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How cells and biomaterials from natural origin are revolutionizing tissue engineering and regenerative medicine

João F. Mano

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How cells and biomaterials from natural origin are revolutionizing tissue engineering and regenerative medicine

João F. Mano[1]

ABSTRACT

Tissue engineering and regenerative medicine aim to restore damaged tissues by combining human cells with biomaterials that provide structure and biological cues. After decades of progress from early scaffold-based approaches to today's biofabrication methods, the field is moving toward therapies that are more precise, more patient-specific, and more biologically faithful. This article presents the key ingredients required to engineer tissues (cells, matrices, biochemical signals and culture conditions) and why biomaterials are central to success. Emphasis is placed on polymers of natural origin, including polysaccharides and proteins sourced from plants, animals and especially the marine environment (e.g., alginate, carrageenans and chitosan), as well as human-derived materials obtained from blood fractions (platelet lysate) and perinatal tissues (amnion, chorion, umbilical cord, placenta). We describe how these macromolecules can be processed into porous scaffolds or, increasingly, into hydrogels-water-rich macromolecular networks that mimic the extracellular matrix. By adding photocrosslinkable groups, natural polymers can be solidified with light, enabling rapid gelation, spatial patterning and 3D bioprinting of complex constructs. We introduce bottom-up tissue engineering, where small cell-laden building blocks assemble into hierarchical tissues, and show how the same technologies used to build healthy tissues can also create 3D disease models for drug testing and precision medicine. Finally, we highlight emerging applications beyond healthcare, including soft biohybrid robotics and cultivated meat.

RESUMO

A engenharia de tecidos e a medicina regenerativa têm como objetivo restaurar tecidos danificados combinando células humanas com biomateriais que fornecem suporte estrutural e sinais biológicos. Após décadas de progresso — desde as primeiras abordagens baseadas em estruturas porosas (*scaffolds*) até aos atuais métodos de biofabricação — o campo evolui no sentido de terapias mais precisas, personalizadas e biologicamente fiéis. Apresentamos os principais ingredientes necessários para a engenharia de tecidos (células, matrizes, sinais bioquímicos e condições de cultura) e explicamos por que razão os biomateriais são centrais para o sucesso. A ênfase é colocada em polímeros de origem natural, incluindo polissacarídeos e proteínas obtidos de plantas, animais e, em particular, do ambiente marinho (como alginato, carragenanos e quitosano), bem como em materiais de origem humana provenientes de frações sanguíneas (lisado plaquetário) e de tecidos perinatais (membrana amniótica ou coriónica, cordão umbilical e placenta). Descrevemos como estas macromoléculas podem ser processadas em *scaffolds* porosos ou em hidrogéis. A introdução de grupos fotorreticuláveis permite a solidificação com luz, possibilitando gelificação rápida, padronização espacial e bioimpressão 3D. Introduzimos ainda a

[1] Academia das Ciências de Lisboa, CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro.

engenharia de tecidos *bottom-up* e mostramos como estas tecnologias podem gerar modelos de doença 3D para testes de fármacos e medicina de precisão, bem como aplicações emergentes como robótica híbrida e carne cultivada.

1. FROM "SPARE PARTS" TO LIVING REPAIRS: A SHORT HISTORY

The idea that we might replace or regenerate damaged tissues is older than modern medicine. Surgeons have long used grafts and transplants, and biologists have studied remarkable natural examples of regeneration. But the modern field of tissue engineering (TE) emerged when scientists began to combine three worlds that traditionally evolved in parallel: cell biology, materials science, and engineering. A landmark moment came in the early 1990s, when the term "tissue engineering" was popularized as a strategy to use cells together with supportive materials to create functional tissues that could repair or replace what disease or trauma had compromised (Langer, 1993).

At first, many TE efforts followed a relatively "top-down" logic: fabricate a porous scaffold, seed it with cells, and encourage those cells to form new tissue. Over time, two key lessons became clear. First, living tissues are not simply collections of cells: they are organized in a hierarchical form, where chemistry, mechanics, and architecture work together across multiple scales. Second, cells are highly responsive to their surroundings. They sense not only biochemical signals such as growth factors, but also physical cues such as stiffness, surface chemistry, and microscopic structure. These ideas are now central to how we design biomaterials and instruct cells (Discher, 2009; Place, 2009).

Today, TE sits within a broader area often called regenerative medicine: a spectrum of approaches that includes cell therapies, gene and RNA therapies, immunomodulation, and bioengineered tissues. Biomaterials remain a core enabler across this spectrum because they can act as temporary "instructions" and "infrastructure" for cells—helping them survive, organize, and ultimately rebuild tissue in the body (Hutmacher, 2000; O'Brien, 2011; Place, 2009).

2. THE ESSENTIAL INGREDIENTS FOR ENGINEERING TISSUES

Although each tissue has its own biology, most tissue engineering strategies can be explained using a simple triad: cells, signals, and structure. "Cells" are the living builders—patient-derived cells, stem cells, or specialized cell types.

"Signals" are the chemical and physical messages that guide what cells do: they include growth factors, small molecules, cell–cell interactions, oxygen and nutrient supply, and mechanical forces. "Structure" is the three-dimensional environment that holds everything together and helps cells organize into tissue-specific architecture. This structure is usually provided by a biomaterial scaffold or hydrogel that mimics, in key ways, the body's own extracellular matrix (ECM) (Discher, 2009; Hutmacher, 2000; O'Brien, 2011; Place, 2009).

In practice, the triad is often expanded into a "toolbox" that includes bioreactors and manufacturing. Bioreactors provide controlled culture conditions—flow, oxygenation, mechanical, or electrical stimulation—so that developing tissues experience a more realistic environment. Manufacturing matters because a promising laboratory material is not enough: we need processes that are reproducible, scalable, and compatible with living cells. This is where modern biofabrication (including 3D bioprinting) has become transformative (Groll, 2019; Mandrycky, 2016; Murphy, 2014).

3. BIOMATERIALS AS TEMPORARY MICROENVIRONMENTS

3.1 What makes a material a "biomaterial"?

A biomaterial is any material designed to interact with biological systems for a medical purpose. In TE, biomaterials are not just passive supports. They can be engineered to present cell-adhesion motifs, bind and release growth factors, degrade over time, or change their properties in response to the body. A central design goal is to capture some of the ECM's "complexity"—its ability to deliver biochemical and mechanical information at multiple length scales (Place, 2009).

Biomaterials used in TE can be grouped into synthetic polymers (such as polyesters used in dissolvable sutures), natural polymers (derived from polysaccharides or proteins), and hybrid materials that combine the advantages of both. Synthetic polymers are attractive because their chemistry and mechanical properties can be tuned with high precision. Natural polymers are attractive because evolution has already optimized them for biological interactions and thus, they are natural present in the normal functioning of living organisms—often giving them inherent bioactivity and biocompatibility (Hutmacher, 2000; O'Brien, 2011; Place, 2009).

3.2 Natural-based polymers: why they matter

Natural-based polymers include polysaccharides (long sugar chains) and proteins. They are widely used because they can resemble the ECM in composition, hydration, and biological signaling. Examples include alginate and chitosan (polysaccharides), and collagen, gelatin, fibrin, and hyaluronic acid (proteins or glycosaminoglycans). Many of these materials can be processed into porous scaffolds, fibers, films, microgels, or hydrogels. Importantly, they can often be chemically modified to tune degradation rate, stiffness, or cell adhesion (Hutmacher, 2000; Silva, 2012).

3.3 Marine-derived materials: a sustainable and versatile source

Marine organisms provide a rich library of structural materials—from seaweed polysaccharides to fish collagens—often harvested from side-streams of the food industry. This can align tissue engineering with sustainability by valorizing renewable resources. Reviews of marine-origin biomaterials highlight how polysaccharides (such as alginate, carrageenan, ulvan, and fucoidan), proteins (including marine collagens and gelatin), and even mineralized structures (such as coral and cuttlebone) can be processed into biomedical scaffolds and hydrogels (Silva, 2012; Silva, 2014).

Marine collagen is a particularly interesting example. Collagen is the most abundant structural protein in mammals and has a long history in medical devices. Marine sources can reduce risks associated with zoonotic transmission and may offer distinct properties due to differences in amino-acid composition and thermal stability. Comprehensive reviews discuss extraction methods, characterization, and applications of marine collagens in wound healing, bone regeneration, and drug delivery (Silva, 2014).

3.4 Human-derived proteins and clinically relevant biological sources

Beyond materials harvested from plants or animals, an important trend is the use of human-derived proteins and tissues to create highly bioactive environments. Blood-derived products are a prime example. Platelets store and release growth factors involved in healing, and platelet-rich plasma (PRP) and platelet

lysate have been explored both as therapies and as components of biomaterials. Blood plasma derivatives can be formulated as hydrogels or combined with other polymers to create personalized, growth-factor-rich matrices for regenerative applications (Santos, 2018).

Perinatal tissues—such as the placenta, amniotic membrane, and umbilical cord—are another valuable source. These tissues are usually discarded after birth, yet they contain ECM molecules and cells with regenerative and immunomodulatory potential. Perinatal tissues and their derivatives can be processed into scaffolds, decellularized matrices, or cell-derived products with applications ranging from wound repair to musculoskeletal regeneration (Deus, 2020). The obtention of biopolymers from perinatal tissues require a processing step of decellularization, permitting the removal of cells from a tissue while preserving the ECM's architecture and biochemical composition. Decellularized materials can provide tissue-specific cues that are difficult to reproduce synthetically. Reviews summarize decellularization methods, how processing affects ECM integrity, and how decellularized scaffolds are used clinically (Crapo, 2011).

4. FROM POROUS SCAFFOLDS TO HYDROGELS: BUILDING "WATER-RICH" CELL NICHES

4.1 Porous scaffolds: the classic approach

Porous scaffolds were the workhorse of early tissue engineering. Their interconnected pores allow cells to migrate, nutrients to diffuse, and new tissue to form. Porosity, pore size, and mechanical strength must be balanced: larger pores can support vascularization and tissue in-growth but may weaken the scaffold. A variety of parameters of the scaffolds, including the polymer nature, degradation kinetics, and architecture influence tissue formation and clinical performance (Hutmacher, 2000; Karageorgiou, 2005; O'Brien, 2011).

4.2 Why hydrogels changed the conversation

Many tissues—especially soft tissues—are mostly water. Hydrogels are macromolecular networks of hydrophilic polymers that absorb large amounts of water, producing a soft, tissue-like environment. Because cells in the body live

in a hydrated ECM, hydrogels can be excellent carriers for cell encapsulation and delivery. Hydrogels also support the diffusion of nutrients and signaling molecules, and their mechanical/viscoelastic properties can be tuned to match different tissues. Hydrogels have become central across drug delivery, wound healing, and TE because they can be engineered to combine softness with structural integrity (Hoffman, 2012). Hydrogels can be formed in many ways: by ionic interactions (as in alginate), by thermal gelation (as in some gelatin systems), by enzymatic reactions, or by covalent crosslinking. Covalent crosslinking is especially useful when long-term stability is needed, but it must be designed to be cell-friendly. This is where light-triggered chemistry has had a major impact (Nguyen, 2002; Yue, 2015).

4.3 Photocrosslinkable macromolecules: "solidifying" hydrogels with light

A powerful idea in modern biomaterials is to chemically modify natural polymers with photocrosslinkable groups—often methacrylates—so that a liquid precursor solution can be converted into a solid hydrogel by exposure to light in the presence of a photoinitiator. This enables in situ gelation (for minimally invasive delivery) and precise control over when and where the material solidifies. A classic review describes photopolymerizable hydrogels for TE, including advantages of light-based crosslinking, photoinitiator choices, and early applications (Nguyen, 2002).

Among photocrosslinkable natural polymers, gelatin methacryloyl (GelMA) has become widely used because it combines gelatin's cell-interactive motifs with photocrosslinkable tunability. Information could be found elsewhere summarizing GelMA synthesis, mechanical tuning, degradation, and applications as a bioink for cell-laden hydrogels and microtissues (Yue, 2015).

Light-triggered gelation does more than simplify handling. It enables spatial patterning: different regions of a construct can be given different stiffness, different biochemical signals, or different cell populations. This is an important step toward reproducing how tissues are organized in gradients and layers rather than being uniform slabs (Groll, 2019; Place, 2009; Yue, 2015).

5. BIOFABRICATION: MAKING TISSUES BY DESIGN

Biofabrication refers to manufacturing strategies that create biological structures with controlled architecture. The best-known example is 3D bioprinting: the layer-by-layer placement of cells and biomaterials according to a digital design. This has accelerated tissue engineering because it helps us move from "cells in a blob" to patterned, geometrically complex, multi-material constructs where different cell types are placed where they are needed (Groll, 2019; Murphy, 2014).

Extrusion printing can handle viscous hydrogels and high cell densities, but it can subject cells to shear stress. Inkjet and droplet-based approaches offer high speed and resolution for low-viscosity inks. Light-based printing (such as stereolithography and digital light processing) can produce fine features and smooth surfaces when using photocrosslinkable bioinks (Groll, 2019; Mandrycky, 2016; Murphy, 2014; Yue, 2015).

Because hydrogels are soft, printing alone maybe not enough for specific applications requiring more structural requirements; in those cases, the structures must be stabilized during and after fabrication. A possible solution is to combine photocrosslinkable hydrogel constructs with 3D-printing of thermoplastic polymeric structures to improve mechanical strength while maintaining cell viability (Pereira, 2015).

6. BOTTOM-UP TISSUE ENGINEERING: ASSEMBLING COMPLEXITY FROM BUILDING BLOCKS

As biofabrication matured, many researchers recognized a challenge: tissues are built from repeating functional units—small building blocks such as lobules, crypts, or microvascular networks. Trying to print or sculpt an entire organ at once can be inefficient and may fail to capture this hierarchy. Bottom-up tissue engineering tackles the problem by first creating small living building blocks (cell spheroids, cell-laden microgels, organoids, or microtissues) and then assembling them into larger, more complex structures (Gaspar, 2020).

This approach can exploit cells' natural tendency to self-organize. For example, aggregates of cells can fuse and remodel their surroundings, forming tissue-like structures with less external "instruction" than in top-down scaffolds. Bottom-up strategies can also improve vascularization by assembling

pre-vascularized modules and can create interfaces—such as bone–cartilage boundaries—by combining different modules in a controlled arrangement (Gaspar, 2020).

A major advantage of bottom-up thinking is flexibility. Different building blocks can be produced in parallel, optimized/matured separately, and then integrated. This modularity could support the development of hierarchical organizations and can reduce the manufacturing burden for large constructs. It also pairs naturally with advanced biofabrication methods that can place building blocks with precision (Gaspar, 2020).

7. FROM REGENERATIVE THERAPIES TO DISEASE MODELS: ENGINEERING TISSUES TO STUDY ILLNESS

An exciting shift in the last decade is the use of TE technologies not only to repair the body, but also to model disease. Traditional cell biology often grows cells on flat plastic dishes. These two-dimensional cultures are convenient, but they can misrepresent how cells behave inside the body, where they interact in 3D with ECM and neighboring cells. Reviews argue that 3D culture models can bridge the gap between simple in vitro assays and animal studies, improving the predictive power of drug screening and mechanistic research (Edmondson, 2014; Pampaloni, 2007).

In cancer research, for example, tumor cells grown in 3D can show different drug responses compared with 2D culture, partly because 3D environments affect oxygen gradients, cell–cell contacts, and matrix interactions. 3D culture systems include the use of spheroids, hydrogel-based models, or engineered microenvironments as platforms to study invasion, resistance, and therapy response (Edmondson, 2014; Pampaloni, 2007).

Organoids—self-organized 3D structures derived from stem cells or patient tissue—add another level of biological realism. They can recapitulate key features of organ development and function, and they are increasingly used for personalized medicine and drug testing. Organoids can be "designed" by combining developmental biology with biomaterials and engineering control (Takebe, 2019).

Organ-on-chip systems extend the concept further by adding microfluidic flow, mechanical stimulation, and controlled interfaces between tissues.

Microfluidic organs-on-chips can recreate aspects of organ-level physiology in vitro, enabling studies that are difficult in animals or 2D culture (Bhatia, 2014).

Recent work emphasizes that biomaterials are not just add-ons in these platforms: they are central to how cells sense and respond. Tumor modeling has increasingly integrated biomimetic hydrogels and perfusable microvessels in organ-on-chip systems to better capture metastatic processes and drug response (Monteiro, 2025).

8. BEYOND MEDICINE: LIVING MATERIALS, SOFT ROBOTICS, AND CULTIVATED MEAT

Once we learn to build living tissues reliably, it becomes natural to ask: where else could these technologies matter? One emerging area is soft robotics and biohybrid robotics, where living muscle tissues, neurons, or engineered cellular assemblies are integrated with synthetic materials to create devices that move, sense, or adapt. Biohybrid systems have been combining biological actuation with engineered structures, to address relevant aspects such as durability, control, and scaling (Cianchetti, 2018; Sun, 2020).

Another frontier is food technology. Cultivated (cell-based) meat aims to produce edible muscle tissue by culturing animal cells and assembling them into tissue-like products. Although the goals differ from medicine, many of the core challenges are familiar to tissue engineers: how to expand cells efficiently, how to provide a 3D scaffold that supports structure and texture, and how to supply oxygen and nutrients at scale (Post, 2012).

These examples point to a broader theme: tissue engineering is becoming a general-purpose technology for building "living systems." As methods mature—especially those that combine biomaterials, hydrogels, and biofabrication—applications may expand into areas such as smart living implants, in vitro testing platforms that reduce animal experiments, responsive living materials for environmental sensing, and engineered tissues that interact with electronics.

9. CONCLUSION

Tissue engineering began as a bold proposal: combine cells with supportive materials to regenerate tissues. Three decades later, that proposal has evolved into

a rich technological ecosystem. We now understand that the biomaterial is not merely a container; it is an active microenvironment that can guide cell fate through biochemical and mechanical signals. Natural-based polymers—including those from marine sources and human-derived proteins—provide powerful starting points for designing bioactive matrices. Hydrogels, particularly photocrosslinkable systems, have become central because they recreate water-rich ECM-like niches and enable precise manufacturing through light-based biofabrication.

At the same time, "bottom-up" assembly and advanced biofabrication are pushing the field toward truly hierarchical, multi-tissue constructs. Perhaps most importantly, the very tools developed for healing are now being used to model disease—offering new ways to test therapies, understand pathology, and move toward personalized medicine. As TE continues to mature, it is likely to influence not only healthcare, but also industries that need controlled living structures—from soft robotics to cultivated food.

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