molecular patterns (DAMPs) that are attached to implant surface are able to interact with pattern recognition receptors on macrophages and dendritic cells (DCs) [38].

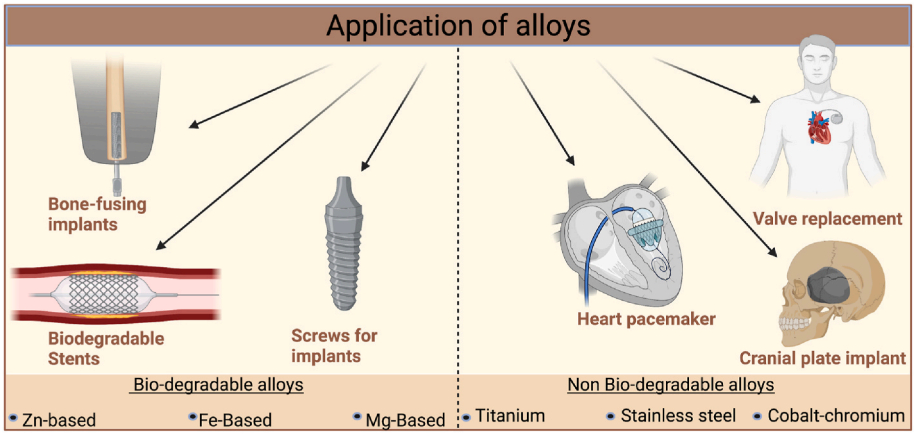

Fig. 1. Non-degradable alloys have made a great impact in clinic and improved patient's lives. Non-biodegradable alloys have been extensively used in clinic for applications such as knee replacement, stents, hip-implants, dental implants, heart pacemakers, cranial plate implants and valve replacement therapies over the years. Degradable Mg, Zn and Fe based implants can also be utilized in some of these applications.

This inflammatory cascade is started from vascularized connective tissue, which are made of endothelial cells (ECs). ECs have a high potential in the regulation of immune and local inflammation around the implant through expression of cell adhesion molecules (CAM). Pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) activate CAM expression. These pro-inflammatory cytokines are secreted from the recruited immune cells. Moreover, it is suggested that increased accumulation of metal debris can directly activate the expression of CAM by ECs. Vascular adhesion molecule 1 (VCAM-1) is an immunoglobulin receptor that increases the affinity between ECs and integrin's on the leukocytes surface, which also accelerates monocytes trans-endothelial migration [20]. Following immune cell recruitment, if any wear debris particles are generated from biomaterials, those are then phagocytosed by macrophages. The act of phagocytosis then activates a cascade of pro-inflammatory mediators such as IL-1β, tumor necrosis factor-alpha (TNF)-α, IL-6, and IL-8. These cytokines are well-known for osteoclast induction which then lead to osteolysis or bone resorption [25,39].

Soon after the inflammatory cascade is initiated, there is an increase in anti-inflammatory mediators such as IL-10 and chemokines (C-X-C motif) ligand 2 (CXCL2). This negative-feedback loop of anti-inflammatory response is to prevent from excessive inflammation and to prevent tissue damage. Notably as the immune response resolves, release of hepatocyte growth factor (HGF) and osteoclast-specific protein vitronectin (VTN) is increased, whereas the expression of chemokine (C-X-C motif) ligand 5 (CXCL5) transcript level is gradually decreased over time. This chemokine is particularly responsible for neutrophil recruitment during acute inflammatory responses and plays a key role in early-stage inflammations and wound repair [40]. Noticeably, mononuclear phagocytic cells can generate reactive oxygen species (ROS), which in turn lead to higher inflammatory responses. Also, NDPH oxidase (NOX) can be activated by neutrophils during the phagocytosis process and lead to generation of ROS [41,42]. ROS can also be physically generated through exogenous events such as pathogen and chemical exposure, which might be associated with the metal implants [42]. Exclusive to the cytotoxic role of ROS, they also regulate cell signaling and suppress inflammasome activity and cytokine expression, which can also lead to inflammation [43].

As it is discussed above, during the implantation process, immune cells are invariably recruited to the site of implants and interact with the implant to mount a response. Occasionally, these responses lead to the destruction of surrounding bone, due to metal hypersensitivity. Metal hypersensitivity promotes bone osteolysis by a complex series of biological events by macrophages, osteoclasts, and osteoblasts [35]. Metal-host reactions vary based on individual body chemistry and biomaterial composition or geometry [22]. The exact mechanism of metal hypersensitivity is unknown; however, recent studies have strived to investigate the inflammatory responses and recruited immune cells. For example, it is well documented that patients with aseptic implant lessening experienced high levels of oxidative stress in peri-implant tissues [35]. Also, it is well documented that patients experiencing aseptic loosening secrete higher levels of pro-inflammatory cytokines and chemokines as compared with successfully implanted patients [44]. Gene expression in peri-implant tissues has been demonstrates an excessive expression of inflammatory mediators, including interleukin 6 (IL6) and interleukin 1-β (IL1-β), and its signal transducer IL6ST [40]. Particularly, the secretion of L-1β plays an important role in implant rejection since it can lead to matrix metalloproteinase expression and intensify osteoclast differentiation and bone resorption [25]. IL-1β secretion is reliant on the danger signals activation through the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. NLRP3 inflammasome can be triggered by both endogenous damages, including mitochondrial and lysosomal destruction, ROS and ionic flux, as well as exogenous danger signals such as implant debris [25,45]. The release of danger cytokines such as IL-1β mediates the expression of cytokines such as IFNγ and IL-17 by $CD4^+$ T helper (Th) cells which in turn leads to delayed-type hypersensitivity (DTH) [44].

IL-6 is released by monocytes and macrophages in the early stages when the body encounters a pathogens. Furthermore, antigen-presenting cells (APCs) like DCs and B cells can produce IL-6 as well [46]. IL-6 induces the secretion of chemokines from smooth-muscle cells and accelerates the recruitment of immune cells [47]. For instance, IL-6 also skews T cells toward T helper type 2 (Th2) through activation of transcription factors that induce Th2 cytokines and also decrease Th1 activation via inhibition of INF-γ [47]. Specifically, APC-derived IL-6 can facilitate naïve $CD4^+$ T cells toward Th2 via upregulation of nuclear factor of activated T cells (NFAT), leading to IL-2 secretion and Th2 production [46]. Furthermore, the contribution of IL-6 in the presence of TGF-β leads to Th17 differentiation [47]. A clinical study on 78 patients with total hip or knee replacement showed that both TNF-α and IL-6 tend to be higher in patients with implant failure [48]. Also, in another study, patients who have received left ventricular assist device (LVAD) have shown elevated levels of IL-6 in implant neighboring tissues. This higher IL-6 led to increased secretion of monocyte-related markers and, finally higher susceptibility to multi-organ failure [49].

Another important factor that plays a role in metal-immune system interaction is Toll-like receptor 4 (TLR4) which can induce the release of inflammatory cytokines, chemokines and type I interferon (INF). Further, these proteins encourage the activation of neutrophils, macrophages and DCs [47]. It has also been shown that innate immunity plays an essential role in metal allergy and also TLR or IL-1 signals that are related to innate immunity play a bigger role in metal allergy compared with TNF signals [50]. Moreover, it is important to study the behavior of non-immune peri-implant cells, like fibroblasts, since they also have a significant impact on the induction of allergic inflammation. For example, dermal fibroblasts are provoked by TNFα and IL-1β and are able to induce the production of matrix metalloproteinase-9 and facilitate DC migration. Also, activated dermal fibroblasts generate prostaglandin E2, facilitating DCs to produce Th-17 related cytokine IL-23 [51]. Overall, it has been reported that aseptic loosening is associated with a noticeable increase in the expression of IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, granulocyte macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) [52,53]. In this review the interaction of different immune cells with metal implants is discussed in the following paragraphs.

2.2. Immune cells involved in response to biomaterial implants

Particulate corrosion product accumulation promotes inflammatory cells, chiefly macrophages and multinucleated giant cells, toward the implant site [35]. Immune cells pass through the extracellular matrix, eliminate debris, and secrete a cascade of cytokines affecting implant performance [54]. Neutrophils are the first responders to implant lesions, whereas macrophages are the most heavily studied phagocytes that respond to implant debris. Neutrophils amount rarely increase in implant adjacent tissues and they are mainly present in patients experiencing infection at the implant site [35], implant loosening [55], or in the early inflammation stages [38]. In the peri-implantitis condition, an excessive number of macrophages and T cells are responsible for the inflammatory response (Fig. 2) [55]. It has been hypothesized that delayed-type hypersensitivity (DTH) mainly resulted from T helper type 1 reactions and interferon-gamma (IFN-γ) secretion [25,26]. Helper T cells are activated when an antigen is presented on class II major histocompatibility complex (MHC) by antigen-presenting cells (APCs). Dendritic cells, an important APC, are also engaged in metal hypersensitivity. Both APCs and T helpers can secrete various cytokines and recruit macrophages, neutrophils, monocytes, and other immune cells. Activated macrophages can promote the activation of more T helper cells, and again with the release of inflammatory cytokines, more macrophages are recalled. Finally, the cycle of cytokine secretion and immune cell recruitment leads to excessive tissue damage [24]. Moreover, the released ions from the implants can form complexes with

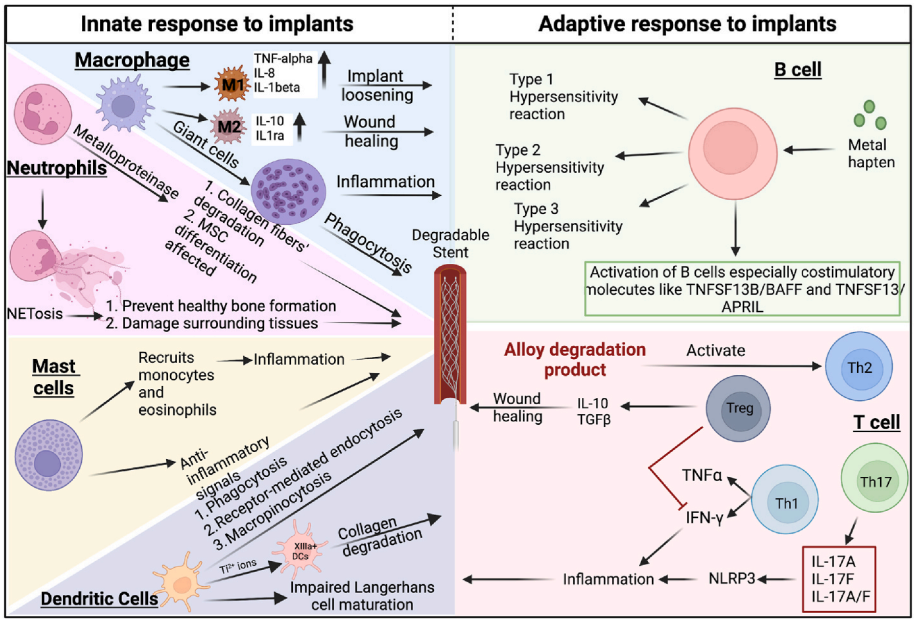

Fig. 2. Implants induce both innate and adaptive immune responses. Innate response - Implant debris can give rise 'danger signal' induced innate immune responses in the form of macrophage, neutrophil, mast cell and dendritic cell activation. This can then lead to failure of these implants but can also be utilized to modulate the innate immune responses. **Adaptive response –** Implants by releasing different ions, and through wound healing processes, can modulate B cell and T cell responses.

native proteins, and these metal-protein complexes activate the immune responses [24]. Metal ions may also act as haptens, bind to self-proteins, mainly serum albumin, and promote conformational changes (Fig. 2) [56]. Thus, hypersensitivity is a complex phenomenon involving various immune cells. Therefore, in this part of the article, the innate and adaptive immune system reaction to metal debris is discussed.

2.2.1. *Innate immune cells' interaction with metal alloys*

The innate immune system provides a non-specific inflammatory responses to implants and facilitates the adaptive immune system to specifically react with biomaterial. Some of the important cells of the immune system are: neutrophils, eosinophils and basophils, mononuclear phagocyte cells including: monocytes, macrophages and dendritic cells, and lymphocytes including: natural killer cells, gamma-delta T cells and innate lymphoid cells [37]. In the following section the cells that are involved in metal-immune reactions are discussed.

2.2.2. *Macrophages and foreign body giant cells*

Macrophages are one of the most important phagocytes reaching the lesion site within 48–96 h. Once in the lesion site, macrophages recruit other immune cells by releasing a variety of cytokines. Therefore, it is of great importance to unravel the macrophages' mechanism of action on implants. Macrophages are typically activated by pathogen- or damaged-associated molecular patterns and play an essential role in the induction of inflammation, which directly affects implant performance and tissue repair [57]. For example, Heise et al., demonstrated that macrophages can attach the oxide layers of stainless steel and Ti-based implants and disrupt the oxide layer. This disruption increases the corrosion rate, followed by metal ion accumulation in the surrounding tissues and immune reactivity [58]. Macrophages range in their function depending on the proteins they express and exist on a spectrum of pro-to anti-inflammatory functions [59]. For example, M1-like cells have a pro-inflammatory phenotype and secretes cytokines like Tumor Necrosis Factor alpha (TNF-α), IL-8, IL-10 and IL-1β and chemokines like monocyte chemotactic protein1 (MCP1) or chemokine (C–C motif) ligand 2 (CCL2) [25,39,60–62]. These cytokines and chemokines are well-known for osteoclast induction followed by osteolysis, and subsequently, implant loosening [25,39]. Moreover, there is a correlation between the high number of peri-implant M1-like proinflammatory macrophages and implant loosening [63], which is possibly a result of phagocytosis of the wear debris particles and activation of a cascade of pro-inflammatory mediators [57].

On the other hand, M2-like sub-phenotypes are responsible for triggering tissue repair and are considered as an alternatively activated cell type, which secretes cytokines like IL-10 and IL1ra and chemokines like osteopontin (OPN). Although the entire ranges of different types of macrophages are necessary for healing resolution [57], M2-like macrophages are anti-inflammatory and facilitate wound healing, while M1-like macrophages accelerate osteolysis and implant loosening [63,64]. For example, numerous amounts of $CD68^{+}$ macrophages (chiefly expressed by M1-like macrophages) are present at the implant site in patients with aseptic loosening. These macrophages are fundamental units in the foreign body reaction, massively infiltrating the inflammation area and recruiting other lymphocytes [65].

One of the important pathways that macrophages utilize is NADPH oxidase (NOX). NOX is a transmembrane enzyme [66] and is the most powerful endogenous source of ROS production [67]. Among different isoforms of NOX, NOX1 and NOX2 play an important role in macrophage differentiation to M2-like phenotype. Infact inhibition of NOX 1 and NOX2 has been shown to significantly decrease ROS formation in macrophages, and impair monocyte ability to differentiate to M2-type macrophage, which then results in dysfunction of wound healing process [68]. Importantly, ROS can positively contribute to osteoclast differentiation and maturation, which is essential for bone remodeling. Also, osteoclasts generate a dramatic amount of ROS through NADPH oxidase activity so that this ROS can degrade bone extracellular matrix in the presence of matrix metalloproteinases (MMPs) [42,69]. Contrarily, a study demonstrated that the poor osteointegration at the bone-implant site of diabetic patients is due to significant expression of NOX and ROS production. The NOX and NOX-induced ROS overexpression impaired angiogenesis and in turn, decreased the number of osteoprogenitors, resulting in poor bone formation at implant site. This study suggested a new area which can be explored further for better implant integration in diabetic patients with hyperglycemia via NOX inhibition strategies [70]. Hence, NOX is a critical factor in macrophage differentiation and need to be studied further in patients receiving implant alloys, especially degradable alloys.

At the implant site, two kinds of multinucleated giant cells are generally found, bone-resorbing osteoclasts and foreign body giant cells (FBGCs) [71]. Macrophages fuse together to develop into bigger cells called foreign body giant cells (FBGCs), large multinucleated cells involved in biomaterial phagocytosis. FBGCs can phagocytose big

particles and they are also responsible for inducing chronic inflammation [57]. Moreover, while FBGCs can secrete anti-inflammatory cytokines such as IL-10 and IL-1ra, the pro-oxidant environment (ROS and degradative enzymes) of implant moiety diminishes the effect of immunosuppressive cytokines [72]. If FBGCs are not able to phagocytose the biomaterial, they remain at the biomaterial surface and form an actin-rich (podosomal) structure on the implant surface. Upon macrophages' fusion to FBGCs, the phagocytic ability of the macrophages diminishes and simultaneously the degradative capacity increases, this process is called frustrated phagocytosis. Then, FBGCs strive to resorb the non-phagocytosable implant by releasing protons, enzymes and ROS, which may lead to resorption of part of the implant. In case of degradable biomaterials, after complete resorption, the associated inflammation will be resolved since it is expected that there will be no foreign body biomaterial remaining [72].

2.2.3. Dendritic cells and langerhans cells

DCs serve as the bridge between innate and adaptive immunity and are responsible for facilitating a diverse range of functions [73–76, 76–79]. DCs are classified as either myeloid (mDCs) or plasmacytoid (pDCs) [80]. DCs patrol the peripheral tissues for possible foreign materials. They are considered the most efficient APCs, with the ability to trigger both pro-inflammatory and anti-inflammatory adaptive immunity. Immature DCs located at the lesion site can entrap potential hazards by three available mechanisms: phagocytosis, receptor-mediated endocytosis, and macropinocytosis. Following antigen recognition, DCs secrete chemokines and migrate to the lymphoid organs, where the naive T cells reside. Naive T cells react to the antigens presented on the DC's surface, mainly through immature $CD83^+$ DCs leading to the development of mature T cells [81–83].

The role of DCs in T cell responses is well understood in the context of pathogens; however, only a few studies have focused on the T cell responses after DCs and biomaterials interact. It has been shown that in damaged tissue, about 25% of the recruited monocytes differentiate into DCs, which confirms the importance of DCs in post-implant immune responses, irrespective of the implant type. Moreover, studies suggest that interstitial DCs and Langerhans precursors gradually infiltrate the peri-implant site peaking at day 10 post-implantation. These DCs express major histocompatibility complex (MHC), costimulatory molecules, and markers such as MHC II, CD11c, CD11b, and CD68 [84,85]. Studies also suggest that DCs are capable of downregulating pro-inflammatory responses in peri-implant sites and accelerating tissue resolution [80]. However, there are concerns about the impact of $XIIIa^+$ DCs on collagen degradation. Interstitial DCs (IDCs) are subsets of DCs which contribute to the pro-transglutaminase clotting enzyme factor XIIIa formation. It has been demonstrated that inflammatory responses at the site of titanium implants and the release of titanium ions recruit an excessive population of factor $XIIIa^+$ DCs, which further provoke collagen degradation [81].

Langerhans cells (LCs), a type of dendritic cell, are mainly resided in the skin epidermis [86,87]. They can preserve oral tissues from infection and also adjust the immunological performance of the mucosa [88]. Studies showed that although the LC precursors ($CD11c^+$ $MHCII^+$) are increased at the implant site, the overall number of LCs is dramatically diminished. This peri-implant decrease in LCs could be interpreted as the immune system dysregulation and impairment in the maturation of LCs, primarily LCs $CD1a^+$ [89].

2.2.4. Neutrophils, mast cells and natural killer T cells

Histological staining of the implant site has demonstrated that in patients suffering from peri-implantitis, there are tremendously higher numbers of polymorphonuclear cells, chiefly neutrophils, in the implant site as compared to the normal tissue [55]. Neutrophils are the first cells migrating into the lesion site. They belong to the polymorphonuclear lineage and originate from bone marrow stem cells. When tissue is damaged or during a pathogen attack, the release of histamine, cytokines, or bio-signals increases the blood vessels' permeability. Following that, neutrophils are triggered to migrate to the injury site from the circulating system [54]. The primary action of neutrophils is the formation of an acute inflammatory microenvironment via granulation, inflammatory chemokine or cytokine secretion, and foreign body or pathogen phagocytosis [90].

It has previously been shown that neutrophils are most active during the acute inflammation phase (2–3 days); however, it is shown that they also participate in tissue resolution [91] and they are present at the implant site for longer periods to contribute to tissue regeneration. Importantly, neutrophils facilitate implant corrosion through the secretion of oxidants (e.g. ROS) [90]. Metal particles activate the production of ROS, which can lead to the recruitment of more quantity of neutrophils. Then, neutrophils develop metalloproteinase, encouraging collagen fibers' degradation and adversely affecting mesenchymal stem cells (MSC) differentiation; thus, bone regeneration is impaired [55].

In addition, neutrophil-metal interaction is not limited to ROS production; neutrophils in contact with the implants trigger the release of a decondensed, web-like structure. This web-like structure is composed of DNA filaments coated with histones and granular enzymes such as myeloperoxidase (MPO) and neutrophil elastase (NE). The web-like scaffold is called neutrophil extracellular traps (NETs), and have recently been determined as stimulators of sterile inflammation with an ability to damage the surrounding tissues [92–94]. Although the connection between NETs formation and bone metabolism has not been fully understood yet, studies demonstrated that NETs interfere with healthy bone formation post-implantation, possibly promoting fibrotic tissue formation [93]. One of the fundamental elements of NETs is histone citrullination (detected by citrullinated histone H3 (citH3)), which is mediated by peptidyl arginine deiminase 4 (PAD4) enzyme. Histone citrullination is an essential posttranslational modification promoting chromatin decondensation in the process of NETs generation [93–95]. It has also been demonstrated that blocking the PAD4 considerably declines the NET structure formation [96]. Once the NET is formed, Deoxyribonuclease 1 (DNase 1) can continuously eliminate the NET scaffold, considered a cytotoxic factor for NETs enzymes and citrullinated histones. Conclusively, both DNase1 and PAD4 blockade exhibit a reducing effect on NET's side effects [93]. Overall, neutrophils via the release of NETs and ROS induce inflammatory responses at the implant site and can lead to inflammation-mediate implant rejection.

Mast cells (MCs) are granular immune cells from the myeloid lineage family, derived from bone marrow hematopoietic cells. They play a key role in anaphylactic and allergic disorders [97]. Mast cells chiefly reside in the connective tissues [98] and are involved in inflammation, tissue repair, and body defense [99]. Mast cells, just like macrophages, might have a binary effect at the implant site. While they can secrete divergent cytokines to recruit eosinophils and monocytes and thus boost inflammatory responses, they also are capable of producing anti-inflammatory cytokines to accelerate inflammation resolution [54]. Currently, there is paucity of evidence of the involvement of these cells in implant rejection, which warrants further investigation. The behavior of the most engaged innate immune cells on metal implants has been discussed so far. However, we need to emphasize that other innate immune cells may also play a role in metal-body reactions. For example, studies on the murine model of skin metal allergy showed that both metal-specific T cells and natural killer T cells are accumulated in the skin of allergic groups [100,101]. Moreover, natural killer cells have the potential to regulate allergies that are induced by haptens, even in T cell and B cell-deficient mice [102].

2.3. Adaptive immune cells' interaction with metal alloys (T cell and B cell)

It is well understood that adaptive immune system is involve in metal-body reactions and this engagement dominantly occur through T cells [103]. The adaptive interaction to metal corrosion products is

modulated by both $CD4^+$ T helper cells and $CD8^+$ cytotoxic T cells [62,104]. $CD4^+$ T cells play a key role in adaptive immune system regulation. The naïve $CD4^+$ T cells are multi-potential precursors capable of differentiating into various lineages of T helper cells such as T helper type1 (Th1), Th2, Th17, and regulatory T cells (Treg) [105,106]. Naive T cell differentiation and proliferation is reliant on the presence of cytokines. IL-12 and IFN-γ play a role in Th1 cell differentiation, and TGF-β, IL-6, or IL-21 particularly induce Th17 cells [107]. Two main subgroups of T helpers that have been shown to be important in metal-implant interaction are T helper type1 cells, secreting IFN-γ; and T helper 17 cells [107], secreting IL-17A, IL-17F, and IL-17A/F [26]. It is suggested that the presence of IL-17A increases the activity of the NLRP3 inflammasome; and also secretion of caspase-1 and IL-1β raise the release of IL-17 [108]. Inflammasomes are multiprotein complexes involved in signal transduction. NLRP3s are capable of inflammation induction and immune responses, followed by the release of cytokines and acceleration in peri-implantitis [103]. Blocking either the inflammasome/caspase-1 pathway or IL-17A expression diminishes the implant debris inflammatory responses [26]. Moreover, macrophages' reaction to metal debris mediated IL-1β production facilitates the proliferation and differentiation of the Th17 cells. It is also unclear how the metal-macrophage inflammasome pathway translates to T cell responses [26]. Similarly, the decrease in IFN-γ augmented the generation of mature IL-1β and IL-17 and boosted the T cell recall. With these data, we can hypothesize that there is a correlation between elevated IL-17 and downregulated IFN-γ, and aggressive T cell responses in the presence of the implants. Meanwhile, the absence of IFN-γ leads to the loss of control over IL-17 secretion, which further affects both innate and adaptive immune systems. Hence, despite the pro-inflammatory nature of IFN-γ, here it serves as a non-pro-inflammatory promoting or protective factor against metal-DTH [25,26].

Moreover, activated $CD4^+$ T cells can modulate macrophage polarization as well. Th1 secretes proinflammatory cytokines such as INF-γ and IL-2, which encourage M1 macrophages. Following M1-like phenotype induction, these cells secrete chemokine and cytokines like L-12, CXC-chemokine ligand 9 (CXCL9) and CXCL10; and consecutively, these molecules induce more Th1 differentiation and hence more proinflammatory reactions. On the other hand, Th2 cells produce anti-inflammatory cytokines such as IL-4 and IL-10 which facilitate macrophages toward M2-like phenotype. And again, M2-like phenotypic macrophages release chemokines like C-chemokine ligand 17 (CCL17), CCL18 and CCL24 to activate regulatory T cells. These, activated T regs can increase Th2 differentiation as well [38]. Thus, T cell-based adaptive immune responses play an important role in developing immune responses against metal-implants. For example, Reiner et al. studied the amount of peripheral blood lymphocytes in patients who have implanted small diameter total joint replacement. They hypothesized that an increase in the level of metal ions or adverse local tissue reactions might lead to changes in the number of blood circulating lymphocytes. This alteration in blood lymphocytes could be used as a diagnostic marker to monitor the implant implications before reaching chronic inflammation. A 15-year follow-up on patients with elevated blood metal ion (Cr and Cr more than 2 μg/L) showed a dramatic decrease in the amount of IFN-γ+ Th1 compared with control group (ceramic-on-polyethylene) and patients without adverse local tissue reactions. No differences in other lymphocyte subgroups were found between samples and also all the groups have shown no systemic adverse effects [104].

Although it had been hypothesized that T-cells, and not B cells are the main suspects for metal hypersensitivity, it was observed that the surface marker activation was unconditionally heterogeneous, indicating that both T cells and/or B-cells likely cause hypersensitivity. Notably, B cells activation without T-cell involvement shows the possible uninvestigated role of B-cells in metal allergy [24]. Conclusively, hypersensitivity is a complex phenomenon involving various immune cells. Moreover, studies are typically performed on rodents, and although mouse models of inflammation well-mimic the human immune system status, the lack of human models experiments may pose concerns [80]. Immune cell interaction with implants is thoroughly discussed elsewhere in Refs. [37,72]. For more details, please refer to those articles.

3. Immune response differences between degradable and non-degradable biomaterials and the importance of implant composition

As it has been discussed so far, implants, as a foreign material for the immune system, evoke inflammatory responses as soon as the material is implanted. In biostable alloys, this inflammation resolves quickly since the phagocyte system cannot digest the biomaterial and this finally leads to fibrous encapsulation. But the engagement of biodegradable materials with the body and specifically the immune system is quite different [109]. Hence, there is an urgent need to study immune system behavior and its interaction with degradable alloy implants. Here, in this review article, we discuss the possible interaction of immune cells with metallic alloys and cover the differences between non-degradable (Table 1) and degradable (Table 2) implants from the immune system perspective.

3.1. Immunological interaction of non-degradable alloy implants and their alloying elements (Ni, Co, Cr)

Among non-degradable metallic implants, there are several allergen-free implants that have been used, such as titanium alloys, stainless steel, and Cobalt–Chromium alloys. It is well documented that tantalum, titanium and vanadium ions rarely induce adverse immune responses [39,120]. Notably, Ti-based alloys (Ti–6Al–4V, Ti–Mo12–Zr6–Fe2, or TiNb13Zr13) rarely generate allergic responses, and the reported allergy cases are possibly due to byproduct contents such as nickel (Ni) [39]. These alloying elements and their reaction with immune cells have been further discussed in the following section (summarized in Table 1).

Nickel (Ni), cobalt (Co) and chromium (Cr) are three common alloying elements that have been used in most traditional non-degradable implants to increase the strength and durability in alloys. Although these three elements are main metals that are susceptible to allergy induction [121], alloying elements such as Mn and Mo (molybdenum) have also been used. Mn and Mo have been shown to increase TNFα secretion and CD86 expression in DCs. And these inflammatory responses are not limited to their particles, and their fully dissolved salt can also induce the secretion of inflammatory cytokines [112]. Among the alloying traces, Ni is considered one of the most allergen element in patients with dermatitis [47]. Both Ni ions and particles can induce inflammation and allergies. Ni ions and particles can pass through the cells via ion channels and phagocytosis pathways, producing inflammatory responses [47,50]. For example, it has been shown that Ni has the potential to induce proinflammatory cytokines and chemokines in human DCs [51]. Also, Ni^{2+} can attach to soluble proteins or surface proteins of APCs so that this Ni-protein system is recognized as antigen by APCs, resulting in T cell differentiation to Ni-specific INF-γ^+ $CD4^+$ and $CD8^+$ T cells [47,50]. Also, nickel has shown binding capabilities to migratory DCs in skin draining mandibular lymph nodes. Interestingly, Ni also binds to conventional DC type 2 (cDC2), and in turn, leads to the activation of T regulatory cells, an immunosuppressive type of T cell [56]. Notably, Ni^{2+} is a physiologically toxic element due to its ability to get oxidized to Ni^{3+} and generate ROS [113]. So, the release of Ni ions from alloy debris must be carefully controlled.

In a another recent study by Chen et al., the peripheral blood samples of implant failure patients were taken for T cell separation. T cell mechanism of Ni-mediated hypersensitivity was studied in patients who have previously shown allergic reactions to Ni-containing CoCrMo. The result confirmed that a conserved glutamic acid in TCR CDR3β sequence provides a potential Ni binding site [122]. Although previous studies discussed the significant role of T cells in Ni-induced inflammation, a surprising study by Sato et al. revealed that even nude mice (lacking

Table 1
Summary of immune cell interaction and inflammatory pathways in non-degradable alloy implants.

Implant Type	Inflammatory pathways and Immune Cell Engagement
Ti-based alloys	
Ti-based alloys (Ti6Al4V)	– Act through RANK/RANKL pathway and trigger the differentiation and activation of osteoclasts [110]. – Osteoclasts are generated from monocyte/macrophage lineage in the presence of RANKL [111].
Common Alloying Elements	
Mn and Mo (molybdenum)	– increase TNFα secretion and CD86 expression in DCs [112]
Ni	– pass through the cells via ion channels and phagocytosis pathways, and produce inflammatory responses [47,50]. – Ni^{2+} attach proteins of APCs and recognized as antigen by APCs, resulting in T cell differentiation to Ni-specific INF-γ^+ $CD4^+$ and $CD8^+$ T cells [47,50]. – Ni binds to conventional DC type 2 (cDC2), leading to the activation of T regulatory cells [56]. – oxidized to Ni^{3+} and generate ROS [113]. – toll-like receptor 4 (TLR4), macrophages and IL-1 play role in Ni allergy [50]. – IKK2/NF–B pathway play role in Ni allergy and inflammatory reactions [114]. – proangiogenic pathway which is mediated by HIF-1 play role in Ni allergy and induce proinflammatory genes, such as IL-6 [114]. – Ni increase the production of nitric oxide (NO) through HIF-2α-dependent pathways [51]. – Activate T regulatory cells [56]. – Engage with T cells, specifically T helper type1 [50]. – Lead to Ni-specific INF-γ^+ $CD4^+$ and $CD8^+$ T cells formation [47,50]. – Trigger proinflammatory cytokines and chemokines in human DCs [51], and bind with cDC2 [56].
Stainless steel	
SS316L rods	– Increase in expression of pro-inflammatory markers such as MD2, TLR-4, and MyD88 [115]. – Increase in level of NF-κB/p65 (RelA) and NF-κB1 (p50) [115]. – Decrease Treg level [115]. – higher level of inflammation compared to titanium alloy implant [115].
CoCr alloys	
CoCr alloy	– osteolysis in CoCr particles is a direct action of inflammatory cytokines [35]. – blood examinations revealed IgE-specific reactions to CoCr samples and the possible role of humoral immunity [35] – Co and Cr bind to proteins and increase the corrosion rate of implants leading to debris induced inflammation [116]. – IFN-γ was inhibited by the cobalt-chromium group [117]. – inflammatory responses in nonimmune cells, like mouse dermal fibroblasts through NO production and iNOS expression [51]. – Co divalent cation produce ROS and decrease the cellular metabolism [118]. – Co ions caused mitochondrial dysfunction and decreased level of oxidative phosphorylation in macrophages leading to inflammatory reactions [119]. – trigger T helper type 2 reactivity [26]. Th2 recognizes Co as a foreign invader and promote the clonal expansion of T cells that can react to Co through antigens presenting cells or hapten [35]. – Co can enter the cellular cytoplasm and lead to oxidation and nitration of different cytosolic proteins, which in turn results in the activation of NADPH oxidase which is one of the main sources of superoxide production in human macrophages [118]. – In vitro CoCr particles reduced proliferation of T and B cells [117]. – low contribution of macrophages, and high engagement of B cells, T cells and plasma cells in peri-prosthetic tissues [35]. – Lead to T helper type 2 reactivity [26]

Table 2
Summary of inflammatory responses and immune cell interaction in biodegradable metallic alloys.

Implant Type	Inflammatory responses and Immune cell engagement
Mg-based alloys	
Mg	– Mg produce hydrogen gas (H_2). H_2 down-regulate the expression of pro-inflammatory cytokines and chemokines such as IL-6, IL-1β, IL-10, IL-12, CCL2, TNF-α, TNF-γ, CAM-1, HMGB-1, PGE2, and nuclear factor-κB (NF-κB) [126]. – magnesium ions can efficiently decrease ROS [17] due to the antioxidant features of the degraded particles [127,128]. – Mg ions down regulate the TLR-4/MYD88 signaling pathway [17]. – Mg is a natural calcium (Ca) antagonist, blocks an excessive activation of N-methyl-D-aspartate (NMDA) receptor and reduces the intracellular concentration of the Ca [129]. This low intracellular Ca halts the activation of phagocytic cells and cytokine production which reduces the inflammation [130]. – down-regulate the production of M1-like and up-regulate M2-like macrophage-related cytokines, and as a result, rapid inflammation resolution and tissue repair can occur [57,131,132].
Examples of Mg Alloys interaction	
RS66 alloy (Mg-6.0Zn-1.0Y-0.6Ce-0.6Zr)	– No acute inflammation [133]. – Neutrophils and macrophages were present at implant site. While the foreign body reaction and the number of neutrophils and macrophages were not elevated [133].
magnesium- particulate debris	– In an in vitro study, release of proinflammatory cytokine TNFα remained unchanged [134]. – Mg particles show no adverse effect on macrophage function in vitro [134].
ZX50 (Mg–5Zn-0.25Ca) and AZ91D (Mg–9Al–1Zn)	– no sterile inflammation [15]. – neutrophils and T lymphocytes in AZ91D alloy was similar to the autologous implants [15]. – magnesium implants have a positive effect on innate immune responses [15].
Common Alloying elements	
Yttrium	– Yttrium element can negatively influence the cellular phagocytosis ability and increase the expression of inflammatory factors [15].
Gd and Ag	– Increase the population of M1-like phenotype; while simultaneously increase M2-like cytokines [57]
Zn-based alloys	
Zn-based alloys	– zinc (Zn) has a positive impact on innate and adaptive immune modulation [135]. – zinc reduce inflammatory responses through ENA-78 and F4/80 which suppress the foreign body reaction [136]. – zinc down-regulate the NF-κB activation, decreasing the production of inflammatory cytokines [30,137]. – High concentration of zinc can lead to changes in metal divalent ion-dependent intracellular signaling pathways, promote oxidative stress and finally lead to cell apoptosis or necrosis of the adjacent tissues [138].
Examples of Zn alloys interaction	
Pure Zn	– no sign of inflammatory reactions [30].
Zn–Li	– Zn–Li leads to moderate inflammation with a non-obstructive neointima, possibly due to various intermetallic chemical species like $LiZn_4$ [139].
Zn–Mg	– Zn–Mg increase the local acute inflammatory profiles in tissues due to the higher rate of degradation and generation of toxic Mg_2Zn_{11} intermetallic by products compared to the pure Zn implant [140,141].
Zn–Al	– Al change the corrosion profile [142]. – Al increased the activity of macrophages [142].

(*continued on next page*)

Table 2 (*continued*)

Implant Type	Inflammatory responses and Immune cell engagement
	– Zn–Al mainly lead to neutrophil and eosinophil infiltration [143].
Zn–Fe	– Higher corrosion rate [144]. – Monocyte/macrophage aggregation [144].
ternary and quinary alloys	better modulate inflammatory reactions relative to pure Zn where tissue healing is concerned [109].
Fe-based alloys	
Fe-based alloys	– Fe can generate hydroxyl radicals (HO) during the corrosion process, specifically when it is in direct contact with the aortic tissue as coronary stents [145]. – Iron clearance take place in lymphatic circulation [146] where adaptive immune cells reside. – Giant cells are the most dominant cells that contributed to the Fe implant inflammatory responses and the highest inflammation was reported in Cr-coated Fe implants [147]. – Most inflammatory infiltrates consisted of lymphocytes, plasma cells, macrophages and occasional multinucleated giant cells [148].
Fe–Ag	– Excessive inflammatory response associated with corrosion and reduced pH at the implant site [8]. – Significant number of macrophages and lymphocytes in the pocket wall [8].
Nitrated-Fe	– Higher number of macrophages and plasma cells compared with Co–Cr alloy [163].

mature T cells) have shown Ni allergy. Hence, Sato et al. suggested that although Th1 cells are important for Ni allergy, Ni inflammation is not limited to the T cell reactions. They also showed that mast cells and TNF-α deficient mice can induce Ni allergy as well. Finally, Sato et al. demonstrated the potential role of toll-like receptor 4 (TLR4), macrophages and IL-1 in Ni allergy [50]. Importantly, Ni contact allergy is chiefly identified as two distinct signaling cascades, IKK2/NF–B pathway and a proangiogenic pathway which is mediated by HIF-1. It has been shown that the induction of proinflammatory genes, such as IL-6, is highly dependent on the HIF-1 pathway [114]. On the other hand, NF-kb activation is started with IKK2-mediated phosphorylation and proteasomal degradation of IB proteins [114]. The transcription factor NF-kb plays a significant role in innate and adaptive immunity and augments the expression of different pro-inflammatory genes [123].

Moreover, it has been demonstrated that Ni activates inflammatory responses in nonimmune cells, like mouse dermal fibroblasts (MDF) with increasing the production of nitric oxide (NO). Importantly, this increase in NO production and iNOS expression has also been detected in implant-neighboring MDF cells when they are in contact with Cobalt (Co) element. The augmentation in NO release mainly happens via HIF-2α-dependent pathways, since Ni mimics hypoxia situation and inhibits prolyl hydroxylase (PHD), which leads to prolyl hydroxylation of hypoxia-inducible factor (HIF)-α catalyzing and HIF activation [51].

In addition to Ni, Co and Cr alloys are also non-physiological elements, and even their slight ion release induces pro-inflammatory cytokines [124]. Moreover, Ni, Co and Cr bind to proteins and these proteins increase the corrosion rate of implants [116] and lead to debris induced inflammation. Also, synergized reactivity in alloys composed of both Ni and Co is also expected [39]. Co ions are produced as a normal electrochemical corrosion of the implants or through intracellular corrosion when Co particles are phagocytosed by immune cells [118]. Although it has been shown that Co, like Ni can potentially activate human toll-like receptor 4 (TLR4) [51], the toxicity of Co is mainly because of ROS production by Co divalent cation [118]. Also, in a study the differences between Co ions and Co particles in ROS formation were studied by Chamaon et al. In this study, cell lines of monocytes and T lymphocytes were contacted with cobalt ions and cobalt particles, and the results revealed ROS production and decreased metabolic activity in cells treated with Co ions, while the cobalt particles were well tolerated. Therefore, according to this study, it is suggested that particle size is an essential factor for ROS formation in the immune cells [118]. Chamaon et al. also showed that in human macrophage cell lines (U937), Co can enter the cellular cytoplasm and lead to oxidation and nitration of different cytosolic proteins, which in turn results in the activation of NADPH oxidase which is one of the main sources of superoxide production in human macrophages [118]. In another study, the effect of Co^{2+} and Cr^{3+} on macrophages' oxidative stress and energy metabolism was analyzed on RAW 264.7 murine macrophages. Murine macrophages were cultured with 6–12 ppm Co and 50–150 ppm Cr ions, and the results demonstrated that with increase of Co ions, the level of oxidative stress, ROS level, and protein carbonyl was significantly increased, whereas Cr ions showed no meaningful changes in oxidative stress induction. Moreover, the oxygen consumption rate (OCR) dramatically decreased in mitochondrial respiration and non-mitochondrial oxygen consumption with the increase of Co concentration. But, no changes in OCR were seen by increase of Cr amount. Co ions caused mitochondrial dysfunction and decreased level of oxidative phosphorylation in macrophages leading to inflammatory reactions [119].

The overlying mechanism of osteolysis induction is contingent on particles' composition and size, and since there are contrary reports, it is difficult to clarify a single mechanism for immune-biomaterial interaction and osteolysis. For example, Keegan et al., in his review, suggested that osteolysis in CoCr particles is a direct action of inflammatory cytokines, while in Ti implants, RANK/RANKL plays an important role. Peri-prosthetic tissue examinations in CoCr implants demonstrated the low contribution of macrophages, while the perivascular increase of B cells, T cells and plasma cells was confirmed [35]. Notably, blood examinations revealed IgE-specific reactions to CoCr samples and the possible role of humoral immunity [35]. While in another study, the effect of titanium and cobalt-chromium alloys on murine immune response and the release of immunoregulatory cytokines was studied both in vivo and in vitro. It was found that the concentration of IL-2, IL-4, and IgG was significantly low in cobalt-chromium samples, whereas IL-2 and IL-4 concentrations were only low in the group with pure titanium particles. The concentration of IgG was not affected in the titanium groups. Similarly, the release of IFN-γ was inhibited by the cobalt-chromium group but not with the titanium group. *In vitro* study demonstrated that the proliferation of T cells in a high concentration (5×10^5 particles per well) of titanium particles was reduced significantly, whereas cobalt-chromium particles had a reduction in the proliferation of T cells in both low (1×10^5 particles per well) and high concentrations (5×10^5 particles per well). Similar results were found in the proliferation of B cells treated with cobalt-chromium particles, whereas the group with titanium particles did not exhibit an impairment in the proliferation of B cells. From these results, it can be concluded that both titanium and chromium-cobalt-based implants can impair the murine immune response and cytokine release [117].

Interestingly, recent studies uncovered the high impact of Tregs and T helper type 2 on the metal-immune responses [115,125]. For example, it has been observed that Co-based alloys (CoCrMo), are able to trigger T helper type 2 reactivity [26]. Th2 recognizes Co as a foreign invader and promote the clonal expansion of T cells that can react to Co through antigens presenting cells or hapten [35]. It is notable that T cell reactivity toward metal implants differs between genders. For example, in similar age groups, female mice experienced two-fold higher T-cell reactivity toward Ni and cobalt (Co) ions as compared to male mice. Male mice produced a considerable quantity of Interferon-gamma (IFN-γ) and a minimal IL-17, while the female mice cytokine secretion profile was flipped, with higher IL-17 and low IFN-γ. In a study, Masui et al. demonstrated the impact of Ti6Al4V and CoCr on a receptor activator of nuclear factor-κB ligand (RANKL), osteoprotegerin (OPG) and inflammatory cytokines induction on murine calvariae osteolysis. RANKL is a member of TNF superfamily and directly trigger the differentiation and activation of osteoclasts [110]. Indeed, osteoclasts are

generated from monocyte/macrophage lineage in the presence of RANKL [111]. On the other hand, OPG, which is a soluble member of TNF receptor superfamily is able to regulate the RANKL activity. Hence, the ratio between RANKL and OPG is an important factor for bone resorption. In Ti6Al4V samples, the ratio between RANKL and OPG was high, whereas CoCr implanted mice have shown a physiological ratio. The physiological RANKL/OPG ratio in CrCo samples suggests that inflammatory cytokines cause osteoclast induction in these implants not RANKL-RANK pathway [110]. The difference between titanium and stainless steel implants on murine immune response was also tested through the analysis of NF-κB expression in the MyD88-mediated pathway in monocytes. In this study, rats were implanted with Ti6Al4V or SS316L rods on their vertebral lamina and blood samples were taken within a month post-operation. It was observed that compared to control and titanium alloy, the levels of pro-inflammatory markers MD2, TLR-4, and MyD88 expression in the stainless-steel alloy consistently increased while the Treg level decreased. Similarly, in the stainless-steel group, NF-κB/p65 (RelA) and NF-κB1 (p50) levels were also increased (Fig. 3). From these results, it was observed that the implantation of non-degradable implants in a rat model can cause both acute and chronic inflammation reactions. This data suggests that stainless steel implants promoted higher level of inflammation as compared to the titanium alloy implant and the control [115], which again confirms that Ti-based implants surpass other non-degradable alloys in terms of immune responses.

3.2. Degradable alloy implants interaction with immune cells

As it is discussed so far, immune responses toward implants are a complex process that involves tissue remodeling and regeneration (Fig. 4). The development of immune responses toward degradable implants adds another level of complexity to tissue growth at the implant site as the implant degrades. Furthermore, immune responses toward degradable alloys are even more complex since the implant has to not only provide weight-bearing functionality but at the same time modulate the immune responses, so that tissue regeneration occurs as the implant degrades. Moreover, immune cells and particularly macrophages must be present at the implant site to engage with phagocytosis and implant corrosion. The sustained release of degraded particles leads to destructive inflammatory environment which could be harmful for the neighboring tissues [109]. Therefore, understanding this complex phenomenon is important to develop optimal properties of degradable alloy by modulating its bulk chemistry, surface properties and

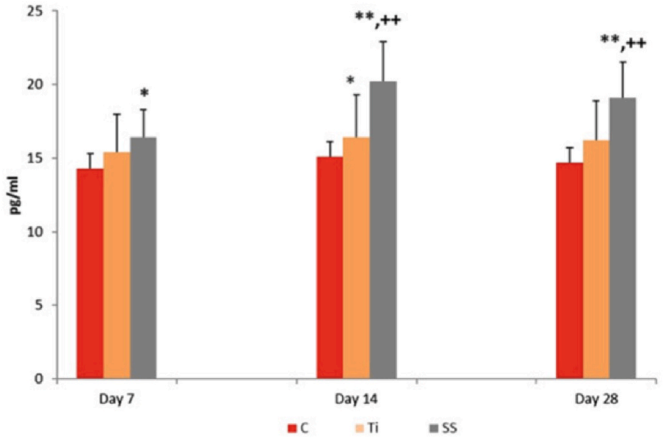

Fig. 3. NFkB expression is modulated in the presence of stainless steel alloy (SS) and titanium alloy (Ti) as compared to the control (c) group, which suggests that SS might be more pro-inflammatory as compared to Ti alloy. Adapted from Akyol et al. World Neurosurg. 2020, 144, e138 [115]. printed with permission from Elsevier.

degradation kinetics. Here, in the remaining sections, we discuss the immune interaction to Mg-, Zn-, and Fe-based biodegradable implants and in section 4 we discusse possible approaches for developing biodegradable implants.

3.2.1. Mg-based biodegradable implants

Mg-based alloys have shown to modulate immune responses and they are promising biodegradable implants as they can decrease inflammatory reactions. However, these immunological interactions have not been extensively studied. It is understood that high amounts of Mg may be tolerated in the body potentially due to alkaline pH during Mg corrosion or maybe because Mg is a vital element in physiological systems and can be metabolized [15], whereas nickel or Co–Cr alloys that are non-physiological and a tiny increase in their amount can lead to pro-inflammatory cytokine secretion and cellular damage [15]. Noticeably, degradable metal implants have been produced with elements that are well-tolerated in the body. Although Mg is a physiologically essential element with good toleration; Mg alone cannot provide the implant with the desired mechanical strengths and degradation rate. Hence, these implants are mostly supplemented with other elements such as Gadolinium (Gd) [149–151] and Silver (Ag) [152–154], which can modulate immune cell function [57].

It has been suggested that Mg-based alloys can down-regulate the production of M1-like and up-regulate M2-like macrophage-related cytokines, and as a result, rapid inflammation resolution and tissue repair can occur [57,131,132]. Interestingly, Costantinothe et al. showed that macrophages' interaction with Mg alloys in the presence of traces such as Gd and Ag increased the population of M1-like phenotype; however, the simultaneous increase of M2-like cytokine release profile led to the acceleration in tissue repair and inflammation resolution [57]. Also, Willbold et al., demonstrated that RS66 alloy (Mg-6.0Zn-1.0Y-0.6Ce-0.6Zr, similar composition with commercial ZK60 alloy), does not show acute inflammatory responses when administrated as a bone implant. This study also suggested that although neutrophils were recruited to the implant site in the first weeks' post-implantation and macrophages were present throughout the observation period of 8 weeks, the foreign body reaction toward RS66 and the number of neutrophils and macrophages were not elevated [133].

In addition to the toxic features of alloying elements, concerns about immunotoxic effect of magnesium-derived particulate debris should also be addressed carefully. The impact of these Mg-related particles was studied on primary murine and human macrophages. Notably, the release of proinflammatory cytokine TNFα remained unchanged and also no differences in the ability of macrophages to promote the proliferation of allogenic T lymphocytes was detected. This study further monitored the influence of Mg-induced particles on the function of macrophages. In Mg-particulate medium, murine and human macrophages were infected with Mycobacterium smegmatis. Overall bactericidal activity of macrophage types remained unaffected in Mg-particle medium. This study suggests that Mg particles show no adverse effect on macrophage function in vitro [134]. However, further studies are needed to investigate Mg particle features in vivo and on other immune cell types. Feser et, al. Demonstrated that pure Mg and Mg-(0.6–1.2)Ca have insignificant effects on dendritic cell function. Murine DCs were incubated with degraded alloys for over 6 days and the results showed minimal increase in DCs migration in Mg-xCa alloys with high Ca content compared with untreated control. Moreover, the secretion of TNFα, CD88 and T-cell proliferation remained unchanged in all samples [112].

Notably, studies demonstrated that even fast-degrading magnesium alloys such as Z×50 (Mg–5Zn-0.25Ca) and AZ91D (Mg–9Al–1Zn) have shown no sterile inflammation and osteolysis [15,155]. Witter et al., claimed that the presence of both neutrophils and T lymphocytes in AZ91D alloy was similar to the autologous implants after 3 and 6 months post operation [155]. This study suggests that there is no specific inflammatory response associated with fast degrading AZ91D implant. In another study, the immune responses toward ZX50-based magnesium

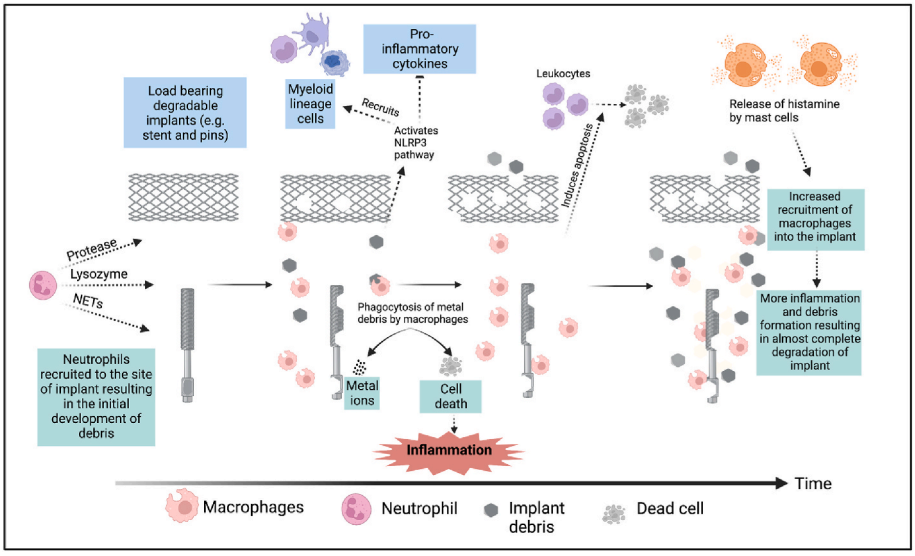

Fig. 4. Timeline of immune response toward degradable implant. As the implant degrades, it leads to recruitment of macrophages, neutrophil, and other innate immune cells. These cells then generate cytokines and can also lead to induction of adaptive immune responses. Designing implants that interact with the immune system for effective degradation of the implant at the same time providing for regenerative signaling are required.

alloy implants were tested. This study evaluated the phagocytic ability of neutrophil granulocytes on a fast (ZX50) and a slow (WZ21, Mg–2Y–1Zn-0.25Ca-0.15Mn) degrading magnesium alloys (Fig. 5). This data demonstrated that magnesium implants have a positive effect on innate immune responses. Importantly, the phagocytic ability of the neutrophil granulocytes slightly increased with no severe irritation in implant groups compared with no implant group. However, with the passage of time, the phagocytic ability was decreased in WZ21 which might be a result of yttrium element accumulation in tissues with phagocytic ability like bone [15]. Yttrium element can negatively influence the cellular phagocytosis ability and increase the expression of inflammatory factors. So, we need to emphasize that Mg implants that contain rare-earth elements need to be used carefully, as they may generate inflammatory responses in some cases [15]. This field can benefit from investigations on the response of other phagocytic immune cells such as macrophages and dendritic cells. Moreover, this field of research can greatly benefit from investigating changes in phagocytic ability over time by including more time points in the study. Overall, both slow and fast degrading magnesium alloys exhibit suitable biocompatibility with low/no systemic inflammation; however, the byproduct elements of metallic alloys, such as nickel and yttrium [15], are able to recall the immune responses [15,57] and thus may raise concerns over their safety profile [15]. In the following paragraph, the possible mechanisms that facilitate tissue resolution and decrease the inflammatory responses in Mg-alloys are discussed.

There are several mechanisms associated with Mg implants' ability in inflammation reduction. For example, in an aqueous environment, like human tissues, Mg alloys react with water and produce magnesium hydroxide ($Mg(OH)_2$) and hydrogen gas (H_2). Hydrogen gas plays a significant role in inflammation reduction. Molecular H_2 down-regulate the secretion of pro-inflammatory cytokines and chemokines such as IL-6, IL-1β, IL-10, IL-12, CCL2, TNF-α, TNF-γ, CAM-1, HMGB-1, PGE2, and nuclear factor-κB (NF-κB) [126]. Moreover, Jin et al. studied the inflammatory response of a JDBM (Mg-2.1Nd-0.2Zn-0.5Zr) alloy on lipopolysaccharide (LPS)-induced macrophages to find the underlying mechanism of macrophages inflammatory reactions. Lipopolysaccharide was added to stimulate the macrophages' inflammatory responses. The study demonstrated that the secretion of inflammatory cytokines such as TNF-α and IL-6 was significantly suppressed in all the sample groups. It is also revealed that at RNA and protein levels, JDBM extract and $MgCl_2$ samples reduced the expression of TLR-4 and MYD88. This downregulation showed the impact of magnesium ions on TLR-4/MYD88 signaling pathway [17], and most importantly, emphasized the difference between Mg alloys and Stainless steel since stainless steel has previously been demonstrated to play a role in the increase of both TLR-4 and MyD88 [115]. Notably, lipopolysaccharide contributes to ROS production, and ROS encourages inflammatory responses through the TLR-4 pathway. Jin et al. showed that magnesium ions can

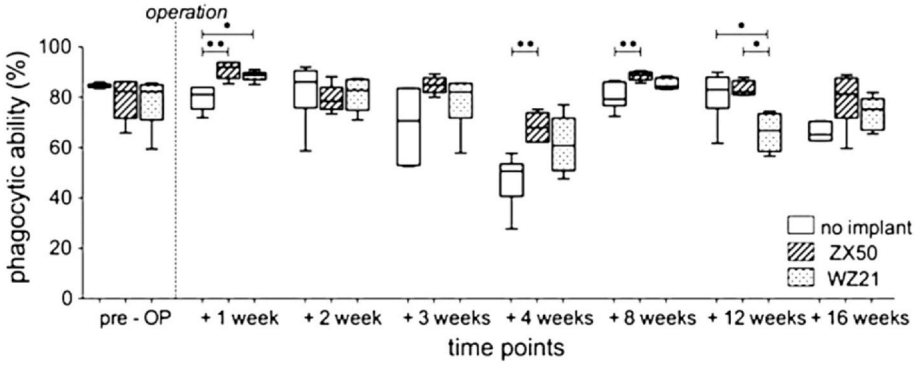

Fig. 5. *Neutrophil phagocytosis at different time points is affected by the type of implant, * - $p < 0.05$; ** - $p < 0.01$.* Adapted from Pichler et al. Jom 2014, 66, 573 [15] printed with permission from Elsevier.

efficiently decrease ROS production (Fig. 6) [17], due to the antioxidant features of the degraded particles of Mg, which further contribute to cell membrane stability [127,128]. Moreover, since Mg is a natural calcium (Ca) antagonist, the high extracellular amount of Mg blocks an excessive activation of N-methyl-D-aspartate (NMDA) receptor and thus reduces the intracellular concentration of the Ca [129]. This low intracellular Ca halts the activation of phagocytic cells and cytokine production which in turn reduces the inflammatory responses [130].

3.2.2. Zn-based biodegradable implants

Similar to the Mg-based alloys, Zn-based implants are also biodegradable candidates which have been recently researched as orthopedic devices as well as cardiovascular stents [5,156]. It has also been demonstrated that Zn-based alloys could exhibit better mechanical strength, a more stable corrosion rate, and higher biocompatibility compared with typical AZ31 (Mg–3Al–1Zn) [16]. In addition, zinc (Zn) is one of the crucial elements for the physiological system and has a great impact on innate and adaptive immune modulation [135]. Zinc also participates in important biological events like gene expression, signal transduction, nucleic acid metabolism and apoptosis. The corrosion process of Zn-based implants do not generate gas which is a big advantage of zinc implants over Mg-based implants. The corrosion layer on the surface of zinc implants is mainly made of $Zn(OH)_2$ and ZnO. These byproducts affect tissue healing and bone resolution by changing the gene profile of the local tissues and chiefly change angiogenesis, vessel tone, inflammation, platelet aggregation and cellular adhesion [138]. Zinc concentration in the neighboring tissues is the most critical aspect, which should stay in the optimal amount. High concentration of zinc can lead to changes in metal divalent ion-dependent intracellular signaling pathways, promote oxidative stress and finally lead to cell apoptosis or necrosis of the adjacent tissues [138]. Moreover, zinc also has a dual potential in apoptosis induction or inhibition based on its concentration. For example, Zn can inactivate caspase-3 and suppress caspase cascade initiation, which leads to apoptosis inhibition. However, the excessive intracellular amount of zinc renders pro-apoptotic features through p38 and potassium channel activation followed by energy metabolism restriction [157]. Hence, it is vital to evaluate Zn degradation rate to better understand their possible interaction with the immune cells.

The degradation rate of pure zinc pins and the body's inflammatory responses toward Zn particles was investigated in a study by Chen et al.

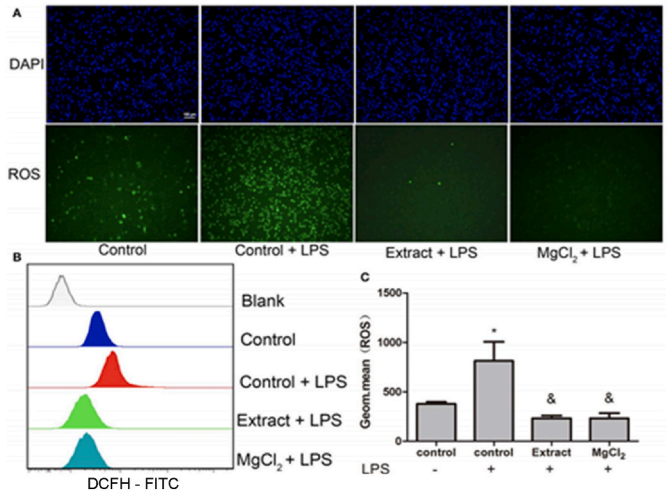

Fig. 6. *Extracts from the alloy and $MgCl_2$ act as antioxidants in macrophages derived from THP-1 cells. (A) Reactive oxygen species (ROS) in cells treated with alloy extract and $MgCl_2$.* ***(B,C)*** *Intracellular ROS expression of cells treated with extract and $MgCl_2$ in the presence of ROS.* Adapted from Jin et al. Front. Immunol. 2019, 10 [17] printed with permission from Elsevier.

[30]. Pure zinc pins were administrated to the colorectum and their rate of degradation was monitored. This in vivo experiment showed that pure zinc implants degrade slowly at a rate of 7.795% per month with no sign of inflammatory reactions. Another study also showed no early inflammatory responses in pure Zn wire implants when they were implanted on the rats' atrial lumen [158]. The mechanism behind zinc ability to reduce inflammatory responses is that zinc implant increases the expression of epithelial neutrophil-activating peptide-78 (ENA-78) and F4/80 in local tissues and in turn, suppresses the acute inflammation associated with implant foreign body reactions. The chemokine ENA-78 is a neutrophil chemotactic factor [136] and plays a key role in neutrophil homeostasis. F4-80 is expressed by various subpopulations of eosinophilic granulocytes and considerably on macrophage subsets [159]. According to these studies upregulation of ENA-78 and F4/80 helps patients to tolerate the implant with minimal inflammatory responses. Also, zinc can increase the A20, a zinc finger transcription factor and thus down-regulate the NF-κB activation, decreasing the production of inflammatory cytokines [30,137].

One of the main concerns regarding the usage of Zn-based biodegradable implants is their long-term degradation profile which may lead to the prolonged presence of corrosion materials. This long-term presence increases the risk of foreign body reactions [160]. In a study, metallic zinc was implanted into the abdominal aorta of rats and the degradation was monitored for 20 months post-implantation. The results showed that zinc wires have a steady corrosion profile with the experimental duration. Rats experienced no local toxicity and the rate of chronic inflammation reduced between 10 and 20 months post-implantation. Zinc oxide, zinc carbonate, and zinc phosphate were the main corrosion products in the surrounding tissues. This study showed that zinc stents successfully worked in arterial moiety and safely degraded within 1–2 years [161].

Nanoparticles are often dislodged from biomaterial implants, which can cause activation of immune cells. In fact, it has been demonstrated that macrophages that phagocytose debris lead to their activation and ultimately pro-inflammatory responses and loosening of the implant. Furthermore, implant byproducts such as ZnO need more investigations in terms of immune cells interaction and inflammatory responses. For example, ZnO nanoparticles have been widely used as a coating in implants coating material to inhibit bacterial adhesion and facilitate osteoblast growth. Memarzadeh et al., showed that ZnO nanoparticle coating are not toxic toward MG-63 cells and maintains the normal morphology of Human mesenchymal cell (hMSC), when they adhere to the implant surface. Also the level TNF-α and IL-6 cytokine do not change in contact with the implant [162]. ZnO can act as a coating on the surface of the Zn alloys and facilitate osteointegration, inhibit the formation of biofilm and slow-down the implant corrosion rate. Also, the release of ZnO nanoparticles (ZnO-NP) is a potential anti-inflammatory agent, decreasing the secretion of pro-inflammatory cytokines at the mRNA level. ZnO-NPs inhibit the expression of myeloperoxidase, the NF-κβ pathway, and mast cell degranulation which again help in inflammation reduction [163]. In another study, Hussein et, al. Studied the effect of ZnO-NPs on diabetic patients and demonstrated that ZnO-NPs treatment efficiently attenuated the level of diabetic related pro-inflammatory agents such as C-reactive protein (CRP) and IL-1α [164]. While the positive impact of ZnO on implant corrosion and inflammation have been documented, ZnO is able to induce ROS [165] which is a demanding concern in the Zn biodegradable context.

Although pure zinc implants have shown to be well tolerated in the body with no acute inflammation, alloying seems to be unavoidable since pure Zn implants are mechanically weak. Studies suggest that aluminum (Zn–Al, mainly neutrophil and eosinophil infiltration) [143], Lithium (Zn–Li, moderate inflammation with a non-obstructive neointima possibly due to various intermetallic chemical species $LiZn_4$) [139] and magnesium (Zn-Mg) [141] as alloying materials increase the local acute inflammatory profiles in the tissues which might be due to the higher rate of degradation in alloy implants compared to the pure Zn

implant [142]. Alloy implants have a higher rate of degradation, so inflammatory cells penetrate easier to the porous corrosion layer formed on the surface of alloy implants [142]. In a study, cell viability decreased in Zn–Al alloys by increasing the amount of Al element. This reduction associated with an increased CD68 and CD11b labeling, showing an increase in macrophages' activity. The elevated macrophage activity is possibly due to changes in implant corrosion profile after Al addition making macrophage penetration to corrosion layer feasible [142].

Surprisingly, the worst inflammatory response was seen in Zn-0.1 Mg alloy implants [141]. Since Mg is biologically compatible, authors suggest that the weak response of the Zn–Mg alloy is possibly the result of changes in their corrosion behavior and generation of toxic Mg_2Zn_{11} intermetallic by products [140,141]. Mg_2Zn_{11} shows resistance toward corrosion and thus, more macrophage infiltration is required to break down the foreign material [140]. *In vivo* comparison between groups of Zn-based alloys (Zn, Zn–Sr and Zn–Mg) with the standard Mg-based alloy (AZ31, Mg–3Al–1Zn) demonstrated that both Zn and Mg implants have similar macrophage infiltration profiles. This similarity was measured with CD11b staining of the adjacent tissues and represented in Fig. 7. Specifically, this study investigated the extent of the inflammatory response as well as the fibrotic tissue formation at the interface of the implant and host. Notably, a small number of inflammatory cells were found at the interface, as observed by immunohistochemistry. Through this study, it was seen that Zn-based biomaterials were comparable to the standard AZ31 magnesium alloy, as far as the amount of macrophage infiltration was concerned [16].

In another study, Zn-0.4Fe, Zn-2.5Fe, pure Zn and pure Fe were implanted in the rat subcutaneous tissue. Both Zn–Fe implants exhibited higher degradation rate compared with pure Zn. The CD11b and CD68 immunostaining demonstrated the monocyte/macrophage aggregation

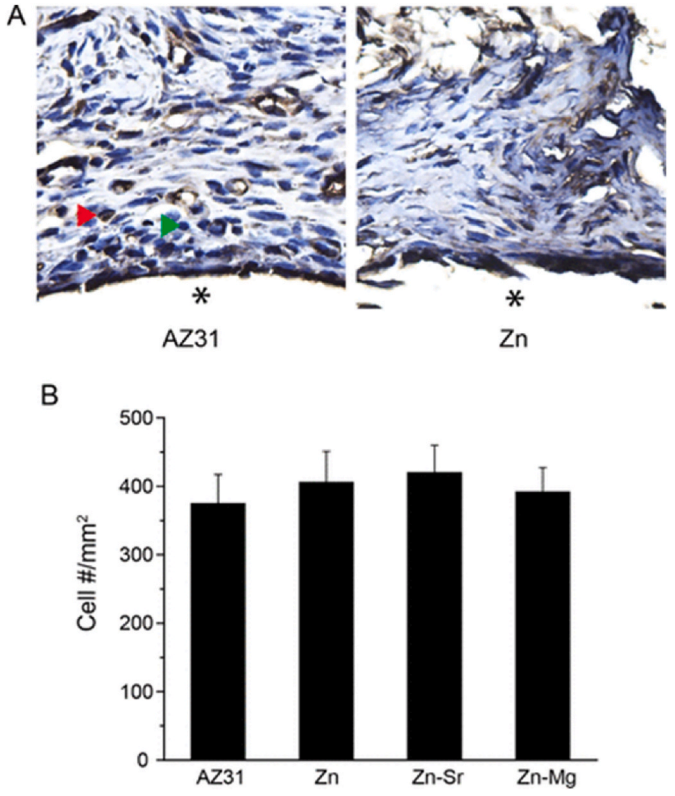

Fig. 7. *Infiltration of phagocytes that are positive for CD11b in 2-weeks post-implant site. (**A**) Representative images of CD11b + cells are shown with red arrow representing CD11b + and green arrow representing CD11b-cell, and (**B**) semi-quantitative numbers of cells at the implant-site.* Adapted from Zhu et al. ACS Appl. Mater. Interfaces 2019, 11, 6809 [16] printed with permission from Elsevier.

which was more significant in Zn–Fe alloys, especially Zn-2.5Fe, compared to pure samples. This numerous immune cell presence in alloyed implants was related to the higher degradation products at the implant site. Finally, authors suggest that this higher macrophage activity in Zn–Fe samples is favorable in the pro-healing process [144]. Shao et al., studied the inflammatory and immune cell reactions toward ternary Zn–Mg–Fe alloy osteosynthesis system. The implants were administrated to frontal bone, mandible and femur of the beagles and the results were monitored for a year. The peripheral blood CD4/CD8a lymphocyte ratio showed no significant changes in Zn–Mg–Fe implant, and the serum levels of IL-2 and IL-4 were also the same as no implant samples. The degradation was similar in frontal, mandible and femur with products including zinc oxide [ZnO], zinc hydroxide [Zn(OH)2], hydrozincite [Zn5(OH)6(CO3)2], and hopeite [Zn3(PO4)2·4H2O] that were all tolerable with no immune reaction [160].

From these studies it can be inferred that binary Zn-based alloys are suitable biodegradable materials from the mechanical strength perspective; however, they may cause inflammatory reactions as well. The inflammation problem in binary Zn alloys attracted scientists to check ternary and quinary Zn-based implants. In a study, Oliver et al. demonstrated that quinary Zn alloys could significantly decrease the inflammation profile compared with binary and ternary alloys. Specifically, this study showed that the quinary Zn–4Ag−0.8Cu−0.6Mn−0.15Zr alloy could impart inflammation resistance features when administrated as an arterial implant. This study suggests that Cu-bearing Zn implants may better modulate inflammatory reactions relative to pure Zn where tissue healing is concerned [109].

3.2.3. *Fe-based biodegradable implants*

Fe seems to be a promising biodegradable metal implant due to its excellent mechanical properties, considerable ductility, malleability, low price and suitable biocompatibility [8,167]. Moreover, Fe is an essential element in human physiological system and contributes to DNA synthesis, oxygen transportation and redox enzyme activities [8]. For example, in 2001, the first temporary Iron stent was added to the aorta of New Zealand rabbits and 6–18 months follow-up showed no pronounced inflammatory reactions or toxicity. The main obstacle was the implant's inability to fully degrade [166]. In order to overcome the slow degradation rate of Fe implants, scientists have developed a vast range of Fe-based alloys. The most common alloying elements are Mn, Al, Co, W, Pd, and Pt [8]. As it has been discussed before, careful observations are needed with alloying traces since they may induce inflammatory reactions. In a study, three implants were generated composed of Fe–35Mn, Fe–35Mn–1Ag and WE43 magnesium alloy was used as a commercial reference. This study demonstrated the impact of Ag and Mn alloying elements on zinc degradation rate and inflammatory responses. Ag supplementation increased the corrosion rate due to microgalvanic corrosion resulting in higher gas pocket formation. These gas pockets might have been developed due to excessive inflammatory response associated with corrosion and reduced pH at the implant site. This gas pocket formation was high in Fe–35Mn 4 weeks post-implantation and decreased only after 12 weeks. Compared to Fe–35Mg, Ag-contained samples induced higher inflammation as compared to the control alloy. This study also showed that Fe products are mainly cleared by macrophages phagocytosis. Notably, Ag group demonstrated high inflammation with significant number of macrophages and lymphocytes in the pocket wall. It is not yet fully understood if the Fe alloy implants will exhibit prolonged inflammation. But long term inflammation in Fe alloys may be due to their microporous nature or enhanced corrosion rate, and further studies are needed in this field [8].

In addition to the toxicity problems with alloying traces, the released degradation products from Fe-based alloys may lead to cytotoxicity and insoluble products may cause excessive ROS production [145]. Also, it has been shown that the formation of iron oxide on Fe implants is a potential danger [157] that needs to be studied more in future studies from the perspective of immune responses. Chen et, al showed that

various amount of Fe_2O_3 in Fe– Fe_2O_3 composite experience different corrosion rates and biological properties. Also, this study demonstrated that Fe_2O_3 can reduce to FeO [168]. Notably, animal studies showed that both FeO and Fe_2O_3 are phagocytosed by macrophages [166,169].

Noviana et al. studied the in vitro and in vivo biocompatibility of the Fe-based implants (Pure Fe wire and Cr coated Fe implant) where Stainless steel (SS316L) was considered as a control sample. This study confirmed higher rate of oxide layer on the surface of Fe-based implants compared with SS316L [147]. Noviana et al. also studied the in vitro cytotoxicity against rat smooth muscle cells which was the same as control sample (SS316L), whereas the in vivo results showed an increase in inflammation (14 days post-surgery) at intramuscular sites compared with SS316L [147]. This study showed that giant cells are the most dominant cells that contributed to the Fe implant inflammatory responses and the highest inflammation was reported in Cr-coated Fe implants. This study suggests that the increase in inflammatory reactions in the first weeks after implantation is a normal wound healing and phagocytosis process and is not considered as a negative immune cell interaction [147].

In another study, the effect of inflammation on the degradation behavior of Mg and Fe implants were monitored in high inflammation condition. It was demonstrated that H_2O_2 altered the surface film behavior of the Mg and CoCrMo samples, but it had minor effects on their long-term degradation behavior. On the contrary, H_2O_2 actively engaged in Fe degradation process, accelerated the degradation and also restrained the formation of corrosion products [170]. This study shows the importance of ROS-induced inflammation in the degradation of Fe implants. Notably, Fe corrosion releases Fe^{2+} participating in Fenton reaction in the presence of H_2O_2. Implant site is abundant in H_2O_2 as a result of wound healing and inflammatory reactions. This oxidative niche around implants accelerates implant corrosion and the generation of metal debris and ions [145]. On the other hand, Fe can generate hydroxyl radicals (HO) during the corrosion process, specifically when it is in direct contact with the aortic tissue as coronary stents. HO has a non-selective behavior and rapidly reacts with molecules, so it can only affect adjacent cells [145]. This oxidative stress lead to eNOS uncoupling and reduction in NO production in neighboring endothelial cells. These findings not only show the deleterious effect of Fe on endothelial cells and smooth muscle cells but also developed new concerns about the biocompatibility of degradable Fe alloys since HO is a potent ROS that play a key role in activation of pro-inflammatory cytokines [41]. Recently Zheng et al. studied the long-term behavior of the absorbable Nitrated-Fe (Fe- 0.05%N) implants in porcine coronary for 7 years where Co–Cr alloy was used as a control [146]. The first important finding was that nearly all the samples were resorbed within 7 years contrary to the Mg alloys that left calcium phosphate deposits in the tissues [171]. There was no difference in the immune cell population between control and Fe samples except for macrophages and plasma cells which is an obvious result of higher phagocytosis in degradable alloys. In this study, Zheng and his colleagues also showed that residual iron elements are located in mediastinal lymph node and they suggest that iron clearance may take place in lymphatic circulation [146] where adaptive immune cells reside, and this needs to be considered for the future investigations. Another recent study by Wegener et al., confirmed the presence of iron particles in popliteal lymph nodes of the Merino sheep when they implanted with a porous iron-based degradable alloy. During the 6 and 12 months of follow-up, blood samples and histological tests showed no significant inflammatory reactions, whereas some individuals experienced inflammatory infiltrates in regional lymph nodes and implant site. Neutrophils and eosinophils were rare in regional lymph nodes and most inflammatory infiltrates consisted of lymphocytes, plasma cells, macrophages and occasional multinucleated giant cells [148]. The predominance of lymphocytes and granulocytes at the iron implant site was also confirmed in another study by Peuster et al. In his study, the pure iron implants were administrated on the descending aorta of minipigs and the 316-L stent was used as control. Macrophages were the main cells contributed with iron stents and the number of multinucleated giant cells remained low. Overall, these studies demonstrate that the macrophages play a key role in iron clearance in the form of ferric and ferrous [169].

4. Future outlook

The development of novel degradable alloys are required that can interact with different cells of the immune system to guide the immune responses. For example, a strategy can be to incorporate proteins, peptides and small molecules within the biodegradable implant, and as the implant degrades these biomolecules can then be released in a sustained manner. These biomolecules can interact with the immune cells and modulate their function. For example, the surface of the alloys can be coated with polymers incorporated with siRNA against NFkB, which when released in a sustained manner can prevent excessive inflammation. Furthermore, the surface of the alloys can also be coated with specialized proteins and polymers [73,74] known to modulate the function of immune cells in a differential manner.

Another strategy can be to modulate the surface topography and the hardness of the alloys such that the interaction of immune cells can be preferentially modulated. For example, it has been demonstrated that immune cells such as macrophage function can be modulated by changing the surface topography and hydrophilicity [172,173]. In addition to the immune response associated with topography and hydrophilicity, it is also important to consider the alloy's mechanical properties when generating novel degradable alloy implants (Fig. 8). Both Zn and Mg-based alloys have shown suitable mechanical properties and cytocompatibility [16]. For example, in a study, the mechanical properties and biocompatibility of Zn-based biomaterials (pure Zn, Zn–Sr, Zn–Mg) were analyzed and compared to the standard Mg alloy (AZ31). It was observed that the Zn–Sr and Zn–Mg alloys had a similar yield strength and ultimate tensile strength to AZ31, but had a higher microhardness and elongation than AZ31. These changes to the microhardness can also modulate immune responses and should be considered as a potential factor in designing these materials. Moreover, release of ions from these novel alloys will also change, which can modulate the immune responses and hence should be studied as well (Fig. 9).

Both innate and adaptive immune cell functions can also be modified by incorporating immunosuppressive molecules. For example, it has been shown that local delivery of rapamycin along with TGFβ and IL-2 can prevent generation of pro-inflammatory T cells [174] and reduce implant rejection [175]. Similar strategy can be utilized for alloy implants and delivery of these factors can then prevent immediate rejection by local generation of immunosuppressive cells. Another strategy can be to locally deliver chemokines that can recruit immunosuppressive T cells to the site of implant and prevent rejection [79,175].

Local modulation of immune cells is also very important in load transfer implants. Load transfer from alloy implants to the tissue requires infiltration of immune cells such as macrophages. These macrophages help remodel the tissue, and then allow for cell types such as fibroblasts to deposit extracellular matrix proteins. However, this deposition of tissue can be affected by the degradation product from the degradable alloy implants. Specifically, if the degradation products can activate macrophages, then the tissue remodeling will restart, and the load-bearing capacity of the degradable implants will be hampered. Therefore, it is paramount to design the degradable implants so that the degradation products are non-activating.

Overall, given that biodegradable implants are being generated for temporary load bearing applications, it is imperative that the immune responses against such implants are optimized and understood before these are clinically translated. There is also a great need to develop new types of degradable alloys which can encourage tissue regeneration at the implant site.

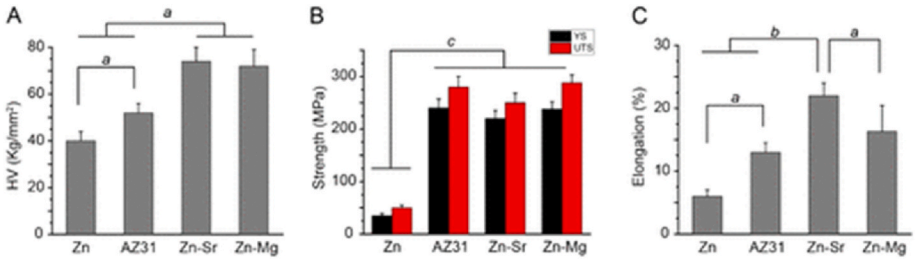

Fig. 8. Mechanical strength of Zn, AZ-31, Zn–Sr and Zn–Mg alloys is shown. Adapted from Zhu et al. ACS Appl. Mater. Interfaces 2019, 11, 6809 [16] printed with permission from Elsevier.

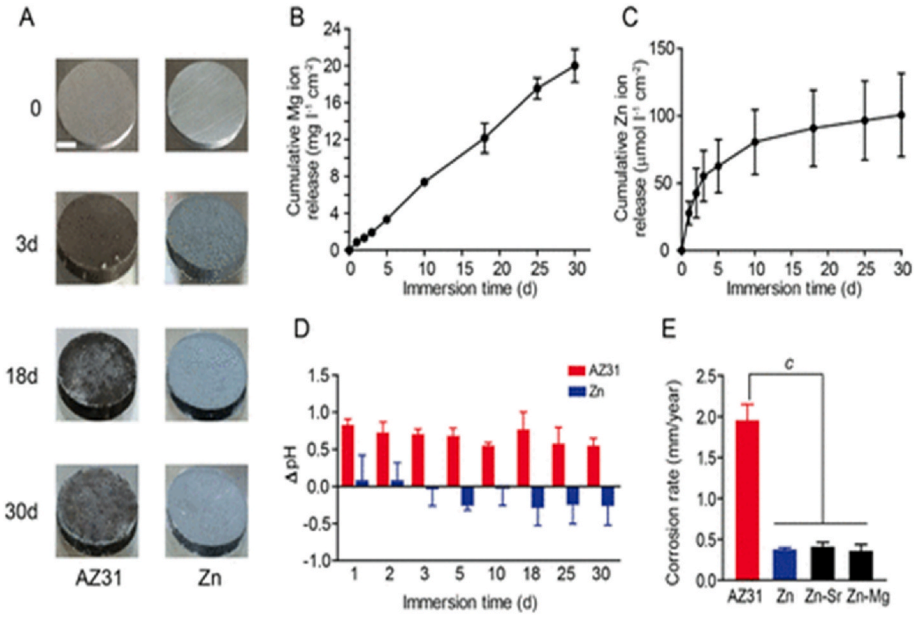

Fig. 9. *AZ31 and Zn materials degrade over time (A), and release ions (B, C), can modify the* pH *in the microenvironment (D) and corrode as they degrade (E).* Adapted from Zhu et al. ACS Appl. Mater. Interfaces 2019, 11, 6809 [16] printed with permission from Elsevier.

Ethics

This manuscript is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Contribution

TK and ES contributed equally to researching and writing this manuscript. APS and APA read and edited the manuscript, and generated figures for this manuscript.

Declaration of competing interest

There are no conflict of interest to declare.

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