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A commentary on the interplay of biomaterials and cell adhesion: new insights in bone tissue regeneration

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Abstract: This article navigates the relationship between biomaterials and osteogenic cell adhesion, highlighting the importance of mimicking the physiological response for bone tissue regeneration. Within this spirit is an initial description of the interaction between osteoblasts and osteoprogenitor cells with the extracellular matrix, explaining the leading role of integrins and cadherins in cell adhesion, and the intracellular signaling pathways elicited. Additionally, there is a focus on the strategies of advanced biomaterials that foster osteogenesis by replicating the native environment, taking advantage of these known specific signaling pathways. The final remarks lay on the need for careful consideration of *in-vitro* and *in-vivo* complexities in biomaterial development.

Abbreviation List

FERM	4.1 ezrin, radixin, moesin
Axin-GSK3β	Axin and glycogen synthase kinase 3 beta
BMP-2	Bone morphogenetic protein 2
Cas	CT10 Regulator of Kinase-associated substrate
ECM	Extracellular matrix
ERK1/2	Extracellular signal-regulated kinases 1 and 2
F-actin	Filamentous actin
FAK	Focal adhesion kinase
Grb2	Growth factor receptor-bound protein 2
GTPase	Guanosine triphosphatase
ILK	Integrin-linked kinase
LRP5/6	Low-density lipoprotein receptor-related proteins 5 and 6
mTOR	Mammalian target of rapamycin
MAPK	Mitogen-activated protein kinase
PI3K	Phosphoinositide 3-kinase
AKT	Protein kinase B
Rho	Ras homolog gene family
p130	Retinoblastoma-like protein 2
ROCK	Rho-associated protein kinase
Src	Sarcoma family of non-receptor tyrosine kinases
Ras	Small GTPases
SOS	Son of sevenless
Wnt	Wingless-related integration site proteins

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Osteogenic Cells' Adhesion and Regulation

When considering regeneration, it becomes evident that there is no better response than that of our own body. Therefore, mimicking its strategies appears to be the best approach for developing successful biomaterials. This proposal requires a thorough and deep understanding of how this perfect system works. With this aim, a closer look at osteoprogenitor cells' interactions with the extracellular matrix (ECM) is the natural first step. We will focus on cell adhesion, the kickoff of osteospecific differentiation, and subsequent osteogenesis. This communication occurs via intracellular signaling pathways related to cadherins and integrins receptors, both mechanotransducers. Cadherins facilitate cell-cell communication, while integrins are behind the interaction between cells and their ECM. The integrin receptor pathway presents two main types: those dependent on the focal adhesion kinase (FAK) complex and those independent of the FAK complex. Also, different phosphorylation sites on FAK can trigger cascades, such as the PI3K-Akt-mTOR, Ras-MAPK-ERK1/2, and p130Cas-RhoA GTPase pathways [1]

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(Fig. 1). The protagonism of FAK is beyond doubt regarding the intricate mechanisms involved in stiffness detection and surface texture of ECM by osteoprogenitor cells. Its three-domain structure of a kinase active domain capped by a FERM domain associated with the cell membrane at the focal adhesion and by the FAT domain on the opposite direction, related to the filamentous actin (F-actin) cytoskeleton fiber, is the cue. The native conformation hides this active domain. Still, in the presence of sufficiently high tension between the F-actin cytoskeleton and the focal adhesion, FAK reversely unfolds and elongates, exposing the kinase domain, causing its phosphorylation and subsequent complexation with Src protein-tyrosin kinase, leading to the activation of the FAK complex. If tensions cease or are insufficient, FAK will fold back and remain in its inactive low-energy conformation [2].

The subcellular mechanisms involved in cell adhesion present a collaborative association. In particular, the adhesion behavior of osteoblastic cells is interconnected rather than isolated. As such, some of the signaling molecules, scaffolding and cytoskeletal elements described at cell-ECM adhesions are also present in adherent junctions (AJ) of cell-cell adhesions, forming a converging signaling network referred to as "adhesive crosstalk" between integrins and cadherins [3]. Activated osteoblasts shape cadherin-connected monolayers after stimulation of β-integrin by ECM microenvironment via stimulation of common signaling proteins like FAK and Rho family GTPases [4]. Although the full extent of their regulation remains unclear, it is increasingly evident that their interaction affects cell spreading, growth, and survival.

Advanced Biomaterials Promoting Osteogenic Cell Adhesion

Functional tissue engineering scaffolds require biomaterials that closely mimic the native extracellular matrix of the target tissue. In this regard, numerous approaches focused on natural ECM molecules incorporation into biomaterials to promote cell adhesion, such as arginine–glycine–aspartic acid (RGD) ligands [5,6]. However, current research focuses on enhancing specific adhesion sites for endogenous cells involved in bone formation. Unlike the non-specific RGD peptide frequently used, a biomaterial could be modified with synthetic ligands with high specificity to osteogenic cells integrins (such as integrins α4β1 and αvβ3), showing increased mesenchymal stem cells and osteoblasts cells adhesion [7]. Moreover, certain soluble growth factors can orchestrate integrin and cadherin activation, giving tissue engineers more powerful tools to control cell fate. Such is the case of a recently developed polyelectrolyte matrix loaded with bone morphogenetic protein 2 (BMP-2), able to induce muscle to-osteoblast-transdifferentiation via N-cadherin/β3-integrin and Cadherin11/β1-integrin crosstalk to regulate transcriptional activities, after cell adhesion [8].

Considering the type of ligand presented and how the overall biomaterial structural design activates intracellular pathways and influences cell behavior is crucial. FAK

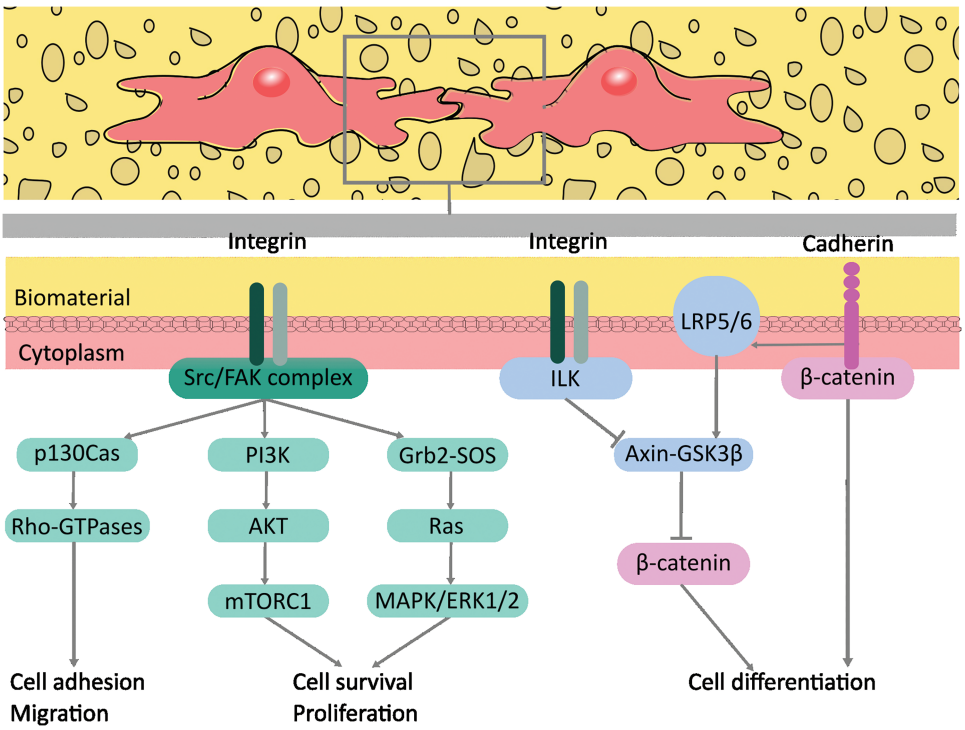

FIGURE 1. Intracellular signaling pathways related to integrins and cadherins receptors that could be activated in the biomaterial-cell interface. Adapted from [1]. The figure was created using free Inkscape software. Abbreviation list: axin and glycogen synthase kinase 3 beta (Axin-GSK3β), CT10 Regulator of Kinase-associated substrate (Cas), extracellular signal-regulated kinases 1 and 2 (ERK1/2), focal adhesion kinase (FAK), growth factor receptor-bound protein 2 (Grb2), guanosine triphosphatase (GTPase), integrin-linked kinase (ILK), low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6), mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), Ras homolog gene family member A (RhoA), Retinoblastoma-like protein 2 (p130), small GTPases (Ras), sarcoma family of non-receptor tyrosine kinases (Src), son of sevenless (SOS).

complex function might be of interest as a target for biomaterial development since its sensibility to the substrate topographical and stiffness information is recognized [2,9]. At this point, there is a common consensus that nanofibrous topographies are much more effective for osteogenic cell adhesion, migration, and proliferation than flat surfaces. The leading hypothesis underlying the intracellular mechanism relies on the fact that osteoprogenitor cells and nanofibers have less focal adhesion, causing lower FAK activity, lower RhoA/ROCK activity, and in turn, decreasing actin polymerization required for translocation of YAP to the nucleus; this, ultimately, impairs the inhibition of Runx2, giving free road to initiate the synthesis of alkaline phosphatase (ALP), the induction of osteogenesis and bone maturation [7]. Moreover, recent findings demonstrate that interconnected porous structures enhance MSCs adhesion and spreading by synergic induction of subunit α5 of α5β1-integrin, cadherin11, and gap-junction gene expression, plus activation of Wnt pathway, involved in mechanical stretching-induced osteogenesis. The Osteonectin gene expression augmented, while the ALP activity increased by a factor of 4 compared to the non-porous substrate [10].

Integrin-related signaling pathways triggered by biomaterials are widely studied. However, adhesion doesn't stop at integrins. Tissue engineers must expand their designs beyond the integrin family to fully unlock the potential of biomimetic approaches. In this regard, developing tunable biomaterials aimed at cadherin-related osteoblasts signaling remains a potential research area.

Perspectives and Conclusion

Along these lines, we discussed the immense importance of cognizance of the underlying mechanisms of cell behavior and communication with their microenvironment. We have emphasized that multiple pathways can be activated by the same surface parameter, providing a bird's eye view of the beautiful complexity of intracellular communication.

The current challenge to our understanding is to investigate how specific biomaterial properties, when studied individually or combined, affect osteogenesis. A critical point is that many studies using biomaterials lack a comprehensive analysis of the biological pathways they activate. Addressing these gaps in research through methods like three-dimensional cell cultures providing more robust organotypic models and high-throughput fabrication with detailed characterization of arrays of engineered biomaterials will enhance our understanding of the key biomaterial parameters necessary for regenerating bone tissue with precision and predictability.

A final remark: *in-vitro* tests offer initial insights into biocompatibility but may only partially capture *in-vivo* complexities, such as systemic factors influence. Different processes such as neo-vascularization, immune response, and degradation are frequently slurred over. Also, proper animal selection is a sensitive issue when reflecting human responses, especially in load-bearing conditions assays. Lastly, navigating the regulatory landscape for new biomaterials represents a bureaucratic challenge that cannot be avoided when the goal is the translation of bench to bedside.

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