

CELL SIGNALLING AND BIOLOGICAL COMMUNICATION AT THE BIOMATERIAL-TISSUE INTERFACE: IMPLICATIONS FOR IMPLANT INTEGRATION AND DRUG DELIVERY

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ABSTRACT. This review presents the interconnected roles of biointerfaces, cell signalling, and biological communication in implant biocompatibility and integration with surrounding tissues. Special focus is given to cell signalling pathways in the immune and nervous systems, as these mechanisms are central to cellular communication and implant acceptance. Key aspects discussed include the roles of signalling molecules, extracellular and intracellular communication, and how engineered biomaterial surfaces can promote tissue healing or, conversely, trigger foreign body responses and implant rejection. Surface modification is emphasized as a strategy to enhance immune compatibility and improve implant performance. Clinical translation is illustrated through spinal graft preparation, highlighting the importance of surface engineering in surgery. Despite advances, the design of bioactive implants that actively support healing remains challenging. Current limitations include insufficient understanding of cell–material interactions, including patient-specific responses. Future directions point toward smart implants capable of real-time sensing, adaptive responses, and integration with regenerative medicine approaches.

Keywords: biomaterials; cell signalling; biointerfaces; implant integration; foreign body response; tissue regeneration; biocompatibility.

INTRODUCTION

Implant rejection still represents one of the major challenges in clinical use of biomaterial solutions. Biointerfaces have a major role in directing the outcomes of an implant's

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acceptance (LIU and WANG, 2014; LI *et al.*, 2025). New implant designs that incorporate specific antigens or immunomodulatory agents (PARK and KIM, 2025) and surface engineering are studied to improve biocompatibility and reduce inflammatory responses (BRYERS *et al.*, 2012). Surface modifications can influence cell adhesion and proliferation, including changes in cytokine secretion profiles or increasing expression of anti-inflammatory genes (AMANI *et al.*, 2024). Surface texturing, bioactive coatings, and different surface modification techniques are studied to provide the fully integrated implant (HOU *et al.*, 2022), including biohybrid systems for smart implants, such as biohybrid regenerative bioelectronics (CARNICER-LOMBARTE *et al.*, 2025). Incorporation of drug delivery systems can realise controlled release of therapeutic agents over time and prevent adverse reactions (FAYZULLIN *et al.*, 2021).

Close relationships between biointerfaces, cell signalling, and implant integration into biological systems have been widely demonstrated (FRANZ *et al.*, 2011). However, cell–material interactions are not fully understood to enable customization in biomaterial design according to specific tissues (HU *et al.*, 2023). Cutting-edge research in mechanisms of cellular communication is focused on modelling and simulation of signal integration and crosstalk, where cells integrate signals from multiple pathways (e.g., Notch, Wnt, MAPK, PI3K-AKT) to monitor dynamic signal integration in live cells (ULLO and CASE, 2023), or to indicate directions for tissue regeneration, like in bone regeneration (DALLE CARBONARE *et al.*, 2025).

This review explores the evolving field of implantable systems and biological communication at the implant interface, including drug delivery systems and their integration with biological tissues. We analysed how implants communicate with the host environment through complex biological processes, including cellular signalling, immune responses, extracellular and intracellular signalling pathways, and interactions with the nervous system. Building on these mechanistic insights, the review considers their implications for clinical translation, with a case study in spinal surgery. Finally, it discusses the key challenges and emerging opportunities that will shape the development of next-generation implantable devices.

IMPLANTABLE DRUG DELIVERY SYSTEM

Drug delivery systems can realise controlled release of therapeutic agents over time (FAYZULLIN *et al.*, 2021). Currently, the FDA has approved a range of drug delivery systems. Recognised issues with biointegration of drug delivery systems are shown in Tab. 1.

Table 1. Recognised issues with biointegration of drug delivery systems (FAYZULLIN *et al.*, 2021) (under an open access Creative Commons CC BY license).

<i>Type of IDDSs</i>	<i>Reported Biointegration Issues that May Be Linked to FBR</i>
Subcutaneous	Implant migration Difficulty with implant removal due to peri-implant scarring Implantation site aseptic inflammation or implant rejection
Infusion pumps as IDDSs	Inflammatory and dystrophic changes in spinal cord Fibrotic transformation of the skin pocket around metallic reservoir of the pump can affect the integrity of the reservoir–catheter connection and result in skin pocket filling with high doses of the drug.

Table 1. continued

Type of IDDSs	Reported Biointegration Issues that May Be Linked to FBR
Ocular IDDSs	Poststeroid cataracts
Intracerebral IDDS (Gliadel)	Peri-implant inflammation
Drug-eluting Stents	Proliferation of neointima and thrombogenic complications (successfully prevented in modern IDDSs)

Implantable biomaterials are recognized by the immune system as foreign entities, initiating a cascade of responses collectively referred to as the foreign body reaction (FBR). The implantation process invariably results in tissue injury and blood extravasation, which prompts an instantaneous influx of inflammatory-mediating cells to the site (KASTELLORIZIOS *et al.*, 2015; CARNICER-LOMBARTE *et al.*, 2021; FAYZULLIN *et al.*, 2021). Rather than merely minimizing immune activation, current biomaterial design increasingly aims to actively modulate immune cell behaviour to promote constructive tissue regeneration and long-term implant acceptance.

Integration with biological systems

Immediately after implantation, biomaterial surfaces become coated with a dynamic layer of adsorbed proteins, which mediates the initial interaction with host cells and largely determines subsequent immune activation, cell adhesion, and tissue integration. Implanted materials elicit a host response, and successful implant design balances immune-mediated tissue integration with minimal chronic inflammation and foreign body reactions (BAKER and CHEN, 2012; FRANZ *et al.*, 2011). Inert biomaterials are recognized as foreign and become encapsulated by fibrous tissue. Triggering specific cellular responses can improve biomaterial integration (KÄMMERLING *et al.*, 2021). After the surgical placement of an implant, multiple reactions are triggered involving interaction with blood components, deposition of a protein layer on the biomaterial, formation of a provisional matrix, immune cell recruitment, acute inflammation, granulation tissue formation, fibrosis, foreign body reaction, and development of a fibrous capsule (KÄMMERLING *et al.*, 2021). Initial implant–host reaction significantly influences the fate of an implant.

The interaction between biomaterials and tissues significantly depends on their surface properties. Surface modification is a commonly adopted approach for better integration of biomaterials within the living environment since it enables tailoring of physical or chemical properties that enhance their compatibility with the human body (HU *et al.*, 2023; BRANKOVIĆ *et al.*, 2024). A range of surface modification methods is widely utilized to improve cytocompatibility, promote cell growth, enhance drug stability, enable targeted delivery, and prevent bacterial contamination (HANAWA, 2011). Biofunctionalisation involves the immobilization of biomolecules such as proteins, peptides, and polysaccharides, or bioactive drugs, whereas biological communication at the implant interface is of major importance for understanding and subsequently controlling this biointegration.

The complex interplay between biomaterial properties, biological communication, intracellular signalling pathways, and tissue responses that collectively determine implant integration, and long-term biocompatibility is schematically illustrated in Fig. 1.

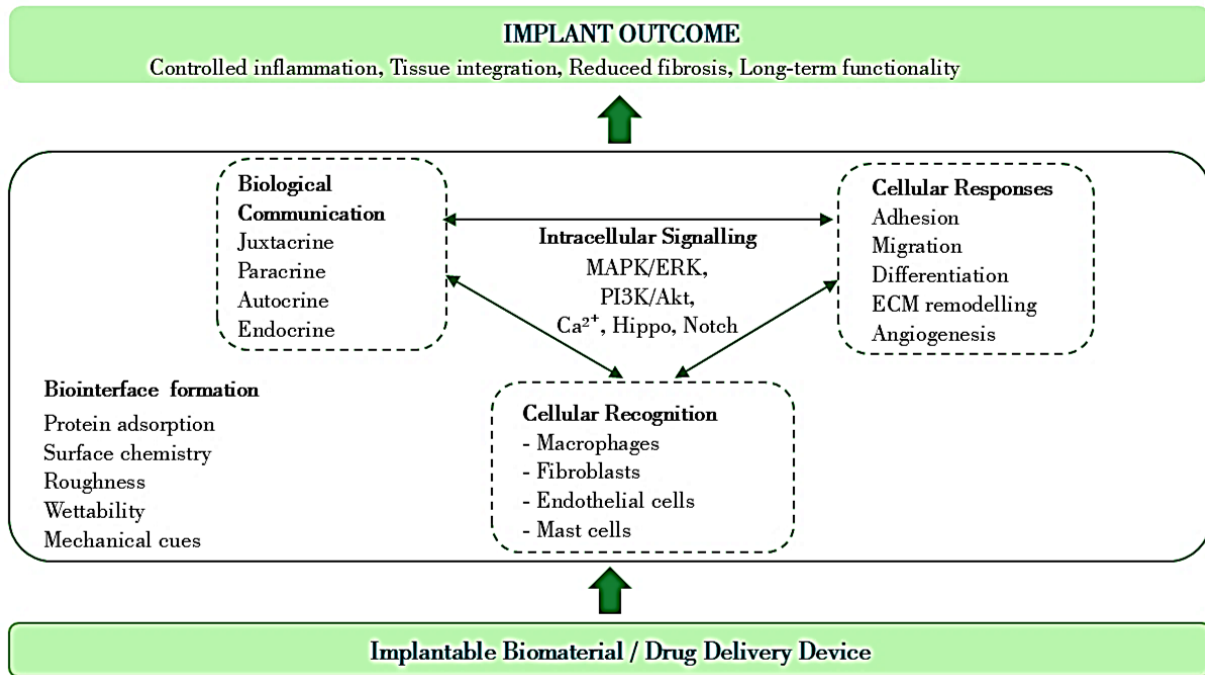


Figure 1: Schematic overview of biological communication at the biomaterial interface illustrating how biomaterial properties regulate cell signalling pathways, immune responses, tissue regeneration, and long-term implant integration.

These initial cell–material interactions establish the biological microenvironment that governs subsequent cell signalling events and ultimately determines the long-term integration and functionality of implanted biomaterials.

BIOLOGICAL COMMUNICATION AT THE IMPLANT INTERFACE

Mechanisms of cellular communication

Cellular communication is fundamental to maintaining tissue homeostasis and coordinating biological responses to implanted biomaterials and drug delivery systems (FRANZ *et al.*, 2011). Following implantation, resident and recruited cells exchange biochemical signals through membrane receptors and intracellular signalling pathways to regulate inflammation, immune activation, extracellular matrix remodelling, angiogenesis, and tissue repair (PERKINS, 2007; YARON-BARIR *et al.*, 2024). The coordinated activity of these signalling networks ultimately determines the degree of implant integration, long-term biocompatibility, and clinical performance.

Key signalling pathways are studied, such as the PI3K/AKT/mTOR pathway that regulates cell growth and metabolism (PENG *et al.*, 2022), including neural stem cell proliferation and differentiation, mechanisms underlying learning and memory, and connections to cancer developments (GUERTIN and SABATINI, 2007). Hippo signalling pathway that regulates cell proliferation and apoptosis and controls the size of organs (FU *et al.*, 2022). Notch signalling pathway (BRAY, 2006; ZHOU *et al.*, 2022), being crucial for cell fate determination and differentiation with recently discovered roles and implications in bladder and liver cancers (SHI *et al.*, 2024). In the context of the immune system, the immunological synapse commonly involves effector cells such as T-lymphocytes or natural killer (NK) cells (ABEL *et al.*, 2018; FERLAZZO *et al.*, 2002).

Cells communicate through several complementary mechanisms, including juxtacrine, paracrine, autocrine, endocrine, and intracellular signalling, each differing in the distance over which signalling molecules act and the mode of signal transmission (CHAFFEY, 2003). These pathways function in an integrated manner to regulate cell proliferation, migration, differentiation, apoptosis, and immune responses, thereby maintaining tissue homeostasis while enabling adaptation to physiological and pathological stimuli.

During implant healing, juxtacrine interactions between immune cells, fibroblasts, and tissue-resident cells contribute to the regulation of inflammatory responses and tissue integration at the biomaterial interface. At the biomaterial interface, these communication pathways coordinate cellular responses to implanted materials by regulating inflammation, extracellular matrix remodelling, angiogenesis, and tissue regeneration. The magnitude and duration of cellular signalling are strongly influenced by biomaterial properties, including surface chemistry, wettability, roughness, stiffness, and nanoscale architecture.

Collectively, these signalling pathways mediate the cellular responses elicited by biomaterial surfaces and therefore represent important targets for designing bioactive implants capable of directing tissue regeneration. Although numerous signalling pathways involved in biomaterial–cell interactions have been identified, their coordinated regulation *in vivo* remains incompletely understood owing to the complexity of the tissue microenvironment and patient-specific biological variability.

Cell signal molecules

Cells communicate through numerous signal molecules, as shown in Tab. 2. Cells use receptors that are commonly some types of proteins to bind to the signalling molecule and subsequently trigger a response.

Table 2. Major signalling molecules involved in intercellular communication.

Primary signalling mechanism	Type of signalling	Reference
NO, CO, H ₂ S	Paracrine and autocrine signalling	(BUSTOS-MORÁN <i>et al.</i> , 2016)
Adiponectin	Paracrine signalling	(SEGRS and DE KEULENAER, 2021)
Interleukin 11	Paracrine signalling	(SEGRS and DE KEULENAER, 2021)
Growth factors (IGF)	Paracrine and autocrine signalling	(BUSTOS-MORÁN <i>et al.</i> , 2016)
Cytokines, Chemokines, coagulation factors	Paracrine and autocrine signalling	(BUSTOS-MORÁN <i>et al.</i> , 2016; SEGRS and DE KEULENAER, 2021)
Hormones, steroid hormones (including vitamin D), estrogen, testosterone, glucocorticoids	Endocrine signalling	(GOUGH, 2010)
Purinergic signalling (autocrine/paracrine)	Nerve signalling and autocrine signalling	(NOVAK, 2003; BUSTOS-MORÁN <i>et al.</i> , 2016)

Cytokines play a critical role in regulating immune functions through established signalling pathways like JAK-STAT, which govern inflammation, cell growth, and tissue regeneration (O'SHEA and PLENGE, 2012). However, many therapeutic agents targeting cytokine activity, such as small molecules and peptide-based modulators, are hindered by poor water solubility and low oral bioavailability, limiting their therapeutic potential (GOKHALE and SATYANARAYANAJAIS, 2014). Haematopoiesis is crucial for immune defence, oxygen delivery, and coagulation, and its disruption is associated with a range of disorders, including cytopenias and hematologic cancers. Pharmacological agents aimed at modulating hematopoietic pathways, such as cytokines, receptor agonists, and signalling inhibitors, also commonly exhibit poor solubility or limited absorption, which can hinder their therapeutic efficacy. Drug formulations that use Amorphous Solid Dispersion (ASD) have been studied to solve these challenges by maintaining active compounds in an amorphous, high-energy state stabilized by polymer carriers (BAIRD and TAYLOR, 2012; MILOSEVIC *et al.*, 2024). This enhances dissolution and maintains supersaturation within the gastrointestinal environment, thereby improving systemic uptake (HANCOCK and ZOGRAFI, 1997). For hematopoietic therapies that require precise and consistent bioavailability, such as kinase inhibitors or growth factor-based treatments, ASD formulations may offer improved pharmacokinetic stability, reduced dosing variability, and enhanced therapeutic impact (SCHITTNY *et al.*, 2020).

Communication in the immune system

The immune response to implanted drug delivery devices is mediated by coordinated interactions between innate and adaptive immune cells (KROESEN *et al.*, 1998; MARSHALL *et al.*, 2018). Following implantation, antigen-presenting cells (APCs), particularly dendritic cells and macrophages, recognize foreign materials and initiate immune signalling. Dendritic cells bridge the innate and adaptive immune systems by processing and presenting antigens to T-lymphocytes through major histocompatibility complex (MHC) molecules. CD4⁺ helper T-cells recognize antigens presented by MHC class II, whereas CD8⁺ cytotoxic T-cells recognize antigens presented by MHC class I. Activated T-cells secrete cytokines that regulate inflammation, recruit additional immune cells, and influence the foreign body response, while B-cells mature into plasma cells that produce antibodies. Together, these cellular interactions determine the host response to implanted drug delivery systems, affecting inflammation, fibrous capsule formation, device integration, and ultimately the performance and longevity of the implant. Types of T-cells and comparison of MHC complex types are given in Tab. 3.

Table 3. Major T-cell subsets and comparison of MHC class I and II antigen presentation pathways.

Cytotoxic T lymphocytes (CD8⁺)	Helper T lymphocytes (CD4⁺)	Regulatory T cells (Treg)
Directly eliminate infected or abnormal cells.	Do not directly eliminate other cells.	Suppress or reduce the activity of other T-cells when necessary and regulate immune responses, preventing immune cells from attacking healthy cells (SAULS <i>et al.</i> , 2025).
Regulate haematopoiesis <i>in vitro</i> (VOJVODIC and POPOVIC, 2010; ABEL <i>et al.</i> , 2018).	Send activation signals to CD8 ⁺ T-cells, B-cells, and macrophages.	Function as immune regulators (KUMAR <i>et al.</i> , 2018).
Recognise antigens and act as effector cells (SAULS <i>et al.</i> , 2025).	Recognise antigens and fight against infections (WILLIAMS <i>et al.</i> , 2018; HIRATA <i>et al.</i> , 2019).	

Table 3. continued

Cytotoxic T lymphocytes (CD8 ⁺)	Helper T lymphocytes (CD4 ⁺)	Regulatory T cells (Treg)
Comparison of MHC type I and II.		
Feature	MHC Class I/ HLA I	MHC Class II/ HLA II
Function	Presents endogenous peptide antigens to CD8 ⁺ cytotoxic T cells.	Presents exogenous peptide antigens to CD4 ⁺ helper T cells (WILLIAMS <i>et al.</i> , 2018; HIRATA <i>et al.</i> , 2019).
Location	Expressed on almost all nucleated cells.	Expressed primarily on professional antigen-presenting cells (dendritic cells, macrophages, B lymphocytes).

Immune synapse

Immune synapses enable communication between T-cells and their target cells, similar to neuronal synapses. They form through the organized interaction of membrane proteins between T-cells and antigen-presenting cells (APCs). The process begins when T-cell receptors (TCRs) recognize peptide–MHC complexes on APCs, triggering T-cell activation while maintaining contact until activation is complete (DUSTIN *et al.*, 2010). The three main types of antigen-presenting cells are: macrophages, B-lymphocytes, and dendritic cells.

Immature T-cells enter lymph nodes and scan for specific peptide–MHC (pMHC) complexes. Upon recognition, they form prolonged contacts with antigen-presenting cells, commit to the cell cycle, and differentiate into effector T-cells (JANEWAY *et al.*, 2001). Antigens are recognized through peptide fragments by T-cell receptors.

Antigen recognition requires presentation by antigen-presenting cells. Innate immunity rapidly recruits immune cells to sites of infection through cytokines and chemokines. Key inflammatory cytokines, including TNF, IL-1, and IL-6, promote cell recruitment, local inflammation, pathogen clearance, and fever. Dysregulated cytokine production is associated with inflammatory and autoimmune diseases (MARSHALL *et al.*, 2018). The absence of a single MHC-I allele, common in cancer cells, increases their sensitivity to NK cell cytotoxicity (ZAMAI *et al.*, 2007).

Cytokines

Cytokines are peptide and glycoprotein signalling molecules that regulate inflammation, immune responses, wound healing, fibrosis, and neuronal function. In peripheral nervous tissue, they are produced by immune and support cells, including macrophages, mast cells, Schwann cells, and endothelial cells. They modulate neuronal excitability and contribute to neuroinflammation by activating signalling pathways and reaching the dorsal root ganglion and spinal dorsal horn, (ZHANG and AN, 2007; MOUDGIL and CHOUBEY, 2011). These cellular responses are particularly relevant to implanted drug delivery devices, as activation of local immune and support cells at the tissue–implant interface drives cytokine release, influencing foreign body reactions, tissue integration, and the long-term performance of the implant.

The balance between pro-inflammatory and anti-inflammatory signalling at the biomaterial interface largely determines whether implantation results in successful tissue regeneration or chronic foreign body reactions.

Extracellular signalling

Extracellular signal molecules typically function at low concentrations and are recognized by high-affinity receptors, usually transmembrane proteins on the cell surface. The binding of a ligand to these receptors initiates a signal transduction cascade, resulting in changes to the cell behaviour. In some cases, receptors are located inside the cell, requiring the signal molecule to cross the membrane to activate intracellular signalling pathways (SU *et al.*, 2024). Diffusion of the signal molecules through the plasma membrane is shown in Fig. 2. Cells communicate using different signalling mechanisms based on the range and mode of signal molecule action, which can belong to contact-dependent signalling and secreted signals (endocrine and paracrine signalling), where different pathways provide the spatial and functional diversity in cell transmission and response to signals (CHAFFEY, 2003).

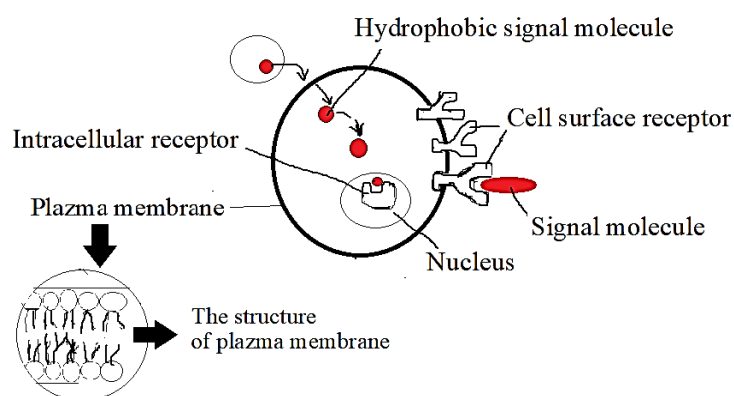


Figure 2. General concept of extracellular signalling.

Cell signalling is central to the biological response to implanted drug delivery devices. Following implantation, resident cells such as macrophages, mast cells, Schwann cells, fibroblasts, and endothelial cells recognize the biomaterial surface through membrane receptors, triggering intracellular signalling pathways that regulate cytokine secretion, immune cell recruitment, extracellular matrix remodelling, and tissue repair (BRYERS *et al.*, 2012, AMANI *et al.*, 2024, DALLE CARBONARE *et al.*, 2025). Communication through contact-dependent, paracrine, and endocrine signalling coordinates the foreign body response and ultimately determines the degree of inflammation, fibrotic encapsulation, tissue integration, and long-term functionality of the implanted device.

Paracrine signalling regulates neighbouring cells through locally released cytokines, chemokines, and growth factors, while autocrine signalling allows cells to respond to their own secreted mediators, thereby controlling proliferation, differentiation, and immune responses. In implanted biomaterials and drug delivery systems, these signalling mechanisms influence the foreign body response, modulating inflammation, tissue integration, and ultimately the long-term acceptance and functionality of the implant.

Endocrine signalling involves hormones that are transported through the circulation to regulate gene expression, metabolism, and tissue homeostasis in distant target organs. In implantable drug delivery systems, endocrine signalling influences tissue repair, angiogenesis, and immune regulation, thereby contributing to implant integration and long-term biocompatibility (FRANZ *et al.*, 2011, KÄMMERLING *et al.*, 2021)

Intracellular signalling

Intracellular signalling enables cells to sense and respond to extracellular stimuli through receptor-mediated pathways (Tab. 2) that regulate proliferation, migration,

differentiation, apoptosis, and other essential cellular functions (EBLEN, 2018). Calcium (Ca^{2+}) is one of the most important intracellular second messengers, with its concentration tightly controlled by transport proteins and ion channels to coordinate gene expression, secretion, metabolism, and other signalling events (REDDISH *et al.*, 2017). In implanted biomaterials and drug delivery systems, intracellular signalling regulates the cellular response to the biomaterial surface, influencing inflammation, tissue regeneration, and ultimately the long-term acceptance and functionality of the implant. Activation of intracellular signalling pathways enables cells to translate physicochemical cues from biomaterial surfaces into biological responses that regulate implant acceptance and long-term biocompatibility. Besides biochemical signals, cells continuously sense mechanical cues such as substrate stiffness, topography, and surface roughness through mechanotransduction pathways, thereby influencing adhesion, proliferation, differentiation, and tissue regeneration, (DISCHER *et al.*, 2009; SARASWATHIBHATLA *et al.*, 2023).

Nervous system communication

Neural signalling regulates bone remodelling through neuroimmune interactions, with mediators such as IL-6 influencing cellular responses that can affect the integration and performance of implanted biomaterials (WAN *et al.*, 2021; ZHANG *et al.*, 2022).

Bone cells participate in immune-mediated regulation within the intrabody microenvironment by releasing signalling factors such as interleukin-7 (IL-7), CXC-chemokine ligand 12 (CXCL12), granulocyte colony-stimulating factor (G-CSF), and prostaglandin E2 (PGE2), which in turn influence nearby nerves (WAN *et al.*, 2021; ZHANG *et al.*, 2022). These signalling molecules serve as crucial mediators of communication between the nervous system and bone tissue. Disruption of this signalling pathway can contribute to the development of various bone disorders.

Evidence indicates that neuron-specific gene expression is closely connected to the structural and functional organization of the entire nervous system (TAYLOR *et al.*, 2021). According to (JIANG *et al.*, 2022), the first group of alterations involves disruptions in critical transcriptional and translational signalling pathways. The second group is characterized by abnormalities in synaptic proteins, and the third group concerns the excessive translation of specific transcripts. At the same time, another key factor is the immunoinflammatory response triggered by reactive glial proliferation and dysregulation of the intestinal microbial community. These signalling pathways contribute to the pathophysiology of ASD through interconnected, cascading effects rather than functioning in isolation (JIANG *et al.*, 2022). Nervous system damage impacts not only neural circuits but also immune responses and signalling processes, which makes the pathology more complex.

CLINICAL TRANSLATION

Spinal surgery

Spinal implantation surgery encompasses a set of surgical procedures aimed at correcting instability, deformities, or injuries to the spinal column (KO *et al.*, 2024). The primary goals are to restore sagittal and transverse balance, preserve or regain neurological function, and alleviate pain (TAN *et al.*, 2023). These interventions often involve the extracorporeal synthesis and fusion of spinal segments using intervertebral screws, rods, and plates, with or without supplementary bone augmentation, typically using polymethyl methacrylate (PMMA) (MOON *et al.*, 2009). Bone remodelling is regulated by the coordinated activity of osteoblasts, osteoclasts, and osteocytes (BOLAMPERTI *et al.*, 2022). Following implantation, the communication among these cells governs the success of the graft. A vital

aspect of achieving durable integration is the careful preparation of the interface between the implant and the host tissue. Thorough surface preparation is essential for ensuring optimal osseointegration (ZHANG *et al.*, 2021). The molecular signalling mechanisms described above provide the biological basis for the clinical performance of implantable biomaterials and drug delivery systems across a wide range of medical applications.

Within this procedure, the bone acts as the natural host tissue that secures the synthetic implants. The preparation of this biological material for reconstructive purposes, particularly in spinal implant surgery, requires a multifaceted approach that combines biomechanical, material, and biological factors to optimize clinical outcomes (SONG *et al.*, 2021). The healthy bone tissue is prepared through decortication, which creates space for the implant. This process stimulates local osteogenic activity and vascularization, as well as enhances cell adhesion, proliferation, and differentiation, thereby increasing the likelihood of successful integration (SHAH *et al.*, 2018). Successful spinal surgery depends on accurate graft placement and well-prepared implant surfaces (Fig. 3).

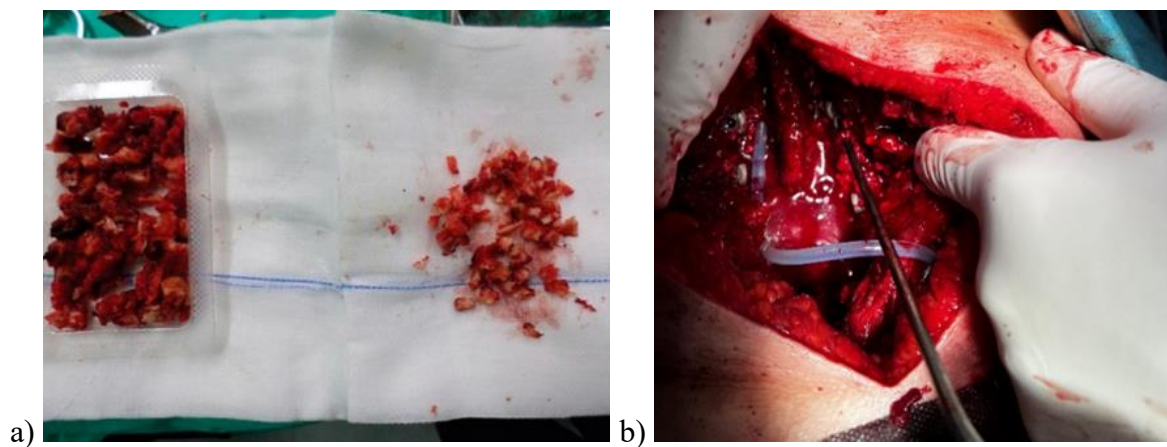


Figure 3. a) Bone graft prepared for surgical intervention ((BOKTOR *et al.*, 2018) under Creative Commons Attribution-Non-commercial-Share Alike License (CC BY-NC-SA)); b) Complexity of positioning the graft during the spinal surgery: exposing the disc while protecting the dura and nervous system.

Surface modification of the bone, particularly through decortication, causes mechanical disruption of the cortical bone layer, exposing the underlying trabecular tissue. This action initiates a local inflammatory response, which represents the first phase in the process of bone healing and implant integration (BATOOL *et al.*, 2021). During the early stages of this response, the damaged tissue releases danger-associated molecular patterns (DAMPs), which activate resident immune cells and draw blood cells to the region (CHEN *et al.*, 2018). The synchronized activation and transition from the inflammatory phase to the regenerative phase create an optimal microenvironment for new bone formation and the integration of the implant into the spinal column's biomechanical framework (CAI *et al.*, 2023). Successful tissue integration depends on maintaining a carefully regulated balance between inflammation and regeneration. While an appropriate inflammatory response is necessary to initiate healing, excessive or persistent inflammation promotes fibrous capsule formation around the implant, whereas an inadequate response may impair tissue repair, leading to incomplete fusion or implant failure. Successful implant integration also depends on rapid vascularization, as adequate angiogenesis ensures oxygen and nutrient delivery while supporting tissue repair and long-term implant functionality. Additionally, during the surgical procedure, it is crucial to preserve the viability of surrounding tissues, such as muscles, ligaments, and blood vessels, to promote healing and reduce the incidence of surgical complications (ZHOU *et al.*, 2025).

Implant surface modification is critical for successful spinal fusion, with titanium and its alloys widely used due to their biocompatibility, mechanical strength, and corrosion resistance (CHEN *et al.*, 2023), (WARBURTON *et al.*, 2020). Some of the commonly used implants in the surgical treatment of spinal disorders include pedicle screws, spinal cages, and spinal rods, which provide essential support to the spine through careful selection and combination (JAIN *et al.*, 2020). Before implantation, implants undergo strict sterilization protocols to eliminate any risk of infection and ensure patient safety. Surface preparation uses physical, chemical, and biological methods to enhance implant biocompatibility and osteoconductivity, including surface roughening and bioactive coatings such as hydroxyapatite or calcium phosphate (GORIAINOV *et al.*, 2018; HOU *et al.*, 2022). These strategies enhance osteoblast adhesion, osteogenic marker expression, and matrix mineralization while reducing fibroblast adhesion, inflammation, and fibrous capsule formation, thereby improving osseointegration and implant stability (BANDYOPADHYAY *et al.*, 2023; CROFT *et al.*, 2023).

CHALLENGES AND FUTURE PERSPECTIVES

Future biomaterials will increasingly be designed not only to provide structural support but also to actively regulate cellular signalling and biological communication to improve long-term therapeutic outcomes. Emerging approaches combining advanced biomaterials, patient-specific implant design, and artificial intelligence are expected to enable personalized implants capable of dynamically adapting to the host biological environment. Despite remarkable progress, several challenges remain at the intersection of biointerfaces, cell signalling, and implant integration. A major issue is the incomplete understanding of cell–material interactions, which limits the controllable design of biomaterials that can direct cellular responses (FLETCHER and OSBORNE, 2022). Similarly, the creation of biomimetic signalling environments that reproduce dynamic, spatially organized, and stimuli-responsive conditions is still underdeveloped (MA, 2008; STERN *et al.*, 2009; BAKER and CHEN, 2012). Another key limitation is the lack of materials with immune tolerance, as most clinically used biomaterials still provoke host responses (FAYZULLIN *et al.*, 2021). Long-term stability and durability of implants also remain problematic, with biochemical and biomechanical degradation affecting their functionality (ZIVIC *et al.*, 2013). Finally, personalisation of implants to patient-specific anatomical and physiological needs is not yet fully achievable (STOJKOVIC *et al.*, 2010).

Promising strategies are emerging. Surface engineering techniques, such as nano- and micropatterning and bioactive coatings, provide better control of cell–material interactions (STERN *et al.*, 2009; CHEN *et al.*, 2015; PETERSEN, 2017; HU *et al.*, 2023; MILENKOVIĆ *et al.*, 2024). Smart biomaterials and dynamic substrates that respond to external stimuli can partially mimic natural signalling environments (LEDET *et al.*, 2018; QU *et al.*, 2023; MILENKOVIĆ *et al.*, 2024). Advances in immune-compatible and biodegradable materials, including extracellular matrix scaffolds (EBLEN, 2018; BATOOL *et al.*, 2021; SONG *et al.*, 2021), self-healing (TOOHEY *et al.*, 2007; QU *et al.*, 2018) and antifouling systems (ZIVIC *et al.*, 2018; SLAVKOVIC *et al.*, 2023), are aimed at improving durability and reducing complications. Additive manufacturing allows the fabrication of personalized implants tailored to patient anatomy (STOJKOVIC *et al.*, 2010), while computational modelling offers insights into the multiscale integration of molecular, tissue, and organ functions (SANTANA-CODINA *et al.*, 2013; MILENKOVIĆ *et al.*, 2025).

The future next-generation smart biointerfaces should integrate biosensors, bioelectronics, and AI-driven design. Biosensors can provide real-time monitoring from cellular to tissue levels (STUART *et al.*, 2010; KASTELLORIZIOS *et al.*, 2015; KOETTING *et al.*, 2015; ANIC *et al.*, 2021;), while AI-based models have already shown promise in predicting implant success (NAZARI *et al.*, 2025). These tools are expected to support better clinical

decision-making and accelerate the development of personalized and adaptive implants. Overcoming these challenges is key to developing implants that not only remain functional over the long term but also adapt to the needs of individual patients and integrate more effectively with the surrounding biological environment. Continued progress in this area will support the development of implantable systems, including drug delivery devices that are regenerative, responsive to physiological changes, and have improved clinical effectiveness.

CONCLUSIONS

The integration of biomedical implants depends strongly on the design of biointerfaces. Cell signalling and biological communication are fundamental regulators of the interactions between implanted biomaterials and the host tissue, governing immune activation, inflammation, tissue regeneration, and long-term implant performance. The coordinated action of autocrine, paracrine, endocrine, juxtacrine, and intracellular signalling pathways enables cells to sense and respond to biomaterial surfaces, ultimately determining whether implantation results in successful integration or an adverse foreign body response. Recent advances in biomaterial engineering, including biofunctionalization, surface modification, nanostructured interfaces, and smart implant technologies, have demonstrated significant potential to modulate these biological processes and improve implant biocompatibility and clinical outcomes.

Despite substantial progress, a major challenge remains the incomplete understanding of the dynamic and multiscale interactions occurring at the biomaterial–tissue interface. The complexity of cellular communication networks, together with patient-specific biological variability, continues to limit the rational design of biomaterials capable of predictably directing tissue responses. Future research should therefore integrate advances in materials science, molecular biology, immunology, computational modelling, and artificial intelligence to establish a more comprehensive understanding of cell–material interactions and their regulatory signalling mechanisms.

A deeper mechanistic understanding of biological communication at the biomaterial interface will support the development of next-generation implantable systems that actively regulate host responses, promote tissue regeneration, minimize chronic inflammation and fibrotic encapsulation, and achieve improved long-term functionality and clinical success. Continued collaboration between biomaterials science, cell biology, immunology, biomedical engineering, and computational modelling will be essential for translating fundamental discoveries into clinically successful implantable technologies.

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