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REVIEW ARTICLE

Beyond Encapsulation: Exploring Macrophage-Fibroblast Cross Talk in Implant-Induced Fibrosis

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The foreign body response (FBR) and organ fibrosis are complex biological processes involving the interaction between macrophages and fibroblasts. Understanding the molecular mechanisms underlying macrophage-fibroblast cross talk is crucial for developing strategies to mitigate implant encapsulation, a major cause of implant failure. This article reviews the current knowledge on the role of macrophages and fibroblasts in the FBR and organ fibrosis, highlighting the similarities between these processes. The FBR is characterized by the formation of a fibrotic tissue capsule around the implant, leading to functional impairment. Various factors, including material properties such as surface chemistry, stiffness, and topography, influence the degree of encapsulation. Cross talk between macrophages and fibroblasts plays a critical role in both the FBR and organ fibrosis. However, the precise molecular mechanisms remain poorly understood. Macrophages secrete a wide range of cytokines that modulate fibroblast behavior such as abundant collagen deposition and myofibroblast differentiation. However, the heterogeneity of macrophages and fibroblasts and their dynamic behavior in different tissue environments add complexity to this cross talk. Experimental evidence from *in vitro* studies demonstrates the impact of material properties on macrophage cytokine secretion and fibroblast physiology. However, the correlation between *in vitro* response and *in vivo* encapsulation outcomes is not robust. Adverse outcome pathways (AOPs) offer a potential framework to understand and predict process complexity. AOPs describe causal relationships between measurable events leading to adverse outcomes, providing mechanistic insights for *in vitro* testing and predictive modeling. However, the development of an AOP for the FBR does require a comprehensive understanding of the molecular initiating events and key event relationships to identify which events are essential. In this article, we describe the current knowledge on macrophage-fibroblast cross talk in the FBR and discuss how targeted research can help build an AOP for implant-related fibrosis.

Keywords: foreign body response, macrophages, fibroblasts, cross talk, material properties, adverse outcome pathways

Impact Statement

Biomaterials are widely used to manufacture medical devices, but implantation is associated with a foreign body response (FBR), which may lead to failure of the implants. Surface properties are related to FBR severity. In this review, we zoom in

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on the cross talk between the two key players, macrophages and fibroblasts, and propose the use of Adverse Outcome Pathways to decipher the causal link between material properties and the severity of the FBR. This approach will help increase a mechanistic understanding of the FBR and, thus, aid in the design of immunomodulatory implant surfaces.

Foreign Body Response Leads to Encapsulation

IMPLANT ENCAPSULATION IS A play with four scenes and different actors. In the first scene, a surgeon makes a wound in which the material is placed.[1,2] The material is immediately colonized by plasma proteins, even before the wound has closed, forming a provisional matrix to which cells can bind. The second scene lasts a few days, and the immune system plays a leading role. There is a flux of neutrophils toward the wound, followed by monocytes which differentiate into macrophages and coordinate the clearance of tissue damage. T cells also play a role in this.[3,4]

In the third scene, which can last weeks to months, the implant is noticed by the diligent macrophages, which cannot clear it and then orchestrate its encapsulation by fibrous tissue. Fibroblasts are recruited and induced to lay down extracellular matrix (ECM), especially collagen type 1. The fibroblasts can also differentiate into myofibroblasts. In the final scene, the graft is encapsulated, and the macrophages remain nearby, often as foreign body giant cells (illustrated in Figure 1). The situation is now stable, the immune system has calmed down again, but the implant may no longer be functional due to the layer of fibrotic tissue around it.

The Foreign Body Response Is a Derailed Wound Healing Response Leading to Implant Failure and Depends on Material Properties

Implants are a boon to millions of patients because they can take over or support essential bodily functions. Think of pacemakers that make the heartbeat, hip implants that allow people to walk, or stents that restart blood flow in occluded vessels. The materials used are often chosen based on their mechanical properties or ease of handling, but once in the body all materials induce the so-called foreign body response (FBR). We explain the different phases of the response; the final stage of the FBR is that fibrous tissue has formed around the implant. This fibrous tissue is rich in collagen, and the fibroblasts that produce it often mature into myofibroblasts that contract the collagen matrix, leading to the characteristic wrinkled surface of a large scar. The FBR is very similar to scar tissue formation, or fibrosis, which we will elaborate about in a moment.[6]

The deposition of this fibrotic layer of ECM can in some cases lead to implant failure. In as many as 7% of women who receive a breast implant, the FBR leads to the formation of such a strong capsule around the implant that it must be surgically removed.[7] Sometimes this is for cosmetic reasons, but often also because of pain complaints. Encapsulation of neuronal implants can lead to a reduction or even complete loss of electrical contact between the implant and surrounding tissue.[8] With hernia meshes, the organs can adhere to the mesh, which can be very painful. The fibrotic response itself can, in some cases, lead to the mesh rolling up completely into a ball of fibrous tissue called a meshoma, which must be surgically removed.[9] The lifetime of glucose sensors is still limited due to the FBR encapsulating the indwelling needle, therewith hampering a reliable glucose reading in the long term.[10]

Being able to control the degree of encapsulation is a great desire of many clinicians and the subject of research by many scientists. The literature shows correlations between material properties and encapsulation.[11–13] Materials that can be easily broken down by the human body, such as natural ECM, used as biological scaffolds remodel themselves based on macrophage polarization initiated by the scaffolds that show mild FBR.[14] Yet, chemical cross-linking of decellularized collagen already leads to an increased

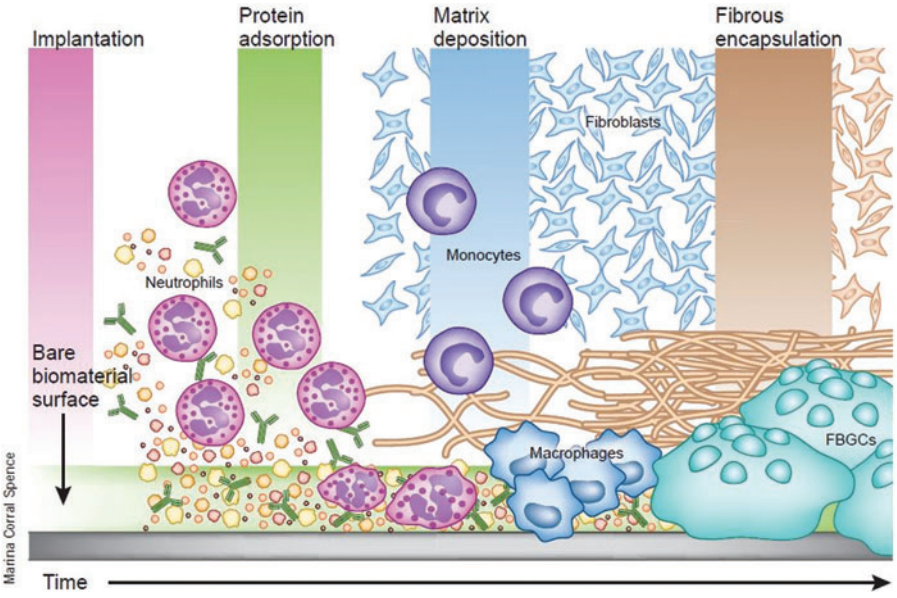

FIG. 1. The stages of the foreign body response. Figure was reproduced with permission from Grainger et al.[5] Color images are available online.

FBR.[15] Material stiffness also seems to affect the encapsulation process, with stiffer materials typically eliciting a stronger response than soft ones.[16,17] Surface topography and chemistry also influence encapsulation, which shows that the magnitude of the FBR can in principle be influenced, but even with the already known causal relationships we are far from solving the problem.

Some studies that show the effect of different biomaterial properties are shown below (Table 1). Systematically analyzing the correlation between material properties and building predictive models that can enable *in vitro* screening of materials offers an opportunity.[18] To do this, we need to gain more insight into the molecular biological mechanism underlying material-induced encapsulation, in other words: which cells interact with the materials and how does that contact or do interactions in general change the process? Insight into this can, for example, be gained from the field of organ fibrosis, in which cross talk between macrophages and fibroblasts appears to be crucial.

Cross talk Between Macrophages and Fibroblasts Plays an Important Role in Organ Fibrosis

Fibrosis occurs in virtually all tissues in the body and, as in the FBR, the massive deposition of collagen by fibroblasts leads to dysfunction of the tissue in question. Macrophages play an important role in the duration and severity of the fibrotic response, with the consensus being that overactivation of macrophages leads to organ fibrosis.[32,33] Where in wound healing the normal activation of macrophages lies in signals released during the injury, the trigger in organ fibrosis is very diverse,[34] for instance, the presence of viruses or asbestos particles in lung fibrosis.[35] Depletion of macrophages alters the course of fibrosis as clearly shown in studies where selective depletion of macrophages using transgenic mice shows a very distinct role of macrophages in organ fibrosis.[36,37] However, careful interpretation is needed of these depletion studies especially in cases where it is performed with liposomal clodronate as they are complicated with toxicity, neutrophil depletion, and tissue specific inefficacies.[38,39]

Macrophages communicate through a very large repertoire of cytokines (Table 2), and it seems that the duration and type of macrophage secretome determine the end result of the fibrotic response. In the literature, macrophages are often classified as M1 or M2 based on intracellular or surface expression of markers and based on difference in cytokine expression pattern. The consensus is that things are not so black and white, but rather that a macrophage is somewhere in a spectrum of phenotypes.[40,41] Macrophages with different secretome lead to different responses of fibroblasts, of which chemotaxis, collagen deposition, and myofibroblast differentiation are considered the three most prominent responses.[42–44]

Several studies have delved into the implication of macrophage phenotype on the fibrotic response. In one such study impact of macrophage depletion was studied in renal fibrosis model where they observed the recruitment of M1 macrophages which was followed up by polarization toward M2 macrophages characterized by high levels of TGF-β1 in a mouse model. Later the depletion of M2 macrophages led to inhibition of fibrosis through the blockage of Epithelial-to-Mesenchymal Transition (EMT).[45] Another study showed the effect of macrophage depletion in induced liver fibrosis with a transgenic mouse model, which led to lower numbers of myofibroblasts and scarring of the tissue.[37]

The fibroblasts process the ligand-mediated signals through their cognate receptors. The ligand receptor pairs are described in Table 2, which nicely illustrates the degree of complexity in cross talk between these two cell types. The actual role of these ligand-receptor pairs has been poorly explored in the context of the fibrotic process *in vivo*.

In the case of liver fibrosis, inhibition of the CCR2 chemokine receptor using an antagonist led to lower monocyte driven recruitment of fibroblasts and thus to fibrosis regression in patients.[74] Given that fibroblasts are also very plastic in their gene expression repertoire and adapt to the specific conditions of the niche in which they are located, it is logical to assume that fibroblasts, like macrophages, are in fact a heterogeneous population of cells whose behavior is a combination of the cytokines released locally by the macrophages and the expression repertoire of their own receptors. In other words, we know that macrophages and fibroblasts play a crucial role, but we do not know the details yet. Further caveats to the limited understanding of

Table 1. Biomaterial Properties That Relate to the Foreign Body Response

Biomaterial parameter	*Experimental groups*	*Effect*[a]	*References*
Surface chemistry	OH group vs. COOH group	Capsule thickness	19
	PDMS vs. hyaluronic acid	Capsule thickness	20
	Polyurethane vs. polyethylene oxide	Capsule density	21
Bulk and surface mechanics	PDMS (200 kPa vs. 20 kPa)	α-SMA expression	22
	Zwitterionic PEG (165 kPa vs. 3 kPa)	Macrophage infiltration	16
	PEG+RGD (840 kPa vs. 130 kPa)	Collagen	23
Topography	Macrotexture (90 μm vs. 4 μm)	Capsule thickness	24
	Microfibers (1.2 μm vs. 0.3 μm)	FBGCs	25
	Microgrooves (50 μm vs. smooth)	Capsule thickness	26
	Aligned fibers vs. random fibers	Collagen deposition	27
	Microtextures (56 μm vs. 200 μm)	Capsule thickness	28
Porosity	Pore size (100 μm vs. 40 μm)	Encapsulation	29
	Pore size (solid vs. 34 μm)	Collagen density	30
	Pore size (100 μm vs. 40 μm)	Macrophage polarization	31

[a]Material groups with highest foreign body response are mentioned first.

Table 2. List of Cytokines Secreted by Macrophages with Their Receptors and Their Effect on Fibroblast Phenotype

Ligand	*Receptor*	*Effect*	*References*
IL-1β	IL-1RI	Pro-inflammatory	46
IL-1RA	IL-1RI	IL-1 β antagonist	47
IL-6	IL-6R, sIL-6R	Both pro- and anti-inflammatory, fibroblast activation	48–50
IFN-γ	IFN-γR	Pro-inflammatory	51
TNF-α	TNFRI, TNFRII	Pro-inflammatory	52
IL-36γ	IL-36R, IL1RaCP	Pro-inflammatory	53,54
IL-10	IL-10R1, IL10R2	Anti-inflammatory, α-SMA downregulation	55,56
IL-33	ST2	Induces an IL-4/IL-13 response	57,58
IL-4	IL-4Rα, IL-13Rα1	Anti-inflammatory, fibroblast activation, & myofibroblast differentiation	59,60
IL-13	IL-4Rα, IL-13Rα1, IL-13Rα2	Anti-inflammatory, fibroblast activation, & myofibroblast differentiation	59–61
CCL3	CCR1, CCR5	Chemotaxis	62
CCL5	CCR1, CCR3, and CCR5	Chemotaxis	63
CCL2	CXCR2	Chemotaxis	64
CXCL-12	CXCR4	Chemotaxis	65
CCL18	CCR6, CCR8	Chemotaxis	66,67
TGF-β1	TGFβ R1, TGFβ R2	Promotes myofibroblast differentiation, both pro- and anti-inflammatory	68–70
PDGFs	PDGFR-α, PDGFR-β	Fibroblast recruitment and proliferation, α-SMA downregulation	71,72
AREG	EGFR	Fibroblast activation	32
FGFs	FGFRs	Fibroblast migration and proliferation	73

the process lie in the fact that peripheral blood macrophages seem to have a different role than tissue resident macrophages.[75,76]

In addition, macrophages also influence fibroblasts by secretion of several different molecules such as miRNAs, metabolites, or matrix metalloproteins, or by laying down an ECM.[77,78] In this article we have decided not to elaborate on those mechanisms, because cytokine mediated signaling is best studied at present. Finally, we must also recognize that macrophages themselves also respond to ligands and ECM proteins and, thus, continuously adapt their phenotype to the circumstances. Many forms of fibrosis have a final phase in which macrophages no longer direct the fibrotic response and in which the fibrous tissue remains stable.[79,80] In a study, the influence of cardiac inflammation on ECM was observed in patients with heart failure patients. Different inflammatory markers were expressed from the cardiac biopsies which correlated with collagen accumulation with high collagen I and III expression.[81]

In fibrosis models, the role of the ECM is intriguing, particularly in its ability to regulate macrophage activation. For instance, in pulmonary fibrosis, IL4 and IL10 stimulate secretion of CCL-18 by macrophages which in turn upregulate collagen production by fibroblasts. Macrophages then bind to this collagen through integrins, and this binding further boosts CCL-18 secretion.[66]

To understand the role of macrophage phenotype in the ECM remodeling, Witherel et al. used classical macrophage polarization protocols and a hybrid approach where both M1 and M2 stimuli were exposed to macrophages simultaneously to study the ECM assembly. Condition medium experiments *in vitro* revealed that M2 stimulated conditions had higher gene expression of matrix proteins *COL3A1*, *COL5A1*, *fibronectin*, *perlecan*, and *versican*, as well as other pro-fibrotic factors *PDGFA*, *VEGFA*, *DACT1*, and *tyrosine kinase protein*, compared to control with no conditioned medium. One key observation taken away from this *in vitro* study was that the matric deposition was less aligned in the fibroblasts with hybrid conditioned medium compared to conventional M1 or M2.[82]

Evidence that Cross talk Plays a Role in FBR

Since cross talk between fibroblasts and macrophages plays a role in wound healing and fibrosis, this process likely also plays a role in the FBR. We have depicted a model for differences in fibroblast-macrophage cross talk in flat versus patterned implants in Figure 2. The literature describes many of the players in wound healing and fibrosis, but the overall picture is still fragmented.[1,2,41,83]

In vitro evidence for cross talk is strongest because the secretome of macrophages changes when exposed to materials of different composition. In the 1980s the Miller lab showed in a series of articles that the secretion of cytokines such as IL-1β and IL10 is different when they grow on surfaces of different chemistry such as polyethylene, polydimethylsiloxane, and polytetrafluoroethylene, and these results have since been confirmed by many other laboratories and with many other materials.[84,85] The expression of the gene-encoding cytokines also appears to be influenced by surface chemistry.[86,87] Analysis of multiple cytokines on the same material, to reveal consistent patterns of pro- and anti-inflammatory profiles, or M1/M2 profiles, has been only partially successful. In some cases, M1 or M2 specific profiles seem to be activated, but more often the data contradict each other or the expression of some of the cytokines is not modulated.

A similar picture emerges when we look at the effect of surface topography. Clear differences can be seen when macrophages are grown on different topographies, but here too the correlation between topographical design and *in vivo*

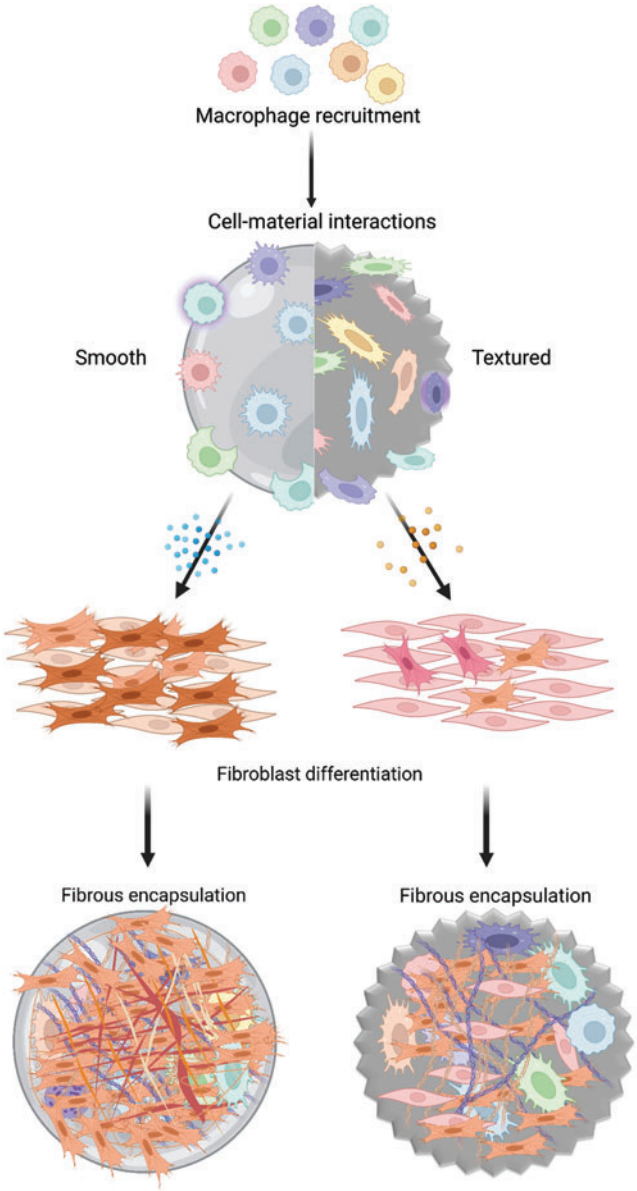

FIG. 2. Model for surface topography-mediated differences in implant encapsulation. (*on left*) Macrophages bind to the smooth implant interface and adapt a typical secretion profile to trigger fibroblast differentiation that leads to thick encapsulation of the materials. (*on right*) Macrophages bind to the textured material and change the cell shape adapts to the surface which creates a distinct secretion profile that modulates the fibrous encapsulation of the material. Color images are available online.

response is not strong.[24,88] The heterogeneity in macrophage response is largely attributed to their diverse origins. Studies indicate that the mode of macrophage polarization significantly influences surface marker expression, cytokine secretion, and gene expression.[89,90] This diversity is evident when considering various cell lines, such as primary monocyte-derived macrophages, RAW 264.7 cell lines, THP-1 monocytes, and others, each exhibiting a unique response to external stimuli. Recognizing this variability underscores the need for a cohesive framework and the establishment of standardized *in vitro* test systems. This standardization could be addressed through guidelines provided by the International Organization for Standardization (ISO) 10993, which offers recommendations for *in vitro* testing of medical devices.[91]

What is clear is the effect of the secretome on fibroblast physiology. These effects are generally tested by exposing fibroblasts to the medium in which macrophages have been grown, so-called conditioned medium, or by physically separating the fibroblasts from the macrophages in a Transwell insert.[42,92–94] Effects are seen on the relevant parameters such as proliferation, migration, differentiation, and cytokine expression. Here too, both chemistry and topography can have an effect.[17,95,96] Cytokine secretion and fibroblast physiology show that biologically relevant parameters can be controlled by material properties. Unfortunately, the correlation between *in vitro* response and *in vivo* encapsulation parameters is sparse.

The molecular biological mechanisms underlying differential cytokines expression are also poorly understood. Macrophages are known to differentially attach to materials with different chemical and topographical properties, and attachment affects, for example, the YAP signal transduction pathway.[97] YAP may then influence the inflammatory response of macrophages.[98] Confinement of macrophages also limits the expression of pro-inflammatory cytokines, which is regulated by the MRTF-A/SRF pathway.[99]

In vivo there is also evidence that cross talk between macrophages and fibroblasts may determine the course of the FBR. Breast implants releasing IL4 showed less TNF-α secretion from macrophages *in vitro* and showed less encapsulation *in vivo*.[100] The relationship with cytokine secretion was further investigated in materials with different pore sizes, where the secretion of pro-inflammatory cytokines by macrophages *in vitro* was correlated with the degree of encapsulation *in vivo*, but no direct evidence was provided that fibroblasts were affected *in vivo* by the macrophages or that the macrophages actually had a different cytokine expression profile *in vivo*.[101]

Doloff et al. implanted surfaces with different topographies and used single cell RNA sequencing technology to demonstrate the difference in cytokine gene expression in macrophages.[24] Immunohistology has also been used in other articles to demonstrate the expression of cytokines in macrophages in contact with surfaces.[102] Functional evidence for cross talk between macrophages and fibroblasts has recently been published. Dondossola et al. proved in a skin flap model that macrophages play a role in fibroblast migration but not in differentiation during the FBR.[103] Vice versa, little research has been done. Fibroblasts also attach to implants and that attachment leads to differences in cytokine expression,[104–106] but there is little evidence that these differences in cytokine expression also occur *in vivo* and that these differences subsequently lead to a difference in macrophage maturation.

Adverse Outcome Pathways as a Means of Mapping Process Complexity

The previous paragraph demonstrates that we are only starting to scratch the surface of the mechanism of macrophage-fibroblast communication in the FBR. It is fundamentally interesting to know the mechanism of cross

talk, but this knowledge can also be applied in a predictive model. For instance, given the negative effect of excessive capsular contracture on breast implant function, we want to be able to predict the relationship between material properties and the degree of encapsulation so that we can engineer a favorable FBR. On the other side of the coin, the physiology of the patient also influences the degree of the FBR and it is also useful to be able to predict the degree of encapsulation for an individual patient. Encapsulation is undesirable or in other words it is an adverse outcome. In the field of predictive toxicology, the mechanisms underlying the development of adverse effects are increasingly being described in so-called Adverse Outcome Pathways (AOPs).[107]

This AOP framework is used to structure data and knowledge into causal relationships, starting from a Molecular Initiating Event (MIE) through several Key Events at different levels in the biological hierarchy and ending in an Adverse Outcome at the organism or population level (as illustrated in Fig. 3). By organizing all available mechanistic information into a chain or network of key events, AOPs can help to identify relevant testing methods or guide the development of novel tests for predicting an adverse outcome. This approach has already led to the successful development of several nonanimal testing strategies, such as for the identification of potential skin sensitizers.[108]

The AOP concept was originally developed as a tool for chemical safety assessment, but in recent years it has also been applied to address other biomedical problems due to its wide range of benefits. For instance, one of the utilities of AOPs is to integrate data from different models. This has proven to be instrumental in describing the COVID-19 pathogenesis, for which several AOPs have been developed to combine the vast quantities of available data from various sources.[109] Besides structuring information on toxicity and disease mechanisms, AOPs can help to define important knowledge gaps that require further research. Moreover, AOP development promotes the incorporation of insights from other fields, as a wealth of biological mechanisms has already been described in the AOP format that can be relevant to multiple pathologies. Due to their modular nature, Key Events can be reused in multiple AOPs and in this way help to identify new, potentially involved pathways.

Although AOPs were at first mostly used to describe pathways triggered by chemical compounds, AOPs are by definition agnostic and can be triggered by any kind of stressor, including biomaterials. Several AOPs have already

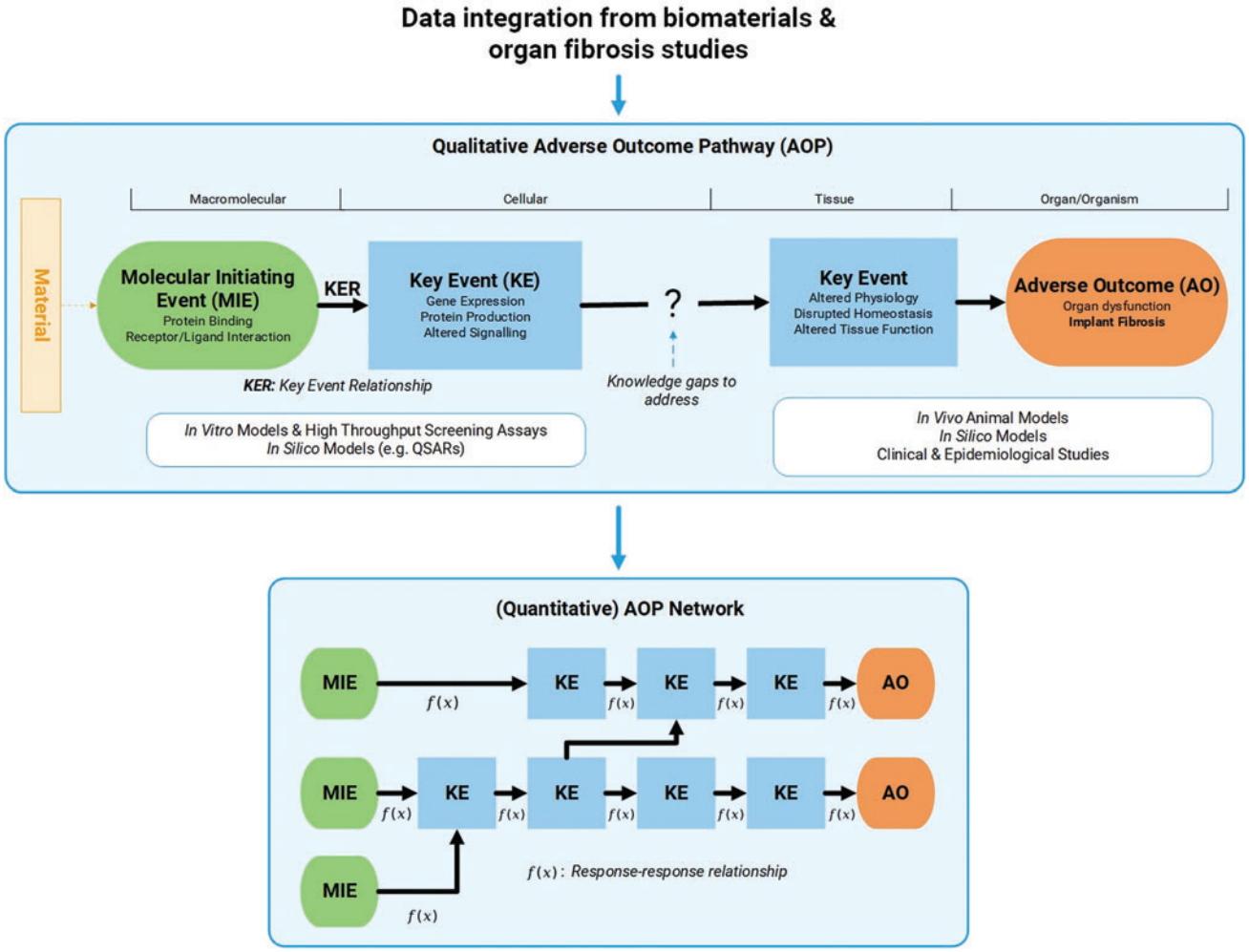

FIG. 3. Illustration of how an Adverse Outcome Pathway could be used to describe and model how macrophage-fibroblast cross talk in the FBR leads to implant fibrosis. FBR, foreign body response. Color images are available online.

been constructed to describe adverse effects caused by nanomaterials, and recently, a study exploring the relationships between metal species (such as hip implant wear debris) and adverse events of medical devices was presented in the AOP format.[110,111] The development of AOPs is governed by a set of guiding principles, for which the reader is referred to these excellent reviews.[112–114]

The prevailing mindset in the field is that if you want to set up an AOP you can start anywhere. To establish an AOP of the FBR, we first must ask ourselves which causal connections there are and which black boxes still exist. One great certainty we have is that all materials induce an FBR. Its degree certainly depends on material properties, implying that there are molecular events triggered by these properties which exhibit a response–response relationship to fibrous encapsulation. A second fact is that the depletion of macrophages leads to less encapsulation, indicating that there are key events taking place in macrophages. Furthermore, it is quite clear that fibroblasts lay down the ECM leading to the loss of function of implants. This matrix production by fibroblasts, in turn, is dependent on cytokines secreted by macrophages. We also know that macrophages change their cytokine expression level under the influence of material properties,[3,115] but we are far from a complete AOP: we certainly cannot yet predict *in vitro* how a material will behave *in vivo*.

We need to think carefully about how AOPs can be used to model fibrous encapsulation. Multiple MIEs likely play a role in the development of the fibrous capsule at different stages of the FBR, some in response to differential adsorption of proteins to the surface, but also in response to material stiffness, porosity, or topography. By building an AOP network based on multiple MIEs and pathways, the antagonistic or synergistic effects triggered by various material properties could be modeled. Eventually, with sufficient quantitative understanding of the key event relationships, such an AOP network could be a starting point for *in silico* modeling approaches.[107, 116]

Steps to be Taken to Map Cross talk in the FBR

To arrive at an AOP describing the role of cross talk, a lot of experimental data will still have to be obtained. First, we will have to map the expression of cytokines in macrophages and fibroblasts around an implant and preferably of all cell types. Because the FBR is a process that takes weeks to months and has many different phases, these data will have to be obtained *in vivo* and then also over time. This will require the use of modern technology that maps proteins and genes at high resolution, such as single cell transcriptomics.[24,117,118] The spatial information in the process is just as important as the expression level, where techniques such as immuno-mass spectrometry, *in situ* sequencing, and tomosequencing combine multiplexing with spatial information.[119–121]

With a map of cells and expression in hand, we will then have to provide evidence for the role of cell types and their subtypes in the FBR. For example, we will have to map out the role of tissue resident versus blood derived monocytes in the FBR.[76,122] The enigmatic role for Foriegn Body Gaint Cells (FBGCs) can also be investigated in this way. These multinucleated cells have been present in implants for a long time, but their role in the process has never been proven nor understood. These questions may be answered with transgenic mouse models in which cell types can be switched off using inducible transgenes. It would be even better if we could specifically ablate individual cells using, for example, optogenetics and study their effect on the surrounding tissue in real time, for example, using skin flap models in the mouse.[103,123,124]

A similar line of research will be needed to provide evidence that those cytokines influence the FBR. Given the large number of cytokines secreted by macrophages, the regulatory mechanism will be complex and individual cytokines are likely to control several subtle components of the FBR. There will also be redundancy in the role of individual cytokines. Targeted inactivation and activation of cytokines and their receptors on the cognate cells will have to map how the morphogenic process of the FBR is controlled by cytokines. This is reminiscent of the way in which targeted genetic engineering has mapped the role of growth factors in the pattern formation of the Drosophila embryos.[125] The analogy also represents the order of magnitude of the task ahead, as generations of geneticists have devoted their life's work to building this scientific understanding.

All the proposed experiments focus on the FBR at the tissue level, but also mapping the molecular mechanism underlying differential expression of cytokines under the influence of different materials is important for our understanding of the process, but also for guiding it. For the time being, this can be unraveled *in vitro* by mapping signal transduction pathways that can be controlled by material properties and the way in which these subsequently lead to phenotypic changes in the cells, including cytokine expression.[104,126]

By large-scale screening of libraries of materials, we can then discover quantitative structure-function relationships and in this way develop *in silico* models that can predict the behavior of cells on materials.[127–130] The predictive value of *in vitro* data could increase if we build more physiologically relevant *in vitro* model systems, in which different cell types are grown together in 3D and with the right nutrients, oxygen tension, etc. Laboratory on chip models can contribute to this.[131] If we then take that a step further and try to link the relationship between the adverse outcome to material properties and we can also include patient-specific and real-time analytical information in predictive models, then we are on our way to a Digital Twin for implant fibrosis.[132]

Authors' Contributions

P.K.S., E.C.A. prepared the review and generated figures, J.d.B., T.v.K., N.B. contributed to the review and reviewed the article. J.d.B. reviewed and oversaw the project.

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