



Immunologic reactions to bone and articular implants

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Received: 16 January 2021 / Accepted: 2 February 2021
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Abstract

Background In recent years the number on implantable devices that have been used in orthopedic surgeries has increased exponentially. As the number of people with orthopedic implants has grown, implant failure has become an increasingly important public health issue. While a significant percent of joint implants fails at between 15 and 20 years some authors suggest that one of the main causes is the interaction between the immune system of the host and the material of the implant

Methods The search engines used for research comprised of PubMed, Google Scholar and Cochrane Library.

Results This review aims to summarize relevant and recent data on the immune reactions that are taking place at the juxtaposition between the implant and the patient's tissue, the time frame in which these immune reactions take place and some of the factors that can influence this reaction. The immune reactions can be divided into: hyperacute immune reactions (anaphylactic shock), acute reactions, the transition between the acute phase and the chronic phase and last but not least chronic immune reactions to such implants.

Conclusion The research being done with regard to implant-related immunology strives to help in solving the problem of long-term implant failure.

Keywords Osteoimmunology · Orthopedic implants · Immunology · Acute immune reaction · Polymorphonuclear · Leukocyte · Chronic immune reaction · Macrophage · Aseptic loosening

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Introduction

In recent years the number on implantable devices that have been used in orthopedic surgeries has increased exponentially. As more and more devices get approved in both Europe and US [1], and the accessibility of those already approved increases, the problem of understanding the effects of these devices and as a consequence, regulating them, is becoming increasingly important [2]. Our understanding of orthopedic implantology has developed over the years. The increasing scientific literature on the microenvironment that forms in close proximity of the implant, has helped to isolate a multitude of elements that contribute to the local and systemic effects that these implants have. As the number of people with orthopedic implants has grown, implant failure has become an increasingly important public health issue. Some studies predict a dramatical increase in revision surgeries performed as a consequence, increasing up to seven times between 2005 and 2030 [3]. From an immunological stand point, implanting any foreign body into a living organism has a multitude

of intricate implications. The cascade of immune reactions that is triggered is dependent of whether at the site of implantation there is an infectious pathogen present as well or not. Thus, the immune reactions of interest can be classified into infectious, non-infectious (reaction to the material that was implanted) and intricate (e.g., continuous activity of polymorphonuclear leukocyte cells triggered by acute immune reaction to the implanted material can reduce the body's capacity to respond to bacterial pathogens), in which the immune response is triggered and maintained by both the material that was implanted and the infectious pathogen involved. While bacterial pathogens cause infectious osteomyelitis, disease characterized by progressive inflammation and subsequent osteolysis, the main focus in recent years is on preventing such infections in taking place. Thus, interest in the study of both bacterial growth dynamics in, in vivo models and the study of the immune reaction in a biofilm versus immune response scenario has started to increase only in recent years [4]. The reasons for needing to study in vivo models versus in vitro ones is due to the fact that in vitro cultures mainly, and at a fast pace, favorize the growth of organisms that do not elaborate an extracellular capsule [4]. When an infectious pathogen is not involved, non-infectious immune based reactions occur. Some studies show that approximatively 20% of joint implant fail at between 15 and 20 years and that the main cause for the long-term failure of total joint arthroplasties implants is immune system based [5]. As time wearing such an implant progresses, debris is produced. The main sources of debris are mechanical wear (having a major role from a quantitative stand point) and by corrosion (producing electrochemical degradation in metallic implant materials) [5]. This debris is responsible for inducing both the nonspecific and the specific immune response. With the wide variety of types of bone implants, and high diversity of biomaterials that comprise them, the clinician's choice of choosing one over another is more important than ever. With regard to biomaterials, in recent years there has also been a shift in the way we perceive them. While at first the main goal in choosing a material for medical usage was to be as "inert" as possible in order not to trigger any immune responses, nowadays, we understand these materials as part of complex systems that we try to integrate into the medical practice (e.g., immunomodulation by surface modification of biomaterial, immunomodulation by incorporating of bioactive molecules). As Williams has put it "a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure" [6]. While there exists a sequential development of the body's immune reaction to

bone implants, the first two weeks are of outmost importance. After in vivo implantation of a medical device, thus in that initial frame time, the innate immune reaction will comprise an acute reaction, the foreign body reaction and even early chronic inflammation [7] (Fig. 1). Even though, there is a field of infectious immunology to be discussed when it comes to bone implants the main focus of this review will be the aseptic immune reactions to such implants.

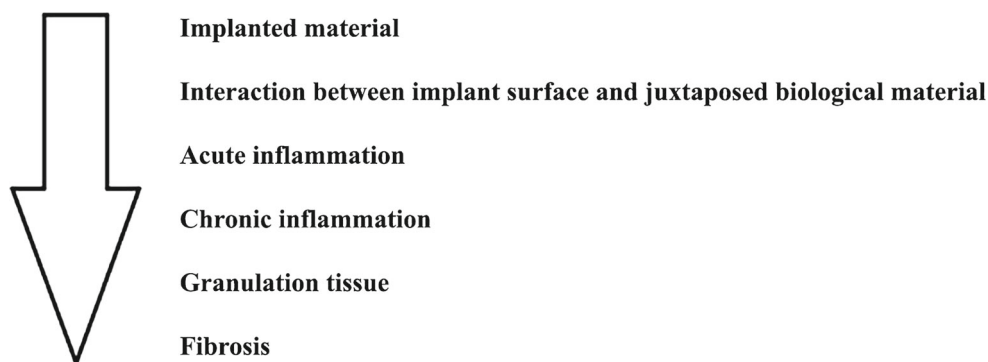
Anaphylactic shock

While hyperacute reactions to bone implants are scarce, there have been reports of patients that have suffered such events during implantation procedures. In the case of such patients the immunologic mechanism is not fully understood, either IgE mediates the immune reaction or it is triggered through direct mast cell activation [8]. We must also pay attention to other materials that we use during such procedures (e.g., latex, antibiotics, anesthetics). For example, there have been report of anaphylactic reactions during surgery induced by bacitracin irrigation [9]. While common symptoms may include diffuse erythema, erythema of the extremities, maculopapular rash, anxiety, edema, apnea, one of the earliest symptoms that can lead to the diagnosis of such a complication is hypotension [8],[9]. For example, multiple published cases of bacitracin associated anaphylaxis report the apparition of hypotension in the first 15 min after irrigation [9]. Another factor to be taken into consideration when talking about hyperacute reactions is underlying mastocytosis. There have been reports of patients with systemic indolent mastocytosis that have developed anaphylactic reactions during cement implantation of total arthroplasties [8].

Acute reactions to bone implants

Immediately after the implantation of the biomaterial, within a few fractions of a second, the material of the bone implant starts to be coated by proteins from both the blood stream and the interstitial fluid. This protein layer that is formed activates the coagulation cascade and interacts in a complex manner with immune cells, platelets and the complement system. This interplay is responsible for the formation of the transient provisional matrix and the beginning of the inflammation that follows [10]. The initiators of the coagulation cascade are the material from which the bone implant is comprised and the damaged tissue around the bone implant. The coagulation cascade's initiators are factor XII (FXII) and tissue factor (TF) which

Fig. 1 Sequence of immune host reactions to medical device implantation



initiate the intrinsic and extrinsic path of the process. FXII is autoactivated by the direct contact with the material that is implanted [11], while TF is released by the damaged tissue around the implant. Activated FXII is known to generate thrombin, which plays an important part in platelet activation. Another important function of thrombin is the cleavage of fibrinogen to fibrin. Fibrin is then responsible for creating a fibrous construct that surrounds the biomaterial. With regard to the complement, it has been shown that the biomaterial is capable of directly activating the complement [12, 13]. Once activated, the complement can take three pathways in inflammation. It has been shown that activation via biomaterial occurs mainly by the classical and alternative pathway, lectin mediated complement activation being less common [12, 13]. All three pathways converge at the level of C3 convertase activation, which lead to the release of C3a and C5a (anaphylatoxins) [14]. The main actor in the acute inflammation reaction is the polymorphonuclear leukocyte (PMN). These cells are attracted towards the site of implantation, migrating from the bloodstream. PMNs are recruited mostly by chemo attractants released by the injured cells, endothelial cells and the activated platelets. At the place where the biomaterial is implanted, the PMN will interact with the protein coated surface of the implant. After engaging with integrins and the pattern recognition receptors, PMN's phagocytic response is triggered and the degranulation process begins [15]. PMNs have multiple roles, releasing proteolytic enzymes and reactive oxygen species, even if these substance's main goal is anti-bacterial, they also have a corroding action on the biomaterial (e.g., polyurethane [16]). The continuous secreting action of PMNs can also lead to depletion, thus the antimicrobial activity of these cells is greatly diminished [17]. This harmful circle is enclosed by the immunoregulatory functions of PMNs. Activated polymorphonuclear leukocyte cells are capable of producing interleukin-8 (IL-8), through the manifest their persistent autocrine attraction of other PMNs [18], and

through the secretion of MCP-1 and MIP-1b they attract monocytes and macrophages [19] (Fig. 2).

Transitioning from an acute immune reaction to a chronic immune reaction

PMNs that have adhered to the biomaterial exercise persistent autocrine function [18]. As previously mentioned, PMN attract other PMN through IL-8 production. This self-perpetuating loop is ended by the other chemokines produced by PMNs. MCP-1 and MIP-1b [19] have a dual role, they attract the cells involved in the chronic immune reaction (e.g., monocytes, macrophages, lymphocytes, immature dendritic cells [20]) and they inhibit the autocrine function of PMNs (Fig. 3). After the PMN job has ended, they are consumed by macrophages [21]. The duration of the acute immune response, even though it depends on the biomaterial that was implanted and on the amount of tissue damaged in the process of implantation, is usually short lived and lasts for a few hours up to a few days [7].

Chronic immune response to bone implants

The cells that have been attracted at the implantation site by the adherent PMNs will be the main constituents of the chronic immune reaction and will perpetuate the immune response [22]. The monocytes will later function as macrophages, change realized through a phenotypic change process. The changed monocytes and the macrophages, that will attach themselves to the biomaterial, will start producing pro-inflammatory substances that, in turn, will attract more immune cells. Such chemokines are IL-8, MCP-1 and MIP-1b [23]. The function of the macrophages is not only pro-inflammatory. Macrophages can be classified in two subsets known as M1 macrophages or pro-inflammatory

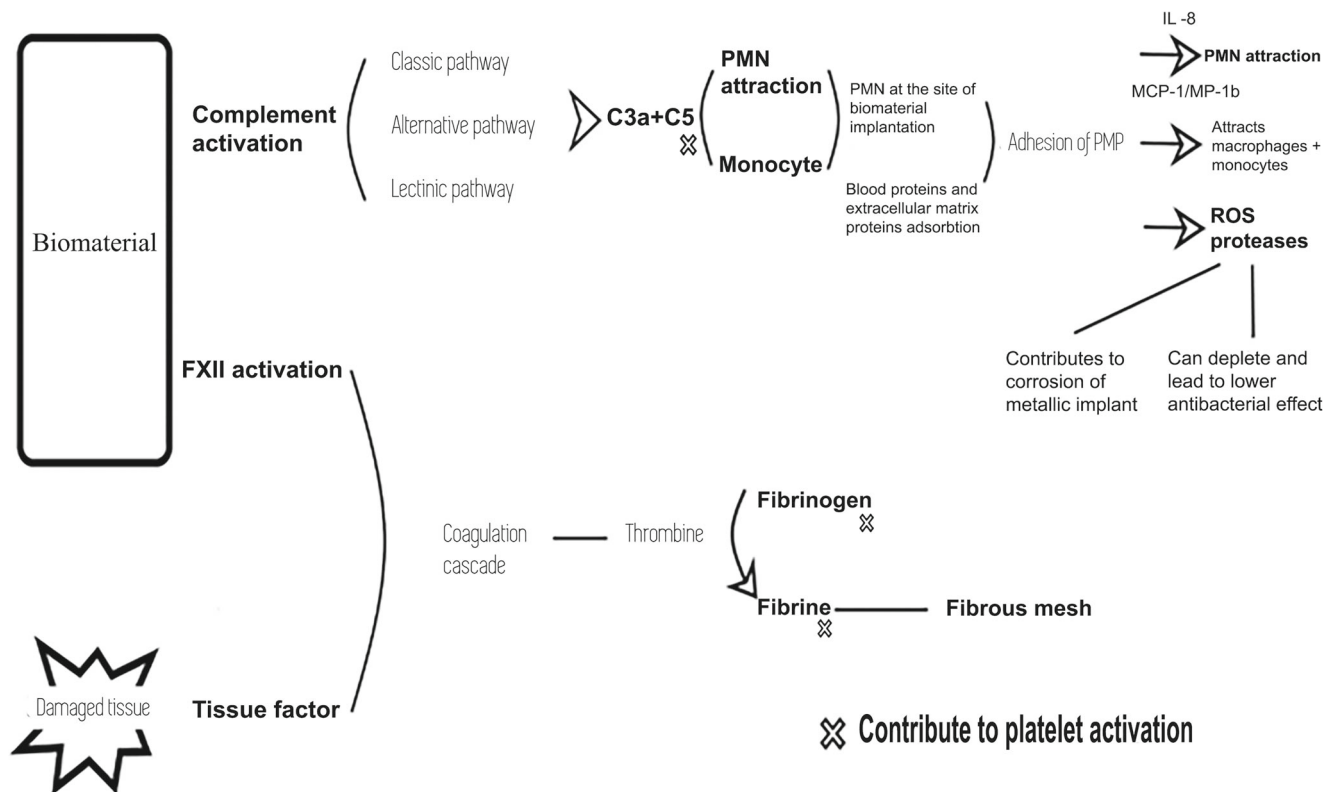
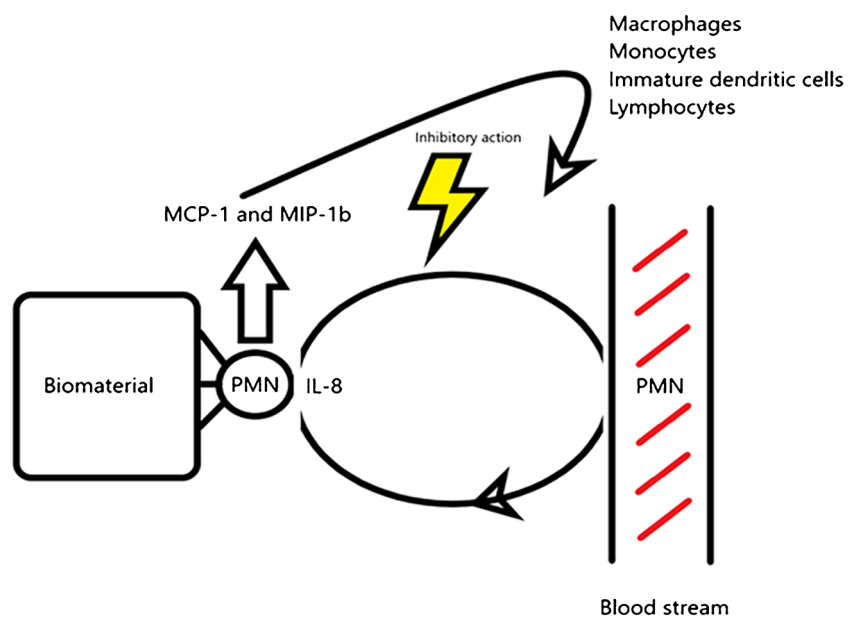


Fig. 2 Acute immune response towards biomaterial

macrophages (they form through classical activation) and M2 macrophages described as having an anti-inflammatory action (formed through alternative activation) [24, 25]. Later on, the M2 macrophages have been also classified into two subsets: regulatory macrophages and wound healing

macrophages [26]. Macrophages have been shown to exhibit phenotypic plasticity; thus, some authors have even claim that the functionality of macrophages is altered by phenotypic changes triggered by progressive changes in their microenvironment [27]. In a normal case, where the eti-

Fig. 3 Inhibitory action of chemokines MCP-1 and MIP-1b on autocrine function of PMN



ological agent is removed, either by phenotypic plasticity or by emigration of M1 macrophages from the inflammation site [28] the pro-inflammatory macrophages, shift in favor of wound-healing and regulatory macrophages. The chronic process of inflammation is biphasic, it has a pro-inflammatory phase dominated by the action of M1 macrophages and another phase in which pro-inflammatory mediators are down-regulated and alternatively activated macrophages promote wound healing [26]. The innate immune response interacts in a complex manner with the adaptive immune reactions. While the macrophage is the key cell in the innate immune response, lymphocytes and plasma cells are the main actors of adaptive immunity. This type of immune response usually has two phases: a stage of sensitization, in which the naive cells are presented the antigen by macrophages, dendritic cells or other antigen presenting cells. A second phase, in which a second contact with the antigen causes the pre-sensitized cells to react. Type IV hypersensitivity and antibody production are examples of such an immune response. Lymphocytes act in a complex manner, while the T helper subset releases cytokines with immunomodulatory action (e.g., T helper 1 cells can activate the M1 subset of macrophages via IFN γ release [26]; T helper 2 subset alongside basophils and eosinophils contribute to the production of IL-4 and IL-13 that stimulate the wound healing macrophages [26]; high levels of IL-10 released by the regulatory macrophages modulate the function of T helper 2 cells that later on release IL-4 [26, 29]) the T cytotoxic cells also have, as the name suggests, a direct cytotoxic action. The presence of monocytes, macrophages and lymphocytes is the hallmark of chronic inflammation and it allows pathologists to differentiate from the foreign body reaction, as the latter is defined by the presence of macrophages and foreign body giant cells [7].

Clinical implications

The continual strive to improve our knowledge on the domain of osteoimmunology is in no small measure due to the fact that the main cause for long term implant failure is considered to be the microparticle induced process of aseptic loosening. There have been various studies performed in order to further our understanding on particle-induced osteolysis [30, 31], and murine models have helped a great deal in that sense [32, 33]. Even though there has been a noticeable advance in preclinical knowledge in this field, in clinical practice, revision surgery and biomaterial design remain our main tools in dealing with this type of complication. In recent years there has been an influx of various types of devices in orthopedic implantology. For example, some implants, such as metal-

-on-metal arthroplasties were first designed with greater over time resistance in mind. However, data from the National Joint Registry for England, Wales and Northern Ireland from 2015 that the 10-year revision rate for metal-on-metal arthroplasties were significantly higher than of metal-on-polyethylene (19.68% cemented and 21.92% non-cemented vs 3.13% cemented and 3.98% non-cemented) [34]. Most of the cases were attributed to metal induced pathology [30]. The heterogeneity of the devices and of the biomaterials comprising them has great impact on the revision rates of the implants. The factors that influence the revision rates can be prosthesis-related (e.g., size of the head in hip arthroplasties [30], prosthesis brand [34]) or material related (e.g., particle size, shape, chemical reactivity [30, 35]).

Conclusion

To sum up, even though aseptic loosening and periprosthetic osteolysis still remain one of the most important factors in long term implant failure important steps are taken in order to further our understanding on osteoimmunology with the hope of creating new solutions for an old problem.

Authors' contributions All authors participated to the coordination and drafting of this manuscript. The authors read and approved the final manuscript.

Availability of data and material Not applicable

Code availability Not applicable

Declarations

Ethical approval Not applicable

Consent to participate Not applicable

Consent to publish Not applicable

Conflict of interest The authors declare no competing interests

References

1. Hwang TJ, Sokolov E, Franklin JM, Kesselheim AS (2016) Comparison of rates of safety issues and reporting of trial outcomes for medical devices approved in the European Union and United States: cohort study. *BMJ* 353
2. Migliore A (2017) On the new regulation of medical devices in Europe. *Expert Rev Med Devices* 53(4):1044–51
3. Wawrzynski J, Gil JA, Goodman AD, Waryasz GR (2017) Hypersensitivity to orthopedic implants: a review of the literature. *Rheumatol Ther* 4(1):45–56

4. Li D, Gromov K, Søballe K, Puzas JE, O'Keefe RJ, Awad H, Drissi H, Schwarz EM (2008) Quantitative mouse model of implant-associated osteomyelitis and the kinetics of microbial growth, osteolysis, and humoral immunity. *J Orthop Res* 26(1):96–105
5. Hallab NJ (2016) Biologic responses to orthopedic implants: innate and adaptive immune responses to implant debris. *Spine* 41:S30–1
6. Williams DF (2009) On the nature of biomaterials. *Biomaterials* 30(30):5897–909
7. Anderson JM, Jiang S (2017) Implications of the acute and chronic inflammatory response and the foreign body reaction to the immune response of implanted biomaterials. In: *The immune response to implanted materials and devices*. Springer, Cham, pp 15–36
8. ten Hagen A, Doldersum P, van Raaij T (2016) Anaphylactic shock during cement implantation of a total hip arthroplasty in a patient with underlying mastocytosis: case report of a rare intraoperative complication. *Patient Saf Surg* 10(1):25
9. Damm S (2011) Intraoperative anaphylaxis associated with bacitracin irrigation. *Am J Health Syst Pharm* 68(4):323–7. <https://doi.org/10.2146/ajhp090238>. PMID:21289327
10. Franz S, Rammelt S, Scharnweber D, Simon JC (2011) Immune responses to implants—a review of the implications for the design of immunomodulatory biomaterials. *Biomaterials* 32(28):6692–709
11. Zhuo R, Siedlecki CA, Vogler EA (2006) Autoactivation of blood factor XII at hydrophilic and hydrophobic surfaces. *Biomaterials* 27(24):4325–32
12. Lhotka K, Würzner R, Kronenberg F, Oppermann M, König P (1998) Rapid activation of the complement system by cuprophane depends on complement component C4. *Kidney Int*
13. Hed J, Johansson M, Lindroth M (1984) Complement activation according to the alternate pathway by glass and plastic surfaces and its role in neutrophil adhesion. *Immunol Lett* 8(6):295–9
14. Sarma JV, Ward PA (2010) The complement system. *Cell Tissue Res* 343(1):227–35. <https://doi.org/10.1007/s00441-010-1034-0>. Epub Sep 14. PMID:20838815. PMCID:PMC3097465
15. Nimeri G, Majeed M, Elwing H, Öhman L, Wetterö J, Bengtsson T (2003) Oxygen radical production in neutrophils interacting with platelets and surface-immobilized plasma proteins: Role of tyrosine phosphorylation. *J Biomed Mater Res Part A* 67(2):439–47
16. Labow RS, Meek E, Santerre JP (2001) Neutrophil-mediated biodegradation of medical implant materials. *J Cell Physiol* 186(1):95–103. [https://doi.org/10.1002/1097-4652\(200101\)186:1<95::AID-JCP1008>3.0.CO;2-0](https://doi.org/10.1002/1097-4652(200101)186:1<95::AID-JCP1008>3.0.CO;2-0). PMID:11147818
17. Patel JD, Krupka T, Anderson JM (2007) iNOS-mediated generation of reactive oxygen and nitrogen species by biomaterial-adherent neutrophils. *J Biomed Mater Res A* 80(2):381–90
18. Park CJ, Gabrielson NP, Pack DW, Jamison RD, Johnson AJ (2009) The effect of chitosan on the migration of neutrophil-like HL60 cells, mediated by IL-8. *Biomaterials* 30(4):436–44
19. Kobayashi SD, Voyich JM, Burlak C, DeLeo FR (2005) Neutrophils in the innate immune response. *Archivum Immunologiae Et Therapiae Experimentalis-English Edition* 53(6):505
20. Yamashiro S, Kamohara H, Wang JM, Yang D, Gong WH, Yoshimura T (2001) Phenotypic and functional change of cytokine-activated neutrophils: inflammatory neutrophils are heterogeneous and enhance adaptive immune responses. *J Leukoc Biol* 69(5):698–704
21. Gilroy DW (2004) The endogenous control of acute inflammation—from onset to resolution. *Drug Discov Today Ther Strateg* 1(3):313–9
22. Hamilton JA (2003) Nondisposable materials, chronic inflammation, and adjuvant action. *J Leukoc Biol* 73(6):702–12
23. Jones JA, Chang DT, Meyerson H, Colton E, Kwon IK, Matsuda T, Anderson JM (2007) Proteomic analysis and quantification of cytokines and chemokines from biomaterial surface-adherent macrophages and foreign body giant cells. *J Biomed Mater Res A* 83(3):585–96
24. Mooney JE, Rolfe BE, Osborne GW, Sester DP, van Rooijen N, Campbell GR, Hume DA, Campbell JH (2010) Cellular plasticity of inflammatory myeloid cells in the peritoneal foreign body response. *Am J Pathol* 176(1):369–80
25. Gordon S, Plüddemann A (2013) Tissue macrophage heterogeneity: issues and prospects. *Semin Immunopathol* 35(5):533–540
26. Mosser DM, Edwards JP (2008) Exploring the full spectrum of macrophage activation. *Nature Rev Immunol* 8(12):958–69
27. Stout RD, Jiang C, Matta B, Tietzel I, Watkins SK, Suttles J (2005) Macrophages sequentially change their functional phenotype in response to changes in microenvironmental influences. *J Immunol* 175(1):342–9
28. Bellingan GJ, Xu P, Cooksley H, Cauldwell H, Shock A, Bottoms S, Haslett C, Mutsaers SE, Laurent GJ (2002) Adhesion molecule-dependent mechanisms regulate the rate of macrophage clearance during the resolution of peritoneal inflammation. *J Exp Med* 196(11):1515–21
29. Stein M, Keshav S, Harris N, Gordon S (1992) Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. *J Exp Med* 176(1):287–92
30. Drummond J, Tran P, Fary C (2015) Metal-on-metal hip arthroplasty: a review of adverse reactions and patient management. *J Funct Biomater* 6(3):486–99. <https://doi.org/10.3390/jfb6030486>. PMID: 26132653. PMCID: PMC4598667
31. Hallab NJ, Jacobs JJ (2017) Chemokines associated with pathologic responses to orthopedic implant debris. *Front Endocrinol* 8:5
32. Goodman SB, Gallo J, Gibon E, Takagi M (2020) Diagnosis and management of implant debris-associated inflammation. *Expert Rev Med Devices* 17(1):41–56
33. Samelko L, Landgraaber S, McAllister K, Jacobs J, Hallab NJ (2017) TLR4 (not TLR2) dominate cognate TLR activity associated with CoCrMo implant particles. *J Orthop Res* 35(5):1007–17
34. Cordova LA, Stresing V, Gobin B, Rosset P, Passuti N, Gouin F, Trichet V, Layrolle P, Heymann D (2014) Orthopaedic implant failure: aseptic implant loosening—the contribution and future challenges of mouse models in translational research. *Clin Sci* 127(5):277–93
35. Hallab NJ, Jacobs JJ (2009) Biologic effects of implant debris. *Bull NYU Hosp Jt Dis* 67(2):182

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