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Unravelling hierarchical patterning of biomaterial inks with 3D microfluidic-assisted spinning: a paradigm shift in bioprinting technologies

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For decades, 3D bioprinting has offered a revolutionising approach to combine living cells and biomaterials to engineer complex, yet functional constructs. However, traditional 3D bioprinting platforms fall short of the ability to pattern complex gradients of biomaterials, cells, and ultimately bio-physical properties to drive tissue formation and regeneration. Recently, 3D microfluidic-assisted bioprinting (3DMB) has risen as a new hybrid approach for the fabrication of physiologically relevant tissues, adopting a microfluidic chip as functional printhead to achieve hierarchical patterning of bioinks and precise control over the microscale architecture of printed constructs, enabling the creation of multi-layered tissues. This review explores recent advancements in graded biomaterial patterning using microfluidic-assisted spinning and novel 3D bioprinting technologies. The physiological hierarchical arrangement of human tissues and the crucial role of biomaterials in achieving ordered assembly is hereby discussed. Lastly, the integration of microfluidic-assisted techniques with new bioprinting platforms is highlighted, examining the latest advancements in tissue regeneration and disease modelling.

KEYWORDS

microfluidic, biofabrication, hierarchical constructs, gradients, functionally graded materials (FGM), bioprinting

1 Introduction

To date, 3D bioprinting platforms are capable of orchestrating the three-dimensional arrangement of living cells and biomaterial inks in a layer-by-layer fashion, for tissue engineering and regenerative medicine (TERM) purposes. The most relevant and widely used 3D bioprinting approaches for the engineering of 3D constructs include inkjet-based (Angelopoulos et al., 2020; Prabhakaran et al., 2022), laser-assisted (Heinrich et al., 2019), and extrusion-based bioprinting (Jeong et al., 2020). The specifics of these 3D bioprinting technologies are beyond the scope of this review and can be found in details elsewhere (Chameettachal et al., 2019; Cidonio et al., 2019; Scognamiglio et al., 2020; Lima et al., 2022; Karvinen and Kellomäki, 2023; Sabzevari et al., 2023).

Typically, 3D bioprinting processes are used to generate three-dimensional structures but fail to precisely tune the spatial distribution of functional elements (Marcotulli et al., 2023), resulting ultimately incapable of mimicking the complex physiological hierarchical structure of complex human tissues (Figure 1A).

In recent years, the emerging of hybrid 3D bioprinting technologies such as the intersection of volumetric bioprinting and melt extrusion (Größbacher et al., 2023), fused deposition modelling (FDM) with integrated electrospinning (Micalizzi et al., 2023), the combination of inkjet printing and electrospinning (Xu et al., 2012) and developing computer-aided design fabrication techniques (Jung et al., 2016) have gained significant attention and demonstrated the potential to revolutionise the fabrication of complex tissue structures by addressing the limitations associated with conventional bioprinting methods (Idaszek et al., 2019; Kosik-Kozioł et al., 2019). Indeed, 3D microfluidic-assisted bioprinting (3DMB) is coming to the fore as a highly promising technology for the graded patterning of bioinks (cells and biomaterials) (Figure 1B), and the precise control over the ultimate tissue architecture and functionality (Davoodi et al., 2020; Swieszkowski et al., 2020). Herein, we explore the recent advancements in hierarchical patterning of biomaterials with microfluidic-assisted spinning and 3D bioprinting, highlighting the biomaterial inks explored so far, with particular emphasis on the promises treasured for future TERM applications.

2 Hierarchy in regeneration and modelling

Biological tissues are organised in ordered structures with multiple degrees of both functional and structural complexity, comprising cells residing within a tissue-specific extracellular matrix (ECM) (Rose and De Laporte, 2018). The complex macromolecular framework of ECM consists of a plethora of proteins, glycosaminoglycans, proteoglycans, and glycoproteins retained in a significant water volume (Salvatore et al., 2021). Biomimetic approaches aiming to recapitulate the architecture of human tissues hold extensive potential across various domains, encompassing drug screening (Wang et al., 2022c), disease modelling (Vanderburgh et al., 2017; Iafrate et al., 2022), organotypic models (Barrila et al., 2010), and tissue repair (Cidonio et al., 2021b; Szklanny et al., 2021). In this domain, hierarchically graded tissues refer to intricate biological structures in which the precise arrangement and coordination of diverse cell types, ECM, and functional components are regulated in a ordered patterning. This graded fashion extends across scales, ranging from the macro-to the micro-environment with stepwise changes that emulate the complexity of the native tissue (Fratzl, 2005; Zhang et al., 2022b).

2.1 Physiological hierarchical arrangement in human tissue

Living organisms present a remarkable level of organisation and structure, characterised by a graded arrangement that span from individual molecules to multicellular assemblies (Figure 1A). This hierarchy encompasses entities of varying dimensions and scales, interconnected through anisotropic relationships (Cidonio et al., 2021a). Within the highly organised framework of the human body, tissues can be typically classified into four major categories: epithelial, connective, muscle, and nervous tissues. Each tissue type serves unique purposes, resulting functional for the homeostasis of the human body (Betts et al., 2021). For instance, epithelial tissue is made of layered protective sheets of cells that

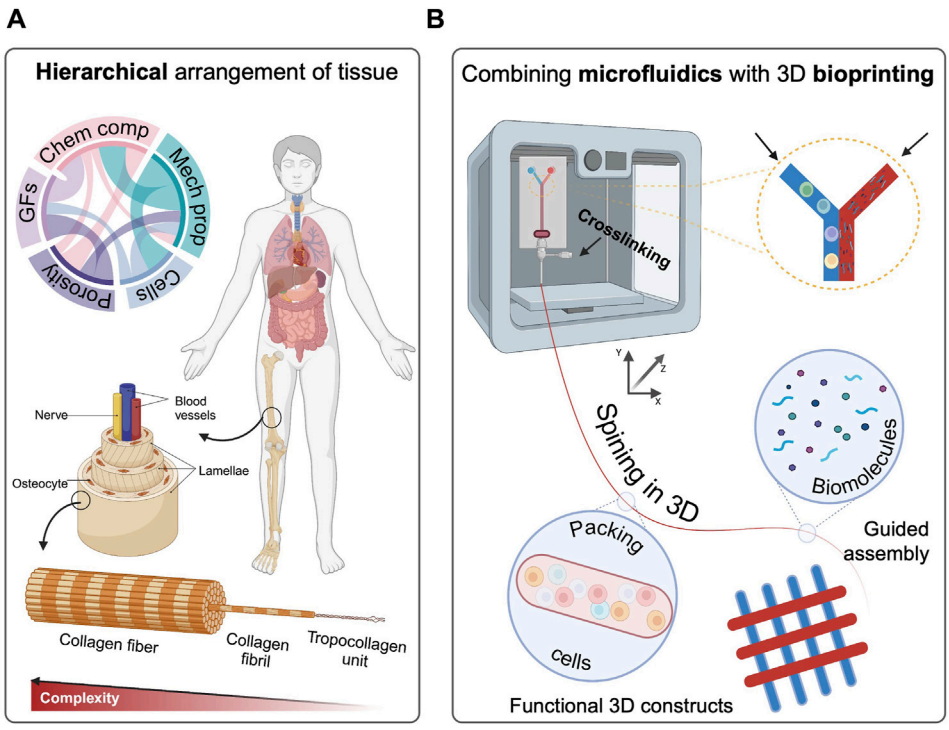

FIGURE 1
(A) Hierarchical physiological arrangement of tissue components, indicating organization level of the human body. **(B)** Combining microfluidic and EBB as a promising approach to mimic the natural architecture. Created with Biorender.com.

cover surfaces of the body, line internal cavities and passages, and contribute to the formation of specific glands (Torras et al., 2018; Gómez-Gálvez et al., 2021; Mohammadi et al., 2023). In the complex stratified system of natural tissues, cells are found to engage in interactions with similar or other cell types, enabling essential communication that drives tissue morphogenesis and function (Song et al., 2019). Abundantly surrounding the cells, the ECM presents a diverse array of adhesion ligands, spatially arranged in 3D, that closely interact with cell surface receptors, transmitting signals (Tueni et al., 2023). The ECM translate biophysical signals and cues to cells, conditioning the mechanotransduction based on mechanical stiffness, and macromolecular composition. The structural features of ECM, such as the stratified organization and fibre arrangement, intensely impact cell behaviour, performance, and tissue function (Ratri et al., 2021). Notably, the anisotropic nature of ECM fibres, which exhibit hierarchical arrangement, can vary significantly across different tissues (Li et al., 2017).

Within every multicellular organism, cells undergo proliferation, leading to the formation and sustenance of tissues that consist of numerous specialized cell types. In these organisms, hierarchical structures are used to enhance self-renewing of the tissues (Derényi and Szöllősi, 2017). Embedded within the intricate hierarchy of multicellular organisms lies a select group of tissue-specific stem cells, distinguished by their remarkable attributes of self-replication and the capacity for differentiation. As cells undergo proliferation, they progressively specialize and acquire distinct functions, orchestrating the tissue development process (West et al., 2021).

2.2 Biomaterial and hierarchical assembly

Biomaterials for TERM applications are typically designed to resemble 3D porous, fibrous, or permeable structures to facilitate the transport of body fluids and gases while promoting crucial cellular interactions, viability, and the deposition of the ECM. Importantly, biomaterials must minimise inflammation and toxicity, demonstrating biocompatible features while ensuring a controlled degradation rate to match the regenerative process (Khan et al., 2022; Bertsch et al., 2023; Liu et al., 2023). Moreover, biomaterials should enhance cell attachment, and proliferation, facilitating the secretion of the ECM and ultimately, tissue repair (Nikolova and Chavali, 2019). Biomaterials derived from plants, animals, microorganisms, and native tissues, hold tremendous potential as scaffolding templates, tailored for specific applications in TERM. These materials mimic the physiological and ordered microstructure of tissue, as well as accelerate cell attachment, growth, and a multitude of functions within the native environment (Huang et al., 2017).

Functionally graded materials (FGMs) are a fitting example of the engineering of ordered systems. FGMs are indeed a class of materials that demonstrate discrete variation in composition, structure or properties throughout the entire volume, imitating the natural transitions between different tissues (Ituarte et al., 2019). The precise patterning and strategic control over ultimate mechanical properties is of great interest for engineering new functional physiological structures. Single- or multi-material FGMs hold the possibility to address common challenges in fabricating hierarchical structures, namely delamination, and cracking (Li et al., 2020). Similarly, biphasic inks including foams and high internal phase emulsion (HIPE) have been introduced to the field of 3D printing, enabling this technology for unequalled control over the creation of the hierarchical constructs with graded pore size. Researchers have reported numerous advantages, due to their superior properties for the hierarchical porous scaffold, resulting in better vascularization, improved cell viability and enhanced oxygen and other crucial nutrients transportation (Search et al., 2023). A number of approaches for fabricating hierarchically porous scaffolds using biphasic inks have been reported in our previous work (Cidonio et al., 2021a).

Today, a new paradigm based on microfluidic technology has emerged as an unparalleled tool capable of providing precise control while ensuring the build-up of consistent and stable 3D structures. Microfluidic systems not only have shown the potential to provide control over placement of the different components, allowing for the production of spatially defined gradients, but also the ability to dynamically modulate flow rates and concentrations enabling real-time adjustments to the tissue construct spontaneously assembling (Pi et al., 2018). Capability to customise the micro-size channels allows microfluidic chips to deliver fibres or 3D structures for tissue engineering and drug delivery purposes. Additionally, microfluidic chips are typically cost-effective, and eco-friendly due to reduced material waste in constructing complex materials with functional properties (Du Chatinier et al., 2021; Prabhakar et al., 2021).

3 Microfluidic spinning technology

Currently, a number of methods are available for producing fibrous materials via spinning technique, including polymer melt (Zhong et al., 2021), dry (Felgueiras et al., 2019), wet (Araki and Miyayama, 2020), and electrospinning (Medeiros et al., 2022). However, the effects of extreme operating conditions such as high pressure, shear, and temperature make these approaches disadvantageous for cell encapsulation, and ultimately, biofabrication. Furthermore, traditional spinning methods impose limitations on the selection of raw materials and hinder the production of fibres with unique structures. Currently, microfluidic technology, as a typical wet-spinning process, has been found capable of generating cell-laden fibres with governable compositions and multiplex structures (Zhang et al., 2022a).

Microfluidic spinning is now used as a fabrication method that enables the precise control of fluids at micro-scale level. By dispersing one liquid into another miscible or immiscible solution, this approach generates individual continuous fibres through physical or chemical reactions within microfluidic channels (Yu et al., 2018). The microchannels design is playing a crucial role in achieving desired fibre characteristics. The formation of functionalised fibres is facilitated by diverse channel geometries, including nested capillaries and microfluidic chips, such as T-junction, flow-convergence, and coaxial structured chips (Tian et al., 2023). Microfluidic spinning currently offers mild and rapid reaction conditions, facilitating the engineering of cell-laden microfibres (Cheng et al., 2017). This technology allows precise control of the preparation process, enabling the production of unique structures like hollow tubes and parallel micro-groove arrays. These structures hold significant promise in TERM

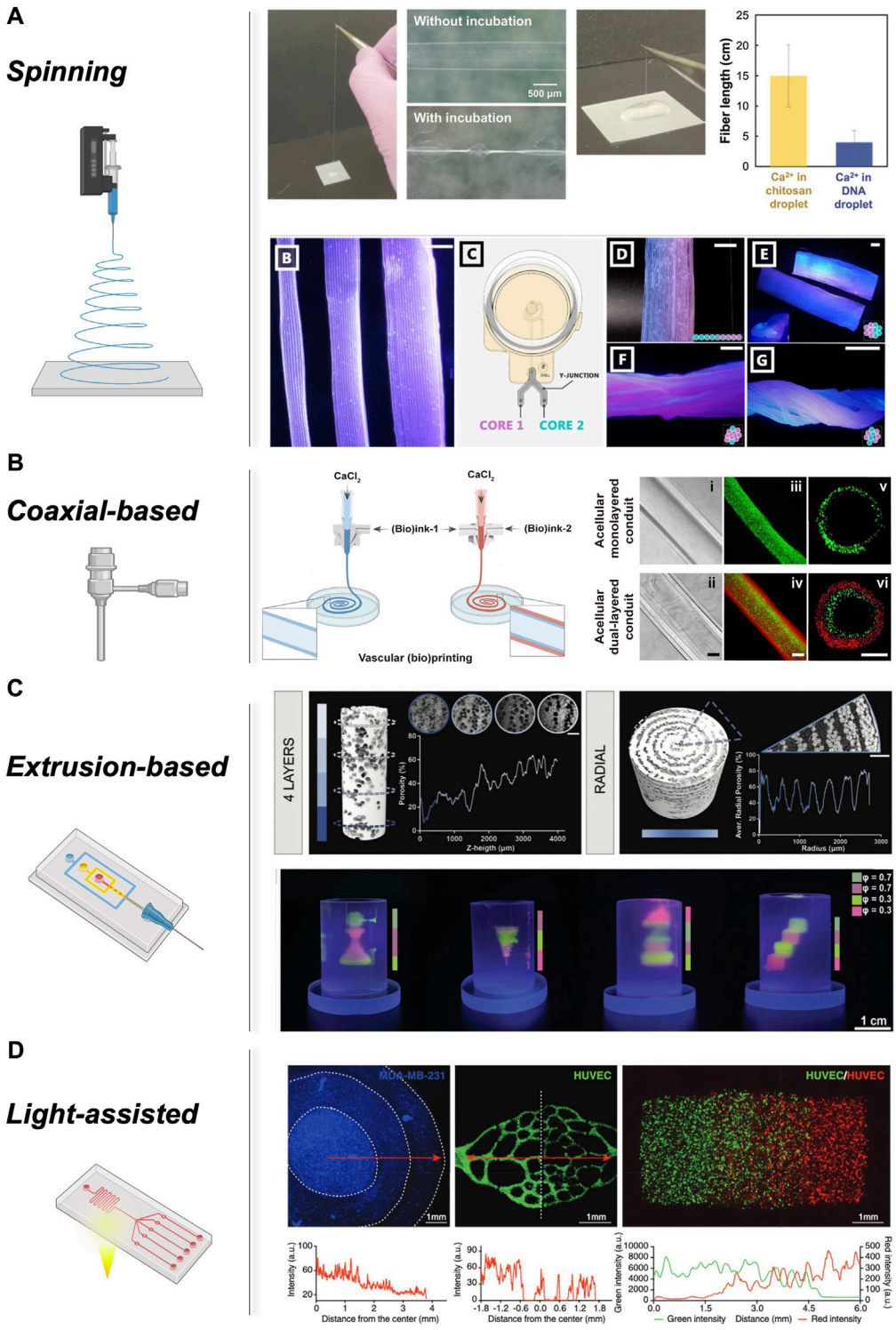

FIGURE 2
Different approaches in microfluidic 3D bioprinting: **(A)** Spun core-shell hydrogel fibre composed of chitosan/DNA IPC and the effect of Ca^{2+} presence in chitosan or DNA on fibre length. Adopted with permission from (Utagawa et al., 2023). Hydrogel fibres with different diameter, microfluidic printhead to fabricate multiple material core extrusion for single-layer, multi-layer and hydrogel bundle printing with gradual color transition, Multi-layered hydrogel bundles with variable core material fibres. Adopted from (Celikkin et al., 2023) under creative common attribution 4.0 license. **(B)** Microfluidic extrusion bioprinting process and different views of the final monolayered, dual-layered, and hollow tubes, using coaxial extruder. Adopted from (Wang et al., 2022a) under Creative Commons Attribution-Noncommercial license. **(C)** Micro-CT analysis for internal topographic of the porous FGMs, Multi-inlet microfluidic chip for alternating printing of GelMA, DexMA/nHA and DexMA emulsion. Complex structures with density gradient. Adopted with permission from (Marcotulli et al., 2023). **(D)** Light-assisted gradient bioprinting within hydrogels, indicating radial gradient in cell density, Encapsulating HUVECs, construct containing RFP-HUVECs and GFP-HUVECs and their fluorescence intensities. Adopted with permission from (Wang et al., 2022b).

applications, such as reconstructing blood vessels (Guo et al., 2021), skeletal muscle (Zhao et al., 2021; Fornetti et al., 2023), bone (Kim et al., 2023), nerves (Chen et al., 2020), and lung (Mazio et al., 2023) tissue. The remarkable advantages of microfluidic spinning have garnered considerable attention from TERM, disease modelling, and drug screening fields, contributing to the generation of a library of biomaterials that can be wet-spun into micro-size fibres. Recently, Utagawa and others developed a rapid approach to generate a core-shell fibre, prepared from interfacial polyelectrolyte complexation (IPC), chitosan, DNA as core and Ca-alginate serving as shell (Figure 2A). The authors showed that the fibre shape can be changed by adjusting the concentration of DNA, providing an adequate environment for HepG2, 3T3, HUVECs, and 3T3 cells co-culturing (Utagawa et al., 2023).

3.1 Biomaterials to spin fibres

Material inks for rapid microfluidic-assisted spinning should be able to instantaneously assemble in continuous microfibres, while preserving biocompatible and biodegradable properties with adequate mechanical strength to support cell encapsulation and maturation (Zhao et al., 2022). A number of polymers have been placed under the spotlight as spinning biomaterials due to their biocompatibility and tuneable properties (Chen et al., 2022). Both natural and synthetic polymers can be adapted to be rapidly extruded using a microfluidic spinning platform. Typically, composite combinations of natural and synthetic polymers have been identified as ideal system for spinning. For TERM purposes, natural polymers, such as alginate, chitosan, hyaluronic acid (HA), collagen, and silk fibroin, are known for their biocompatibility and biodegradability. However, they generally exhibit weak mechanical strength. On the other hand, synthetic polymers offer strong mechanical properties and well-defined compositions but may suffer from limited biocompatibility. Synthetic polymers such as GelMa, polyethylene glycol (PEG), 4-hydroxybutyl acrylate (4-HBA), poly (ethylene glycol) dimethacrylates (PEGDMA), gelatin–hydroxyphenylpropionic acid (Gtn-HPA), poly (lactic-co-glycolic acid) (PLGA), and poly (caprolactone) (PCL) are highly versatile in mechanical strength, degradation rate, and cell interaction capabilities (Park et al., 2016; Gopinathan and Noh, 2018; Sung and Kim, 2020). Crucially, the material solution flowing through microfluidic channels must undergo instantaneous solidification, resulting in the microscale formation of fibres with precise geometrical structures (Perazzo et al., 2017; Zhao et al., 2021) with specific thixotropic properties. A number of methods are employed for solidification, including, chemical cross-linking (Andreazza et al., 2023), solvent exchange (Wu et al., 2022), ionic crosslinking (Mukherjee et al., 2023) and photo-crosslinking (Sang et al., 2023), with the last two being the most relevant.

3.2 Ionic crosslinking to rapidly gelate microfluidic-designed fibres

Ionic cross-linking is a popular approach to guide nearly instantaneous gelation of the spun fibre. This approach is based on the controlled interactions between negatively charged carboxyl groups, typically found in alginate-based materials, with multivalent cations present in cross-linking solutions (e.g., Ca^{2+}, Al^{3+}, and Mg^{2+}) (Cidonio et al., 2020). Alginate (Zdiri et al., 2022), k-carrageenan (Kong and Ziegler, 2013), gellan gum (Gomes et al., 2023) and similar composites (Celikkin et al., 2023) are among the biocompatible polymers that have been spun into fibres. Microfluidic systems can be engineered to allow the divalent ions-rich solutions to be flushed coaxially with reactive biomaterials to facilitate rapid fibre formation (Fratini et al., 2023). However, the complete dependence on divalent ions for crosslinking holds certain disadvantages since ionic interactions are unregulated, and the loss of Ca^{2+} ions might result in an inconsistent gel matrix across different sections of the 3D printed object (Janarthanan et al., 2022).

3.3 Photocurable biomaterials for microfluidic spinning and processing

Photo cross-linkable polymers can be rapidly crosslinked upon exposure to specific wavelengths of light, enabling precise control over the crosslinking process (Xie et al., 2019; Thijssen et al., 2023). This technique is commonly employed for the crosslinking of methacrylated materials such as GelMA (Sharifi et al., 2021), PEGDA (Tan et al., 2008), and 4-HBA (Abdallah and Hadi Mohammed, 2023). In this process, a microfluidic system is utilized to facilitate the controlled flow of photopolymerization monomers and photo-initiators through the outlet. Herein, light is applied to trigger polymerization, resulting in the formation of micro-sized fibres or the rapid gelation of extruded materials. Typically, this method has been found to allow the fabrication of complex structures and facilitates the incorporation of bioactive molecules for enhanced cellular responses (Perazzo et al., 2017; Tian et al., 2023).

4 Microfluidic-assisted bioprinting for disease modelling and tissue regeneration

Microfluidic spinning holds tremendous advantages (Figure 2). The unparalleled ability to tune the fibre diameter, as well as the possibility to include multiple inlets comprising biomaterial and cells is appealing. However, single fibres are limited in recapitulating the complex physiological architecture of human tissues. 3D bioprinting has recently come to the rescue, with a number of different microfluidic-assisted approaches. Coaxial wet-spinning technology (Figure 2B) has been the first to explore the potential of single fibre spinning for the patterning of cellular and biochemical components (Han and Steckl, 2019). However, with the advent of microfluidic-based systems, a complex generation of hierarchical fibrous structures has been demonstrated. The possibility to engineer complex features thanks to the use of passive mixers and flow-focusing junctions is appealing and possible with microfluidic printheads for EBB (Figure 2C) and light-assisted (Figure 2D) platforms.

4.1 Coaxial-based 3D bioprinting technologies

Coaxial-based 3D bioprinting (Figure 2B) offers a continuous method for creating tubular micro-fibres generated from a concentric nozzle assembly that allows the simultaneous extrusion of two distinct solutions. By carefully selecting the hydrogel materials, the mechanical properties of the tubular structures, including toughness, stretchability, and compression resistance, can be precisely tailored to meet specific requirements (Millik et al., 2019; Liang et al., 2020; Bosch-Rué et al., 2021). Moreover, by increasing the number of coaxial orifices, vascular-like fibres can be easily fabricated. The coaxial technology is primarily relying on the use of instantaneous crosslinking of alginate (core) when exposed to divalent cations (sheet) while flowing. Indeed, Wang and co-workers utilized coaxial-driven 3D bioprinting to develop a mechanically stable double-layer hollow hydrogel (alginate and gelatin) for recreation of the vein and artery tissues. In this study, the core flow of $CaCl_2$ enabled the *in situ* physical cross-linking of the alginate component in the (bio) ink. This cross-linking approach played a crucial role in preserving the tubular shape of the conduits. Furthermore, a bath containing a $CaCl_2$/microbial transglutaminase (mTG) solution was utilized to reinforce the cross-linking of the bioprinted tubes. To mimic the structure and functionality of a native vein, a monolayered conduit was bioprinted with human umbilical vein smooth muscle cells (HUVSMCs) on its outer surface and perfused with HUVECs in the inner lumen. Following an additional week of incubation under similar culture conditions, a hollow venous conduit with a confluent endothelial layer inside and a thin, smooth muscle sheath on the outer surface was successfully constructed for further analysis (Wang et al., 2022a).

4.2 Microfluidic chip-driven extrusion-based bioprinting

Extrusion-based technology (Figure 2C) can be used in combination with microfluidic printheads to generate complex hierarchical structures. Recently, Marcotulli *et al.* demonstrated the printability of an oil-in-water emulsion using a new microfluidic printhead. The emulsion consisted of a cyclohexane-based organic phase dispersed in an aqueous phase composed of 20% w/v DexMA and 15% w/v Pluronic F-68, along with 1% w/v Irgacure 2,959 as a photoinitiator. Following the printing process, the samples were exposed to UV light at a wavelength of 365 nm to induce cross-linking. Thus, further architectural complexity was aided by the use of agarose-based support bath, demonstrating the ability of the new microfluidic-based technology in combination with FGMs to print highly complex physiologically-relevant structures (Marcotulli et al., 2023). More recently, extrusion-based microfluidic printing has been used to fabricate unique scaffolds infused with Chinese herbal medicine and a living microorganism for enhanced wound healing. The scaffold, composed of *Panax notoginseng saponins* (PNS) and microalgae *Chlorella pyrenoidosa* (MA), demonstrated controlled release of PNS, leading to improved cellular processes such as adhesion, proliferation, migration, and tube formation *in vitro*. Moreover, *in vivo* experiments with diabetic mice demonstrated the ability of scaffolds to alleviate local hypoxia, enhance angiogenesis, and accelerate wound closure after 14 days, highlighting the potential application for wound healing and tissue repair applications (Wang et al., 2023). Recently, a novel microfluidic-based bioprinting approach has been developed to house a highly efficient static mixer capable to spin multilayered microstructure fibres, demonstrating a continuous chaotic spinning with precise control over the internal structure of the deposited fibre (Chávez-Madero et al., 2020).

4.3 Microfluidic-driven light-assisted bioprinting

The versatile nature of microfluidic can be used to engineer new deposition approaches to aid light-based bioprinting (Figure 2D). Recently, Fournie *et al.* introduced a novel printhead design that utilizes hydrodynamic confinement for efficient microfluidic injection in the printing area. In this setup, an optical fibre is coupled to a 405-nm laser and integrated into the printhead. The adjustable power is used for photopolymerization during material injection. Unlike conventional approaches, the light is directly delivered within the printhead, near the fluidic delivery system, to guide rapid crosslinking (Fournié et al., 2023). Furthermore, Miri and others introduced a novel stereolithography bioprinting platform by incorporating a dynamic patterning system and a microfluidic device with pneumatic valves, where they achieved precise layer-by-layer bioprinting of 3D constructs. Utilizing vascular endothelial growth factor (VEGF)-loaded PEGDA and cell-laden GelMA, the authors successfully fabricated diverse hydrogel constructs which showed promise in neovascularization in a rat model (Miri et al., 2018). Creating complex tissue structures with gradients is a significant challenge in tissue engineering. Few methods have effectively achieved these gradients, which are crucial for functional engineered tissues. Thus, Wang and co-workers developed a composable-gradient Digital Light Processing (DLP)-based 3D bioprinting system that integrates a microfluidic mixer to generate continuous or discrete gradients of desired inks in real-time. In this work, various planar and 3D structures with gradients of materials, cell densities, growth factor concentrations, hydrogel stiffness, and porosities were successfully fabricated, highlighting the great, yet fully unexplored potential in biomedical application (Wang et al., 2022b).

5 Conclusion and future perspectives

To date, the complex hierarchical arrangement of the human body has not been yet recapitulated, slowing down the development of new therapies to regenerate damaged tissues. Microfluidic and 3D bioprinting can synergistically work towards the assembly of functional tissues, exploiting their combinatorial effect to generate complex and hierarchical constructs. Microfluidic spinning platforms can drive the ordered micro-assembly, resulting now capable of controlling mechanical flow, cells, drug and other molecules patterning, gradient building, and mixing. However, this approach fails to offer the fabrication of large and three-dimensional macro assemblies. Thus, the coupling of

microfluidic chip as printheads with multi-axial computer-assisted manufacturing technology can rescue the current inability of modern biofabrication methodology to assemble hierarchically graded functional tissues. Nevertheless, microfluidic-assisted bioprinting add significant value to the creation of physiologically complex structures by providing spatial distribution of cells, biomaterials, and signalling factors (Peng et al., 2016), including engineered micro-fibrous vascularized tissues (Zhang et al., 2017). This precise control ensures that the manufactured structure closely resemble native tissues in terms of their organization and function.

Although microfluidic-assisted 3D bioprinting is now pacing to new unexplored frontiers in the patterning of cells and biomolecules, it is crucial to acknowledge the current limitations and challenges in terms of scalability, reproducibility, and long-term functionality of the fabricated constructs. Further research and development are needed to address these issues and optimize the integration of microfluidic spinning with biofabrication techniques for disease modelling and tissue regeneration. While microfluidic-assisted 3D bioprinting yet holds great promise, the ultimate clinical translation requires extensive validation and robustness testing in the years to come. Nevertheless, the innovative nature and the unparalleled potential of this technology to revolutionize tissue engineering and reduce animal testing should not be unnerved, facilitating and gardening new interest in the development of a better coupling of microfluidic and 3D bioprinting towards the engineer of hierarchical physiological tissues.

Author contributions

SM: Conceptualization, Data curation, Investigation, Visualization, Writing–original draft. GC: Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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