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Induction of sterile type 2 inflammation

Dimitri A. de Kouchkovsky,

Department of Immunobiology Yale University School of Medicine, New Haven, CT 06520, USA

Sourav Ghosh,

Department of Pharmacology, Yale University. Sourav Ghosh is at the Department of Neurology, Yale University

Carla V. Rothlin

Department of Immunobiology Yale University School of Medicine, New Haven, CT 06520, US

Department of Pharmacology, Yale University. Sourav Ghosh is at the Department of Neurology, Yale University

Abstract

Microparticle debris from prosthetic implants has been shown to induce a type 2 inflammatory response through a Burton's tyrosine kinase-dependent signaling pathway.

Total joint replacements are some of the most common surgical procedures performed in the United States. Over a million total hip and total knee replacement procedures are performed annually and these numbers are expected to grow to 3.5 million and 500,000 yearly, respectively, by 2030 [1, 2]. In the US there are currently about 7 million people living with hip or knee implants [3]. While well-tolerated, these implants are nonetheless recognized by the immune system, both directly at their interface with tissues as well as indirectly through the formation of wear debris or microparticles (MP) which are micrometer-sized particles generated in the context of normal use of the artificial joint [4]. This immune response is typically understood in the context of a type IV hypersensitivity reaction in which macrophages are skewed towards an inflammatory phenotype, where they secrete inflammatory cytokines such as interleukin (IL)-1 β , IL-6 and IL-12. This ultimately results in a type 1 immune response characterized by the production of additional inflammatory cytokines such as interferon gamma (IFN γ) and tumor necrosis factor-alpha (TNF α) as well as the recruitment of more macrophages to site of the insult. At the interface of the implant and the host tissue, this reaction is described as the foreign body response. Recruited macrophages are unable to phagocytose the implant, leading to cell fusion and formation of foreign body giant cells and fibrous encapsulation of the implant. The role of MPs in the initiation of type 1 immunity remains controversial because of the difficulty to control for the presence of endotoxin, a potent type 1 immunity inducer. In this issue of *Nature*

Corresponding authors: carla.rothlin@yale.edu and sourav.ghosh@yale.edu.

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Materials, William Gause and colleagues use a model of sterile MP injection to reveal that the response to implant-derived MPs is more complex than previously described.

Gause and colleagues use MPs made of a cobalt chromium alloy, a common metal used in implants, and show that they are sufficient to trigger a type 2 immune response through the release of IL-33 by macrophages [5]. They establish a model of intra-peritoneal MPs injection followed by analysis of the peritoneal exudate cells after 48 hours. They show recruitment of eosinophils and alternatively activated macrophages in addition to the upregulation of several genes associated with type 2 immunity such as IL-4, IL-5, IL-13, as well as Arg1, Ym1 and Relm α . These findings expand on previous results showing that sterile titanium MPs, another metal used in implants, could serve as adjuvants and skew the immune response to peptide antigens towards type 2 immunity [6]. Interestingly, the researchers still observe upregulation of IL-6 and IFN γ but not iNOS, IL-12 or IL-17 suggesting a complex response of the immune system to implants with elements of both type 1 and type 2 immunity.

Using a combination of pharmacological inhibition of IL-33, genetic knock out of IL-33 and its receptor, Gause and colleagues show that this type 2 response is triggered by IL-33. Mechanistically, IL-33 production is shown to be controlled by a spleen tyrosine kinase (SYK) and Burton's tyrosine kinase (BTK) signaling axis (Figure 1). The induction of type 2 response following MP injection is lost in BTK-deficient mice as well as mice treated with the BTK inhibitor ibrutinib but is rescued by the addition of exogenous IL-33. The authors then investigate the source of IL-33. They demonstrate in *in vitro* cultures that peritoneal macrophages can produce IL-33 in response to MPs and peritoneal fluid. Additionally, adoptive transfers of wildtype macrophages in the BTK-deficient mice show these cells are sufficient to restore the response to MPs. Interestingly, the anti-parasitic response is intact when the authors disrupt this pathway of IL-33 activation using a mutant form of BTK. This finding raises exciting questions about the initiation of type 2 immunity. IL-33, in conjunction with IL-25 and thymic stromal lymphopoietin, has been implicated in the induction of type 2 immunity in the context of parasitic infections as well as allergic diseases such as asthma [7]. The authors describe the BTK-dependent production of IL-25 in their model as well, but it can be rescued with the addition of exogenous IL-33, thus suggesting that IL-33 is upstream of IL-25 in this pathway. Type 2 innate lymphoid cells (ILC2s) are key players in the initiation of anti-parasitic or allergic response [8] and yet do not contribute in this model. The researchers show ILC2s do not produce IL-33 nor the downstream cytokines IL-4, -5 and -13 in response to MP injection. Although not exclusively, ILC2s are primarily found at barrier organs such as the skin, gut and lungs and one could hypothesize that their absence in the context of the sterile inflammation at non-barrier sites induced by MPs leads to the activation of other type 2 immunity-inducing pathways. It remains to be tested if these differing induction pathways lead to qualitatively different immune responses downstream, particularly in the context of the chronic inflammation induced by long-lasting implants. Another interesting area of exploration is the induction of sterile inflammation at barrier surfaces where ILC2s will be present, as is seen with inhalation of small particles such as silica or asbestos.

The authors also translate their findings to the relevant tissue type, in this case the joint. They show that intra-articular injection of MPs into the knees of mice replicates the type 2 immunity induction seen in their intra-peritoneal model. Importantly, through pharmacological inhibition, they implicate the SYK-BTK-IL-33 axis in the MP-induced intra-articular inflammation, thus offering potential therapeutic avenues. Finally, they compare the type of the inflammatory response following primary and revision joint replacements in patients, taking care to remove all revisions with a potential septic etiology. They are able to show a similar type 2 immunity signature in the joints undergoing revision surgery through histology and mRNA levels, raising interesting questions about the contribution of this immune response to implant failure. This work not only enriches our knowledge of type 2 immunity initiation, especially in the context of sterile inflammation, but also lays the foundation for therapeutic interventions targeting this novel immune axis.

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Figure 1. Schematic of the type 2 inflammatory response to wear debris associated with implants.

Wear debris or microparticles (MP) can be released by artificial implants (1). The frustrated phagocytosis of MPs (2) leads to the activation (phosphorylation) of SYK and BTK, death of macrophages (3) and release of IL-33 (4). IL-33, in turn, drives the induction of a type 2 inflammatory and fibrotic response to the prosthetic implant (5).