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Review

Immune response against the biomaterials used in 3D bioprinting of organs

Amir Elalouf

Bar-Ilan University, Department of Management, Ramat Gan 5290002, Israel

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ABSTRACT

Regenerative medicine has developed promising approaches for healing and replacing defective and damaged organs or tissues with functional ones. Three-dimensional (3D) bioprinting innovation has integrated a potential to design organs or tissues specific to the patient with the capability of rapid construction to fulfill the storage of organs and the need for transplantation. 3D bioprinting of organs has the main goal to develop a structural and functional organ or tissue mimic to the original one. The highly complex fabrication of tissue engineering scaffolds containing biomaterials, tissue models, and biomedical devices has made it possible to print small blood vessels to mimic organs to reduce organ or tissue rejection. 3D bioprinting has the concept of bioinks containing biomaterials that may trigger the immune responses in the body. Nevertheless, foreign body response (FBR) is mediated by various cell types such as B-cells, dendritic cells, macrophages, natural killer cells, neutrophils, and T-cells, and molecular signals such as antibodies (Abs), cytokines, and reactive radical species. Typically, the biomaterial is shielded by the fibrous encapsulation that is regulated by molecular signals. This review explored the progress in 3D bioprinting of vital organs and basic immune response against the biomaterials used in this approach. Thus, evaluating immune response against biomaterials used in 3D printed organs is necessary to mitigate tissue rejection after the transplantation.

1. Introduction

The global demand for organ transplantation has been growing rapidly since the late 1990s, due to the increasing incidence of vital organ failure, greater success rate, and improved post-transplant outcomes [1]. Subsequently, the waitlist for transplantation has increased dramatically. Fig. 1 illustrates the number of organ allocations waiting, transplants, and donors lists in the U.S. in the last two decades. The waitlist has been continuously growing due to many factors such as insufficient donors, organ allocation criteria, quality and age of accessible organs, and comorbidities. In 2019, about 112,568 individuals were waiting for organ transplants. According to UNOS (United Network for Organ Sharing), only 39,718 patients have been transplanted since the available donors for 2019 were only 19,267 patients [2]. The remaining organs were obtained from deceased donors [3]. Nevertheless, advancements and progress in biomedical engineering and new technologies have provided potential solutions to overcome the transplant crisis. In the last decade, organ engineering has introduced an innovation of three-dimensional (3D) bioprinting to fulfill the organ requirement in transplantation [4].

3D bioprinting is a biomedical technique used to create a 3D structural architecture of the functional tissues or organs to layer the precise deposition or positioning of cells with the biomaterials [4]. This biomedical technique integrates live cells, biomaterial, and regulated motor systems to form complex structures [5]. The main goal of 3D bioprinting is to imitate structural and functional tissues or organs with their innate environment to resemble the original tissues or organs that are ultimately used for organ replacement. 3D bioprinting has created an opportunity to develop various allogeneic biological structures from the small blood vessels to mimic functional organs to minimize the risk of organ rejection [4]. Probably, the rejection is mostly triggered by the allogenic organ transplant [6].

Previously, the immune system was considered to defend only against viral or bacterial infections. However, it is known the immune response is

Abbreviations: 3D, three-dimensional; ADSCs, adipose-derived stromal cells; Abs, antibodies; AVN, atrioventricular node; EC, endothelial cells; ECM, extracellular matrix; FBR, foreign body response; FRESH, freeform reversible embedding of suspended hydrogels; GelMA, gelatin methacryloyl; HA, hyaluronic acid; HCs, hepatocytes; HepG2, hepatocellular carcinoma cell; hiPSC, human induce pluripotent stem cells; hiPSC-HPCs, human induce pluripotent stem cells-derived hepatic progenitor cells; iPS, induce pluripotent stem; LaBP, laser-assisted BioPrinter; LIFT, laser-induced-forward-transfer; MSCs, mesenchymal stem cells; PCs, progenitor cells; PCL, polycaprolactone; PEG-DA, polyethylene glycol-diacrylate; PEUU, polyester urethane urea; PLA, polylactic acid; SAN, sinoatrial node; SCs, stem cells; SMC, smooth muscle cells; UNOS, United Network for Organ Sharing; VICs, valve interstitial cells.

E-mail address: amir.elalouf@biu.ac.il.

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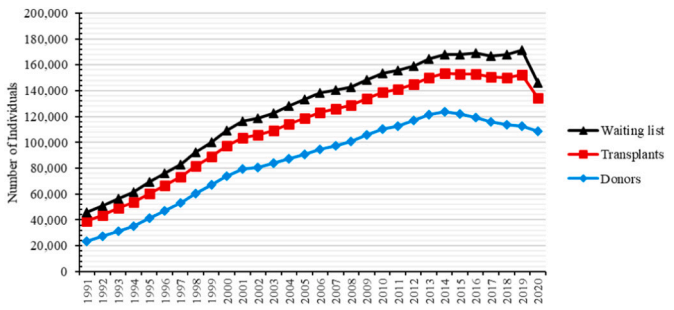

Fig. 1. The number of organ allocation waiting, transplants, and donors lists in the U.S. (1991–2020).
Source: U.S. Department of Health and Human Services.

triggered by any foreign particle, trauma, or biomaterial implantation. The structural and physiological functions of biomaterials in medical applications depend on biocompatibility. Thus, various cell types such as dendritic cells, B-cells, macrophages, natural killer cells, neutrophils, and T-cells, and molecular signals such as antibodies (Abs), cytokines, and reactive radical species can mediate immune responses [7,8]. Amongst, innate immune effector cells, particularly macrophages, play a critical role in defending against foreign particles and initiating molecular signals to protect the body from the biomaterial by fibrous encapsulation. The adaptive immune system, specifically T cells, is now being studied for its function in guiding macrophage responses to biological and synthetic materials [8]. To the best of our knowledge, no previous study has demonstrated immune response related to the biomaterials used in the 3D bioprinting of organs. Thus, this review provides the prevailing knowledge on the progress in the 3D bioprinting of organs, discusses the immune responses against the biomaterials, and also contributes to understand the possible immune response after the transplantation of 3D bioprinted organs.

2. Standard roadmap for 3D bioprinting of organs

With the advent of 3D printing in the late 1990s, surgeons began to 3D print custom prosthetics, kidney bladders, and dental implants. In the following years, the term "3D printing" was coined for this process, which used the printing of living cells, active biomolecules, and biomaterials. The fabrication of organs and tissues using 3D bioprinting is similar to additive manufacturing in that layers of bioink are deposited to create a 3D structure [9]. Bioink is the material that comprises biomaterial, growth factors, hormones, and additives, used by the 3D bioprinters to build bioengineered or artificial live tissues. Fig. 4 is showing the biomaterials used in bioinks of 3D printing organs and their components. 3D bioprinting has three main technologies (a) Inkjet/droplet bioprinting. (b) Extrusion-based bioprinting. (c) Laser-assisted bioprinting [10].

Fig. 2 illustrates a schematic diagram of the main 3D bioprinting techniques. (A) Thermo inkjet-based bioprinting uses an electric current pulse to ionize thin film resistors and then propels the droplets onto substrates with a pressure pulse. (B) Piezoelectric transducers create transient pressure that reacts to pressure fluctuations by ejecting droplets. (C) In pressure-assisted bioprinting, a solution, paste, or dispersion (as a biomaterial) is formulated into a continuous filament, which is then extruded through a microscale nozzle orifice or a microneedle. (D) In laser-based bioprinting, there are three components: a laser source pulse, a receiving substrate, and a ribbon. Through laser irradiation, liquid biomaterials evaporate from the ribbon, reaching the receiving substrate as droplets [10,11].

Fig. 3 shows the standard roadmap for 3D bioprinting of organs. 3D printing of organs starts with the magnetic resonance images of the patient's organs for constructing a 3D map of a particular patient's organ. Induce pluripotent stem (iPS) cells obtained from the patient's skin, isolated fibroblasts can convert into any cell type. iPS reprogrammed for developing specific cells of the particular organ [12]. For instance, in 3D heart printing, iPS cells are reprogrammed for the Purkinje cells, contracting cardiomyocytes, pacemakers, and vascular system cells such as cardiac fibroblasts. Combining the reprogrammed cells and custom formulated bioinks creates a bioprint of a patient's heart based on specific cell types. 3D bioprinting technologies (Fig. 2) accomplish the bioink in a layer-by-layer manner to print the artificial organs that pretend to be the original analog. Bioprinted organs remain for several days in a static condition bioreactor culture that supports the organ tissues and muscles for proper development and maturation. After that, the mature 3D bioprinted organs are ready for clinical transplantation. Cell viability, performance, and matric properties of transplanted organs are measured using custom sensors [13].

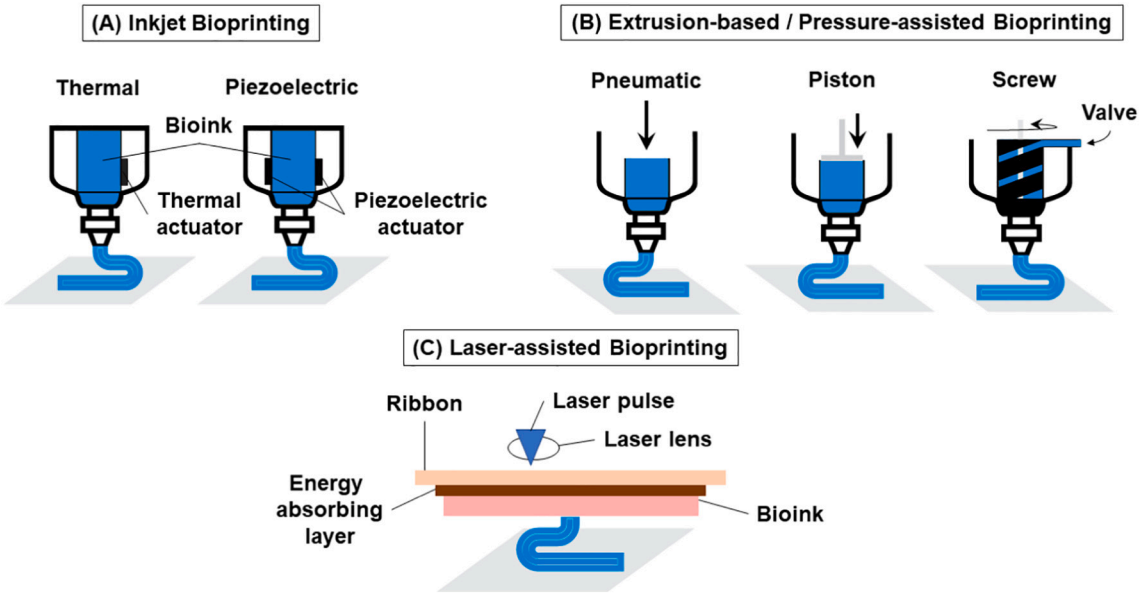

Fig. 2. Schematic diagram of the main 3D bioprinting approaches.

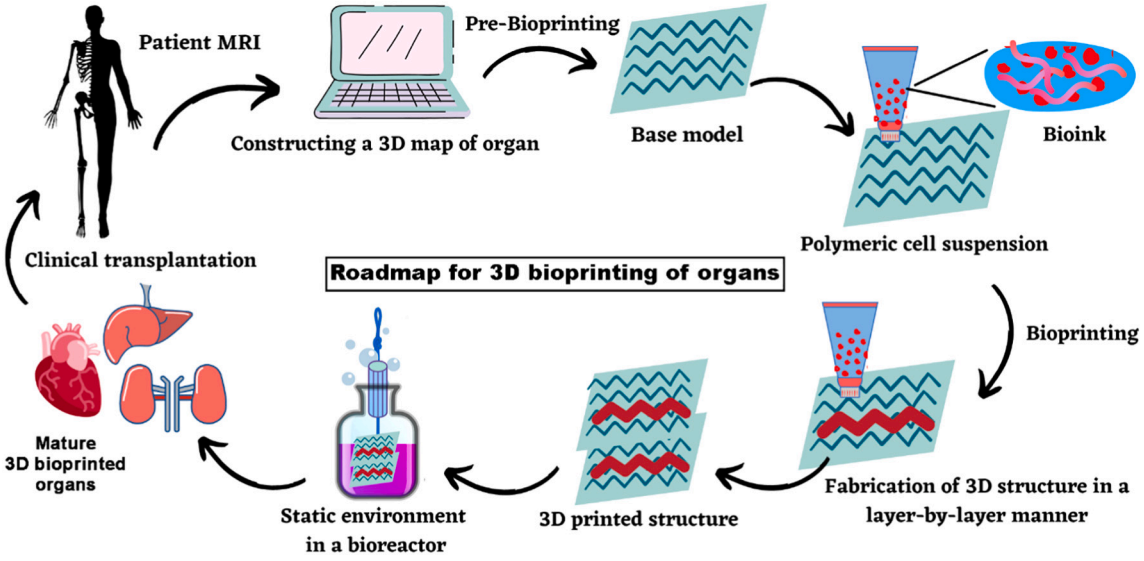

Fig. 3. Standard roadmap for 3D bioprinting of organs.

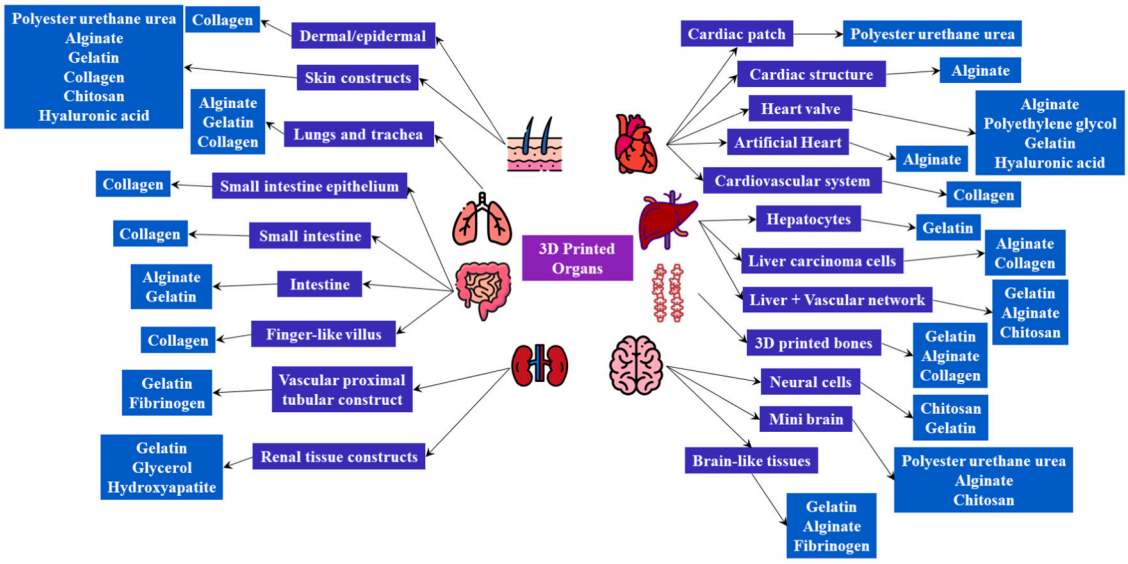

Fig. 4. Schematic diagram of 3D printed organs, their components, and biomaterials.

3. 3D printing of organs

3.1. Heart

The heart is the first muscular and functional organ that develops during the embryonic stage. It pumps the blood unidirectional from atrioventricular valves to semilunar valves. The human heart has a contractile wall, four valves, four chambers, complex vascularization, and a cardiac conducting system. The heart wall consists of three layers: the outer pericardium, middle myocardium, and inner endocardium. The pericardium is a serous fibro sac with double membranes that protect the heart by keeping it from blood overfilling and outer walls anchoring. The myocardium is a dense muscle layer responsible for cardiac contraction and relaxation, made up of cardiomyocytes. The majority of the endocardium comprises endothelial cells (EC) and is accountable for the blood-heart shield to protect the heart chambers and valves [14]. The four human heart valves are the tricuspid, pulmonary, mitral, and aortic valves, while four human heart chambers consist of the left and right aorta and ventricles.

Moreover, the complex cardiac vasculature system consists of small micro-circulation and prominent vessels. The cardiac conducting system, also known as the cardiac electric system, consists of Purkinje fibers, the bundle of His, the atrioventricular node (AVN), and the sinoatrial node (SAN) [13]. Congestive cardiac failure, cardiovascular disorders, and coronary artery disorders are the prominent reasons for mortality and morbidity. A few therapies are available to resolve and reverse the core disease causing heart failure, notably cardiomyocyte depletion, which permanently compromises myocardial contractile functionality [15]. Traditional approaches such as allografts, prostheses, autografts, and xenografts have various adverse cardiovascular diseases. In this regard, tissue engineering is a novel method for constructing engineered tissues to restore congenital disabilities. 3D bioprinting is the most recent innovative and successful approach for imitating structural and functional cardiac tissues [5,16].

Contractile 3D bioprinting heart must contain all the components such as cardiac muscles, left and right cambers valves, and pulsing pumps necessary for the proper functioning. Cardiac muscles have been bioprinted by different techniques in various studies [14,17]. Gaebel et al. composed a cardiac patch by Laser-Induced-Forward-Transfer (LIFT) cell printing technique for seeding human mesenchymal stem cells (MSCs) and human umbilical vein EC in pattern with the polyester urethane urea (PEUU). They examined the cardiac patches *in vitro* and *in vivo* to the infracted region of the rat heart. Ligated cardiac patches significantly improved vessel formation, capillary density, and cardiac wound healing, leading to improved function of the infarcted hearts [17]. In another study, Gaetani et al. constructed a cardiac structure using a 3D printing approach with the human cardiac-derived cardiomyocyte progenitor cells (PCs)-loaded alginate hydrogel. A homogenous cell distributed scaffold was constructed with this approach used for the *in vitro* applications. 3D printed scaffold found an obligation for the cardiac lineage, thereby up to 89% cell viability for seven days of culturing [14].

Different studies have bioprinted the aortic valves with varying compositions of bioink [18–20]. In a paper by Hockaday et al., the innate axisymmetric and anatomic aortic valve was 3D printed with the alginate supplemented polyethylene glycol-diacrylate (PEG-DA) hydrogels seeded with porcine aortic valve interstitial cells (VICs). Seeded cells with scaffolds resulted in 100% viability and rapid fabrication to support cell engraftment [18]. In 2013, Duan et al. bioprinted aortic valve conduits with incorporated and encapsulated dual cell types in alginate/gelatin hydrogel. They confirmed that aortic valve hydrogel conduits encapsulated fabrication is possible with 3D bioprinting. Accordingly, aortic VIC was encapsulated in the leaflets and smooth muscle cells (SMC) in the root of the 3D bioprinted aortic valve. Both cell types were viable; interestingly, VICs elevated the vimentin expression while SMC elevated the alpha-smooth muscle actin expression in the bioprinted aortic valve [19]. In 2014, Duan and his co-workers also synthesized a 3D bioprinted encapsulated heart valve with human aortic VICs and hybrid hydrogels methacrylated gelatin and methacrylated hyaluronic acid (HA). These encapsulated cells with hybrid hydrogels represented high cell viability and reconstructed the original matrix by the glycosaminoglycans and collagen deposition [20].

Chang et al.'s review reported that different studies used collagen 1 as a biomaterial for printing the microvascular and cardiovascular systems of the heart [21]. The vascular system is necessary for cell viability, nutrient transport, and waste removal. In a study, encapsulated cartilage PCs in alginate were printed in tubular channels to mimic the natural coronary vascular system [22]. The cardiac conduction system is necessary for sending contraction signals to the cardiac muscles. The cardiac conduction system is complicated for bioprinting. Nevertheless, cardiac tissue 3D micro physiologic models support future bioprinting of the whole heart, but the exact bioengineering mechanism for the cardiac conduction system has not been established. The idea is to reprogram iPS cells to become early cardiac PCs, then Purkinje cells and pacemakers. The reprogrammed iPS cells will then be used to create biofabricated hearts with artificial SANs, AVNs, and Purkinje fibers, essential components of the cardiac conduction mechanism [13].

Following the previous studies, Hinton et al. (2015) used the free-form reversible embedding of suspended hydrogels (FRESH) technique for bioprinting a 3D heart of a 5-day-old chick embryo. In this technique, fluorescently labeled alginate was used with computer-aided design modeling to recreate the intricate trabecular architectures of an entire heart. It was not an operative heart, but it was the first promising approach for creating a detailed large-scale 3D external and internal biological architecture [23]. In a study by Lee et al., fabricated collagen was used to 3D print the human heart from capillaries to complete the heart using the FRESH technique. The gelatin support bath controlled the pH of FRESH 3D printed hearts precisely similar to the patient heart. Human cardiomyocyte-printed cardiac ventricles exhibited coordinated contractions, lateral action potential dissemination, and up to 14% wall thickening at peak systole [24]. Recently, an artificial human heart was printed by the FRESH technique. The alginate was used as a biomaterial to generate an adult human heart with elastic modulus and is mechanically tunable for future medical applications [25].

3.2. Liver

The human liver consists of highly specialized tissues with hepatocytes (HCs) as a significant cell type that performs various functions such as red blood cell degradation, hormone production, plasma protein synthesis, detoxification, and glycogen storage regulation. The liver has four lobes, each composed of hepatic lobules. Hepatocyte plates radiate from a central vein to form the approximately hexagonal lobules. The liver sinusoids bind the central vein to the portal triads, allowing oxygen-rich blood from the hepatic artery to combine with nutrient-rich blood from the portal vein. The liver has two major cell types: parenchymal cells and non-parenchymal cells. The parenchymal cells are made up of HCs, which constitute 70–85% of the liver. While the non-parenchymal cells are made up of phagocytic Kupffer cells, hepatic stellate cells, and sinusoidal EC [16,26]. HCs have high proliferation that makes the liver a regenerating organ even after colossal damage. Correspondingly, many attempts have been made to develop biomimetic fabricating liver tissue with different tissue engineering techniques. However, traditional approaches have not achieved volumetric, highly adhesive liver tissues [27]. Hence, 3D bioprinting can facilitate liver fabrication with higher cells [28].

In the initial research, Wang et al. constructed a 3D hepatocyte gelatin hydrogel structure with the assembly of more than 30 layers by using rapid prototyping technology. HCs were viable and physiologically active for more than two months [29]. Shengjie et al. used the double-nozzle bioprinting technique to fabricate a metabolic functional and anatomical liver with the vascular network. The vascular network was formed by encapsulating adipose-derived stromal cells (ADSCs) within gelatin/alginate/fibrinogen hydrogel and surrounded by HCs loaded gelatin/alginate/chitosan hydrogel. The findings of this construct indicated that the double-nozzle assembling method could be an effective tool for fabricating complicated frameworks of the liver with unique intrinsic and extrinsic structures [30]. In another study, micron-organ devices were developed by the 3D fabrication of human liver hepatocellular carcinoma cell (HepG2) loaded with alginate hydrogel for *in vitro* drug metabolism models [31]. Hardwick et al. constructed a 3D hepatic tissue consisting of parenchymal and non-parenchymal cells using an automatic 3D fabrication bioprinter. Liver tissue was in organized form with the ability to store both glycogen and lipids. This 3D bioprinted hepatic tissue can be utilized in drug discovery and development and other biochemical studies for six weeks [32].

Bhise et al. developed a liver-on-a-chip platform with encapsulated 3D human hepatic HepG2/C3A spheroids within the photo cross-linkable gelatin methacryloyl (GelMA) hydrogel for the assessment of drug toxicity. The 3D-printed hepatic organ remained functional for thirty days with secreting alpha-1 antitrypsin, ceruloplasmin, albumin, and transferrin and showed an effective toxic response mimicking animal models [33]. In another study, a 3D collagen hydrogel triculture model with implanted human iPS cells (hiPSC)-derived hepatic PCs (hiPSC-HPCs), adipose-derived stem cells (SCs), and human umbilical vein EC was developed. The 3D triculture construct has higher liver-specific gene expression, improved metabolic product secretions, higher cytochrome P450 induction, and improved morphological organization [34]. Many studies have successfully printed 3D structures, but no one addressed the poor mechanical properties of the cell-loaded hydrogels. Lee et al. (2016) used polycaprolactone (PCL) to enhance mechanical properties and collagen laden with human lung fibroblasts, human umbilical vein EC, and HCs to form 3D printing bioink. The bioink was fused in the frameworks of PCL canals to induce the growth of liver cells and the formation of capillary-like networks [35].

In 2017, a custom-made bioinkjet was used for 3D printing liver by Arai et al. for studying the HCs functions. They construct the

galactosylated alginate hydrogel with attached HCs to form a monolayer for 3D bioprinting of liver tissues effectively used in the culture system [36]. Primary HCs are difficult to culture for a long time in constructing artificial livers. In a study conducted by Kim et al., the liver was printed using mouse primary HCs laden with alginate. The cells in the 3D-printed liver remained alive for fourteen days with increased gene expression of *Foxa3*, *HNF-4α,* and *Albumin*. The primary HCs in the liver construct can be cultured for the long term and used for drug screening [37]. Leva et al. (2018) used the LIFT technique for printing at targeted hepatocyte cancer cells. For 3D bioprinting, porous collagen scaffolds were used to study cell viability and examine specific cell structures inside the scaffolds [38].

In 3D bioprinting of the liver, one of the significant problems is vascularization. Limited studies have tried to develop a vascular system in the liver tissue model. Herein, it is now possible to create the vascular system by sacrificial printing, present extrusion, and coaxial printing in 3D-printed organs and tissues. In a recent study, the present extrusion technique constructed multicellular, heterogeneous, and multi-material architectures simultaneously. Kang et al. used preset extrusion and 3D-bioprinted hepatic lobules with HCs, EC enclosing the HCs, as well as a lumen in the middle, with sodium alginate to mimic the portal vein structure *in vivo* [39].

3.3. Bone

Bones are the physical structures to support and integrate the body. Bone is metabolically active and maintains the mineral homeostasis in the continuous process of bone turnover in which bone formation and resorption occur. The major cellular components of the bone tissues are the osteoblasts, osteoclasts, and osteocytes. Osteoblasts are involved in the deposition of mineral matrix and are located on the surface of bones. During the process of mineralized matrix deposition, osteoblasts deposit in the matrix, convert into osteocytes, and form networks by connections. Osteoclasts are the multinucleated cells, counterparts of the osteoblast, involve in the destruction of cells by resorbing minerals in the bone turnover process [40]. Healthy bones are an essential part of life quality; however, bone diseases are common and lethal, necessitating the development of predictive technologies to assist in pre-clinical drug screening and patient care. Bone tissue engineering provides a long-lasting solution to construct a personalized bone that can assimilate and grow within the patient body. The bioengineered constructed bone can also mimic the structure and function of the required bone to reduce the immunogenicity and morbidity risk of the allogeneic and autologous grafts, respectively [41]. Recently, 3D printing of bones has produced custom-shaped functionalized-reproducible bone tissues by the patient's requirements [42].

In a recently published review, Beheshtizadeh et al. mentioned different studies that attempted extrusion bioprinting and powder-based 3D printing of bones. For 3D printing of bones, biomaterials such as gelatin, hydroxyapatite, methacryloyl, PCL, polylactic acid (PLA), poly (lactide-*co*-glycolide), and polyvinyl alcohol were utilized with different cell types such as human MSCs, Human umbilical vein ECs, and adipose SCs [43]. In another review by Genova et al., various studies reported replacing defective bones with 3D printed bone constructs. The studies used biomaterials such as acrylonitrile butadiene styrene, alginate, collagen I, II, hydroxy-apatite, methacrylate gelatin, polycaprolactone, PEG-DA, and PLA for 3D printing of bone defects [44].

3.4. Brain

The brain is a highly complex, segmented, oxygen and nutrition-demanding organ responsible for regulating the physiological and cognitive functions of the body [45]. The brain structure is complicated and divided into three main parts: forebrain, midbrain, and hindbrain, with a complete vascular system. During growth, the vascular system assists and guides the formation of neuronal pathways in the brain, and vascular EC form a protective gate (blood-brain barrier) to regulate the flow of materials into the central nervous system (CNS) [46]. Microfluidic brain models investigate numerous phenomena such as disease states, electrophysiological properties, microenvironmental environments, and physiological interfaces. Recently, 3D tissue models have generated significant attention to developing a human brain mimic to morphology and physiology. However, these methods are time-consuming and difficult to replicate since minor variations in the starting cell number and culture conditions will result in many variations in the final tissue composition and function. 3D bioprinting has offered an exciting innovation to automate the tissue engineering of neural and vascular-related cells to construct long-lasting neural tissues and brain models for therapeutic applications [47,48].

The choice of bioink and cell types are the main concerns in 3D brain printing. Neural SCs or neural PCs are the most important cells, but due to their insufficient amount for 3D printing of neural construct, alternate cell sources are required. Gao et al. formulated ADSCs like neuron cells with porous scaffolds such as chitosan and gelatin. The ADSCs were differentiated into neural cells and proven to be biocompatible *in vitro* studies [49]. A study conducted by Han and Hsu provided a potential 3D printing strategy for a mini-brain. Regarding bioink, natural and synthetic biomaterials have been mentioned to be biocompatible. Polysaccharide-based natural biomaterials such as agarose, alginate, chitosan, and carboxymethyl hydrogels were applied in recent studies for the 3D neural constructs. However, synthetic biomaterial like polyurethane has also been used in 3D bioprinting and differentiation of neural SCs [48]. Recently, researchers of Tsinghua University have printed a brain-like tissue construct adequate for maintaining neural cells and a potential model for drug testing. In this study, biomaterials sodium alginate, fibrinogen and gelatin were used in different concentrations laden with primary neural cells for 3D printing of brain-like tissue construct [50].

3.5. Skin

Skin is the largest organ in the human body that performs many physiological functions. The skin provides fencing and protecting functions from mechanical disturbances, toxic chemicals, ultraviolet radiation, and pathogens. It involves passive functions such as maintaining nitrogen concentrations, oxygen, and hydrogen gases, preventing dehydration, and thermoregulation. Because of its accessibility and wide surface area, the skin has been seen as a drug delivery channel [51,52]. The skin has multiple layers, but three layers are the most important: epidermis, dermis, and hypodermis. The epidermis is the outer layer of the skin that generates the skin tone and serves as a waterproof barrier. Beneath the epidermis, the dermis includes sweat glands, hair follicles, and tough connective tissues. The hypodermis (deeper subcutaneous tissue) consists of connective tissues and fats [53]. Skin burns are a common cause of trauma, and the focus of health treatment has changed over time from survival to facilitating better functional outcomes. Surgical excision of injured skin and restoration of the burn injury with the help of skin replacements are typical burn treatments, particularly in the case of extensive burn injuries. Conventional skin replacements lack all skin cell forms; hence it is challenging to recreate native skin physiology. Lately, 3D bioprinting involves burning injury reconstruction with cell deposition in layers and scaffold biomaterials over the burned areas [54].

In a study by Lee et al., an extrusion printer was used for printing dermal/epidermal-like distinctive layers in a 3D collagen hydrogel with primary adult human epidermal keratinocytes and primary adult human dermal fibroblasts. Collagen type-I precursors were printed with ten layers to generate epidermis and dermis structures. Cells were highly viable, proliferating on both planar and non-planar layer surfaces. However, the printed structure was unable to establish intercellular junctions and generate tissues [55]. In another study, Laser-assisted BioPrinter (LaBP) was used for 3D printing of skin by 20 layers of

keratinocytes and 20 layers of fibroblasts embedded in collagen. 3D skin construct had a similar structure to the epidermis and dermis. It was cultured for ten days and analyzed to form adhering and gap junctions, which are significant for tissue cohesion and morphogenesis [56].

Michael et al., in a separate study, exploited LaBP to generate a cellularized skin substitute. They fabricated bi-layered structures *in vitro*, then implanted them *in vivo* using the dorsal skinfold chamber in nude mice. These skin structures formed epidermis and dermis layers. A multi-layered epidermis was composed of the printed keratinocytes after the initiation of differentiation and stratum corneum. Meanwhile, the printed fibroblasts could migrate collagen into a stabilizing matrix (Matriderm®). 11 days after transplantation, several blood vessels from the wound bed were also observed [57]. Lee et al. printed *in vitro* skin substitutes by bioprinting keratinocytes (HaCaT) and fibroblasts ((HFF-1) on collagen layers. The manually deposited constructs formed concave shapes and shrank, although printed skin samples do not alter their shape and dimensions. 3D printed skin tissue resembled *in vivo* human skin tissue in morphology and biology [58].

Fetah et al. reviewed 3D bioprinting of organ-on-chip and specified four studies [59]. Three studies [56,60,61] printed skin structures on chips with collagen having embedded skin or SCs, while one study [62] printed skin with alginate and pluripotent stem cell-derived EC. Fayyazbakhsh and Leu recently published a brief review on the 3D bioprinting of skin substitutes. They mentioned almost all the studies that printed the skin constructs with skin cells (fibroblast, human amniotic epithelial cells, keratinocyte, mammary PCs, and neonatal fibroblast) and biomaterials (alginate, chitosan, collagen, gelatin, HA, polyurethane, and silk) [63].

3.6. Lung and trachea

The lungs have two sections: the airway and the vasculature. The airways are the 23 generations of the branched network, the essential components of the pulmonary system (in a proximal-distal axis). The conducting zone extends from the main bronchi to the terminal bronchioles (0.5 mm in diameter), in which no gas exchange occurs. The respiratory bronchioles contain alveolar sacs and alveoli. Alveoli are small, interconnected spheres with a diameter of about 200 μm [64]. Different local phenotypes resulting from region-specific epithelial differentiation that occurs along the proximal-distal axis facilitate the requisite physiological functions of the lungs. The tracheal and upper airway epithelium comprises mucous secretory and columnar ciliated cells, capturing the inhaled particles. At the same time, bronchioles have cuboidal secretory cells (club cells) that protect the bronchiolar epithelium by secreting club cell secretory protein [65]. In contrast, the trachea (1.5–2 cm in diameter) is a simple and semi-flexible tube that extends from the larynx behind the sternum ranging 10–13 cm in length, then divides into right and left bronchi. The trachea also has 16–20 C-shaped cartilaginous rings on the anterior side and a soft membranous trachealis muscle on the posterior side. The mucosa is a moist, smooth tissue that lines the inside layer of the trachea [66].

Although the lung is often surgically categorized as a solid organ, it is more beneficial to see the whole respiratory tree as a branching series of tubes for tissue engineering purposes. Thus, advances and drawbacks found in the bioprinting of other tubular organs may be used to guide prospective lung bioprinting studies. Since the ultimate aim of 3D bioprinting lung tissue engineering is to create lung tissues that resemble natural lungs, a thorough understanding of lung anatomy and scaffold characteristics is needed to comprehend and identify 3D bioprinting parameters [67]. The ability to build hollow structures with several layers of various cells and materials is perhaps the most significant advantage of 3D bioprinters in lung and airway tissue engineering. Galliger et al. [67] mentioned different studies that utilized the 3D printing of lungs. Studies used alginate, collagen I, gelatin, PCL, and various combinations in 3D printing of lungs and trachea. Recently, Kang et al. (2021) devised a 3D alveolar barrier model by a 3D bioinkjet printer with alveolar cells and collagen. The 3D construct can be used in tissue responses against influenza infection [68].

3.7. Intestine

The intestine is mainly involved in food digestion and absorption of nutrients and water into the blood circulation. The human intestine is the longest part of the gastrointestinal tract, divided into two sections: small intestine and large intestine. The small intestine is metabolite and nutrient absorption, while the large intestine is involved in water reabsorption and electrolytes recovery. Intestine also acts as an effective barrier against harmful microorganisms. Moreover, the intestine has a critical role in immunity due to microbiota [69]. The intestinal wall consists of four layers: serosa, muscularis propria, submucosa, and mucosa. The serosa, also known as the adventitia, is a loose connective tissue membrane that contains nerves and blood vessels. The muscularis has two smooth muscle layers: an inner circular layer and an outer longitudinal layer, involved in peristalsis. The submucosa is a connective tissue underneath the muscularis and comprises stromal cells and dense lymphatic vessels and arteries that absorb the nutrients. Lastly, the mucosa lines the lumen and is involved in absorption [69,70].

For patients with severe intestinal impairment, intestinal transplantation remains a life-saving choice. Significant strides have been made towards producing replacement tissues and organs, including the intestine, using innovative tissue engineering methods to avoid transplant-related issues. The latest paradigm is to seed a biocompatible support material (scaffold) with a target cell population to produce viable replacement tissue [71]. Recently, researchers printed 3D intestinal tissue composed of human primary intestinal epithelial cells and myofibroblasts with biomaterials. The architecture and structure of the 3D construct mimicked the original human intestine [72].

Wang et al. developed a collagen scaffold to generate an *in vitro* self-renewing human small intestinal epithelium converted into the small intestine *in vivo*. This system allowed primary human intestinal cells to grow and differentiate, revealing that, in addition to 3D topography promoting cell organization, adequate chemical gradients were required for cell segregation in a stem/proliferative zone and unidirectional migration and differentiation along the crypt-villus axis [73]. Galliger et al. cited studies that operated 3D printing of intestines and other hollow organs. The studies used biomaterials such as alginate, fibrin, gelatin, GelMA, and PCL for 3D printing of the intestine and other digestive system organs like the liver [67]. In a recent study, a finger-like villus structure was constructed using a 3D printer with epithelial cell-laden collagen. Compared to pure cell-laden collagen, villus construction with a comparable villus geometry, *in vitro* cellular activities showed that the suggested cell-laden collagen/extracellular matrix (ECM) villus structure provides a more significant epithelial layer resembling the intestinal structure. Based on the findings, it is believed that using an ECM-based 3D villus model to create a more realistic physiological small-intestine model will be beneficial [74].

3.8. Kidneys

Kidneys are significant organs involved in the excretion of waste products from the body. The basic structural and functional units of the kidney are the nephrons. Nephrons have the bowman's capsule that encloses the glomerulus involved in blood filtration and generating urine. The urine is collected in the tubular structure of nephrons, which drains into the bladder *via* collecting tubules and ureters. The process of micturition removes the urine from the body *via* the urethra [75]. Kidneys and their vascular system are composed of different types of cells. Kidneys have the minimal ability to regenerate due to adult SCs. However, embryonic kidneys have self-assembling and generating capacity during the process of reaggregation. Dissociated kidney cells can form renal organoids, which are cell aggregates containing many types of renal cells. When kidney organoids are implanted subcutaneously,

similar effects are found [75]. Patients have two options in case of kidney failure, dialysis, and transplantation. But these are not the permeant solutions over time. Thereby scientists are trying to improve the kidney supply by using other sources such as kidneys from other mammals, implantable bioartificial kidneys, and 3D printing.

In a study by Steensma and Bennett, convoluted renal proximal tubules were 3D printed using two bioinks: silicone ink and fugitive ink. These constructed 3D proximal tubules had dramatically improved epithelial shape and functional features compared to constructed 2D models [76]. In a study by Lin et al., the vascularized proximal tubular construct was 3D printed with adjacent conduits lined with mingling endothelium and epithelium. The construct was embedded in a permeable ECM containing gelatin and fibrinogen to investigate renal reabsorption studies [77]. Recently, Carreno-Galeano et al. printed renal tissue constructs using formulated bioink composing hydroxyapatite, glycerol, and gelatin. The formulated bioink provided a microenvironment specific to the kidney that supported the maturation of human kidney cells and the formation of tissues. The cells of the bioprinted renal construct were highly viable and proliferating. Meanwhile, the renal construct mimicked the structure and function of native renal tissues [78].

4. Immune response and encapsulation of implanted biomaterial

Biomaterial implantation indues the immune response of the body. Implants release degrading products that alter the biomaterials' surface and actives the immune system [8]. The immune system of the host interacts with the biomaterial-based on the tissue surrounding the implant. This tissue determines the induction of innate immunity and adaptive immunity to the implant [79]. A study described that the surface roughness and wettability of titanium implants increased the adaptive immune response towards the helper T-cells with inflammation and enhanced the recruitment of SCs [80]. Thus, a detailed understanding of the immune response to synthetic materials has been established. Fig. 5 illustrates the immune response after the implantation and encapsulation of the biomaterial. In the classical foreign body response (FBR), macrophages gathered around the foreign object and formed giant cells. Fig. 6 is showing immune responses against the biomaterials used in 3D printing of organs and their components.

Biomaterial implants activate foreign immunity after a surgical procedure [81]. Herein, cell-biomaterial hybridization stimulates the inflammatory response associated with the innate immune system. Within nanoseconds, the first contact of biomaterial with the tissues triggers the release of proteins from the blood vessels and intestinal fluid. Various proteins (such as fibronectin) absorb the biomaterial surface and activate the complement system, coagulation cascade, immune cells, and platelets. After platelet and monocytes recruitment, monocytes differentiate into macrophages and adhere to biomaterials with platelets and monocytes [82]. Subsequently, macrophages activate to form giant cells [83], along with monocytes and platelets secrete cytokines and chemokines to recruit fibroblasts or MSCs. Finally, fibroblasts, or MSCs, create lymphoblastic tissues surrounding the biomaterial surface and mediate the formation of capillary beds and collagen accumulation [84,85].

4.1. Alginate

Alginate is a promising biomaterial use for the 3D printing of different organs [14,18,19,22,23,25,30,31,36,37,39,44,48,50,62,63,67]. In hum ans, the first clinical trials of alginate gels were based on the findings of animal tests that proved effective and safe for use [86]. It was reported in 1994 that calcium alginate dressing induced the FBR and created a problematic hemorrhage and long-lasting adverse effects [87]. However, FBR can mitigate against alginate by chemical modification (triazole group addition) [88] and used in hydrogel composite (alginate gelatin borax hydrogel) [89]. Meanwhile, alginate, like other biomaterials, induces inflammation. Yang and Jones reported an innate immune response trigger by the macrophage receptors. They found that sodium alginate activated the macrophage-like cells (RAW264.7) *via* the NF-κB

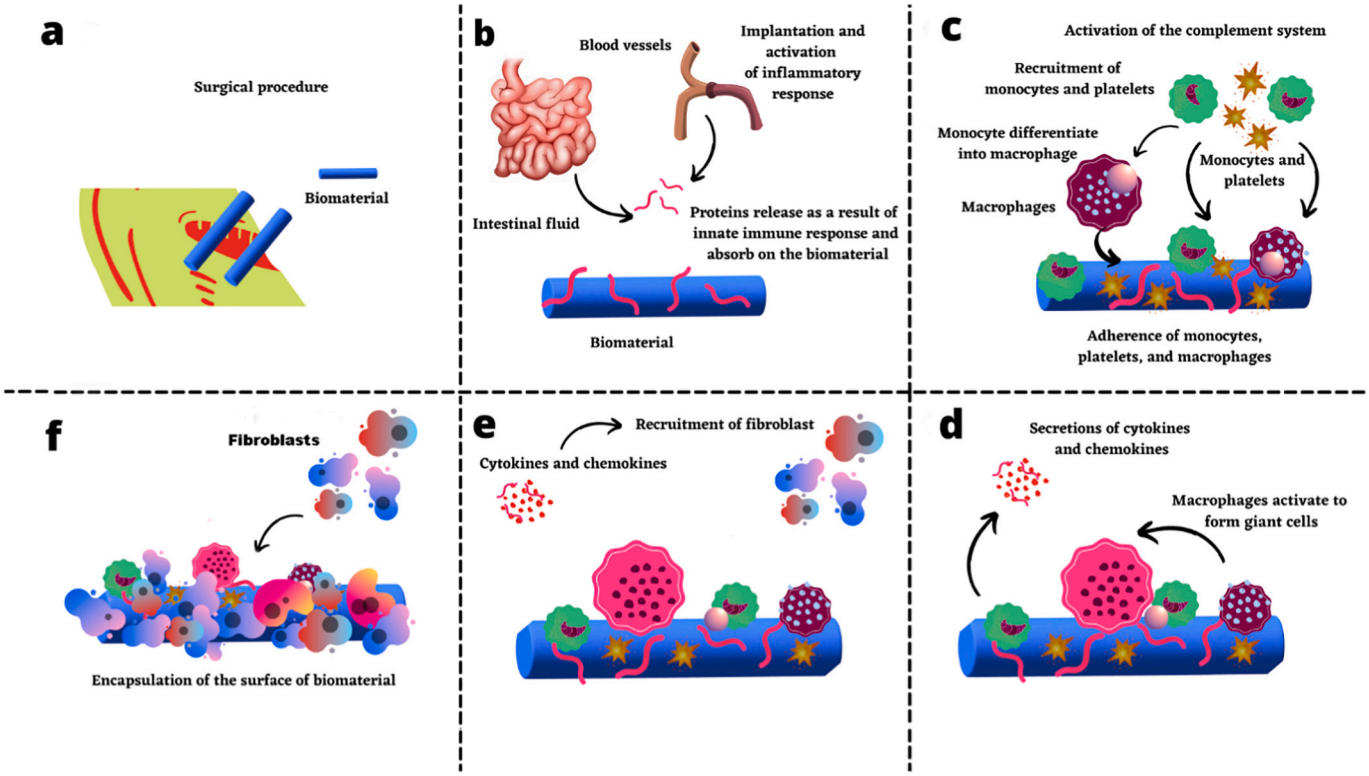

Fig. 5. The immune response after the implantation and encapsulation of biomaterial.

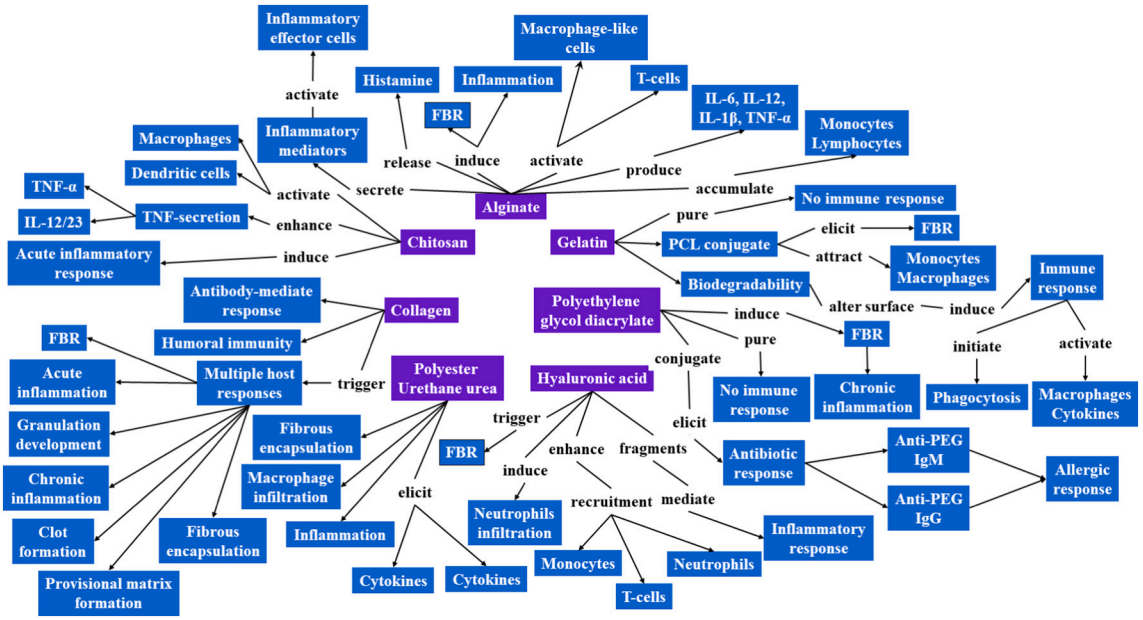

Fig. 6. Illustration of the immune responses against biomaterials used in 3D printing of different organs.

pathway. Pro-inflammatory cytokines such as IL-6, IL-12, IL-1β, and TNF-α were produced depending on the dose and duration [90]. Impure alginate has also provoked the immune system against impurities. Accordingly, alginate purification is necessary to prevent the activation of the immune response, but purification that can remove all the contaminants in alginate is still not possible. Even a minute amount of contaminants can promote the FBR [91].

Few days after the implantation, immune cells and activated macrophages such as basophils surround the alginate into the body. In the acute inflammatory stage, neutrophils and macrophages are recruited, and histamine releases from the mast cells. No immune cell adheres to the surface of alginate until impurities in the alginate biomaterial trigger the innate immune response. It senses through pattern recognizing receptors on the cells leading to chronic inflammation by activating macrophages *via* the NF-κB pathway and intensifying humoral response by producing chemokines and cytokines [91,92]. In chronic inflammation, monocytes and lymphocytes become accumulated around the alginate. Lymphocytes first adhere to the alginate surface then are predominately attached to the macrophages. Studies suggested that the T-lymphocytes assist the adhesion and fusion of macrophages to the surface of the biomaterial. Moreover, lymphocytes and macrophages also secrete inflammatory mediators such as chemokines ENA-78, IL-8, MCP, and MIP-1β, and cytokines TNFα, IL-6, and IL-1β. These recruits activate inflammatory effector cells such as monocytes, natural killer cells, neutrophils, and T-lymphocytes. *In vivo* studies have reported active T-cells during the inflammatory response against the alginate; however, *in vitro* studies have reported no lymphocyte response against the alginate biomaterial [85,91].

4.2. Gelatin

Gelatin has been used in combination with other biomaterials in bioprinting various organs such as aortic valve conduits, heart valves, liver tissues, bones, brain, skin, lung, trachea, intestinal tissues, and renal tissues [19,20,24,29,30,33,43,44,49,50,63,67,77,78]. Immune response against the pure gelatin is not found; however, gelatin conjugated with PCL elicits the FBR. An *in vitro* study reported that the PCL with random orientation attracted monocytes and macrophages in higher density. This random trend orientation of fibers in PCL scaffolds elicited an intense FBR *in vivo* study on rats [93]. Gelatin is a natural polymer and has the property of biodegradability due to the presence of specific enzymes. During the biodegradability of the gelatin, macrophages become active and subsequently activate the cytokines to initiate phagocytosis [94]. Degradation mediators such as acidic substances and lytic enzymes release after the adsorption of macrophages on the surface of gelatin; this makes the gelatin surface susceptible to biodegradation. The release of the degraded product alters the gelatin surface and induces the impact of the immune response [85].

4.3. Polyethylene glycol diacrylate

PEG-DA has been supplemented with alginate in hydrogel to form 3D-printed aortic valve and bone constructs [18,44]. PEG hydrogels induce the FBR, particularly *in vivo* chronic inflammation, after two weeks of implantation due to the crosslinked hydrophobic polyacrylate chains to form PEG-DA polymers [95]. In a study by Dobner et al., nondegradable PEG hydrogel injection into the ventricle of the rat elicited FBR after three months of the injection; however, the FBR mechanism was not clear [96]. Free PEG has shown no or weak immunogenicity response. Meanwhile, conjugate macromolecules with PEG elicit the antibiotic response against the small portion of the PEG and the whole PEGylated structures [97]. Critical features such as terminal end-groups, length, and branching trigger the immunogenicity against the PEGylated structures. Anti-PEG Abs have notably binding affinities in decreasing order with the PEG end groups: tert-butoxy (–O-(CH3)3) > butoxy (–O-(CH2)3-CH3) > methoxy (–O-CH3) > amino (–NH3+) > hydroxy (–OH) [98,99].

Further, hydrophilicity also influences the immunogenicity against the PEG core structures, such as anti-PEG IgM against the PEG-shell-containing hydrophobic inner core with polymeric micelle, and no response against the similar PEGylated micelles containing hydrophilic inner core [100]. A study on rodents reported that the anti-PEG Abs induction occurs through the type-2 T-cell independent mechanism. The anti-PEG immunogenicity is not studied. However, evidence of anti-PEG Abs, memory immune responses, and anti-PEG IgG suggests a difference in anti-PEG immune responses between humans and animals. The reasons behind anti-PEG Abs, memory immune responses, and anti-PEG IgG are still unclear. It needs further research to understand better the mechanism of anti-PEG immunity in humans [101]. Shimizu et al. state

that about 20% of healthy humans pre-exist the anti-PEG Abs. Thus, pre-existing and induced anti-PEG Abs trigger the allergic response and eliminate the body's PEGylated structures [102].

Different strategies have been investigated for reducing FBR against PEG biomaterial. For example, chemical modification (zwitterion addition) [103], alterations in mechanical properties (Young's modulus reduction) [104], and mixing of PEG hydrogel with cells (MSCs addition) [105] can reduce the FBR in humans.

4.4. Hyaluronic acid

Immune cells and ECM components are responsible for maintaining homeostasis and inflammation in the body. Inflammation is an essentially biological process during the wound healing process. During this process, monocytes' recruitment and chemokines, cytokines, and growth factors secretion are also crucial. HA has been used in the 3D printing of heart valves and skin, as discussed above [20,63]. After the implantation, HA fragments interact with the HA receptors present on the cells that mediate the inflammatory response in the body. Such HA-binding receptors TLR-2 and TLR-4 belong to the TLR family that recognize the HA fragments and trigger the pro-inflammatory responses to maintain homeostasis and injury repair [106].

HA signaling and interaction is a complex process involved in the inflammatory and immune response. In this process, CD44 is the primary cellular receptor, and TSG-6 and SHAP (HC) are the soluble proteins involved in the immune response. At the inflammatory site, CD44 enhanced expression linked with the increase in the recruitment of T-cells, neutrophils, and monocytes [107,108]. After the CD44 knockout in mice, a study showed aggravated inflammation, prolonged macrophage and neutrophil infiltration, elevated pro-inflammatory cytokines expression, slower apoptotic neutrophil clearance, impaired TGFβ1 activation, and HA fragments accumulation at the site of injury. That leads to the reduction in the proliferation of fibroblasts and the deposition of collagen [109,110]. TSG-6 and SHAP (HC) are the extracellular proteins that modify the HA into a bioactive complex. TSG-6 transfers the HC to HA [111] and also mediates the cross-linking of native HA [112]. In contrast, SHAP involves the stabilization of ECM [113]. The expression of TSG-6 up-regulates in many types of cells like fibroblasts and monocytes in the presence of IL-1 and TNF-α under the pro-inflammatory conditions. Neutrophil infiltration is induced by the HA while reduced by the TSG-6 [114].

HA is selected as a biomaterial for human use due to its 30 years of usage as a substitute for artificial tear, a cosmetic product, an intra-articular injection for osteoarthritis. Hylaform, HA dermal filler, has been found to trigger FBR in humans. Interestingly, chemical modification in the HA can also improve the mechanical properties of HA derivatives that enhance its range of biomedical applications [89]. FBR may also alter for HA derivatives. In a study conducted by So et al., acrylated HA hydrogel injected into rats showed no inflammation in the cells surrounding the injected hydrogel after four weeks [115]. While in adamantane-modified HA hydrogel implantation in the ovine heart, the minimal foreign body giant cells were found in implanted hydrogel surroundings after eight weeks [116]. In another study, adamantane-modified HA hydrogel was injected immediately after the MI induction into the rat's heart. After the first week, it was observed that IL-10 inclusion decreased the macrophages in the surrounding HA hydrogels [117]. This reaction can trigger the influence of FBR after the implantation of biomaterial. After implanting MSCs loaded hyaluronan-based HYAFF11 scaffolds in rats 111 and porcine 112 models, the FBR response was also found. Time analysis also creates an impact on the observation of FBR. Kim et al. reported acute inflammation after four weeks of HA hydrogel implantation, which was not found at eight weeks [118]. Similarly, Tian et al. observed foreign body giant cells six weeks after the HA hydrogel implantation in the rat brain; thereafter, it was not observed [119].

4.5. Polyester urethane urea

PEUU has been used in 3D bioprinting of cardiac patches [17], brain [48], and skin [63]. A study by Fujimoto et al. reported fibrous encapsulation around the PEUU scaffolds at the 4th, 8th, and 12th weeks. Moreover, macrophage infiltration and inflammation were minimal in PEUU [120]. The PEUU can prevent complications such as implant failure and chronic inflammation from integrating with the host tissue [89]. Moreover, it was found that in *in vivo* models, PEUU elicits the cytokines, chemokines, and growth factors release [121] and do not provoke the macrophages accumulation, tissue necrosis, or capsule formation [122].

4.6. Collagen

Collagen is an important biomaterial in the 3D printing of the heart, liver, hepatocyte cancer cells, bones, skins, lungs, trachea, and small intestinal epithelium discussed above. After the implantation, collagen triggers the multiple host responses in the body, such as acute inflammation, chronic inflammation, clot formation, fibrous encapsulation, foreign body reaction, granulation tissue development, and provisional matrix formation. The thrombin clot develops and encapsulates the implanted collagen, which also functions as a temporary matrix surrounding it in the early stages of healing [123]. The blood proteins deposit on the collagen surface, provide structural and functional components necessary for the collagen's healing process and ensure the FBR [124]. Different chemotactic cytokines, mitogenic agents, and growth factors modulate the macrophages and other cells' activity necessary for the inflammatory and healing processes. Since the FBR and inflammation progress, macrophages migrated to the site of implantation that is mediated by chemokines and chemoattractants. IL-1, leukotriene, platelet-derived growth factor, and TGF-β are the chemoattractants released by the platelets and blood clot [125].

It has been found that in the host body, Abs against the biomaterial such as collagen is already present and known as an antibody-mediated response. Low immunogenicity, which induces the antibody response, has also been found against collagen when interspecies collagen is injected into the body [126]. Epitopes in the telopeptide region at each end of the tropocollagen molecule focus on immune response against collagen. The immunologic profile of the collagen molecule is influenced by the conformation of the helical component and the amino acid sequence on the surface of the polymerized collagen fibril. As a result, the immunogenicity difference between polymerized collagen and its smaller counterpart is due to the decreased accessibility of antigenic determinants during the polymerization process [127].

Humoral immunity is only reported in a limited number of individuals against the type-1 collagen biomaterial after its implantation. A simple serological test can quickly determine allergic reactions against the collagen [127]. Moreover, the concept of immunogenicity against collagen also implements the collagen molecules made up of acellular ECM. The adverse effects of immune response encounter acellular scaffolds are also not necessarily belonging to the collagen molecules. Acute immunological responses or acellular ECM rejection are frequently caused by incomplete decellularization, which leaves residual oligosaccharide α-Gal or deoxyribonucleic acid [128].

4.7. Chitosan

Chitosan is derived from chitin, a natural polysaccharide obtained from crustacean carapaces. Chitosan has been used for 3D printing of liver, neuron cells, mini-brain, and skin [30,48,49,63]. Oliveira et al. found that macrophages and dendritic cells represent different responses to chitosan towards anti-inflammatory phenotype and pro-inflammatory attributes, respectively. Macrophages and dendritic cells were cultured on chitosan films for interaction analysis. Chitosan activated both macrophages and dendritic cells without T-cell proliferation [129].

Almeida et al. examined the cytokine secretion profile of human monocytes/macrophages with biodegradable PLA, PLA/calcium phosphate glass, or chitosan scaffold for 3D printing. TNF-secretion was enhanced by chitosan, with the scaffold geometry influencing the quantities of TNF-α and IL-12/23 released. More pro-inflammatory cytokines were secreted when chitosan scaffolds with large holes were used [130].

Chitosan scaffolds induced an acute inflammatory response, confirmed by a study appraising the chitosan biocompatibility in mice. Neutrophiles significantly reduced at the site of implantation by 12 weeks [131]. Azab et al. stated less inflammatory response in rats after the subcutaneous and intraperitoneal injection of chitosan [132]. Peluso et al. explained the stimulatory effect of chitosan on the production of macrophage nitric acid and chemotaxis *in vitro*. Moreover, *in vivo* study confirmed chronic inflammation and fibrosis in the surrounding tissues of implanted chitosan after 14 days by transmission electron microscopy images [133]. Although chitosan initiates the macrophages to produce monokines such as IL-1 and colony-stimulating factor, it increased the cytolytic activity of peritoneal macrophages that produce pro-inflammatory cytokines, such as TNF-α and IL-1β [134].

5. Conclusion

3D bioprinting of organs has a remarkable potential to develop scale-up functional organs due to recent technology, biomaterial, and cell culture. The versatility of 3D bioprinting has enlarged its biomedical applications from *in vitro* organ or tissue models for medical research studies to organ repairing and transplantation. In the field of 3D bioprinting of organs, different studies have attempted to 3D print human organs, and no doubt, soon, the functional 3D printed organ will be transplanted into the living body. However, challenges in this field are still present.

Previous studies mainly focused on the biomaterial FBR, infection, and toxicity after the implantation. This study discusses the immune response relevant to the biomaterials used in 3D bioprinting organs or tissues. Immune response against the biomaterials in 3D printed organs is so challenging that biocompatibility testing is mandatory for implanting biomaterials. Protein adsorption on the biomaterial surface triggers the FBR that recruits the macrophages and develops fibrous capsulation around the implant. In this review, we discussed the possible immune responses against each biomaterial used to construct 3D bioprinted organs. Ongoing studies disclose more details related to immune responses against the biomaterials, such as immune-modulation, macrophage activation, and polarization. Thus, it is necessary to examine the FBR and other immune responses against the implanting biomaterials to find ways to mitigate immune rejection against the 3D printed organs.

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Declaration of Competing Interest

None.

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