Exploring the Overlooked Roles and Mechanisms of Fibroblasts in the Foreign Body Response

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Significance: Foreign body response (FBR), wherein a fibrotic capsule forms around an implanted structure, is a common surgical complication that often leads to pain, discomfort, and eventual revision surgeries. Although believed to have some mechanistic overlap with normal wound healing, much remains to be discovered about the specific mechanism by which this occurs.
Recent Advances: Current understanding of FBR has focused on the roles of the immune system and the biomaterial, both major contributors to FBR. However, another key player, the fibroblast, is often overlooked. This review summarizes key contributors of FBR, focusing on the roles of fibroblasts. As much remains to be discovered about fibroblasts' specific roles in FBR, we draw on current knowledge of fibroblast subpopulations and functions during wound healing. We also provide an overview on candidate biomaterials and signaling pathways involved in FBR.
Critical Issues and Future Directions: While the global implantable medical devices market is considerable and continues to appreciate in value, FBR remains one of the most common surgical implant complications. In parallel with the continued development of candidate biomaterials, further exploration of potential fibroblast subpopulations at a transcriptional level would provide key insights into further understanding the underlying mechanisms by which fibrous encapsulation occurs, and unveil novel directions for antifibrotic and regenerative therapies in the future.

Keywords: foreign body response, fibroblast, fibrosis, implant

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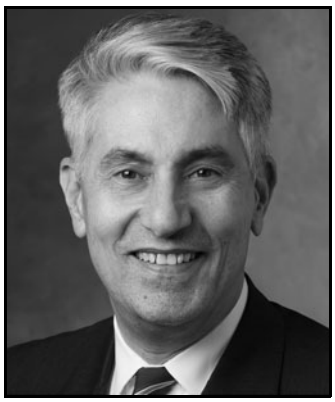

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SCOPE AND SIGNIFICANCE

With uses in the fields of orthopedic, cardiac, and plastic and reconstructive surgery, to name a few, the global implantable medical devices market is considerable. Unfortunately, foreign body response (FBR), an immune reaction that leads to dense scar tissue formation around the implant, is a common surgical complication. Multiple articles have been published on FBR; however, fibroblasts, a key player in this process, has often been overlooked. This review will summarize key contributors and mechanisms of FBR, focusing on fibroblast morphology and function.

TRANSLATIONAL RELEVANCE

Current research aims to further understand the mechanisms that underlie FBR with the hope of developing treatment modalities that reduce fibrotic capsule formation. Some researchers have focused

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on elucidating how the various cell types and signals at different stages of FBR result in fibrotic capsule formation, while other groups are exploring biomaterials and implant coatings with antifibrotic properties. Research from both basic science and engineering may lead to the development of novel antifibrotic strategies.

CLINICAL RELEVANCE

FBR is a common clinical complication that may lead to pain, discomfort, and device failure. In the context of breast implants, revision surgery is the standard treatment for FBR; however, patients frequently experience recurrence. That said, investigations into biomaterial candidates and molecular therapies derived from an increased understanding of the cell types and fundamental mechanisms that lead to FBR show promise as potential future directions in the management and treatment of this condition.

BACKGROUND

With applications ranging from drug delivery, tissue replacement and reconstruction, biosensors, scaffolds for tissue engineering, and prostheses, implantable devices and materials have become a ubiquitous component of modern medicine.[1] In 2021, the global implantable medical devices market reached a value of $120 billion USD and is expected to rise in value to $168.3 billion USD by 2027.[2] Though offering significant benefits clinically, use of these materials often results in an inflammatory reaction known as FBR. This reaction is characterized by a series of stages: (1) provisional extracellular matrix (ECM) formation; (2) acute inflammatory stage; (3) chronic inflammatory stage; and (4) fibrotic capsule formation.[3] The eventual fibrotic capsule that forms around the implant often leads to pain, discomfort, and eventual revision surgery.[4]

Capsular contracture, a form of FBR, remains one of the most common complications of breast implant surgery (Fig. 1). Although the percentage of patients experiencing capsular contracture varies based on procedure and implant type, an estimated 8–15% of patients receiving breast implants will experience capsular contracture.[5] Reoperation is currently the standard treatment for patients experiencing capsular contracture; however, reported recurrence rates have reached up to 54%.[4] Alongside breast augmentation and reconstruction, complications related to FBRs also result in device failure and extraction in orthopedic, cardiac, and dental implants, to name a few.[6–8]

Numerous reviews have been published on FBR; however, most discuss FBR through the lens of either the immune system or the biomaterial. Although both are major contributors to FBR, another key player, fibroblasts, is often overlooked. In this study, we begin our discussion with wound healing given its similarities with the acute stage of FBR. We then proceed with an overview of FBR, followed by a discussion of key cell types involved, focusing particularly on fibroblasts. As much remains to be explored regarding the morphology and function of fibroblasts in the context of FBR, we draw on current knowledge of fibroblast subpopulations and functions during wound healing. Although not the focus of this work, we will also touch briefly on biomaterials and signaling pathways involved in FBR.

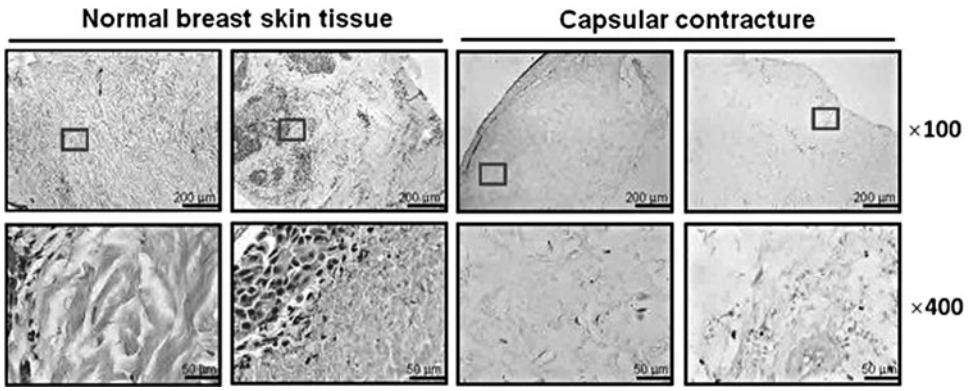

Figure 1. Capsular contracture as an example of foreign body response. Capsular contracture is the clinical term for fibrous encapsulation that occurs among patients who receive breast reconstruction or augmentation surgery. In this study, normal breast tissue (*left*) is compared with capsular contracture (*right*), using H&E staining. H&E, Hematoxylin and Eosin. Boxes indicate the areas from which magnified x400 images were captured. Taken with permission from "Extracellular matrix (ECM) structure in tissue from patients with capsular contracture" (panel A) by Kuo et al.[62]

DISCUSSION

Wound healing

During normal wound healing, a series of overlapping stages is involved: hemostasis and inflammation, cell proliferation and matrix deposition, followed by maturation and tissue remodeling (Fig. 2).[9] Immediately after injury, the coagulation cascade controls bleeding from damaged blood vessels. Inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β) build in the wound bed, bringing in neutrophils and monocytes during the first week postinjury. Neutrophils remove bacteria and cellular debris from the wound, while monocytes activate into macrophages.[10,11] In addition to their phagocytic role in the inflammatory phase, macrophages also stimulate numerous processes involved in the proliferative phase.

During proliferation and matrix deposition, endothelial cells reform capillaries to repair damaged vasculature, while fibroblasts begin depositing collagen and other components of the ECM that forms within the wound at this time.[10] Activated fibroblasts known as myofibroblasts also initiate wound contracture through TGF-β1 signaling.[9] Finally, during maturation and remodeling, the temporary matrix is gradually replaced by one that is more organized and structured. This stage is considered critical to ensure proper wound healing.[9]

FBR overview

There are many parallels between normal wound healing and FBR. During FBR, the process similarly begins with an inflammatory response. The presence of the biomaterial, however, often results in a progression of the acute response into a chronic condition. In this study, we will provide an overview of FBR and will then proceed to discuss specific cellular components of the process in detail in sections to follow (Fig. 3).

When a device is implanted into the body, damage of vascularized connective tissue at the surgical site releases a variety of plasma proteins, including vitronectin, fibrinogen, complement, and fibronectin, which get adsorbed to the biomaterial

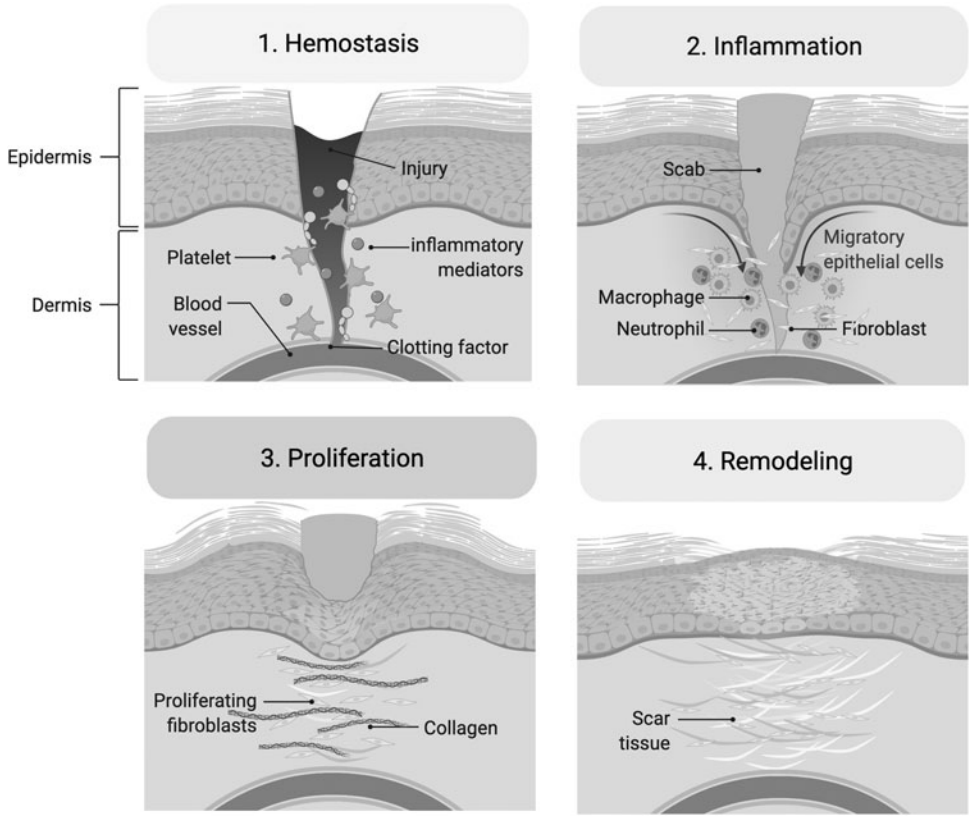

Figure 2. Stages of wound healing. Wounds undergo a series of stages before scar formation. 1. Hemostasis: the coagulation cascade controls bleeding and platelets clot off the injury site. 2. Inflammation: macrophages and neutrophils remove bacteria and debris, while also stimulating processes during the proliferative phase. 3. Proliferation: endothelial cells reform capillaries and repair vasculature, while fibroblasts at the wound site secrete collagen and contribute to ECM formation. 4. Remodeling: the ECM matrix is gradually replaced by one that is more organized and structured, resulting in the observed scar. ECM, extracellular matrix. Adapted from "Wound Healing," by BioRender.com (2022). Retrieved from http://app.biorender.com/biorender-templates

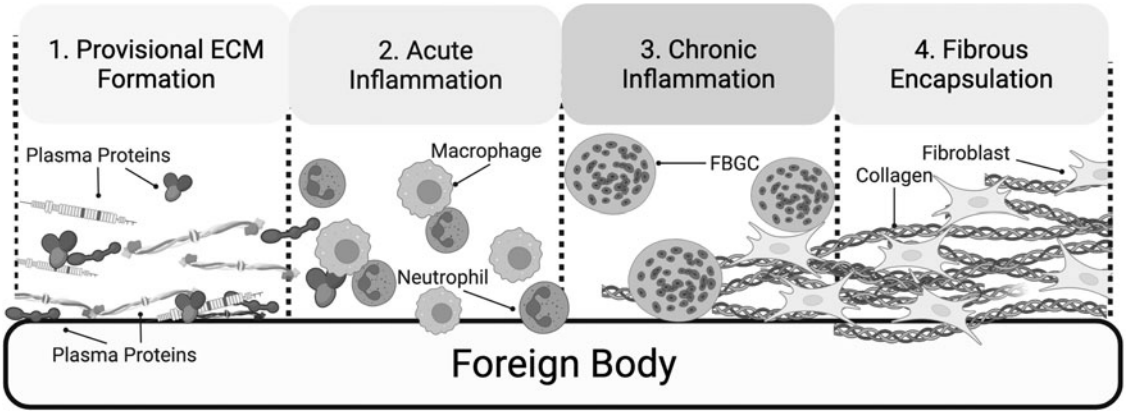

Figure 3. Stages of foreign body response. 1. Provisional ECM formation: Plasma proteins released due to damaged vasculature get adsorbed by the foreign body, forming a provisional matrix around the implant. 2. Acute inflammation: Acting as a source of bioactive agent, the provisional matrix attracts immune cells, including neutrophils and macrophages to the implant site. These attempt to phagocytose the foreign body. 3. Chronic inflammation: Due to the continued attempt by macrophages to phagocytose the implant, these cells undergo additional differentiation, forming FBGC, which continue to attempt to degrade the implant in a process known as frustrated phagocytosis. 4. Fibrous encapsulation: fibroblasts attracted to the implant site by immune cell signaling deposit a collagen-rich ECM that surrounds the implant. FBGC, foreign body giant cell.

surface.[12,13] These proteins form what is known as a provisional matrix on the surface of the implant. The matrix acts as a source of bioactive agents comprising cytokines, growth factors, and chemoattractants, which leads to the recruitment and proliferation of a number of cell types involved in wound healing, such as immune cells and fibroblasts.[3] While macrophages and neutrophils attempt to phagocytose the foreign body, fibroblasts attracted to the implant by immune cell signaling deposit a collagen-rich ECM that surrounds the implant, completing the final two phases of FBR: granulation tissue deposition and fibrotic capsule formation.

FBR is a complicated and dynamic response, incorporating different cell types, materials, and signaling pathways (Fig. 3). We begin our discussion of FBR at the acute phase, where the macrophage is the predominant cell type, before delving into fibroblast subpopulations and functions in more detail.

Macrophage involvement

During normal wound healing, M1 macrophages release inflammatory cytokines, such as TNF-α and interleukin (IL)-6, antimicrobial peptides, and reactive oxygen species.[14] As this type of macrophage is phagocytic, it plays an important role in clearing debris and bacteria initially from the wound bed. In contrast to M1 macrophages that play a proinflammatory role in repair, M2 cells release anti-inflammatory mediators (TGF-β, IL-10, platelet-derived growth factor), which help stabilize the wound environment and promote angiogenesis, ECM deposition and remodeling, and cell proliferation.[15,16] Although macrophages are often placed into these binary categories, evidence suggests that macrophage phenotypes fall on a continuum with M1- and M2-type macrophages on either end.[14]

An important distinction between normal wound healing and FBR is the formation of multinucleated cells from macrophages.[17] Over the course of multiple days, as they continue attempting to phagocytose the foreign body, macrophages undergo additional differentiation and proceed to fuse into multinucleated foreign body giant cells (FBGCs). FBGCs surround the implant and are believed to secrete compounds such as reactive oxygen species and enzymes in an attempt to degrade the implant.[17] This process is known as frustrated phagocytosis.

During the acute inflammatory phase of FBR, mast cells release IL-4 and IL-13, attracting monocytes to the surgical site.[18] These monocytes differentiate into macrophages, which become the primary immune cell type in the implant bed during the chronic inflammatory phase.[3] There is conflicting evidence available regarding the phenotype of macrophages involved in FBR.[19] Some studies indicate that M1 macrophages are the primary macrophage subtype in all stages, while other *in vitro* assays indicate that formation of FBGCs relies on IL-4 and IL-13 signaling, both strong modulators of M2 type macrophages.[17] Other studies also indicate that macrophages associated with FBR lie in between the phenotypes of M1 and M2 macrophages.[19]

Following the acute and chronic inflammatory phases of the FBR, granulation tissue forms

around the implant, slowly transitioning to the formation of a chronic fibrotic capsule that will persist around the implant for as long as it is in the body.[3] Diverse cell types, including fibroblasts, keratinocytes, immune cells, endothelial cells, thrombocytes, and adipocytes, are involved in fibrotic capsule formation; however, it is believed that fibroblasts play the central role.[20]

Fibroblast involvement

Historically, fibroblasts were considered a homogeneous group of spindle-shaped cells that deposit collagen and are present in fibrotic tissue. However, growing evidence suggests that fibroblasts are a heterogeneous cell population exhibiting diverse morphologies and functions.[21,22] For one, fibroblasts demonstrate diversity at different sites of the body. Fibroblasts within the muscle, heart, gastrointestinal tract, and skin all exhibit specialized functions.

Murine dermal fibroblast heterogeneity. Notably, heterogeneity is also seen within a given tissue. In the dermis, for instance, fibroblasts exhibit different ECMs and distinct functional activities within the reticular and papillary dermis layers (Table 1).[21] During wound healing, reticular fibroblasts contribute to formation of the fibrillar ECM and participate in the initial stages of repair. Meanwhile, papillary fibroblasts demonstrate key roles in hair growth regulation, piloerection control, and are only recruited during the late stage of wound healing when re-epithelialization occurs.[21] Further multiomic analysis of neonatal murine skin cells revealed two additional specialized fibroblast subpopulations: (1) the dermal papilla defined by *Lamc3*, *Alx4*, *Bmp3*, *Sobp*, and *Draxin*; and (2) the preadipocyte defined by *Fabp4*, *Adipoq*, *Adig*, *Fabp12*, and *CD36*.[23]

In the context of murine wound healing, our group has identified four additional fibroblast lineages. *Engrailed-1* (*En1*)-positive and *En1*-negative fibroblasts are predominantly found on the mouse dorsum.[24] Meanwhile, paired-related homeobox 1 (*Prrx1*)-positive and *Prrx1*-negative fibroblasts are analogously present in the ventral dermis.[25] During wounding, *En1*-positive and *Prrx1*-positive fibroblasts are considered the dorsal and ventral scar-forming fibroblasts, respectively. When these fibroblast populations are ablated, cutaneous wounds heal with decreased scarring.

Murine skin has some capacity to regenerate and produce skin appendages such as hair follicles (HFs). Exactly how murine dermis regenerates and undergoes wound-induced hair follicle neogenesis (WIHN) is not well understood. It has been hypothesized that stem cells within HFs may be the primary contributors.[26–28] One study explored the concept of hair follicular stem cells (HFSCs) through single-cell RNA sequencing (scRNAseq) analysis of young and aged murine skin.[28] Aged HSFCs transplanted into young dermis were able to regenerate HFs, while young HFSCs transplanted into aged dermis failed to do so. These results suggested that the niche environment plays a crucial role in establishing cellular properties within the dermis.

Table 1. *Dermal fibroblast subpopulations*

Subtype	Role
Fibroblasts within murine dermis	
Reticular	Fibrillar ECM formation; initial stages of wound repair[21]
Papillary	Hair growth regulation; piloerection control; late stage of wound repair[21]
Dermal papilla (*Lamc3, Alx4, Bmp3, Sobp,* and *Draxin*)	Hair follicle development[23]
Preadipocyte (*Fabp4, Adipoq, Adig, Fabp12,* and *CD36*)	Skin repair, regeneration, adipogenesis[23,30]
En1-positive	Dorsal scar-forming, profibrotic fibroblast[24]
En1-negative	Dorsal proregenerative fibroblast[24]
Prrx1-positive	Ventral scar-forming, profibrotic fibroblast[25]
Prrx1-negative	Ventral proregenerative fibroblast[25]
Hic1-positive extrafollicular	Hair follicle regeneration[27]
Crabp1-positive upper wound	Wound-induced hair follicle neogenesis[26]
Fibroblasts within human dermis	
Hypothesized types and subtypes	
Reticular dermis; deep dermis; upper dermis[31]	1. Dermal cell, ECM homeostasis
Alternatively: 3 major subtypes and 10 subtypes[33]	2. Immune surveillance and inflammatory promotion
	3. Specialized roles (dermal papilla, dermo-hypodermal junction

Growing evidence suggests that fibroblasts are a heterogeneous population of cells that vary in morphology and function. In this study, we highlight the different fibroblast subpopulations identified within murine and human dermis as an example of fibroblast heterogeneity.

Adig, adipogenin; *Adipoq, adiponectin*; *Alx4, ALX homeobox 4*; *BMP3, bone morphogenetic protein 3*; *Crabp1, cellular retinoic acid-binding protein 1*; ECM, extracellular matrix; *En1, engrailed-1*; *Fabp12, fatty acid-binding protein 12*; *Fabp4, fatty acid-binding protein 4*; *Hic1, HIC ZBTB transcriptional repressor 1*; *Lamc3, laminin subunit gamma 3*; *Prrx1, paired-related homeobox 1*; *Sobp, Sine oculis-binding protein homolog.*

Interestingly, complementary fate mapping within murine dermis performed by another group demonstrated that progenitor cells from HFs contributed very little to wound regeneration.[27] Instead, their single-cell profiling of murine skin indicated that it was wound activation along with exposure to a permissive environment that activates a latent regenerative capacity of fibroblasts within the wound bed. They conclude that *Hic1*-lineage-comprising extrafollicular fibroblasts were the primary cells contributing to HF regeneration within the permissive microenvironment.

In parallel, another study compared recently published scRNAseq data of small scarring wounds with wounds that regenerated to identify a potential subpopulation of fibroblasts that contributed to WIHN. They identified a novel upper wound fibroblast within the regenerative condition that expresses retinoic acid-binding protein Crabp1.[26]

Heterogeneity also exists within the myofibroblast subpopulation. Characterized by a contractile phenotype, myofibroblasts within the wound bed participate in the organization of the new collagen-rich ECM into a mechanically resistant scar.[9] The cell progenitors of myofibroblasts for many tissues fall under the umbrella term of "fibroblasts"; however, variation is seen depending on organ type.[29]

In the context of skin, a recent study analyzing mouse dermal wound healing and aging established that there were two classes of myofibroblasts: smooth muscle actin $(SMA)^+$ and collagen 1^+ cells.[30] These cell groups varied in their cellular origins, with one expressing adipocyte precursor (AP) cell markers, and the other expressing high levels of CD29 ($CD29^{High}$). Interestingly, AP cells were shown to be derived from *En1*-lineage fibroblasts, and during wound healing, a large proportion of APs expressed profibrotic markers, such as CD26 and CD9.[30] Myofibroblasts also varied in spatial organization, with APs spread throughout the wound, whereas $CD29^{High}$ cells were localized mainly at the outer, superficial areas of the wound.

Human dermal fibroblast heterogeneity. Although there have been diverse murine fibroblast populations described to date, fibroblast subtypes present in human dermis are less well understood.[31,32] Recent studies are emerging that indicate human fibroblasts exhibit similar heterogeneity to that present in mice, although conclusions currently vary between groups (Table 1). In one study, five distinct fibroblast subpopulations were found in human skin using spatial and single-cell transcriptional profiling.[31] Their work demonstrated the following subpopulations of fibroblasts: three subtypes in the reticular dermis, a preadipocyte population within the deep dermis, and one population in the upper dermis.

More recently, another group reanalyzed transcriptomic data from ~14,000 human adult dermal fibroblasts and assigned them to 3 major types and 10 subtypes.[33] Major types functioned in (1) dermal cell and ECM homeostasis; (2) immune surveillance and inflammatory promotion; and (3) more specialized roles such as in the dermal papilla or dermo-hypodermal junction. A recent study conducted scRNAseq of human eyelid skin. These data confirmed the presence of reticular and papillary fibroblasts previously described.[34]

The group harvested eyelid skin from human patients across different ages, which revealed gradual increases in photoaging-related and chronic inflammatory changes with age. Interestingly, this team found that fibroblasts had the highest extent of age-related transcriptional variability of all the clusters they identified in their analyses. They determined transcription factor *HES1* expression within fibroblasts declined during aging. Inhibition of *HES1* decreased cell proliferation, and increased inflammation and cell senescence.

Although little consensus has been achieved about specific subpopulations that make up human fibroblasts, these studies illustrate the growing evidence of human fibroblast heterogeneity.

Fibroblast heterogeneity within FBR. As mentioned, much remains to be explored regarding the morphology and function of fibroblasts in the context of FBR. When macrophages begin releasing TGF-β into the implant bed during FBR acute phase, fibroblasts migrate to the area and surround the biomaterial's surface.[3,35,36] The mechanism by which fibroblasts localize to the implant site is not yet well understood. Once there, similar to normal wound healing, the fibroblasts attempt to re-establish the tissue architecture and mechanical integrity of the implant site by replacing the temporary fibrin with collagen-rich ECM. In parallel, some fibroblasts transition into myofibroblasts.[37] Altogether, fibroblasts and myofibroblasts become the primary cells surrounding the implant 4 weeks after implantation of the biomaterial.[38] In cases where FBR is severe, the capsule surrounds the entirety of the implant, effectively walling off the foreign material from the rest of the body.

Biomaterials

Many factors influence protein adsorption, a key component of provisional matrix formation during FBR.[3] It has been established that different

features of the biomaterial influence protein adsorption and alter the magnitude of the FBR. Furthermore, the degradation of the biomaterial itself has also been shown to be an important contributor of FBR. In the case of dental implants, for instance, ions and particles that get released from the material have been shown to further evoke an immune response, leading to bone resorption and peri-implant disease.[39] Below, we will summarize investigations in the following features of a given biomaterial: chemical composition and coatings, implant topography, and implant stiffness (Fig. 4).

Materials and coatings. Materials used in implants are variable and dependent on their applications in the body. For instance, electrode arrays require coating conductivity, while joint replacements need to meet the demands of weight-bearing impact and locomotion. Meanwhile, extensive research is being conducted to develop materials that invoke a subdued FBR while still providing the desired function. Figure 5 illustrates the difference in FBR created by two different materials: poly(ethyleneglycol) (PEG) and poly-DL-serine (PSer) hydrogels.

The development of novel, low-fouling polymers has been a significant focus. Some polymers such as PEG, poly(ethylene oxide) (POE), and polyhydroxymethacrylate (PHEMA) result in a lower fibrotic response; however, these materials still demonstrate a degree of protein adsorption and cell adhesion.[40] Zwitterionic polymers, particularly ones used to coat implants, have been shown to produce intrinsically low FBR responses, and are a promising option for hydrogel-based cell therapies. Novel materials are also in development. One set of compounds known as triazole-modified alginates, has been shown to incur lower inflammation and fibrosis markers.[41] Another compound makes use of composite materials known as immobilized liquid interfaces and has a repellent liquid such as perfluorocarbon liquid at its surface.[42] Preliminary results for both materials suggest they hold promise in decreasing FBR in future implant development.

In addition to the implant material itself, others are conducting research into coating implants with antifibrotic drugs. For instance, microstents coated with pirfenidone, an antifibrotic agent, implanted in rats demonstrated decreased fibrotic capsule formation relative to controls.[43]

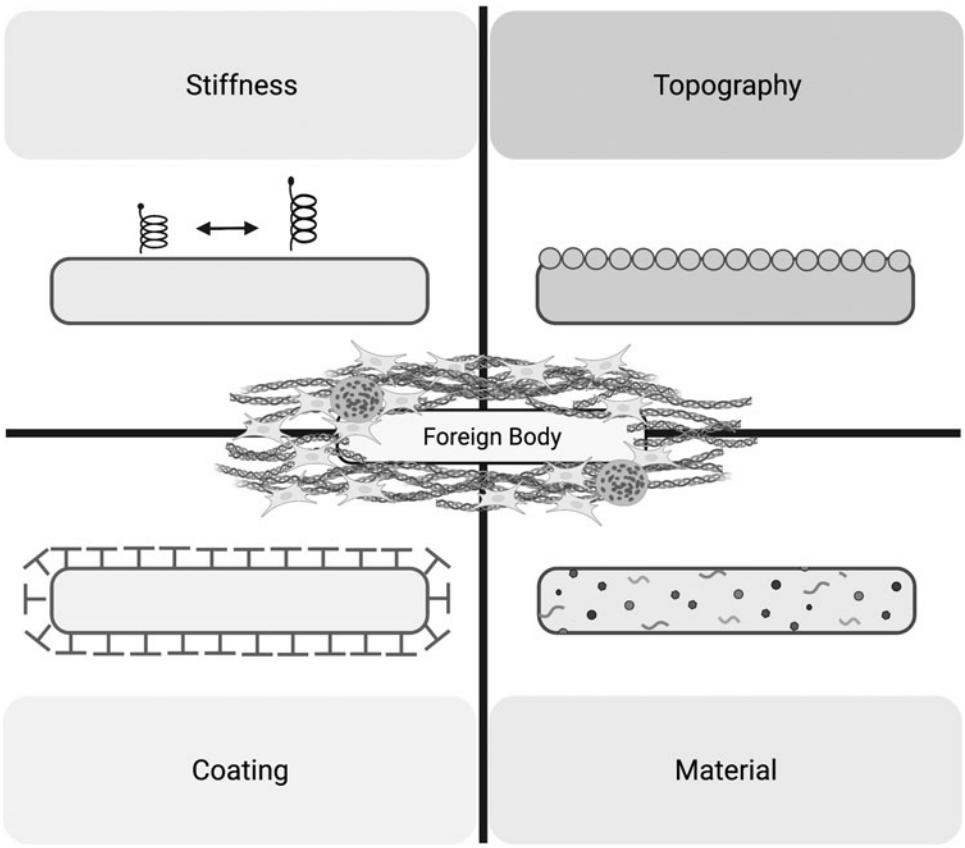

Figure 4. Examples of biomaterial modification used to modulate foreign body response. Changes to stiffness, topography, coating, and material have all been shown to alter implant foreign body response.

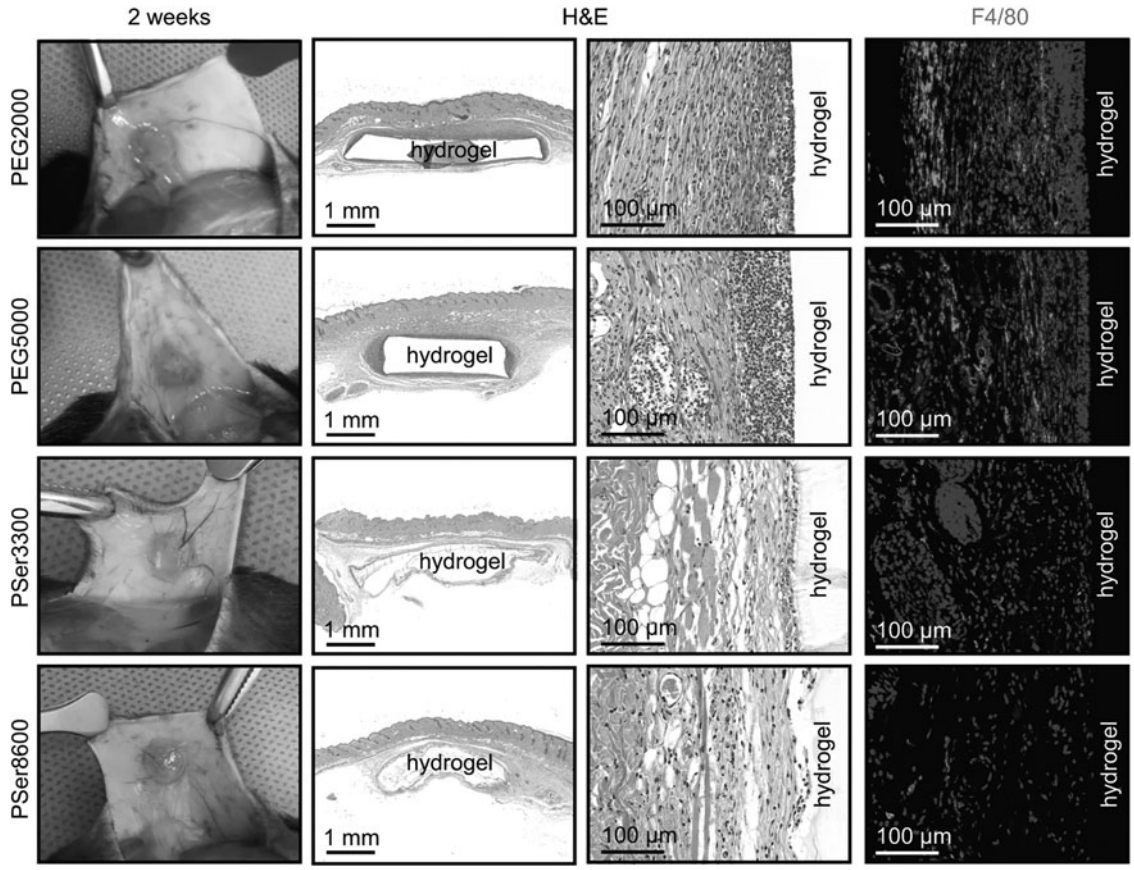

Figure 5. Comparison between foreign body response formation around PEG and PSer hydrogels as an example of the effect of biomaterial on fibrotic capsule formation. A visible reduction in the thickness and density of the fibrotic capsule is seen with the use of PSer hydrogels (*bottom* two *rows*) when compared with PEG hydrogels (*top* two *rows*). PEG, poly(ethyleneglycol); PSer, poly-DL-serine. Taken with permission from "Explantation and staining images of PEG and PSer hydrogels after subcutaneously implanted in mice for 1 week (a) and 2 weeks (b)" (panel B) by Zhang et al.[63]

Topography. Altering the surface architecture is another widely explored strategy to modulate immune response and fibrosis associated with FBR. In the context of breast implants, smooth, micro, and macrotextured implants are currently available.[44] However, macrotextured implants have been associated with breast implant-associated anaplastic large cell lymphoma.[45] A detailed investigation of the effect of surface topography on fibrotic capsule formation recently described that there appears to be a "goldilocks" surface roughness that reduces foreign body capsule formation.[44] Any lower or higher, and the immune system responds more significantly.

Stiffness. Often, tissues in which implants are placed have a stiffness that can be substantially lower compared with the implant itself. Breast implants, for example, although they may appear soft as they are often filled with a liquid or gel, have an outer shell that is a 1,000 times stiffer compared with the dermis.[46] Mismatch in the stiffness between the tissue and implant can lead to mechanical activation of inflammatory and fibroblastic cells seen in FBR. Indeed, a soft silicone coating with an elastic modulus similar to that of dermis around implants placed in mice led to a decreased fibrous encapsulation when compared with stiffer implants of the same size and shape.[46]

Signaling and FBR

Various signaling molecules have been associated with FBR, although further investigation is needed to grasp a more complete understanding of the specific pathways involved in the different stages of FBR. We will describe profibrotic and mechanotransduction pathways believed to direct fibroblast function and fibrotic capsule formation, specifically.

Fibrotic signaling. It is well known that TGF-β promotes fibrosis in many tissues, and numerous studies have demonstrated elevated TGF-β levels during fibrotic capsule formation.[47] TGF-β signaling primarily functions through transmembrane

Table 2. *Potential therapeutics to target foreign body response*

Therapeutic compound	*FBR fibrotic pathway targeted*	*Model tested*	*Reference*
Pirfenidone	TGF-β	Rat; daily injection; 8 weeks	Gancedo et al[57]
Decorin	TGF-β	*In vitro*; decorin-modified titanium surface	He et al[58]
CWHM-12	TGF-β	Mouse; mini osmotic pump; 7 and 28 days	Noskovicova et al[46]
Roxatidine	MAPK	Mouse; oral gavage with roxatidine for 14 days postimplant surgery; 90 days	Ji et al[59]
Verteporfin	YAP; mechanotransduction	Rabbit; injection within implant pocket upon implantation; 60 days	Yi et al[60]
AM-111 (brimapitide)	JNK	Guinea pig; drug administered 30 min before cochlear implantation; 90 days	Eshraghi et al[61]

Below we outline therapeutic strategies tested in implant models targeting antifibrotic pathways associated with FBR.
FBR, foreign body response; JNK, c-Jun-N-terminal kinase; MAPK, p38 mitogen-activated protein kinase; TGF-β, transforming growth factor-beta; YAP, yes-associated protein 1.

receptor serine/threonine kinases to activate Smad proteins, signaling intermediates that in turn activate transcription of profibrotic target genes.[48] However, TGF-β also acts through Smad-independent pathways, including extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun-N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3′-kinase (PI3K)–protein kinase B (AKT) pathways.[49] Inhibition of TGF-β has been shown to decrease fibrotic capsule formation in mice, and its association with a variety of signaling pathways underscores the multiple avenues investigators could take in inhibiting TGF-β to subdue FBR.[46]

Although it does play a role in fibrosis, TGF-β is also crucial for multiple homeostatic processes, including embryogenesis, angiogenesis, immune modulation, and cell differentiation.[50] In human studies, inhibition of TGF-β1 signaling at the levels of its isoforms and receptors has failed numerous times due to systemic complications, and has been shown to impede tissue healing.[50,51] It is therefore believed that the development of a phased, lineage-targeted approach bodes more promise as a therapeutic option.

Mechanotransduction. Mechanotransduction allows cells to respond to mechanical cues through electrochemical signaling. There are a number of extracellular and cellular components that act as mechanosensors, which transmit signal to cells and lead to transcriptional changes when under mechanical stress.[52] It has been previously shown that sustained mechanical load to an incision increased fibrotic response and hypertrophic scar formation in a mouse model, indicating that mechanical stress plays a key role in scarring and fibrosis.[53] The importance of mechanical stress in FBR has been similarly demonstrated.[54]

Key contributors to detecting mechanical stress are transmembrane proteins known as integrins. Formed with different alpha and beta subunits, integrins bind to a variety of ECM proteins, act as bidirectional cell receptors transmitting signals across the plasma membrane, and control cytoskeletal organization.[55] There are many integrins with various functions in FBR, ranging from immune cell recruitment and FBGC formation, to fibroblast recruitment and activation. Integrins can sense extracellular forces applied to the cell by the biomaterial in proximity to it, and in turn facilitate communication and coordination of these cell types during the acute and chronic stages of FBR.[56]

Importantly, additional mechanotransduction pathways alongside mechanical-sensing integrins may present essential areas of exploration in the field of FBR. YAP, Hippo, and Rho/ROCK signaling have all been shown to play key roles in mechanotransduction signaling in wound healing.[24] Given parallels seen between wound healing and FBR, exploration of these pathways in the context of foreign materials may provide additional possibilities for potential drug targets in the future. A few studies exploring inhibitors of fibrotic and mechanotransduction pathways have been conducted, although further study will be necessary to identify effective antifibrotic therapies that could be used in patients. A list of these compounds along with their targeted pathways and FBR models used are summarized in Table 2.

FUTURE DIRECTIONS AND CONCLUSIONS

As alluded in this study, FBR continues to be a serious clinical complication for which the mechanisms are not completely understood. Although the field has elucidated cell types and signaling molecules responsible for the acute and chronic stages of FBR, gaps remain in appreciating the roles of fibroblasts. Although we are aware of their function in forming the fibrotic capsule around a foreign biomaterial, the exact mechanisms providing fibroblasts with the necessary cues remain elusive.

Furthermore, given the heterogeneity in both morphology and function of fibroblasts described

within healthy and wounded dermis, one is left contemplating whether subpopulations of fibroblasts are also seen in the context of FBR. Indeed, many parallels are already appreciated between wound healing and FBR, and so it would not come as a surprise if a similar spectrum of fibroblast morphology and function is seen upon biomaterial implantation. Exploration of potential fibroblast subpopulations at a transcriptional level would provide key insights into answering this question, and these investigations may also provide deeper understanding of the nuances of different fibrotic and mechanical signaling pathways involved.

In addition, although a number of animal models exist to study FBR, the field would benefit from the use of transgenic animal studies along with genetic engineering approaches that could add necessary depth to decipher the mechanisms and subpopulations of fibroblasts associated with fibrotic encapsulation. Altogether, these future perspectives may help unveil novel directions for antifibrotic and regenerative therapies in the future.

TAKE-HOME MESSAGES

- The global implantable devices market is a multi-billion-dollar industry.
- A common surgical complication known as FBR results in the formation of a fibrotic capsule around the implanted medical device, leading to pain, discomfort, and device failure.
- FBR is an immunologic reaction that involves multiple cell types and signals at the implant site.
- During the acute phase of FBR, immune cells, including neutrophils and macrophages attempt to phagocytose the implant.
- Meanwhile, signals released by immune cells attract fibroblasts to the implant site. They deposit a collagen-rich, fibrotic matrix around the implant, effectively walling it off from the rest of the body.
- Although fibroblasts are believed to be key players in fibrotic capsule formation, the specific fibroblast subpopulations involved, and the roles that these play in FBR is not well understood.
- Research into different biomaterials and implant coatings to reduce fibrotic capsule formation due to FBR is ongoing.
- Increased understanding of the fibroblast subpopulations involved in FBR, and the mechanisms by which these fibroblasts form a fibrotic capsule around the implant may allow for the development of novel antifibrotic and regenerative therapies.

SUMMARY

Used in most surgical specialties, implants have become a ubiquitous component of modern medicine. Although the use of implants has benefited countless patients, an inflammatory reaction known as FBR remains a common and significant surgical complication. The field has gained an increased understanding of the cell types and signaling molecules that participate in the different stages of FBR; however, specific details regarding the role fibroblasts play remain elusive. In parallel to the work currently being conducted to develop antifibrotic biomaterials and implant coatings, a deeper understanding of the subpopulations of fibroblasts and mechanisms by which they are involved in FBR may provide the field with additional avenues for antifibrotic and regenerative therapies.

AUTHORS' CONTRIBUTIONS

J.B.P. wrote the article. M.F.G., A.F.S., D.C.W., and M.T.L. edited the article. Written consent was received from all authors to submit the article and all authors accept complete responsibility for the contents of the article.

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AUTHOR DISCLOSURE AND GHOSTWRITING

The authors declare no competing or financial interests.

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Abbreviations and Acronyms

Adig = adipogenin
Adipoq = adiponectin
AKT = protein kinase B
Alx4 = ALX homeobox 4
AP = adipocyte precursor
Bmp3 = bone morphogenetic protein 3
Crabp1 = cellular retinoic acid-binding protein 1
ECM = extracellular matrix
En1 = engrailed-1
ERK1/2 = extracellular signal-regulated kinase 1 and 2
Fabp12 = fatty acid-binding protein 12
Fabp4 = fatty acid-binding protein 4
FBGC = foreign body giant cell
FBR = foreign body response
H&E = Hematoxylin and Eosin
HES1 = Hes family BHLH Transcription Factor 1
HF = hair follicle
HFSC = hair follicular stem cell
Hic1 = HIC ZBTB transcriptional repressor 1
IL = interleukin
JNK = c-Jun-N-terminal kinase
Lamc3 = laminin subunit gamma 3
MAPK = p38 mitogen-activated protein kinase
PEG = poly(ethyleneglycol)
PHEMA = polyhydroxymethacrylate
PI3K = phosphatidylinositol 3′-kinase
POE = poly(ethylene oxide)
Prrx1 = paired-related homeobox 1
PSer = poly-DL-serine
scRNAseq = single-cell RNA sequencing
SMA = smooth muscle actin
Sobp = Sine oculis-binding protein homolog
TGF-β = transforming growth factor-beta
TNF-α = tumor necrosis factor-alpha
WIHN = wound-induced hair follicle neogenesis
YAP = yes-associated protein 1