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Crosstalk between T cells and fibroblasts in biomaterial-mediated fibrosis☆

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A B S T R A C T

Biomaterial implants are a critical aspect of our medical therapies and biomedical research and come in various forms: stents, implantable glucose sensors, orthopedic implants, silicone implants, drug delivery systems, and tissue engineered scaffolds. Their implantation triggers a series of biological responses that often times lead to the foreign body response and subsequent fibrotic encapsulation, a dense ECM-rich capsule that isolates the biomaterial and renders it ineffective. These responses lead to the failure of biomaterials and is a major hurdle to overcome and in promoting their success. Much attention has been given to macrophage populations for the inflammatory component of these responses to biomaterials but recent work has identified an important role of T cells and their ability to modulate fibroblast activity and vice versa. In this review, we focus on T cell-fibroblast crosstalk by exploring T cell subsets, critical signaling pathways, and fibroblast populations that have been shown to dictate biomaterial-mediated fibrosis. We then highlight emerging technologies and model systems that enable new insights and avenues to T cell-fibroblast crosstalk that will improve biomaterial outcomes.

Introduction to interplay between T cells and fibroblasts

Biomaterials play a critical role in medicine and biomedical research by enabling different therapeutic strategies. They include soft tissue implants, metal implants, glucose sensors, intraocular lenses, and vascular stents, improving patient outcomes and quality of life. Additionally, biomaterials have also driven innovations in drug delivery systems, improving the efficacy and targeting of therapeutic agents. Their unique properties and versatility enable groundbreaking applications in regenerative medicine and wound healing. However, biomaterials usually trigger a series of biological responses upon implantation, often leading to an inflammatory foreign body response (FBR) and fibrotic encapsulation, which can compromise the functionality of the implanted material [1–7] (extensively reviewed by [8–10]).

The FBR is a complex cascade of events involving the recruitment and activation of immune cells, and crosstalk between the immune and stromal compartments governs the FBR [11]. The FBR occurs across four stages: (1) blood-material interactions, (2) acute inflammation, (3) chronic inflammation, and (4) fibrotic encapsulation phase. Shortly after implantation, protein adsorption occurs, where protein from the blood adsorbs to the biomaterial's surface directing the tissue-resident and early innate immune cells, including neutrophils, which are recruited upon implantation and contribute to acute inflammation. This inflammation recruits monocytes that differentiate into macrophages and activate tissue-resident macrophages at the implant site. Macrophages play a significant role in dictating the outcomes of implanted biomaterials. They exhibit different phenotypes that influence the tissue response to implanted materials, among them is fusing into foreign body giant cells (FBGC) and exacerbating the inflammatory response [12–14]. The subsequent step involves fibrotic encapsulation, where a collagenous capsule forms around the implant via activated myofibroblasts [15], leading to isolation and failure of the biomaterial implant. Studies have demonstrated that macrophages are crucial for orchestrating proinflammatory responses to biomaterials. Surprisingly, macrophages appear dispensable for generating a fibrous capsule around biomaterials based on not exclusively being responsible for promoting capsule formation, implicating a role for adaptive immunity in responses to biomaterials [16].

The adaptive immune system, comprised primarily of T cells, B cells, Natural Killer cells, γα T cells, and Innate-like lymphocytes, confers antigen-specific and long-lasting immune responses [17]. Unlike innate immunity, which provides immediate non-specific defense, adaptive immunity responds to particular epitopes on antigens. It offers long-lasting memory of earlier encounters with antigens via the development of memory T and B cells along with antigen-specific antibodies. The role of adaptive immunity in biomaterial-mediated fibrosis has recently been appreciated and explored to identify critical populations of lymphocytes that contribute to implant success [18–20] (Fig. 1). However, lymphocytes do not exist in isolation and more studies have begun investigating the intersection of lymphocytes with fibroblast activation.

Fibroblasts are responsible for the deposition and turnover of the

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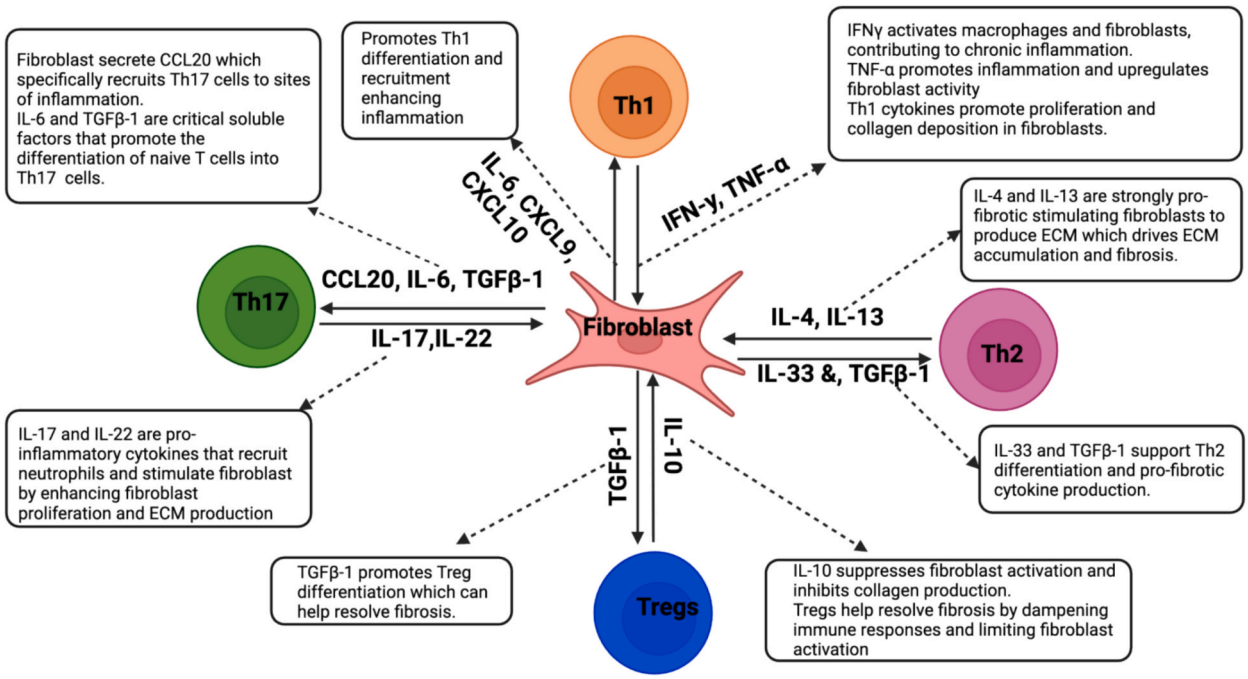

Fig. 1. Outline of T cell subsets and fibroblast crosstalk via cytokines, chemokines, and growth factors.

extracellular matrix (ECM) and play a pivotal role in tissue development, repair, and fibrosis. During tissue repair and wound healing, fibroblasts undergo activation in response to biophysical or biochemical cues, leading to new ECM deposition and tissue remodeling [21]. In the case of implanted biomaterials, the new ECM can either facilitate the biomaterial's function by de novo tissue synthesis integrating with the

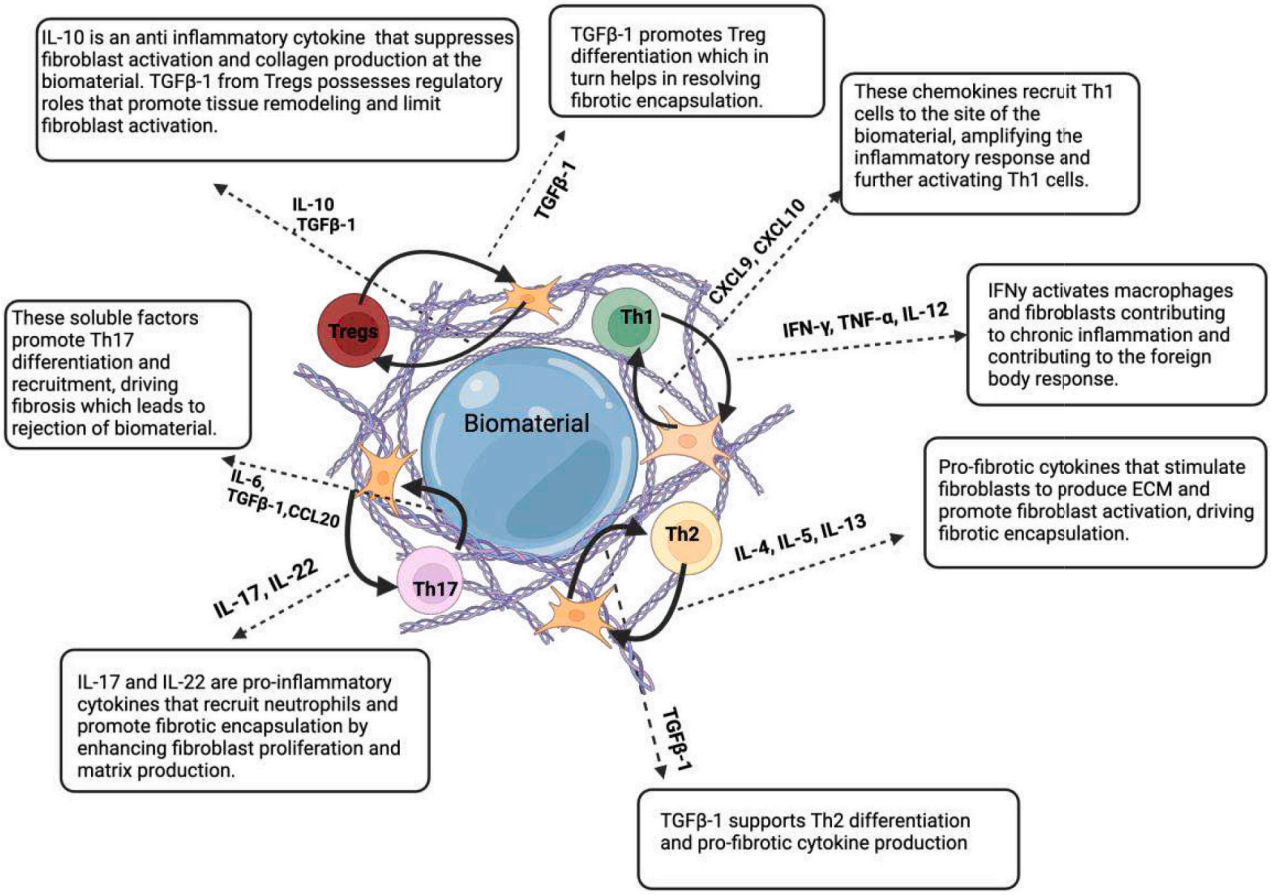

Fig. 2. Outline of T cell subset and fibroblast crosstalk in biomaterial-mediated fibrosis.

biomaterial or promote rejection and failure by isolating the biomaterial with a fibrotic capsule [22]. Throughout the response to implanted biomaterials, fibroblasts communicate with immune cells, dictating one another's phenotype and fate.

The crosstalk between T cells and fibroblasts plays a significant role in the response to biomaterials. Fibroblasts are responsible for regulating extracellular matrix deposition, crosstalk with immune cells, and applying contractile forces on the surrounding tissue. However, their dysregulation can lead to fibrotic outcomes and compromise the function of implanted materials. Within the cellular crosstalk between fibroblasts and immune cells, T cells have emerged as a critical cell population. This review highlights the recent understanding of T cell crosstalk with fibroblasts in biomaterial-mediated fibrosis and future directions to better understand the dynamics of this relationship. Understanding the specific mechanisms of T cell-fibroblast interactions can provide insights into curbing biomaterial-mediated fibrosis and improving the integration and success of biomaterials in medical applications.

T cell diversity in biomaterial-mediated fibrosis

T cell development occurs in the thymus before migrating to secondary lymphoid tissues [11]. T cells undergo antigen-specific activation, mediate activation of other immune cell populations, kill infected host cells, and regulate immune responses. They are divided into two classes: cytotoxic T cells and helper T cells (T_H). Cytotoxic T cells express CD8 and are chiefly tasked with killing infected cells. T_H expresses CD4 and are known for producing soluble factors that aid in orchestrating cell function and phenotype that drive immune responses to antigens [23]. T_H can be broken down further into T_H subtypes: Th1, Th2, Th9, Th17 and regulatory T cells (Tregs). Each T_H subset is defined by activating signals, key transcription factors, specific contexts in which they arise, and cytokines they release. It has been demonstrated that each of these T_H subset plays a role in promoting either biomaterial-mediated fibrosis or repair, and these outcomes are informed by interactions with fibroblasts (Fig. 2).

T helper type1 cells (Th1)

T helper type 1 cells (Th1) activate macrophages towards a pro-inflammatory phenotype, and their presence typically correlates with localized inflammation against intracellular pathogens. Th1 cells promote a type 1 response and secrete IFN-γ, TNF-α, and IL-12, which are associated with acute inflammation [23]. Recently, studies have shown that elevated IFN-γ levels in human synovial fluid are associated with foreign body reactions in hip arthroplasty [24]. A subsequent study has demonstrated the existence and upregulation of IFN-γ in response to rough silk breast implants on rabbits for six months; researchers observed the same results when implanted in mice. IFN-γ contributes to the polarization of macrophages towards a pro-inflammatory phenotype, which is well associated with releasing reactive oxygen species, pro-inflammatory cytokines, and chemokines, creating an inflammatory microenvironment at the implant site [25]. In addition, Th1 cells contribute to the exacerbation of biomaterial-mediated fibrosis by activating fibroblasts. IFN-γ plays a role in stimulating fibroblasts to produce collagen and other ECM proteins. Cassini and colleagues have shown that Th1 cells can drive fibrosis during FBR yet also seem to contribute to angiogenesis [26].

It has been reported that during *peri*-silicone implantation, capsule formation was one of the most frequent postoperative complications in patients receiving silicone mammary implants. In this study, the authors studied immune response activation by phenotypic and functional characterization of lymphocytes accumulated within the tissue. They compared systemic cellular composition in the peripheral blood and intracapsular lymphocytes, where they showed a predominance of CD4 + cells. The most noticeable result they found was that intracapsular T cells secreted a litany of cytokines (i.e., IL-17, IL-6, IL-8, IFN-γ, and TNF-α). Furthermore, they observed an inverse correlation between the severity of capsular fibrosis and the number of T-regulatory cells in the fibrotic tissue. These results indicate that silicone implants trigger a local immune response through activated Th1/Th17 cells. This response promoted fibrosis due to these cytokines, potentially due to the impaired function of local T regulatory cells [27].

Furthermore, Th1 cells can interact with regulatory T cells (Tregs) to balance the immune response. In a study by Zhang et al. (2021), the interplay between Th1 cells and Tregs was crucial in regulating fibrosis around biomaterial implants. Tregs were necessary to temper the pro-inflammatory effects of Th1 cells, preventing chronic inflammation and excessive fibrosis. In summary, Th1 cells play a vital role in FBR, mediating the initial immune activation and the chronic inflammatory response. Their interaction with macrophages and cytokine production are critical contributors to the FBR. By understanding the mechanisms underlying Th1 cell activation and function in the context of biomaterial-mediated fibrosis, researchers can develop strategies to modulate this response, potentially enhancing the success of the implants. In addition, targeting the Th1 cell pathway presents a promising strategy for mitigating the adverse effects of the FBR. Approaches such as local delivery of anti-inflammatory cytokines, modulation of antigen presentation, and engineering of biomaterial properties to dampen Th1 activation [28].

T helper type 2cells (Th2)

Th2 cells are characterized by the production of IL-4, IL-5, and IL-13. These cytokines can modulate the immune response by promoting a type 2 response. They are historically associated with allergies, asthma, parasitic infections, and immune responses to tumors. While Th2 cells promote inflammation in the context of allergies and asthma, Th2 cells also participate in tissue regeneration and repair by resolving inflammation, yet ineffective management of type 2 responses leads to biomaterial-mediated fibrosis. The role of Th2 cells in being either regulatory or inflammatory still depends on a few variables, such as tissue context or duration of Th2 activation.

Th2-mediated IL-4 is an essential inducer in the activation of anti-inflammatory macrophages, which enables healing and remodeling around implanted material [29]. Th2 cytokines are necessary for pro-regenerative biomaterials. Sadtler and colleagues have shown that regenerative biomaterial scaffolds require mTORc2-dependent Th2 cells in functional tissue regeneration [20]. Hotchkiss and colleagues have shown that intramedullary implantation of titanium rods results in local and systemic changes in inflammatory profile. More specifically, they found changes in macrophage levels surrounding implants depending on implant wettability. Increased initial macrophage populations were correlated with an increase in Th2 [30].

The role of Th2 cells in the mechanistic development of FBR can be either inflammatory or regulatory. Interleukin-4 (IL-4) and interleukin-13 (IL-13) produced by Th2 cells in the chronic inflammatory phase enhance macrophage fusion to form foreign body giant cells, which release reactive oxygen species and enzymes that degrade the implanted material [11]. Some groups have portrayed a proliferation of Th2 cells in a fibrotic environment, demonstrating a connection between Th2 cells and the FBR. Martin and colleagues found that biomaterials prepared with xenogeneic serum components elicit a robust type 2 response with increases in eosinophils, $CD4^+$ T cells, and type 2 cytokines, such as IL-4, IL-5, and IL-13, impairing tissue repair. The production of IL-5 enhances and promotes the activation and recruitment of eosinophils, specialized immune cells that participate in allergic responses and defense against parasites. In this study, they conclude eosinophils contribute to the inflammatory process associated with FBR [12].

Other research studies have investigated the importance and role of Th2-associated cytokines cells in the FBR. Balb/c mice were implanted with three biomaterials: elastane (PEU), polyethylene terephthalate

(PET), and silicone rubber. Notably, IL-13 expression was not detected during harvest time, suggesting that Th2 cells may not be as necessary as previously thought for promoting anti-inflammatory responses [31]. Allman and colleagues found that porcine small intestine submucosa (SIS) promoted tissue repair and elicited a dominant Th2 immune response in a mouse model [32]. Using the renal ischemia–reperfusion murine (IRI) model, Marques and colleagues found that Th2 and Th1 are incredibly important in the pathogenesis of renal IRI. IL-4 deficient (i.e., Th2 deficient) mice displayed more severe impairment in renal function with elevated IL-12 [33].

Lastly, regulating and promoting the resolution of Th2 activation can determine whether the type 2 immune response is pathogenic or protective. Th2 cells play a pivotal role in biomaterial-mediated fibrosis by producing IL-4 and IL-13, which drive fibroblast activation and ECM production, while chronic production of those cytokines can also promote fibrotic encapsulation. They also interact with macrophages and other immune cells to amplify the fibrotic response. Recent studies underscore the importance of these cells in fibrosis and suggest potential therapeutic targets to mitigate the fibrotic response. Further research into regulating Th2 cells and their cytokines could improve outcomes for biomaterial implants.

T helper type17 cells (Th17)

Th17 cells are a critical player in the foreign body response (FBR) and biomaterial-mediated fibrosis. In a study by Chung and colleagues, a urinary bladder matrix-based scaffold and a synthetic polycaprolactone (PCL) biomaterial were implanted and used to study immune cell responses to biomaterials. The PCL implant triggered a foreign body response, with enriched Th17 cells and IL-17 expression, demonstrating their critical roles in driving the fibrotic response. This study revealed how Th17 cells interact with senescent cells to contribute to fibrosis. These findings suggest that cellular senescence sustains excess fibrosis and connects chronic IL17 production and fibrogenesis during FBR [18]. In the study referenced earlier by Wolfram and colleagues, intracapsular T cells produced IL-17, IL-6, IL-8, TGF- β1, and IFN-γ, suggesting that Th17 contributed to capsule formation with silicone implants [27]. This provides more evidence that Th17 contributes to biomaterial-mediated fibrosis. Contrasting studies by Hotchkiss et al. have shown that there seems to be a reduced percentage of pro-inflammatory Th17 cells surrounding Ti implants compared to sham operations at three days after implantation; however, fewer differences were found by day seven [30].

Contrary to their pro-fibrotic effects, Th17 cells have been involved in tissue regeneration and repair following implantation, a promising avenue for future research and therapeutic applications. Studies have shown that IL-17 stimulates the production of angiogenic factors such as vascular endothelial growth factor (VEGF), enabling the formation of new blood vessels and improving perfusion, essential for tissue regeneration [34]. However, Th17 cells also show regulatory functions that help modulate the intensity and duration of the response. Regulatory mechanisms involving Th17 cells, derived from cytokines such as IL-10 and IL-22, limit excessive inflammation, thus enabling tissue repair. On the other hand, it has been shown that Th17 has dynamic crosstalk with senescent cells, where they can engage in tissue repair or fibrosis. Th17 cells and senescent fibroblasts engage in a positive feedback loop. In summary, Th17 cells have been observed at both acute and chronic times in the FBR to biomaterial implants. These findings highlight the potential role of Th17 cells in mediating the immune response and subsequent biomaterial-mediated fibrosis. Further research into the specific mechanisms and interactions of Th17 cells within the FBR could provide valuable insights for developing targeted therapies to improve biocompatibility and reduce adverse fibrotic outcomes in biomaterial implantation.

Regulatory T cells (T_{reg})

Tregs, a subset of T_H characterized by their expression of forkhead box p3 (Foxp3) and immunosuppressive roles, they have emerged as essential regulators of immune responses in various contexts. Critical studies have found that Tregs are generated in response to TGF-β1 and are involved in self-tolerance and immune suppression (as reviewed [35]). For example, Tregs can suppress multiple forms of autoimmune disease. Recent studies have begun to unravel the role of Tregs in modulating FBR and fibrosis, thus offering new insights into how to improve outcomes of biomaterials. Tregs tend to inhibit pro-inflammatory responses and promote tissue repair by suppressing the activation and effector functions of innate and adaptive immune cells. One thing to note is that the differentiation and activation of Tregs depend on the activation of Foxp3 via TGFβ-1 signaling. The role of Tregs in the foreign body response (FBR) is the subject of debate due to conflicting evidence regarding their impact. Some studies suggest that Tregs play a beneficial role by promoting tissue regeneration in various tissues, such as the lungs [36], cardiac muscle [37], bone [18], and skin [38]. However, contrasting findings indicate that Tregs possess a dual nature, which could potentially impact the outcome of FBR.

Interestingly, a study by Dievernich and colleagues has shown an increase in Treg level in FBR, compared to other cell subsets when polypropylene meshes are used as surgical implants for abdominal wall hernia repair. This outcome was associated with complications with pain being the primary clinical presentation [39]. While Tregs are not typically associated with fibrosis, their ability to secrete TGFβ-1, as shown in this study, indicates that dysregulation of Tregs might enable fibrotic outcomes. However, it could also be true that Treg abundance was in response to the FBR of polypropylene meshes, not causing it. Determining the Treg relationship as either being in response to or causing the FBR is critical.

Other studies have found Tregs were higher in capsules with less fibrosis. Tregs corresponded to fibrotic capsules where there was a total reduction of myofibroblast, macrophages, and TGFβ-1. Artsen and colleagues depicted Tregs and other T cell subtypes present after mesh implantation and identified an inverse relationship between fibrosis and Tregs, depicting a protective and anti-fibrotic role [40]. Wang and colleagues conducted an experiment utilizing an injectable drug-releasing microgel, which effectively promoted the conversion of pro-inflammatory Th17 cells into anti-inflammatory Tregs in vitro. Furthermore, in vivo treatment with these microgels led to a significant reduction in cardiomyocyte apoptosis and a decrease in inflammatory responses following MI. These results indicate that promoting this T cell conversion promoted vascularization and preserved cardiac function [41].

In summary, Tregs are essential for regulating and controlling the inflammatory response during FBR by suppressing pro-inflammatory cytokines and limiting excessive fibroblast activation. Future studies should seek to understand how Tregs mediates these effects and develop therapeutic approaches that enhance Tregs function and differentiation to improve biomaterial integration and reduce fibrosis. Interestingly, Tregs have been further categorized into several Treg populations, each with their own distinct phenotype. They include Foxp3 + Tregs cells, TR1 cells, and TR17 cells, each with distinct functions and mechanisms of action.

FoxP3 + Tregs cells

FoxP3 + Tregs cells serve a key role as mediators of immune suppression by secreting anti-inflammatory cytokines (IL-10), which inhibit pro-fibrotic immune responses and excessive fibroblast activation [42]. Foxp3 + Tregs are standard Treg subsets defined by the expression of the transcription factor FoxP3. These cells are primarily involved in maintaining immune tolerance and preventing autoimmunity [43]. One of the ways in which Tregs provide their regulatory role is by dictating the phenotypes of other cell populations, including macrophages.

Macrophages play a significant role in the immune response to biomaterials, undergoing phenotypic transitions that dictate the outcome of fibrosis. Initially, macrophages adopt a pro-inflammatory M1 phenotype, producing cytokines such as TNF-α and IL-6, which drive inflammation and tissue damage. Over time, a shift towards the anti-inflammatory M2 phenotype occurs, promoting wound healing and tissue remodeling. FoxP3 + Tregs have been shown to regulate this transition, thereby influencing the fibrotic response to biomaterials [44].

Similarly, Tregs have also been shown to regulate non-immune cell populations, including fibroblasts by promoting fibroblast apoptosis and limiting excessive ECM accumulation under certain conditions [45]. This indicates that the effect of Tregs on fibroblasts is context-dependent and influenced by factors such as biomaterial composition, local immune signaling, and the timing of Treg recruitment. One promising strategy for controlling Treg-mediated fibroblast activation is modifying biomaterial properties. This entails altering surface chemistry, stiffness, or topography of biomaterials that can modulate Treg recruitment and function, thereby affecting fibroblast activity. For example, hydrophilic biomaterials have been found to favor a more balanced immune response, reducing excessive fibrosis while still ensuring adequate immune regulation. In biomaterial implantation, FoxP3 + Treg cells are crucial for modulating the immune response by regulating macrophages, effector T cells, and dendritic cells. They achieve this suppression through the release of immunosuppressive cytokines, notably IL-10 and TGFβ-1. Research by Sadtler and colleagues indicates that collagen-based biomaterials can maintain prolonged activation of FoxP3 + Tregs at the implant site, which fosters a fibrotic environment that ultimately results in chronic fibrous encapsulation and diminished functionality of the device [46].

Outside the context of biomaterials and looking at other examples of fibrosis such as cardiac fibrosis, FoxP3 + regulatory T cells are recognized as potent inflammation inhibitors. Kalelkakis and colleagues examined whether adoptively transferred Tregs could prevent the development of cardiac fibrosis caused by elevated blood pressure. They discovered that significant left ventricular fibrosis was notably reduced in mice that received the adoptively transferred Tregs [47]. This finding indicates that FoxP3 + cells suppress fibrosis in other contexts as well, implying that inflammation plays a crucial role in developing cardiac fibrosis and suggests that Tregs are a therapeutic strategy for addressing cardiac fibrosis as well. Foxp3 + Tregs play a complex and context-dependent role in implant fibrosis. While their immunosuppressive functions help mitigate acute inflammatory damage, their secretion of profibrotic cytokines (i.e. TGFβ-1) and modulation of fibroblast and macrophage activity can lead to excessive fibrous encapsulation. Continued research on regulating the timing and abundance of FoxP3 + Tregs in the context of implant fibrosis offers new opportunities in curbing biomaterial-mediated fibrosis.

Type i regulatory T cells (TR1) cells

TR1 cells are characterized by their high IL-10 production and play a unique role in fibrosis modulation [48]. Unlike conventional Tregs, TR1 cells do not express Foxp3 [49]. However, their regulatory functions are exerted by dampening effector T cell responses and modifying fibroblast activity. Gregori has reported that activated TR1 cells play a role in immunoregulation via their abundant IL-10 secretion and low to moderate TGFβ-1 [50]. TR1 cells inhibit fibroblast proliferation and collagen synthesis, thereby reducing fibrotic tissue accumulation around biomaterials. Additionally, recent research focused on TR1 cells demonstrates their ability to suppress Th1 and Th17 responses associated with inflammatory and fibrotic reactions. TR1 cells play a more significant role in immune responses by modulating T and B effector cell populations. A Study by Groux and colleagues has shown that TR1 cells provide antigen-specific peripheral tolerance and dampen pathogenic effector T cell populations [51]. On the other hand, Short et al. demonstrated that the adoptive transfer of TR1cells into severe combined immunodeficient (SCID) mice resulted in accelerated wound closure on day 7, which corresponded to reduced fibrosis by day 28 [52].

The specific role of TR1 cells in biomaterial-mediated immune responses remains understudied and has not been explored fully. While TR1 cells are known for their immunosuppressive function primarily through IL-10 production and suppression of effector T-cell activity, interaction with biomaterials has not been fully elucidated. Key questions remain about how biomaterials influence TR1 differentiation, abundance, and crosstalk with other immune and stromal cells, particularly fibroblasts. Further research is needed to determine whether biomaterials can actively promote TR1-mediated peripheral tolerance and how this might be leveraged to modulate fibrotic or inflammatory responses in tissue engineering and regenerative medicine applications.

T regulatory 17 (TR17) cells

T regulatory 17 (TR17) cells are a subset of regulatory T cells that undergo differentiation and begin expressing IL-17, a feature previously considered to be unique to Th17 cells, indicating that TR17 cells may play a dual role in inflammation and immune regulation. Their role in biomaterial-mediated fibrosis, the foreign body response (FBR), and fibrosis at large is not yet well-defined, but they may have important implications. While macrophages and foreign body giant cells have been extensively studied in the context of biomaterial-mediated fibrosis, IL-17 expressing T cell populations have emerged as a significant contributor to FBR. Studies have identified innate lymphoid cells (ILCs), γδ + T cells, and CD4 + T cells as primary sources of IL-17 in response to biomaterial implants. For instance, research from Elisseeff and colleagues involving human breast implants and murine models has demonstrated that these cell types significantly contribute to IL-17 production, which in turn promotes a fibrotic response to the implanted materials [18]. Further research is needed to determine whether TR17 cells are a contributing factor to IL-17 expression in response to biomaterials, driving pathways such as senescence that are proving to be contributing factors to biomaterial-mediated fibrosis.

In summary, Tregs and their respective populations are essential for regulating and controlling the inflammatory response during FBR by suppressing pro-inflammatory cytokines and limiting excessive fibroblast activation. Future research should seek to understand how Tregs subsets, especially TR17 cells, mediate these effects and lead to the development of therapeutic approaches that enhance Treg function and differentiation to improve biomaterial integration and reduce fibrosis.

Influence of mechanical properties on T-cell and fibroblast phenotypes during biomaterial-mediated fibrosis

The mechanical properties of biomaterials, including stiffness, viscoelasticity, and elasticity, play a crucial role in modulating cellular behavior, immune responses, and ECM remodeling. These properties also significantly influence the crosstalk between fibroblasts and T cells and the outcome of fibrosis. These mechanical properties of biomaterials can regulate cell adhesion, activation, and differentiation, shaping the immune response and fibrotic remodeling.

Stiffness

Biomaterial stiffness is a key determinant of fibroblast and T cell activation and function. It has shown that cells respond differently to varying mechanical cues, with softer substrates favoring Th1 differentiation [53], stiffer substrates promote Treg differentiation [54]. In comparison, stiffer substrates enhance T cell proliferation and expression of activation markers which were YAP-dependent, a key mechanosensitive transcription factor [55]. Fibroblasts are also highly mechanosensitive and respond to matrix stiffness by altering their phenotype and secretory profile. In stiff environments, fibroblasts adopt a myofibroblast-like phenotype characterized by increased α-SMA expression and excessive ECM deposition [13,56]. This fibrotic

phenotype is associated with enhanced secretion of pro-inflammatory cytokines (e.g., IL-6, TGF-β), which can potentially modulate T-cell responses.

Conversely, softer substrates maintain fibroblasts in quiescence, reducing pro-inflammatory signaling and potentially promoting reduced immune cell activation. Modulating substrate stiffness affects T-cells and fibroblast crosstalk, either skewing them pro-regulatory or triggering biomaterial-mediated fibrosis. A study by Hinz and colleagues has shown that the softening of implant surfaces and inhibition of the activation of TGFβ-1 reduce the fibrotic encapsulation of subcutaneous implants in mice, and given previously reported findings above, may have corresponded to altered Treg abundance [57]. On the other hand, lower substrate stiffness has been shown to reduce focal adhesion formation and integrin signaling in fibroblasts, leading to decreased deposition and fibroblast proliferation. Dupont and colleagues have reported that when fibroblasts are cultured on a soft substrates, they exhibit lower YAP/TAZ nuclear localization, preventing excessive extracellular matrix production [58].

Viscoelasticity

Viscoelasticity refers to a material's ability to exhibit viscous (time-dependent deformation) and elastic (immediate deformation) responses when subjected to stress. The viscoelastic nature of a biomaterial can significantly impact the body's immune response post-implantation. Studies have shown that the mechanical properties of biomaterials, including viscoelasticity, can modulate the behavior of immune cells such as macrophages. Macrophages are among the first responders to implanted biomaterials and play a pivotal role in dictating the subsequent healing or fibrotic response, as reported earlier. Research indicates that macrophages can sense the stiffness of their substrate through mechanisms involving cell membrane deformation and curvature-sensing proteins like Baiap2. This sensing leads to cytoskeletal remodeling and can influence the inflammatory response, potentially affecting fibrosis outcomes [59]. Additionally, within the implant compartment, fibroblasts respond to mechanical and biochemical cues from the implant surface. Chaudhuri has reported that stiffer biomaterials promote fibroblast activation and myofibroblast differentiation, which enhance ECM deposition around the implant [60].On the other hand, Cameron and colleagues have shown that biomaterials exhibiting stress relaxation allow cells to reduce fibroblast activation and fibrotic activity [61].

Furthermore, the viscoelastic properties of the extracellular matrix (ECM) have been found to influence T-cell function. By engineering ECMs with tunable stiffness and viscoelasticity, research by Mooney and colleagues has demonstrated that mechanical cues can direct T cell phenotype and function. Specifically, ECM viscoelasticity regulates T cell activation pathways, such as the AP-1 pathway, which is critical for T cell fate decisions [62].These findings suggest that biomaterials' viscoelasticity can modulate immune responses by influencing T cell behavior, thereby impacting FBR and fibrosis. Fibroblasts are highly sensitive to mechanical cues from there, biomaterial with high viscoelasticity tends to reduce fibroblast activation and myofibroblast differentiation compared to stiffer.

Fibroblast Contribution to biomaterial-mediated fibrosis

Fibroblasts play a crucial role in the body's response to implanted biomaterials, determining whether tissue repair and biomaterial integration occur or biomaterial-mediated fibrosis. Following the implantation of a biomaterial, the body initiates an inflammatory response characterized by the activation of the complement system and the recruitment of immune cells. This initial phase sets the stage for fibroblast activation. Local fibroblasts at the injury site are activated in response to various signaling molecules, including growth factors and cytokines released by immune cells and platelets [63]. Fibroblasts will proliferate and undergo differentiation into myofibroblasts, a more active form characterized by the expression of alpha-smooth muscle actin (α-SMA) and contractility [64].

The properties of the biomaterial themselves significantly influence fibroblast behavior. Factors such as surface roughness, chemical composition, and the presence of bioactive molecules can modulate the fibrotic response. In smooth metallic surfaces promote a less aggressive fibrotic response, while rough surfaces enhance fibroblast adhesion and activation, leading to increased fibrosis. Dolloff and colleagues demonstrated that the surface topography of silicone breast implants influences the foreign body response, with smoother surfaces reducing fibrosis [63]. Similarly, Zhu and colleagues explored how macro-, micro-, and nanostructures of biomaterial surfaces affect chronically implantable devices, highlighting the importance of surface engineering in modulating fibroblast activity [65].

Fibroblasts play a pivotal role in biomaterial-mediated fibrosis, contributing to forming a fibrous capsule around implants. Their roles in migration, proliferation, ECM production, and interaction with immune cells underscore their importance in this context. However, they do not exist in a vacuum and understanding how they function in the context of immune cell activation, particularly T cells, may identify mechanisms underlying fibroblast activity and their interactions with biomaterials that can lead to the development of improved strategies to enhance implant integration and reduce fibrotic complications.

T Cell-Fibroblast Cross Talk during FBR-associated fibrosis

The interaction between fibroblasts and immune cells, particularly T cells, plays a pivotal role in developing biomaterial-mediated fibrosis. These interactions are mediated through cytokines and direct cell–cell contact. For instance, Th2-mediated cytokines such as IL-4 and IL-13 stimulate fibroblast proliferation and ECM production. Conversely, Th1 cells produce IFN-γ, which can augment fibroblast activity and promote myofibroblastic differentiation, highlighting the complex regulatory mechanisms[66,67].The properties of the biomaterial itself, such as surface roughness, chemical composition, and the presence of bioactive molecules, also influence fibroblast behavior and the overall fibrotic response.

Direct cell–cell contact between fibroblasts and T cells further modulates the fibrotic response. Fibroblasts express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), facilitating their interaction with T cells. This contact can activate intracellular signaling pathways in both cell types, influencing their behavior and function. For instance, the engagement of ICAM-1 on fibroblasts with its ligand LFA-1 on T cells can enhance the production of pro-inflammatory cytokines, creating a microenvironment conducive to fibrosis [66]. Cytokine signaling is a primary mechanism through which fibroblasts and T cells interact. Th2-mediated cytokines (e.g. IL-4 and IL-13) can upregulate TGFβ-1 expression in fibroblasts, enhancing their fibrotic activity [68]. Conversely, Th1 cytokines like IFN-γ can inhibit fibroblast activity, demonstrating the complex interplay between pro-fibrotic and anti-fibrotic signals [66]. In addition, chemokine signaling also plays a role in fibroblast-T cell interactions. Chemokines produced by fibroblasts can recruit T cells to the implantation site, where they exert their effects. For example, CCL2 (monocyte chemoattractant protein-1) produced by fibroblasts can attract T cells expressing the CCR2 receptor, facilitating a localized immune response and fibrosis, yet what effector function those recruited T cells take on relies on other factors, such as other cytokines secreted, tissue site, and biomaterial properties [68].

Fibroblast and T cells interact closely during the fibrotic response, enhancing ECM deposition and tissue remodeling. T cell subsets, specifically Th2 and Th17, produce IL-4, IL-13, and IL-17, respectively, stimulating fibroblast proliferation and collagen synthesis. Fibroblasts, in turn, enhance T-cell activation and differentiation through cytokines production and antigen presentation. Fibroblasts express major

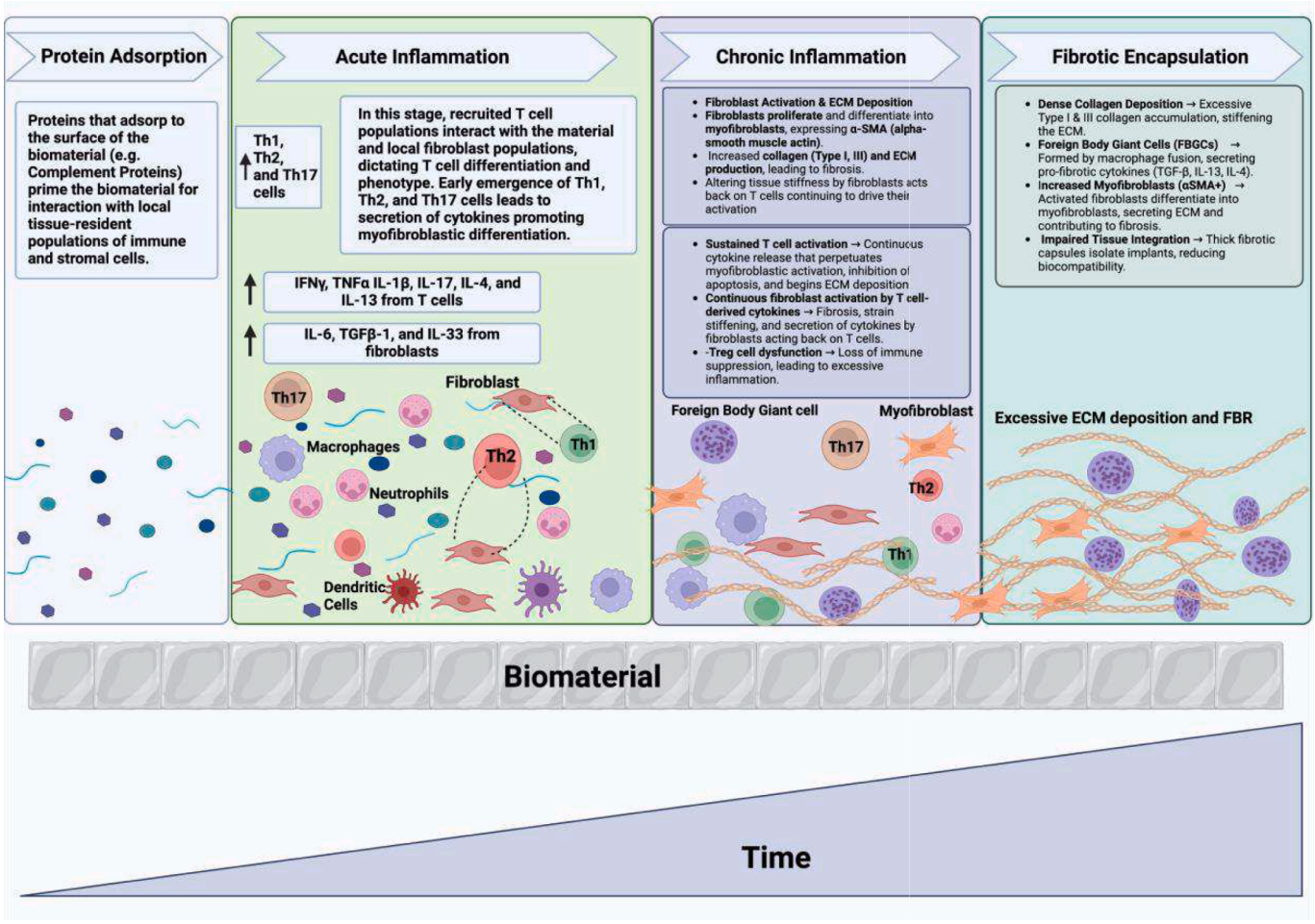

Fig. 3. Timeline of T cell-fibroblast crosstalk in the context of implanted biomaterials.

histocompatibility complex (MHC) I and II and costimulatory molecules, enabling them to interact with T cells and and promote T cell activation via antigen presentation [69]. Fibroblasts serving as non-professional antigen presenting cells has been shown to be a necessary pathway in driving the emergence of pathogenic T_H cells leading to cardiac fibrosis [67]. Mao and colleagues, on the other hand, have shown that pro-inflammatory cytokines such as IL-17 or TNF-α suppress fibroblast activation and fibrotic responses. Targeting the crosstalk between fibroblast and T cells portrays a promising therapeutic intervention in fibrotic disease and biomaterial integration [70]. Conflicting reports about cytokines activating and suppressing fibroblasts reinforce the need to better understand how context-dependent fibroblast and T cell crosstalk is, as factors that might explain these contradictions may come down to tissue-specific differences, the timing of cytokine expression, and the heterogeneity of fibroblasts that will respond differently to various cytokines [71]. Understanding the factors that drive this crosstalk will aid in inflammation resolution and regulation and help us better determine the effects of cytokine signaling in fibroblasts.

Saxena and colleagues conducted experiments to show that Tregs play a dual role in contributing to or suppressing cardiac fibrosis. Tregs co-cultured with cardiac fibroblasts resulted in decreased alpha-smooth muscle actin (αSMA) and matrix metalloproteinase-3 (MMP-3) expression and attenuated fibroblast-mediated contraction of collagen pads. This result suggests that Tregs may be necessary for regulating fibroblast activation [72]. Tregs potentially have a critical dual role in releasing the pro-fibrotic TGFβ-1 and, consequently, inhibiting Th17-mediated fibrosis with the help of Il-10 secretion [73]. Moreover, IL-10 produced by Tregs *in vivo* and *in vitro* significantly inhibits collagen synthesis by cardiac fibroblasts [74]. This correlates with other reports showing pronounced anti-fibrotic features of IL-10 in models of wound healing and Crohn's disease [75].

Recently, studies have shown that Tregs and cancer-associated fibroblasts (CAFs) jointly promote tumor immune tolerance and tumorigenesis. Sun and colleagues demonstrated that IL1RL1/ST2 signaling in Treg cells dampened the antitumor activity of IL-33. They further portrayed that the amphiregulin (AREG) axis enables Treg cells to promote the profibrotic and immunosuppressive functional state of the profibrotic and immunosuppressive functional state of CAFs [76]. A review by Gasparini and colleagues summarizes that IL-4 and IL-13 contribute to inflammation and fibrosis in Systemic sclerosis (SSc). They play a role in the inflammatory phase transition to a fibrotic state. These cytokines mediate the interaction between the inflammatory cells of innate and adaptive immunity, specifically T cells, both CD4 + and CD8+, and fibroblasts [77].

Fibroblasts and T cells also have been shown to interact in autoimmune disorders, such as Rheumatoid arthritis (RA). In the synovium during RA, synoviocytes elicit the differentiation of Th17 cells from naïve CD4 + T cells by producing cytokines such as lL-6 and TGF-β1. Additionally, the synoviocytes suppressed apoptosis of T cells by increasing survival signals and decreasing apoptotic signals [78]. Synoviocytes consistently interact with infiltrating immune cells, especially T cells, thereby increasing differentiation, activation, and survival of T cells [79]. In their review, Yoshitomi reported that increased migration of T cells to the synovium promoted interaction between T cells and synoviocytes [80]. In RA synovium, Th17 cells produced IL-22 and enhanced synoviocyte proliferation. Furthermore, Th17 cells expressed

IL-6, IL-8, MMP1, and MMP3 production when co-cultured with synoviocytes of patients with RA, implying that Th17 is a vital T cell subtype in the pro-inflammatory feedback loop with synoviocytes during RA [81]. Thus, highly proliferative synoviocytes influence the function of the T cells by cells by expressing cytokines, chemokines, and cell adhesion molecules that promote inflammatory responses in RA.

A study showed that several cytokines and T cells produce extracellular matrix deposition by fibroblasts. Th2-type cytokines, such as IL-13, enhance collagen synthesis in fibroblasts [82]. Interestingly, an experiment by Wynn and colleagues demonstrated the role of Th2 cytokines in fibrosis, and the study was conducted using a mouse model of lung fibrosis. The study demonstrated that IL-13 is a critical mediator of fibrosis, as IL-13 knockout mice exhibited significantly reduced fibrosis in response to lung injury. This finding underscores the pro-fibrotic role of Th2 cytokines and their influence on fibroblast behavior in fibrosis that may extend to biomaterial-mediated fibrosis [83]. Kato-Kogoe and colleagues in their study, used human gingival fibroblasts (HGF) to investigate the possible effects of fibroblast-derived soluble factors on the differentiation of naïve T cells and the subsequent fibroblast responses. After a co-culture between naïve T cells and allogeneic dendritic cells in the presence of culture supernatant from stimulated HGF, T cells exhibited a Th2-shifted phenotype whereby they produced more IL-13 and IL-5 compared with IFNγ [84]. Recent work revealed that co-culture of T cells and autologous SSC skin fibroblast promoted fibroblast apoptosis, which was inhibited by a neutralizing IL-17A antibody. The data suggests that the IL-17A upregulation might play a role in modulating T cell-mediated anti-fibrotic and pro-apoptotic effects in co-cultured autologous skin fibroblast [85].

The complex interplay between T cells and fibroblasts significantly influences the outcomes of biomaterial-mediated fibrosis. This crosstalk is critical for the immune response to implanted biomaterials and the subsequent fibrotic encapsulation that can hinder the functionality of biomaterial implants. Fibroblasts and T cells engage in a dynamic and reciprocal relationship essential for tissue repair and immune modulation that can be engineered to improve biomaterial outcomes. One approach is to modulate the immune response by targeting specific cytokines or signaling pathways involved in fibroblast activation derived from T cells. For example, IL-13 inhibitors or IFN-γ agonists could reduce fibroblast activation and ECM production, thereby minimizing fibrosis [28]. Another promising strategy is designing biomaterials that modulate immune responses to favor anti-fibrotic outcomes. This can be achieved by engineering biomaterial surfaces to promote the adsorption of anti-inflammatory cytokines or the recruitment of regulatory T cells (Tregs), which can inhibit fibroblast activation. For instance, biomaterials coated with TGF-β inhibitors or IL-10 could promote a more favorable immune response and reduce fibrosis [86]. While some dynamics of T cell-fibroblast crosstalk have not been fully explored in response to biomaterials, studies investigating their relationship in other fibrotic disorders may shed light on how those dynamics may occur in the context of biomaterial-mediated fibrosis. Understanding the mechanisms of T cell-fibroblast crosstalk (Fig. 3) opens potential strategies to mitigate fibrotic responses to biomaterials.

Conclusion and future directions

In conclusion, the roles of T cells, fibroblasts, and their crosstalk are pivotal in the context of biomaterial-mediated fibrosis. Their interactions influence the inflammatory milieu and determine the extent and nature of ECM deposition and biomaterial fate. Complete tissue regeneration in adult mammals is not common, but it has been shown to occur and studied in two specific models using the African Spiny Mouse and Axolotls [87,88]. To better understand how biomaterial-mediated fibrosis occurs and how to reverse it, these animal models can be valuable tools in understanding and identifying vital molecular targets. Seifert and colleagues have shown that African spiny mice regenerate skin scarlessly, even during adulthood, promoting autotomy to escape predators. In addition, they show that the regenerative capacity in the African Spiny Mouse was extended to ear holes where the mice exhibited complete regeneration of hair follicles, sebaceous glands, dermis, and cartilage. Fibroblasts are crucial in orchestrating the regenerative process by producing extracellular matrix components that aid tissue repair and wound closure and more work is needed to understand how T cells modulate fibroblast phenotype during tissue regeneration [89]. Brant and colleagues' study highlighted the crucial roles of fibroblasts and immune cells, particularly T cells, in regeneration. Fibroblasts were found to be instrumental in orchestrating tissue remodeling, while T cells played a vital role in modulating the inflammatory response and promoting tissue regeneration [90]. In addition, a study by Godwin and colleagues, using the axolotl model, investigated the immune response during limb regeneration, where the formation of specialized ECM guides tissue patterning and cellular migration [91]. These studies point towards a promising research direction: gaining a deeper understanding of the fibroblast-T cell crosstalk in the context of fibrosis and tissue regeneration. This understanding could potentially lead to the development of novel therapeutic strategies to improve biomaterial design and improve outcomes.

Investigating T cell subsets in the foreign body response (FBR) and shedding light on the mechanisms hold promises for advancing the understanding of immune-mediated reactions toward biomaterials. As discussed above, Tregs have been shown to suppress inflammation and promote tissue repair by secreting anti-inflammatory cytokines. Investigating the delicate balance between these T cell subsets and their interactions with fibroblasts and other immune cells is paramount, as it can provide valuable insights and identify novel therapeutic targets. In addition, exploring the temporal and spatial dynamic of T cell recruitment and their regulation in response to biomaterial implantation is vital for understanding the FBR. The spatial dynamics of the FBR can be investigated by spatial transcriptomics and multiplexed imaging, both of which have seen dramatic improvements over the last several years. Additionally, studying the temporal dynamics of the FBR can be investigated by leveraging transgenic mouse models that enable tracking and controlling the expression of inflammatory markers, including fluorescent reporters of inflammatory cytokines and their conditional as well as tissue-specific deletion.

Future research efforts should unravel the regulatory mechanisms that dictate temporal and spatial dynamics of T cell-mediated responses, which can inform better biomaterial design and lead to better outcomes. The tools to interrogate these regulatory mechanisms include integrating multiomics approaches such as transcriptomics, epigenomics, proteomics, and metabolomics. These approaches enable comprehensive profiling of fibroblast-T cell interactions and regulatory networks during tissue regeneration. By combining these high-throughput approaches, researchers can shed light on the molecular mechanisms underlying the crosstalk between fibroblasts and T cells in biomaterial-mediated fibrosis in new ways. Single-cell transcriptomics provides valuable information on the gene expression patterns and regulatory networks operating within fibroblasts and T cells during tissue repair and biomaterial-mediated fibrosis. Epigenomics allows researchers to investigate dynamic changes in chromatin structure and epigenetic modification that regulate gene expression in fibroblast −T dynamic during tissue regeneration. Epigenetic profiling techniques such as chromatin immunoprecipitation sequencing (ChIP-seq) and assay for transposase-accessible chromatins sequencing (ATAC-seq) have shown that epigenetic alteration occurs within fibroblast and T cell populations in tissue repair and wound healing [92].

Lastly, new research directions should also consider integrating and advancing computational modeling and artificial intelligence (AI) −driven simulations, which will also significantly predict fibrotic outcomes based on biomaterial properties and immune system interactions. Machine learning algorithms trained on large-scale experimental datasets can identify key molecular signatures and signaling pathways driving fibrosis. AI-powered image analysis of histological and

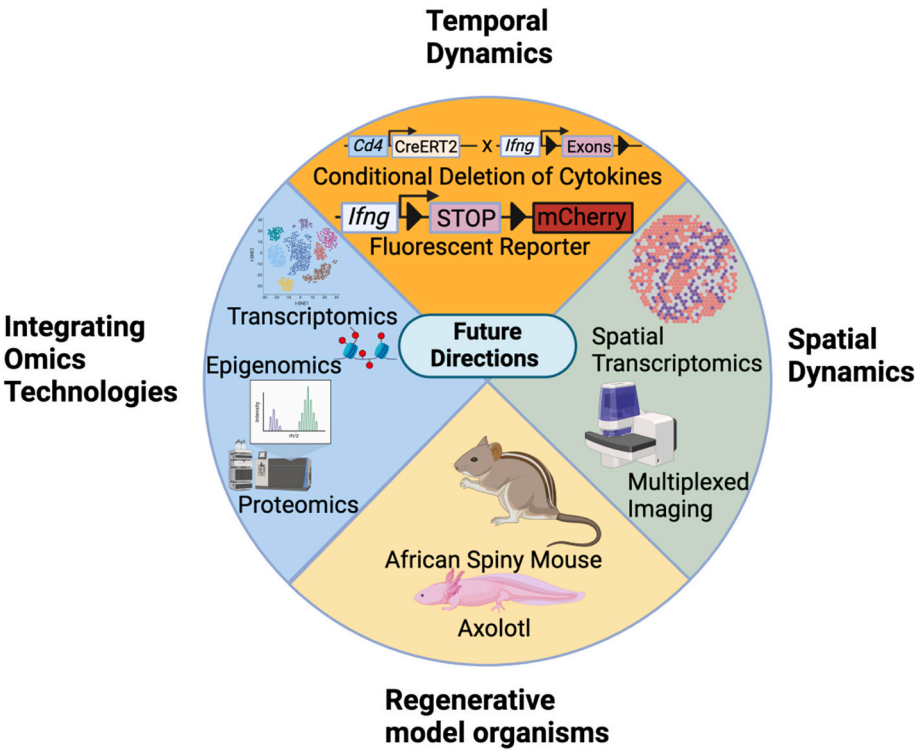

Fig. 4. Potential future directions that could provide a better understanding of Fibroblast-T cell crosstalk in biomaterial-mediated fibrosis.

immunofluorescence-stained tissues will facilitate high-throughput quantification of fibrosis severity, cellular distribution, and biomaterial degradation. Additionally, agent-based modeling and network-based approaches will help simulate complex immune-stromal dynamics, offering predictive tools for optimizing biomaterial design to minimize fibrosis. Thus, by integrating transcriptomics, proteomics, and metabolomics data and employing computational modeling and artificial intelligence, researchers can comprehensively understand the crosstalk between fibroblasts and T cells during biomaterial-mediated fibrosis (Fig. 4). By leveraging these approaches, we will realize the array crosstalk mechanisms between T cells and fibroblasts in biomaterial-mediated fibrosis and guide new avenues for biomaterial development that improve their performance and health outcomes.

CRediT authorship contribution statement

Mathew Kibet: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Daniel Abebayehu:** Writing – review & editing, Visualization, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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