

Review

Lymphocytes and their Involvement in the Foreign Body Response to Biomaterials and Tissue Repair

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Abstract

Lymphocytes, long regarded as central actors of adaptive immunity, are increasingly recognized as key regulators of the foreign body response (FBR) to biomaterials. Their presence shapes the chronic phases of inflammation, fibrosis, angiogenesis, and regenerative outcomes after implantation. This review summarizes the roles of T cells, B cells, and natural killer (NK) cells in biomaterial-associated immune responses, with a particular focus on protein adsorption, antigen recognition, cytokine secretion, and downstream interactions with macrophages, fibroblasts, and endothelial cells. Evidence indicates that T-cell polarization into Th1/Th17 subsets promotes pro-inflammatory reactions, while Th2 and regulatory T cells (Tregs) support constructive remodeling and resolution. B cells contribute through antibody production and cytokine release, which may foster fibrosis or support debris clearance. NK cells serve as early stress sensors, releasing cytotoxic mediators and pro-angiogenic factors that influence vascularization and tissue repair. Collectively, lymphocytes are pivotal but underexplored players in biomaterial integration. Incorporating lymphocyte biology into material design and surface modification strategies offers promising avenues to guide immune cascades toward predictable and regenerative outcomes.

Keywords: Lymphocytes, biomaterials, foreign body response, tissue regeneration, immunomodulation, review.

Introduction

The implantation of any biomaterial triggers a highly orchestrated sequence of host reactions, collectively referred to as the foreign body response (FBR). This cascade begins within seconds after implantation with

the adsorption of plasma proteins and the formation of a provisional matrix composed of fibrin, fibronectin, and immunoglobulins. These early events are followed by acute inflammation, dominated by neutrophils and monocytes, and later by chronic inflammatory processes, tissue remodeling, and in some cases, fibrotic



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encapsulation that can isolate the implant from surrounding tissues (1-4). Traditionally, the central focus of biomaterial immunology has been on innate effector cells such as macrophages, foreign body giant cells, and granulocytes, as they are the first responders that directly interact with material surfaces (1-5). However, it has become increasingly evident that the long-term fate of implants –whether successful integration, stable regeneration, or fibrotic failure– depends critically on the involvement of adaptive immune cells.

Among these adaptive immune populations, lymphocytes –particularly T cells, B cells, and innate-like natural killer (NK) cells– play decisive roles in the chronic and late phases of biomaterial-tissue interactions (1-4, 6). Lymphocytes extend their influence beyond simple immune surveillance; they act as regulators of the inflammatory milieu and determinants of whether remodeling is constructive or pathological. Their contributions include cytokine secretion, cross-talk with antigen-presenting cells, antibody production, and the modulation of stromal cells such as fibroblasts and endothelial cells. These activities collectively shape angiogenesis, extracellular matrix deposition, and the balance between resolution *versus* persistent inflammation.

T lymphocytes are of particular importance in this context. CD4⁺ T-helper cells differentiate into distinct subsets that orchestrate divergent outcomes. Th1 and Th17 cells release pro-inflammatory cytokines such as interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and IL-17, which drive chronic inflammation, amplify neutrophil recruitment, and promote fibrotic encapsulation (7). In contrast, Th2 cells produce IL-4, IL-5, and IL-13, which promote alternative macrophage activation, angiogenesis, and extracellular matrix turnover, thereby supporting tissue integration. Regulatory T cells (Tregs) secrete IL-10 and transforming growth factor- β (TGF- β), counterbalancing pro-inflammatory cascades and maintaining tissue homeostasis. Importantly, the balance between effector T cells and Tregs often

determines whether the FBR culminates in regeneration or fibrosis (3, 8-11).

B lymphocytes contribute to biomaterial responses through antibody production, immune complex formation, and cytokine secretion. Adsorbed and conformationally altered proteins at biomaterial surfaces may serve as antigens, leading to the generation of antibodies and subsequent complement activation. Such mechanisms can reinforce chronic inflammation and promote fibroblast activity, ultimately driving fibrosis (7). Furthermore, plasma cell infiltration has been documented in the degradation zones of collagen membranes, indicating an ongoing B-cell response during the remodeling phase.

NK cells, while traditionally associated with anti-viral and anti-tumor defense, also play roles in biomaterial integration. They are activated in response to stress-induced ligands or altered MHC class I expression in cells adjacent to biomaterials. NK cells release cytotoxic molecules such as perforin and granzymes, but they also secrete IFN- γ and vascular endothelial growth factor (VEGF), thereby influencing macrophage polarization and angiogenesis (6). Depending on the context, NK cells may thus either promote vascularization and constructive remodeling or contribute to chronic tissue damage.

Taken together, lymphocytes should no longer be considered passive latecomers in biomaterial immunology. Instead, they act as central regulators of the chronic phase of the FBR, exerting both beneficial and detrimental effects depending on their subset activity and the microenvironment created by the biomaterial surface. Understanding the nuances of lymphocyte biology at biomaterial interfaces is essential for the rational design of next-generation biomaterials that actively shape immune responses. Such materials may be tailored to promote Treg and Th2 polarization, limit pathogenic B-cell responses, and harness NK-mediated angiogenesis. This immune-centered approach provides a promising avenue to minimize fibrosis, enhance tissue regeneration, and improve the predictability of clinical outcomes (2, 3, 8-11).

Basic Knowledge about Lymphocyte Subtypes

T lymphocytes. T lymphocytes constitute the majority of circulating lymphocytes and are indispensable for adaptive immune responses. Upon activation, naive T cells differentiate into several specialized subsets, each of which has a distinct cytokine profile and function that can profoundly influence the host reaction to biomaterials. Th1 cells are characterized by the secretion of IFN- γ and TNF- α , which drive the classical activation of macrophages toward a pro-inflammatory M1 phenotype. While essential for pathogen clearance, persistent Th1 activity in the context of implanted biomaterials often sustains chronic inflammation and contributes to fibrotic capsule formation (2, 6). In contrast, Th2 cells release cytokines such as IL-4, IL-5 and IL-13, which promote alternative M2 macrophage activation, stimulate angiogenesis, and facilitate extracellular matrix deposition. These processes are associated with more favorable outcomes for biomaterial integration when appropriately regulated (7).

A further subset, the Th17 lineage, is defined by secretion of IL-17 and IL-22. These cytokines amplify neutrophil recruitment and sustain pro-inflammatory conditions, particularly under sterile inflammatory settings such as those provoked by certain biomaterials (2, 6). If unchecked, Th17 activity may impair constructive remodeling and prolong tissue injury. Balancing this response, Tregs secrete anti-inflammatory mediators including IL-10 and TGF- β , which suppress excessive immune activation and foster resolution and regeneration (2, 3, 8-11). Finally, CD8⁺ cytotoxic T cells recognize and destroy stressed or antigen-presenting cells. While this cytotoxic activity may contribute to clearance of damaged cells, in some contexts it exacerbates tissue injury and delays integration. Collectively, the interplay between effector subsets and Tregs is a decisive determinant of whether the FBR culminates in fibrosis or in successful healing (2, 12).

B lymphocytes. In contrast to T cells, B lymphocytes mediate humoral immunity through differentiation into

plasma cells and the production of antibodies. Their relevance in biomaterial immunology arises from the ability to recognize conformationally altered proteins that adsorb to material surfaces. Such recognition can result in the generation of antibodies directed against neoepitopes, leading to immune complex formation and complement activation (7). This cascade may amplify inflammation, recruit additional immune cells, and contribute to chronic tissue reactions at implant sites. Beyond antibody production, B cells secrete cytokines such as IL-6, which influence macrophage polarization and fibroblast activation, thereby shaping the extracellular matrix environment. Depending on the context, B-cell responses can be beneficial by clearing debris and supporting resolution, or detrimental by driving fibrosis and perpetuating chronic inflammation (6).

Natural killer cells. NK cells represent a distinct subset of innate-like lymphocytes that rapidly respond to cellular stress at the biomaterial interface. Unlike T or B cells, NK cells do not require antigen priming. Their activation is often triggered by reduced major histocompatibility complex (MHC) class I expression or the presence of stress ligands on host cells adjacent to implants. Once activated, NK cells exert cytotoxic effects through the release of perforin and granzymes, thereby eliminating compromised cells (2, 6). They also secrete IFN- γ , which enhances macrophage and dendritic cell activity and shapes subsequent adaptive responses. Importantly, NK cells release pro-angiogenic mediators such as VEGF, which support neovascularization and may improve integration of biomaterials into host tissue (2, 3, 6). Nevertheless, NK cell responses are highly context-dependent. Under favorable conditions, NK-mediated angiogenesis contributes positively to tissue repair, whereas excessive or dysregulated activation can exacerbate tissue damage, inflammation, and fibrosis (2, 3, 6, 13).

Taken together, these findings underscore that all lymphocyte subsets –T, B, and NK cells– play integral and distinct roles in shaping biomaterial-tissue

Table I. *Lymphocyte subsets and their main functions at biomaterial interfaces.*

Subset	Main cytokines	Effects on macrophages/fibroblasts	Impact on regeneration/fibrosis	References
Th1	IFN- γ , TNF- α	M1 activation, fibroblast stimulation	Chronic inflammation, fibrosis	(8, 9, 22)
Th2	IL-4, IL-5, IL-13	M2 activation, ECM remodeling	Angiogenesis, regeneration	(10, 23)
Th17	IL-17, IL-22	Neutrophil recruitment, sustained inflammation	Tissue damage, fibrosis	(11, 22)
Treg	IL-10, TGF- β	Suppression of effector cells, wound resolution	Tolerance, constructive remodeling	(12, 26)
CD8 ⁺ T cells	Perforin, granzymes	Cytotoxicity, clearance of stressed cells	Tissue damage if persistent	(13, 25)
B cells	Antibodies, IL-6	Immune complex deposition, fibroblast modulation	Fibrosis, plasma cell infiltration	(29, 35)
NK cells	IFN- γ , VEGF, perforin, granzymes	Macrophage activation, angiogenesis support	Balance of clearance vs. regeneration	(27, 30, 36)

IFN: Interferon; TNF: tumor necrosis factor; IL: interleukin, ECM: extracellular matrix; VEGF: vascular endothelial growth factor.

interactions. Understanding the nuances of their activity provides essential knowledge for the rational design of immunomodulatory biomaterials that promote constructive tissue remodeling and minimize adverse outcomes. For a compact overview of hallmark lymphocyte subsets, their key cytokines, and their predicted impact on regeneration versus fibrosis at biomaterial interfaces, see Table I.

Protein Adsorption and Lymphocyte Activation at Biomaterial Interfaces

Immediately after implantation, the surface of any biomaterial is rapidly coated with a dynamic layer of host proteins derived from blood plasma and interstitial fluids. This adsorbed protein layer forms within seconds to minutes and represents the true biological identity of the biomaterial. It is not the underlying synthetic or natural material itself that cells encounter, but rather this layer of proteins, which undergoes continuous conformational changes and exchange processes. The characteristics of this layer –its composition, structure, and stability– are therefore decisive not only for the adhesion and activation of innate immune cells such as neutrophils and macrophages, but also for the engagement of lymphocytes in the subsequent phases of the foreign body response to biomaterials (14, 15).

Among the most relevant proteins are immunoglobulins, fibrinogen, fibronectin, albumin, vitronectin, and components of the complement cascade. Immunoglobulin adsorption is particularly significant because it directly links to the activation of B lymphocytes. Structural alterations of IgG molecules upon adsorption to hydrophobic or charged surfaces may expose Fc domains, making them accessible to Fc receptors on immune cells. This facilitates immune complex formation and the initiation of antibody-mediated immune responses, which can reinforce chronic inflammation at the biomaterial-tissue interface (16). Such processes have been observed for both synthetic polymers and natural collagen-based scaffolds, indicating that the phenomenon is broadly relevant across material classes.

The complement system represents another critical mediator connecting protein adsorption with lymphocyte activity. Adsorbed and denatured proteins can activate the classical, lectin, or alternative pathways, generating fragments such as C3b, iC3b, and the potent chemoattractant C5a. While complement activation initially drives neutrophil recruitment, it also indirectly engages lymphocytes by enhancing antigen uptake and presentation by dendritic cells and macrophages (17). Complement-derived signals can influence the balance of T-cell polarization, for example by promoting Th1/Th17 responses in a pro-inflammatory environment or

Table II. Protein layer composition and immunological consequences.

Protein	Conformational changes	Target cells	Lymphocyte effect	References
Immunoglobulins (IgG)	Fc domain exposure	B cells, APCs	Antibody production, immune complexes	(17, 29)
Complement (C3b, iC3b, C5a)	Fragment generation	APCs, T cells	Indirect activation, Th1/Th17 polarization	(18)
Fibrinogen	Fragmentation, TLR activation	Dendritic cells	Th1/Th17 polarization	(19)
Fibronectin	Conformational change (RGD sites)	Dendritic cells, T cells	Tolerogenic DCs → Treg induction	(20)
Albumin	Surface passivation	—	Dampens immune activation	(20)
Vitronectin	Stabilized adsorption	NK cells, T cells	Supports adhesion, angiogenesis	(21)

APC: Antigen-presenting cells; RGD: Arg-Gly-Asp tripeptide motif.

supporting regulatory T-cell activity when complement activation is controlled and limited in duration.

Fibrinogen and fibronectin adsorption also plays a central role in shaping the adaptive immune response. Both proteins are important ligands for integrins on dendritic cells, and their conformational states can determine dendritic cell maturation and cytokine secretion profiles. Mature dendritic cells, in turn, direct the polarization of T cells. For instance, fibrinogen fragments are capable of activating Toll-like receptor signaling on antigen-presenting cells, driving a Th1/Th17-type immune response characterized by persistent inflammation (13). By contrast, fibronectin adsorption in specific conformations may favor tolerogenic dendritic cell phenotypes, which guide the expansion of regulatory T cells and contribute to immune resolution. This illustrates how the physical and chemical properties of a biomaterial surface –hydrophobicity, charge, roughness, and topography– can indirectly shape adaptive immune pathways through protein-mediated mechanisms.

The dynamic nature of the adsorbed protein layer is another critical factor. Proteins continuously exchange between the adsorbed layer and the surrounding fluids, a phenomenon known as the Vroman effect. This means that proteins with higher affinity may replace those initially bound to the surface. Over time, the evolving composition of the layer modifies the immunological cues presented to

lymphocytes and antigen-presenting cells (18). For example, early fibrin adsorption may trigger strong pro-inflammatory activation, but subsequent enrichment with albumin or vitronectin can dampen these signals and promote more tolerogenic conditions. Such temporal dynamics of the protein layer add another level of complexity to lymphocyte activation at biomaterial interfaces.

Taken together, these insights highlight that the protein layer serves as a critical immunological interface, not only guiding innate immune cell adhesion but also dictating how lymphocytes are recruited, activated, and polarized. The conformational stability and biochemical composition of adsorbed proteins ultimately influence whether a Th1/Th17-driven inflammatory cascade dominates, whether antibody production by B cells and complement activation perpetuate chronic inflammation, or whether regulatory mechanisms prevail and support tissue integration and regeneration. Understanding these processes provides a key opportunity for biomaterial design: by engineering surfaces to control protein adsorption and conformation, it may be possible to guide lymphocyte responses toward tolerance and constructive tissue remodeling rather than chronic inflammation and fibrosis (19). Major components of the adsorbed protein layer, typical conformational changes upon adsorption, and their immunological consequences for lymphocyte activation are summarized in Table II.

Table III. *Lymphocyte responses to different biomaterial classes.*

Biomaterial type	T-cell responses	B-cell responses	NK-cell responses	Consequences	References
Bone substitutes	Th1/Th17 inflammation vs. Th2/Treg regeneration	Antibody/immune complexes	Limited	Balance regeneration vs. fibrosis	(22, 23)
Collagen scaffolds	Strong T-cell infiltration; source-dependent	Plasma cell infiltration	Moderate in xenogeneic collagen	Variable integration; fibrosis risk	(24)
Titanium implants	Mild T-cell infiltration; risk with contamination	Minimal	IFN- γ release, angiogenesis	Stable integration unless peri-implantitis	(25, 30)
Magnesium implants	Th1/Th17 activation; potential Treg expansion	Limited	Strong activation via Mg ²⁺	Angiogenesis vs. fibrosis	(26, 27)
Synthetic polymers	Acidic degradation prolongs T-cell activity; hydrophilic coatings \rightarrow tolerance	Antibody recognition of modified epitopes	Minimal	Outcome dictated by chemistry	(28)

IFN: Interferon; Mg: magnesium.

Interactions of Lymphocytes With Biomaterials

A comparative overview of reported T-, B-, and NK-cell responses across major biomaterial classes and their typical consequences for integration *versus* fibrosis is provided in Table III.

T-cell interactions. The role of T lymphocytes in shaping host responses to biomaterials has gained increasing recognition, particularly because their cytokine profiles determine whether inflammation is resolved or perpetuated. In the case of bone substitutes, such as xenogeneic or allogeneic grafts and synthetic calcium phosphates, pro-inflammatory Th1 and Th17 responses have been associated with impaired osteoconduction and fibrotic encapsulation. By contrast, polarization toward Th2 and Tregs correlates with enhanced osteogenesis and constructive remodeling of the bone-implant interface (20–22). Several preclinical studies have demonstrated that hydroxyapatite-based and biphasic calcium phosphate scaffolds can attenuate Th1/Th17 activation and instead promote a tolerogenic milieu that supports vascularized bone regeneration. Across biomaterial classes, the balance of Th1/Th17-driven inflammation *versus* Th2/Treg-associated resolution and remodeling is summarized in Figure 1.

Collagen scaffolds show more variable immunological profiles, as they differ in both source and processing.

Bovine pericardium-derived membranes often elicit strong T-cell infiltration, reflecting their xenogeneic origin and higher risk of immunogenic epitopes. These responses may include enhanced Th1 and Th17 polarization, leading to more intense chronic inflammation. By contrast, fish-derived collagen scaffolds appear less immunogenic, displaying reduced T-cell infiltration and lower rates of fibrotic remodeling (23). The observed differences underline the importance of antigenicity and protein conformation in determining T-cell engagement.

Titanium implants are widely used in orthopedics and dentistry, where they typically induce only mild T-cell infiltration under physiological conditions. However, when titanium surfaces are contaminated with organic residues, wear particles, or bacterial biofilms, the adaptive immune system can be strongly activated. In these cases, persistent T-cell infiltration contributes to peri-implantitis, which is characterized by chronic inflammation, bone resorption, and loss of osseointegration (24). These findings suggest that surface cleanliness and biofilm control are central not only for infection prevention but also for avoiding T-cell-driven chronic inflammation.

In the case of magnesium-based implants, degradation and ion release create a unique immunological scenario. Local alkalization due to hydroxide formation and elevated magnesium ion concentrations stimulate Th1 and Th17 activity, which can amplify inflammation in the short term.

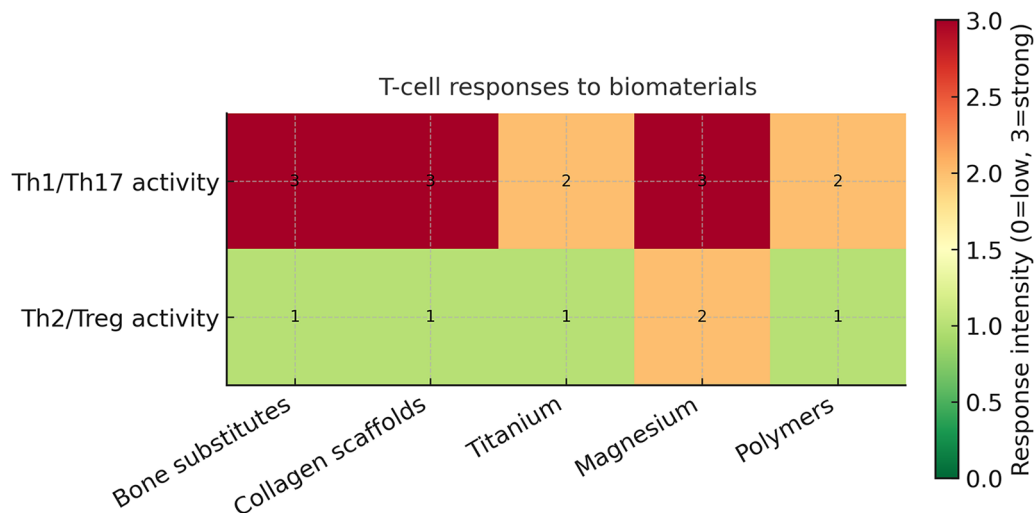


Figure 1. T-cell responses to biomaterial classes. Heatmap summarizing Th1, Th2, Th17, and Treg activities in response to bone substitutes, collagen scaffolds, titanium, magnesium, and synthetic polymers. Color gradient indicates intensity of pro-inflammatory vs. pro-regenerative activity (0=low, 3=strong).

Nonetheless, controlled and gradual degradation has been shown to expand Treg populations, shifting the immune balance toward tolerance and tissue regeneration. This dual effect positions magnesium implants as promising but challenging candidates for bioresorbable implantology, requiring fine-tuning of degradation kinetics to promote immune homeostasis (25-27).

Finally, synthetic polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers elicit T-cell responses that are highly dependent on their chemical composition and degradation profiles. Acidic degradation products, particularly lactic and glycolic acid, prolong T-cell activation and contribute to sustained inflammatory signaling. In contrast, hydrophilic modifications and zwitterionic coatings have been shown to dampen T-cell activity and favor tolerogenic responses (28). Such design strategies illustrate how polymer chemistry can directly shape adaptive immunity by controlling the microenvironment at the implant interface.

B-cell interactions. The involvement of B cells in biomaterial responses has historically been underestimated, but mounting evidence indicates that they significantly influence

long-term outcomes. For bone substitutes, B-cell activation may be triggered by the release of danger-associated molecular patterns (DAMPs) from necrotic tissue residues or surface-bound antigens. This can lead to antibody production, immune complex deposition, and complement activation, which in turn amplify chronic inflammation and fibrosis (29). B-cell-associated readouts at biomaterial interfaces, including antibody production, plasma cell infiltration, immune-complex formation, and fibrosis risk across material classes, are summarized in Figure 2.

Collagen membranes frequently display plasma cell infiltration during their degradation, reflecting ongoing B-cell and humoral activity. These responses suggest that collagen degradation products may act as antigens, continuously stimulating antibody production and influencing remodeling outcomes (23).

In contrast, titanium and magnesium implants exhibit less pronounced B-cell responses under physiological conditions. Nevertheless, in chronic inflammatory lesions, B-cell clusters and plasma cell activity have been detected, indicating that persistent antigenic stimulation or biofilm-associated antigens can engage humoral immunity in these settings (24, 27).

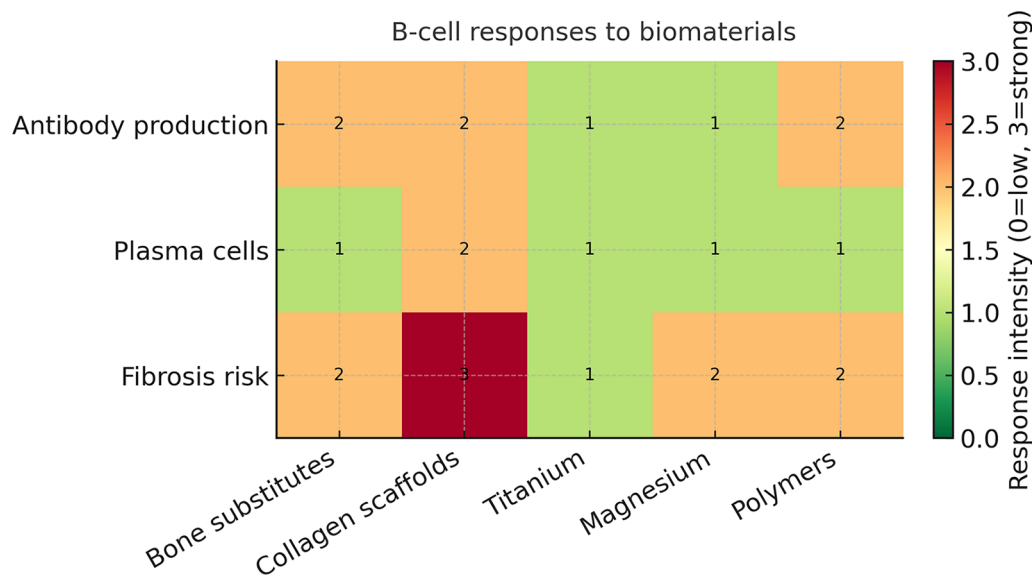


Figure 2. B-cell responses to biomaterial interfaces. Heatmap depicting antibody production, plasma cell infiltration, immune complex formation, and fibrosis risk across biomaterial classes. Color gradient indicates intensity of pro-inflammatory vs. pro-regenerative activity (0=low, 3=strong).

NK-cell interactions. NK cells, though less frequently studied in biomaterial contexts, contribute significantly to tissue remodeling and angiogenesis. NK-cell responses across biomaterial classes, including cytotoxicity, IFN- γ release, pro-angiogenic activity, and potential links to fibrosis, are summarized in Figure 3.

For calcium-phosphate bone substitutes based on hydroxyapatite (HA), beta-tricalcium phosphate (β -TCP) or biphasic materials (BCP), the host response is predominantly macrophage/multinucleated giant cell (MNGC)-driven; direct NK-calcium phosphate (CaP) data are scarce, but IFN- γ -secreting NK cells can boost macrophage VEGF and thereby indirectly promote angiogenesis (30, 31). Bioactive glasses create an immunomodulatory, pro-angiogenic milieu supportive of constructive remodeling; NK-specific readouts are limited but compatible with these effects (32, 33).

For titanium implants, NK cells have been reported to secrete IFN- γ , which promotes macrophage activation and indirectly influences osteogenesis and angiogenesis. Their contribution is generally beneficial under sterile conditions, but dysregulated NK activity may exacerbate inflammation (2, 34, 35).

In collagen scaffolds, NK cell responses are typically limited. However, xenogeneic collagen sources can recruit NK cells, likely through recognition of stress-induced ligands on infiltrating or damaged host cells. This activity can either aid clearance of compromised cells or contribute to prolonged inflammatory reactions (23).

Magnesium implants represent a particularly interesting case for NK biology. The release of Mg²⁺ ions has been shown to enhance NK cell activation, resulting in increased IFN- γ production and VEGF secretion. These functions support angiogenesis and tissue integration, but if magnesium degradation is uncontrolled, excessive NK activation may drive fibrotic encapsulation and limit constructive remodeling (25-27).

Role of Blood Concentrates in Regenerative Medicine With Focus on Lymphocytes

Blood-derived concentrates such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have become widely applied in regenerative medicine and dentistry. Their clinical benefits are traditionally attributed to the high

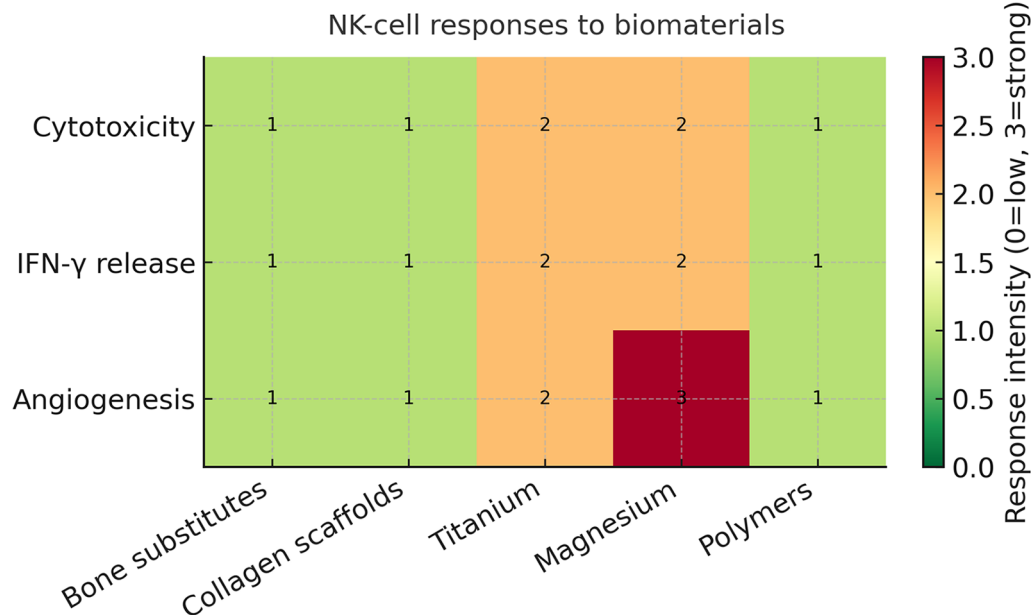


Figure 3. NK-cell responses to biomaterials. Heatmap visualizing cytotoxicity, IFN-γ release, angiogenesis promotion, and fibrosis risk in relation to material type. Color gradient indicates intensity of pro-inflammatory vs. pro-regenerative activity (0=low, 3=strong).

concentration of platelets and the release of growth factors such as platelet-derived growth factor (PDGF), VEGF, and TGF-β. These molecules promote angiogenesis, fibroblast proliferation, and extracellular matrix deposition. However, recent studies emphasize that the cellular fraction of these preparations, particularly lymphocytes, also plays a decisive role in shaping the host response and in orchestrating regenerative outcomes (36, 37). Reported effects of PRP/PRF on T cells, B cells, and NK cells –including key mediators and clinical implications– are summarized in Table IV.

T lymphocytes contained within PRP and PRF can secrete anti-inflammatory cytokines such as IL-10 and IL-4. These mediators drive macrophage polarization toward the M2 phenotype, which is associated with tissue remodeling, angiogenesis, and constructive biomaterial integration. In addition, T regulatory cells present in blood concentrates contribute to limiting excessive inflammation and promoting resolution, thereby improving the microenvironment for wound

healing (38). Conversely, elevated levels of Th1 and Th17 cells may release pro-inflammatory cytokines such as IFN-γ and IL-17, which can prolong the inflammatory phase and compromise the regenerative potential of the concentrate (34). This duality highlights the importance of carefully balancing T-cell subsets in clinical preparations.

B lymphocytes, though less abundant in PRP and PRF, contribute indirectly to regenerative processes. By producing antibodies, they assist in the clearance of necrotic matrix components and potential microbial antigens, thereby reducing persistent inflammatory stimuli. Moreover, B-cell derived cytokines such as IL-6 can modulate macrophage and fibroblast activity, linking humoral immunity to tissue repair pathways (39).

NK cells, as innate lymphocytes, provide an additional dimension to the regenerative effects of blood concentrates. NK cells release cytotoxic molecules that enhance antimicrobial defense in wound beds and secrete angiogenic mediators, particularly VEGF,

Table IV. *Effects of blood concentrates (PRP/PRF) on lymphocytes.*

Lymphocyte subset	Role in PRP/PRF	Cytokines/mediators	Clinical consequence	References
T cells	Promote M2 macrophages, Treg activity	IL-10, IL-4	Enhanced healing, reduced inflammation	(31, 33, 34)
B cells	Clearance of damaged matrix	Antibodies, IL-6	Reduced necrotic debris; fibrosis risk	(35)
NK cells	Antimicrobial defense, angiogenesis	IFN- γ , VEGF, perforin	Accelerated vascularization, antimicrobial effect	(36, 37)

IFN: Interferon; IL: interleukin.

which accelerates neovascularization. Their activity complements the pro-regenerative signals of platelets and macrophages, especially in early wound healing phases where rapid vascularization is critical for biomaterial integration (40-43).

Clinical and preclinical evidence suggests that preparations containing a balanced fraction of lymphocytes accelerate wound healing and improve the integration of biomaterials by modulating both innate and adaptive immune responses. However, an overrepresentation of pro-inflammatory Th1/Th17 subsets may be detrimental by maintaining a persistent inflammatory state. These findings underscore the need to optimize protocols for PRP and PRF preparation with attention not only to platelet counts but also to the lymphocyte composition. By tailoring lymphocyte content, clinicians may harness the full immunomodulatory potential of blood concentrates, thereby achieving more predictable regenerative outcomes (44).

Conclusion

Lymphocytes are increasingly recognized as essential regulators of biomaterial-associated immune responses (Figure 4). Beyond the early involvement of neutrophils and macrophages, adaptive immune cells decisively influence the chronic phase of the FBR. T cells are central to this process because their subset-specific cytokine profiles determine the balance between inflammation and regeneration. Pro-inflammatory Th1

and Th17 subsets sustain chronic inflammation, fibrosis, and impaired integration, whereas Th2 and Tregs promote anti-inflammatory conditions, angiogenesis, and tissue repair (2, 6). B lymphocytes also contribute by producing antibodies against denatured or altered proteins at material surfaces, which can result in immune complex deposition, complement activation, and chronic inflammation. At the same time, B-cell-derived cytokines such as IL-6 can modulate macrophage polarization and fibroblast activity, thereby influencing extracellular matrix turnover and fibrosis (2, 6). NK cells act as rapid stress sensors in the peri-implant environment. Through the secretion of IFN- γ they activate macrophages and dendritic cells, while their release of VEGF promotes angiogenesis and supports tissue integration. Depending on the degradation kinetics of a material, NK activity may therefore tip the balance between regeneration and fibrotic encapsulation (2, 3, 6, 10).

A decisive factor in this process is the dynamic protein layer that immediately forms on biomaterial surfaces upon implantation. The composition and conformational stability of adsorbed proteins orchestrate immune recognition and lymphocyte activation, linking material properties to adaptive immunity and long-term outcomes (13). These insights emphasize that future biomaterial design must extend beyond classical considerations of biocompatibility and macrophage or granulocyte responses. By steering lymphocyte activity toward Treg and Th2 phenotypes, limiting pathogenic B-cell responses, and harnessing NK-mediated angiogenesis,

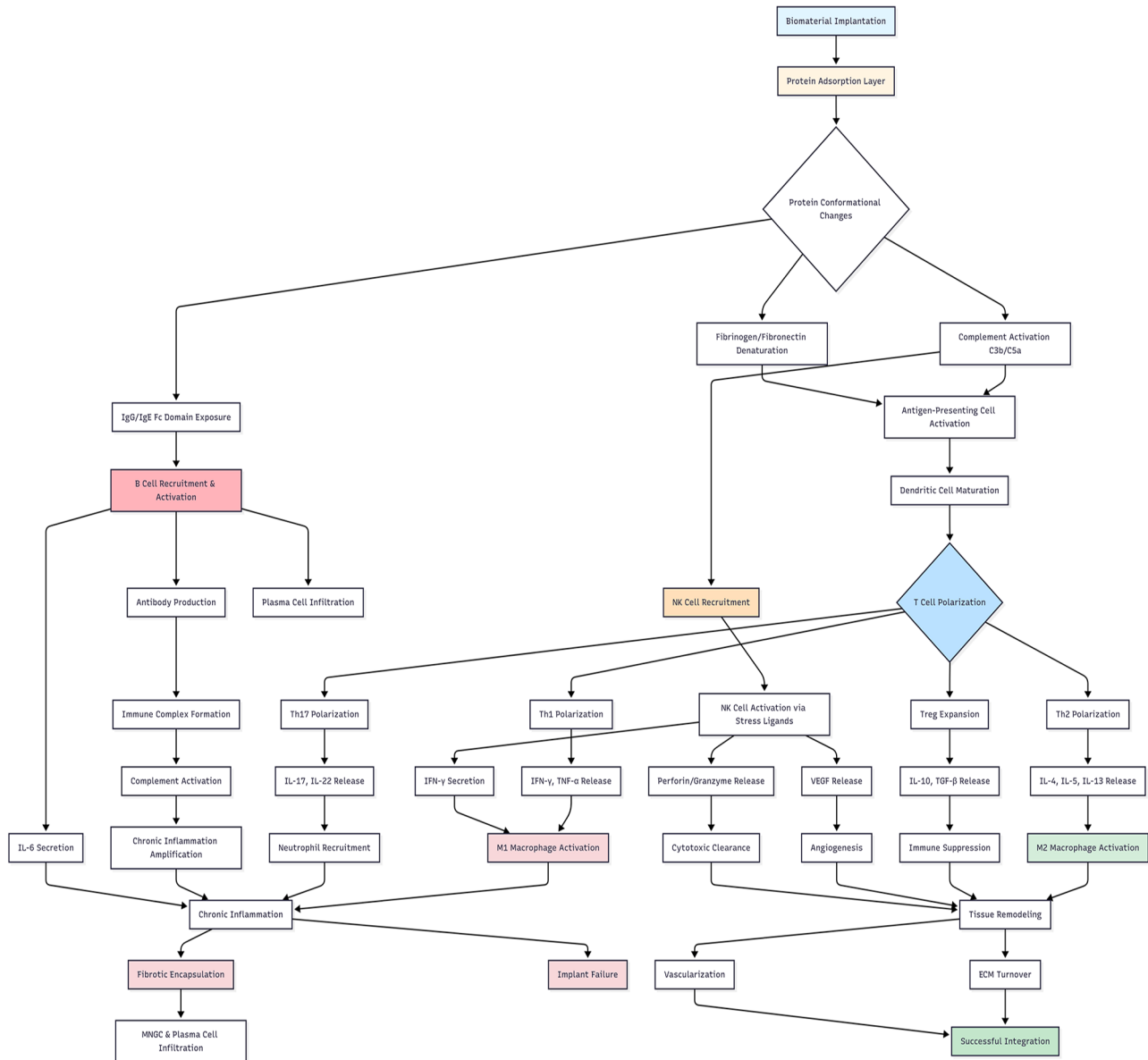


Figure 4. Lymphocyte responses to biomaterials and interactions with other immune cells. Flowchart illustrating the adaptive immune cascade following biomaterial implantation. Protein adsorption with conformational changes (IgG/IgE Fc exposure, complement C3b/C5a generation, fibrinogen/fibronectin denaturation) activates APCs and triggers lymphocyte recruitment. B cells produce antibodies, differentiate into plasma cells, and secrete IL-6, leading to immune complex formation, complement activation, and chronic inflammation amplification. T cell polarization via activated DCs generates four distinct subsets: Th1 cells (IFN- γ , TNF- α) drive M1 macrophage activation and chronic inflammation; Th2 cells (IL-4, IL-5, IL-13) promote M2 macrophage polarization and tissue remodeling; Th17 cells (IL-17, IL-22) recruit neutrophils and sustain inflammation; Tregs (IL-10, TGF- β) suppress immune activation and support resolution. NK cells, activated by stress ligands, release IFN- γ (enhancing M1 activation), VEGF (promoting angiogenesis), and perforin/granzymes (cytotoxic clearance). Pro-inflammatory pathways converge to cause fibrotic encapsulation with MNGC and plasma cell infiltration, leading to implant failure. Pro-regenerative pathways result in ECM turnover, vascularization, and successful integration. Color coding: blue=initial events; pink=B cells; light blue=T cell polarization; orange=NK cells; red=M1/adverse outcomes; green=M2/favorable outcomes. APCs: Antigen-presenting cells; C3b/C5a: complement components 3b/5a; DCs: dendritic cells; ECM: extracellular matrix; IFN- γ : interferon-gamma; IgE/IgG: immunoglobulin E/G; IL: interleukin; M1/M2: classically/alternatively activated macrophage; MNGC: multinucleated giant cell; NK: natural killer; TGF- β : transforming growth factor-beta; Th1/Th2/Th17: T helper type 1/2/17; TNF- α : tumor necrosis factor-alpha; Treg: regulatory T cell; VEGF: vascular endothelial growth factor.

Table V. Strategies to modulate lymphocyte responses in biomaterial design.

Strategy	Target subset	Mechanism	Example modification	References
Hydrophilic/zwitterionic coatings	Tregs, Th2	Reduce protein denaturation, promote tolerance	Zwitterionic hydrogels resist FBR	(28)
Controlled Mg degradation	Tregs vs. Th1/Th17	Ion release kinetics modulate balance	Alloy composition adjustment	(26, 27)
Decellularization & crosslinking control	B cells	Reduce antigenicity of xenogeneic collagen	Tilapia vs. bovine collagen	(24)
Nano/micro surface topography	T cells, NK cells	Modify DC maturation, angiogenesis	Titanium implant design	(25, 30)
Growth factor delivery (PRP/PRF)	All lymphocytes	Cytokine-driven immunomodulation	PRF-derived IL-10, VEGF	(31–37)

FBR: Foreign body response; IL: Interleukin; PRF: platelet-rich fibrin; PRP: platelet-rich plasma; MG: magnesium; DC: dendritic cell.

it will be possible to develop immunomodulatory biomaterials that promote constructive remodeling and more predictable clinical success (5). Finally, practical strategies to steer lymphocyte activity toward constructive remodeling in biomaterial and surface design are summarized in Table V.

Conflicts of Interest

All 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.

Authors' Contributions

Conceptualization: M.B. and O.J.; resources: M.B. and O.J.; data curation: M.B. and O.J.; writing – original draft preparation: M.B. and O.J.; writing – review and editing: M.B. and O.J.; visualization: M.B. and O.J.; funding acquisition: M.B. and O.J. All Authors have read and agreed to the published version of the manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (Microsoft Copilot) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning-based image enhancement tools.

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