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Small Tissue Chips with Big Opportunities for Space Medicine

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Abstract

The spaceflight environment, including microgravity and radiation, may have considerable effects on the health and performance of astronauts, especially for long-duration and Martian missions. Conventional on-ground and in-space experimental approaches have been employed to investigate the comprehensive biological effects of the spaceflight environment. As a class of recently emerging bioengineered *in vitro* models, tissue chips are characterized by a small footprint, potential automation, and the recapitulation of tissue-level physiology, thus promising to help provide molecular and cellular insights into space medicine. Here, we briefly review the technical advantages of tissue chips and discuss specific on-chip physiological recapitulations. Several tissue chips have been launched into space, and more are poised to come through multi-agency collaborations, implying an increasingly important role of tissue chips in space medicine.

Keywords

microfluidics; spaceflight; microgravity; radiation; drug development

1. Introduction

Space exploration and travel are both exciting themselves and are of great scientific values and implications for human beings (Schwartz, 2020; Board and Council, 2012). In the past half-century, space travel and exploration have progressed substantially through the efforts of the National Aeronautics and Space Administration (NASA) and other governmental agencies and private companies, as exemplified by the human landing on Moon in 1969, Perseverance rover landing on Mars in 2021, and the International Space Station (ISS). The ISS has orbited the Earth at an approximate altitude of 400 km and a speed of 28,000 km per hour for the past two decades. Recently, due to the advent of reusable rockets such as SpaceX Falcon 9, the cost of launching a spacecraft has been reduced by approximately 50%

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and continues to decline, which makes personal space travel possible and perhaps popular in the near future. The field and market of space travel and exploration seem to burgeon in the next decade.

However, the biological effects of the spaceflight environment may overshadow space exploration, especially for long-duration and Martian missions (Afshinnekoo et al., 2020). The spaceflight environment, different from that on Earth, is primarily characterized by microgravity and high-energy radiation (Fig. 1a), which broadly affects biological systems and may lead to pathological conditions (Nicogossian, 2003). Microgravity can result in alterations of multiple organs/tissues, affecting the immune and musculoskeletal systems as well as renal and cardiac functions (Nicogossian, 2003). Some physiological alternations undermine the health and performance of astronauts, including the losses of muscle and bone masses (Lee et al., 2020). It is because that microgravity is unable to provide necessary mechanical stimuli to maintain tissue homeostasis and regeneration (Grimm et al., 2016; Juhl et al., 2021; Comfort et al., 2021). Also, microgravity leads to changes in the blood flow, such as flow turbulence and local density, which is associated with a rare venous thrombosis in an astronaut after working in the ISS for 2 months (Auñón-Chancellor et al., 2020). Microgravity was suggested to alter stem cell differentiation and gene regulation (Nagaraja and Risin, 2013; Zhang et al., 2018). For example, human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), onboard the ISS under microgravity for approximately 6 weeks, altered the expressions of 2,635 genes (Wnorowski et al., 2019).

Space radiation is another important feature of the spaceflight environment and a conundrum in space medicine (Chancellor et al., 2014). Space radiation has been associated with DNA damage (Dubrova et al., 2000), cancer (Sridharan et al., 2016), and other diseases (Wakayama et al., 2021; Mishra and Luderer, 2019). Away from the earth, space radiation may include energetic protons, alpha particles, and high-energy, and high-charge (HZE) nuclei, which may affect the welfare of astronauts during deep-space travels. In low-Earth orbit (LEO, with an altitude of 2,000 km or less), the space radiation is partially shielded by the Earth’s magnetic field.

It remains challenging to investigate the complicated space-related biological effects and develop space medicine. One obstacle is to recapitulate the microgravity and space radiation on Earth. Many on-ground approaches have been developed to resemble microgravity, including clinostat, random positioning machine, diamagnetic levitation, and drop towers (Ferranti et al., 2020), as well as to simulate galactic cosmic rays (GCR). In particular, the NASA Space Radiation Laboratory at Brookhaven National Laboratory is the only operating facility in the US for GCR simulation (Slaba et al., 2021; Norbury et al., 2019). A range of studies on GCR-induced biological effects has been carried out in this facility, including behavioral effects (Kiffer et al., 2019), omics datasets (Beheshti et al., 2018), and plants and plant propagules (Zhang et al., 2022). However, some on-ground approaches are limited to either short time scales or incomplete simulation. Furthermore, the on-ground approaches and datasets may be challenging to investigate the combined effects of space radiation and microgravity (Wakayama et al., 2021; Furukawa et al., 2020).

In addition to the on-ground approaches, the ISS and other in-space facilities have been used to investigate the limits of life in space and the habitability of Mars (De Vera et al., 2019; Poghosyan and Golkar, 2017). Of note, space radiation on the ISS is mitigated due to the shielding effect of the Earth's magnetosphere (Fig. 1a). Due to the orbiting motion, the ISS is subject to microgravity around 1×10^{-6} m s^{-2}, which is much lower than that on Earth, around 9.81 m s^{-2}, thus suitable for microgravity studies. The ISS has hosted approximately 3,000 experiments from a diverse range of disciplines, including biology, technology, and physics, to benefit space exploration and fundamental biomedical research (Witze, 2020; Thirsk et al., 2009). However, the ISS and other in-space facilities are restricted by the accommodating/loading capacity, limiting the weight and footprint of research instruments. Also, the hands-on operation of astronauts is often limited. These experimental limitations in spaceflight probably lead to reduced complexity, oversimplification, and the narrowed scope of experiments, representing a major challenge in exploiting space-induced biological effects and space medicine.

Tissue chips or microphysiological systems (MPS) are promising toolsets for space biomedicine (Fig. 1b), primarily due to their relatively small footprints, the capability to recapitulate tissue-level physiology, and the possible automated operations (Low and Giulianotti, 2020; Low et al., 2021; Zhang et al., 2017; Mu et al., 2013a; Zhang et al., 2009). In the microchannels of tissue chips, surface tension and viscous forces dominate, benefiting fluid-handling and transportation (Nijhuis et al., 2022). Yet gravity is still playing a role in the microchannel (Huh et al., 2007; Giorello et al., 2020; Sun et al., 2019). In particular, continuous mass-dependent separation of particles has been carried out in microfluidic chips (Huh et al., 2007). Other gravity-induced phenomena have been reported, including the flow-focusing of liquids with unmatched densities (Giorello et al., 2020) and the participation of bacteria (Sun et al., 2019). Thus, it is still promising to deploy tissue chips in space for exploiting microgravity-related biological effects. Also, tissue chips will be a valuable alternative to animal models for in-space and on-ground studies.

NASA and the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) have collaborated with the ISS-National Laboratory (ISS-NL) along with other agencies to launch an array of tissue chips into the ISS and perform a range of biomedical experiments in space (Table 1). These tissue chips in the ISS promote the understanding of the molecular and cellular mechanism of spaceflight environment-related biological effects (Fig. 1c).

In this review, we describe the technical fundamentals of tissue chips and their promising utility in space medicine. In particular, tissue chips are characterized by small footprints, tissue-level anatomy, and long-term maintenance of the tissue functions, thus highly promising for studying long-term space travel-related biological effects. We also review promising examples of tissue chips for space medicine, including drug development and fundamental biomedicine research, such as cancer biology.

2. Tissue chip techniques

Tissue chips are bioengineered microdevices that originate from microfluidic chips (Bhatia and Ingber, 2014; Mitchell, 2001) and can recapitulate essential physiological features at the tissue level, such as the breathing lung alveoli (Huang et al., 2021; Huh et al., 2012a; Huh et al., 2010) and glomerular filtration (Valverde et al., 2022; Ashammakhi et al., 2018; Mu et al., 2013b). The on-chip recapitulation of tissue-level physiological features are achieved by the combination of human cells, mammalian extracellular matrix (ECM) (Moses et al., 2021), advanced microfabrication, and well-controlled environmental cues (Viravaidya et al., 2004; Thompson et al., 2020). Also, tissue chips can integrate multiple cell types and tissue/organ-analogs for investigating the metabolic pathway of drugs and the toxicity of metabolites, superior to single-tissue/cell models (Miller and Shuler, 2016; Zhang et al., 2017; Skardal et al., 2017; Nahmias et al., 2007; Trapecar et al., 2021; Herland et al., 2020; Novak et al., 2020). This feature of tissue chips also allows the construction of quantitative pharmacokinetic-pharmacodynamic (PK-PD) models (Sung and Shuler, 2009; Esch et al., 2011; Lee et al., 2017).

Tissue chips are expected to offer a more realistic and accessible physiological environment and predict human responses better than two-dimensional (2D) Petri dish-based cell culture and some animal models. It has been increasingly recognized that animal models exhibit physiological and pathological conditions distinct from human beings, thus leading to a high rate of failure in clinical trials (Akhtar, 2015; Horejs, 2021). Also, compared with animal models, tissue chips are characterized by well-controlled and decoupled experimental conditions and convenient real-time imaging. Depending on the substrate materials and fabrication techniques, tissue chips can be high in cost and thus largely used for low- to moderate-throughput screening (Leung et al., 2022). However, the cost of tissue chips can be lowered by adopting affordable fabrication techniques (Winkler et al., 2020). Tissue chips have been recognized as a potential lower-cost alternative to animal models (Huh et al., 2013) and hold great promise for facilitating clinical trials and speeding up drug development (Caplin et al., 2015; Ma et al., 2021). Tissue chips may further enable the integration of various types of biosensors for *in-situ*, continually, and automatically monitoring of on-chip cellular responses (Zhang et al., 2017; Aleman et al., 2021; Lima et al., 2014; Miller et al., 2021). Due to all these technical benefits, tissue chips are one of the most promising technical platforms for exploiting space medicine. To deploy tissue chips in space is worth taking all necessary costs. Below, we discuss the space medicine-related technical benefits of tissue chips, including relatively small footprints, long-term preservation of tissue functions, and heterogeneous cellular composition, as well as other promising biomedical utility of tissue chips in space, such as cancer biology and drug development.

2.1 Relatively small footprint

Compared with conventional approaches, tissue chip-based systems, including tissue chips and peripherals, may be of relatively small footprint and thus be suitable for loading into the space-limited ISS and other spacecrafts. Tissue chips are usually not larger than the size of a palm, a huge reduction of footprint compared to conventional bioreactors. The relatively

small footprint of tissue chips is due to advanced microfabrication approaches, including lithography (McDonald et al., 2000; Whitesides et al., 2001) and recently, three-dimensional (3D) printing (Ching et al., 2019; Au et al., 2016; Rahmani Dabbagh et al., 2022). The advanced fabrication approaches allow the construction of precise microstructures in the length scales of a few to a few hundreds of micrometers, such as networks of microchannels and micropillar arrays.

Notably, tissue chips also require external power sources, tubing, and regulating systems, which are oftentimes much larger than the chips themselves yet still contribute to a small footprint compared with conventional approaches. For example, a kidney chip system required four syringe pumps, two incubators and tubing over 30 meters, accounting for a total volume of approximately 1,350 L (Yeung et al., 2020). Through optimizing the external perfusion and environmental control systems, the size of a tissue chip-based device can be reduced from approximately 1,350 L to 45 L, which fits well the launch capsule and the limited experimental space in the ISS (Yeung et al., 2020). The footprint of the tissue chip-based systems may be further reduced through continued engineering innovations, for example, capillary phenomena-based sequential liquid-manipulation (Yafia et al., 2022).

The tissue chips with microchannels and micrometer-sized structures may provide other size-related benefits. These microstructures are comparable to the size of cells, thus beneficial for manipulating cells, such as patterning and trapping (Mu et al., 2013a; Ma et al., 2018). Also, the mass/heat-transport is usually faster on a small length scale than on a large one (Dittrich and Manz, 2006). Flow phenomena under small scales, such as multistream laminar flow and multi-phase droplets, provide flow-based approaches for manipulating cells, which reduces the system complexity (Mu et al., 2009; Teh et al., 2008; Mu et al., 2014).

2.2 Long-term culture

Tissue chips enable the long-term cell culture and the preservation of tissue-level physiology, resulting from the bioengineered on-chip environment that is physiologically relevant. The long-term on-chip cell culture benefits the investigations of non-acute biological effects of the spaceflight environment (Vernetti et al., 2016; Qiu et al., 2018; Sieber et al., 2018), and allows the investigations of non-acute cellular responses, which is important for the pathogenesis of chronic diseases. In addition, the launch of a spacecraft may experience unexpected changes and delays (Yeung et al., 2020), which can be mitigated by the long-term self-contained culture capacity of tissue chips. Most of current tissue chips enable cell culture for 3–4 weeks, but the more recent multi-agency collaborative effort is to extend the culture period for at least 6 months, which supports eight tissue chip-based projects that are supposed to function in an automated manner and are projected to be onboard the ISS (Tagle, 2022). Below we discuss two exemplary tissue chips that can support cell culture and tissue-level functions for around 1 month.

One liver chip consists of human hepatocytes, non-parenchymal cell lines, and collagen hydrogels, maintaining metabolic functions for at least 28 days (Vernetti et al., 2016). The liver chip reveals the acute toxicity of 180-μM troglitazone and 210-μM nimesulide within 2–4 days, characterized by sharply decreased albumin and urea, increased reactive oxygen

species (ROS), and cellular apoptosis. More importantly, the 28-μM troglitazone did not lead to significant cellular apoptosis until 14 days. This result underscores the importance of long-term on-chip culture for uncovering non-acute and chronic drug toxicity.

Another vessel chip maintained endothelial barrier functions over 1 month; the long-term on-chip culture is attributed to the physiologically relevant microenvironment, including substrate stiffness and laminar flow (Fig. 2a–c) (Qiu et al., 2018). In particular, the vessel chip employed an agarose-alginate interpenetrating-polymer-network (IPN) hydrogel with Young's modulus of roughly 20 kPa, mimicking that of the tissues surrounding the vessels (~35 kPa) (Huynh et al., 2011). In contrast, a stiffer material of ~50 kPa, silicone rubber polydimethylsiloxane (PDMS), led to significantly increased permeability; a softer one of ~1 kPa was not feasible to form an endothelial barrier. The long-term preservation of vascular barrier function enables investigations of the interactions between pathological red blood cells and endothelial cells. The vessel chips demonstrated that pathological *Plasmodium falciparum*-infected blood cells alone led to increased vascular permeability, which does not require the participation of other types of cells, such as immune cells. This result thus provides insights into a long-standing controversy regarding the cellular mechanism of malaria (Frevert and Nacer, 2014).

2.3 Heterogenous cellular composition

Tissues are composed of heterogonous cells. The complex and dynamic interactions between these cells are key to tissue homeostasis and disease pathogenesis. For example, the respiratory system, including the alveoli and large and small airways, contains more than 40 types of cells; the lung alveolus alone contains two types of epithelial cells, macrophages, endothelial cells, and fibroblasts, among others (Franks et al., 2008). Tissue chips employ microstructures and microchannels to incorporate and pattern multiple cells to resemble the complex anatomical and physiological characteristics, thus promising to decipher the role of cellular interactions at the tissue level (Mertz et al., 2018; Huh et al., 2012b). In particular, epithelial and endothelial cells were cultured in individual yet interconnected channels, recapitulating the tissue interface in the lung alveoli (Huh et al., 2012b) and the nephron (Mu et al., 2013b).

One bone marrow chip reconstitutes a complex population of bone marrow cells to recapitulate the hematopoietic niche and to model radiation toxicity and potential countermeasures of drugs (Fig. 2d, e) (Torisawa et al., 2014). This bone marrow chip exploited an *in vivo* approach, *i.e.*, 8-week subcutaneous implantation, for forming trabecular bone-like tissues with a central region of blood-filled marrow. The reconstituted bone marrow resembled the morphological, biochemical, and cellular aspects of natural bone marrow. The cell population residing in the bone marrow included hematopoietic stem cells (HSCs), hematopoietic progenitor cells (HPCs), and all other differentiated blood cells, such as erythrocytes, lymphocytes, and myeloid cells. The complete set of bone marrow cells was suggested to work collectively to maintain hematopoietic functions and mimic the response to radiation.

The reconstituted bone marrow was incorporated into a microfluidic chip, where on-chip perfusion provided physiological flow stress and delivered nutrients and water-soluble

chemicals for keeping cells' self-renewal and differentiation for more than 1 week. After exposing to 1- and 4-Gy doses of γ-radiation, the bone marrow chip exhibited a dose-dependent decrease in the proportion of HSCs, HPCs, lymphoid cells, and myeloid cells. This on-chip result is nearly identical to that of live mice yet not observed with a static stroma-supported model. Also, colony-stimulating factor (G-CSF), a therapeutic agent for radiation toxicity (Hérodin and Drouet, 2005), can increase the number of hematopoietic stem cells and progenitor cells in the bone marrow chip. These results imply the potential of the bone marrow chip, as a useful alternative to animal models, for mimicking radiation responses and screening anti-radiation drugs.

In addition to using mouse cells, some bone marrow chips can be composed of all human cells (Aleman et al., 2019; Chou et al., 2020), thus minimizing potentially biased results due to species differences. One study used multiple bone marrow-derived cells, including sinusoidal endothelial cells, arterial endothelial cells, mesenchymal stromal cells (MSCs), and MSCs-differentiated osteoblasts, to construct 4 distinct bone marrow niches within an integrated, recirculating perfusion system (Aleman et al., 2019). Another study employed two microfluidic channels to recapitulate hematopoietic and vascular morphologies, respectively (Chou et al., 2020). The on-chip results, such as ionizing radiation-induced decrease of bone marrow cells, quantitatively matched human radiation sensitivity.

2.4 Cancer biology

Tissue chips can be deployed in space to empower other fundamental biomedical research in space, such as cancer biology (Krüger et al., 2019). It is primarily because of the space environment that impacts cancer cell behaviors and perhaps carcinogenesis and is often challenging to replicate on ground. Tissue chips have been exploited to reconstruct key tumor features and investigate the pathogenesis, metastasis, and potential treatments for several cancers (Mu and Zhang, 2022; Sontheimer-Phelps et al., 2019), paving the way for in-space investigation.

Microgravity has been shown to affect the behavior of cancerous breast cells (MCF-7), such as invasion, adhesion, migration, vinculin expression, and apoptosis, compared to normal breast cells (MCF10A) (Monti et al., 2021). Some regulating genes and signaling pathways have been suggested to involve microgravity-induced cellular alternations (Ma et al., 2014; Arun et al., 2017). Moreover, cancer cells in space tend to form 3D tissue-like spheroids that may capture some tissue-level features and facilitate testing anti-cancer drugs (Grimm et al., 2018; Aleshcheva et al., 2016).

An all-glass tissue chip has been used to investigate skin melanoma cell line A375 under short-term (2 hr) simulated microgravity using a 3D clinostat (Przystupski et al., 2021). The simulated microgravity was found to increased caspase activity and reduce proliferation of cancer cells, which may be linked to apoptosis and are consistent with previous results (Arun et al., 2017; Kossmehl et al., 2003). Although these results are interesting, more efforts are most likely needed to extend the culture and simulation period.

2.5 Drug development

The biological effects of the space environment are also important to medication and drug development (Braddock, 2020; Giulianotti and Low, 2020; Eyal and Derendorf, 2020). The bioavailability, metabolic pathway, and pharmacokinetics of drugs in space may differ from those on Earth (Eyal and Derendorf, 2019). Also, the drug-drug interactions (DDIs) may lead to the compromised performance of astronauts. For example, the combination of sleep aids and anti-emetics involves cumulative central nervous system (CNS) depression, and such sedation may be problematic for extravehicular activity (spacewalk) (Berman and Eyal, 2019). Furthermore, most DDIs potentially encountered in space have not been fully investigated. Thus, it is desirable to avoid non-established drug combinations in space and to develop a space-related clinical decision support (CDS) system (Berman and Eyal, 2019). Tissue chips in space are promising to verify the efficacy of drugs and the potential crosstalk. In particular, some vessel chips with on-chip mechanical stimuli and sensors may be useful for screening drugs in space for vascular diseases (Ribas et al., 2017; Sadlowski et al., 2018; Giulianotti and Low, 2020).

The spaceflight environment leads to rapid physiological alternations that resemble the effects of expedited aging, including changes in telomere length, cardiovascular dysregulation, neurodegeneration, and a mosaic of somatic mutations (Afshinnekoo et al., 2020). These accelerated physiological alternations could shorten the required experimental time of tissue chips for observing disease development and cellular responses to drug candidates, thus promising to expedite drug discovery (Giulianotti and Low, 2020). Of note, it remains unclear if in-space aging and disease development's mechanisms are the same as the terrestrial ones. Nevertheless, tissue chips enable further exploration to compare the mechanisms on-Earth and in-space.

Some PDMS-constituted tissue chips may suffer from the bulk absorption of small hydrophobic molecules due to the porosity and hydrophobicity of the polymer network of PDMS (Toepke and Beebe, 2006). The bulk absorption may bias the concentration of drug candidates within the microchannels, thus leading to challenges in predicting cellular responses. There are several approaches to ameliorate this issue, including surface modification (Ren et al., 2010), a simulation-facilitated experimental approach (Grant et al., 2021), and the adoption of other polymeric materials for fabricating tissue chips, such as Teflon and thermoplastic polypropylene (Ren et al., 2011; Sun et al., 2019; Pourmand et al., 2018; Shaegh et al., 2018).

3. Conclusion and perspective

In summary, the tissue chip techniques as versatile bioengineered small-footprint physiological models have exhibited particular advantages in understanding biological effects in space for developing space medicine. The huge potential of tissue chips in space is in part reflected in the ongoing projects supported by the multi-agency collaboration. As tissue chips are naturally multi-disciplinary, the collaboration between scientists and engineers with diverse backgrounds and between different regulating agencies would be key to future success. Tissue chips are still in their infancy, yet we envision them playing an increasingly important role in space exploration and space medicine.

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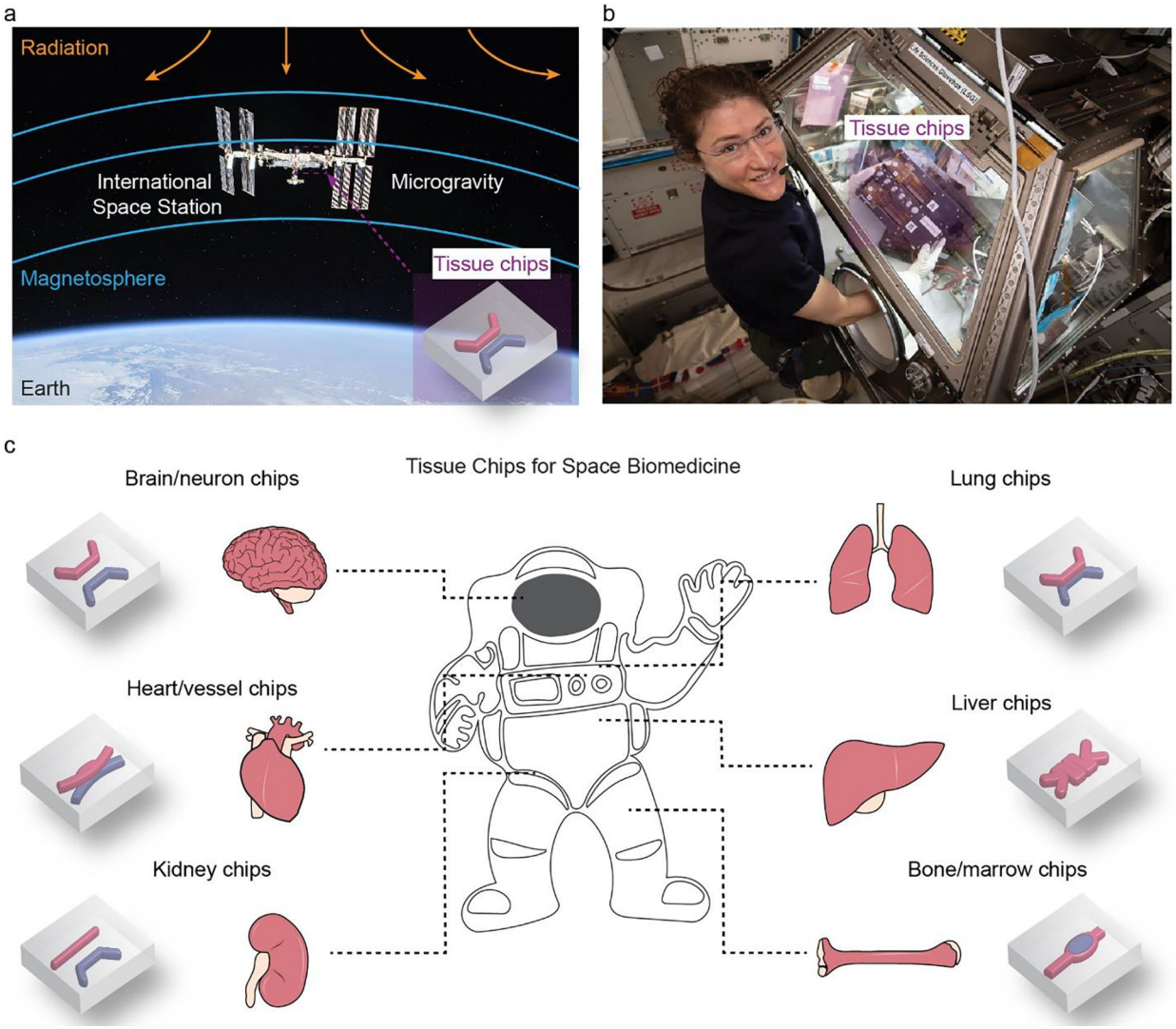

Fig 1.

a. Tissue chips are a promising tool for understanding the biological effects of spaceflight environments, including microgravity and radiation. Photograph credit (iss056e201352): NASA/Roscosmos. **b**. Astronaut Christina Koch operated kidney chips in the International Space Station (ISS). The reduced footprint and improved automated manipulation of liquids make tissue chips compelling. Reproduced with permission (Yeung et al., 2020). Copyright 2020, John Wiley and Sons. **c**. Overview of tissue chips for recapitulating multiple tissue-level physiological functions. Microchannels and in-chip microstructures are labeled in red and blue. Multiple tissues can be incorporated into one chip.

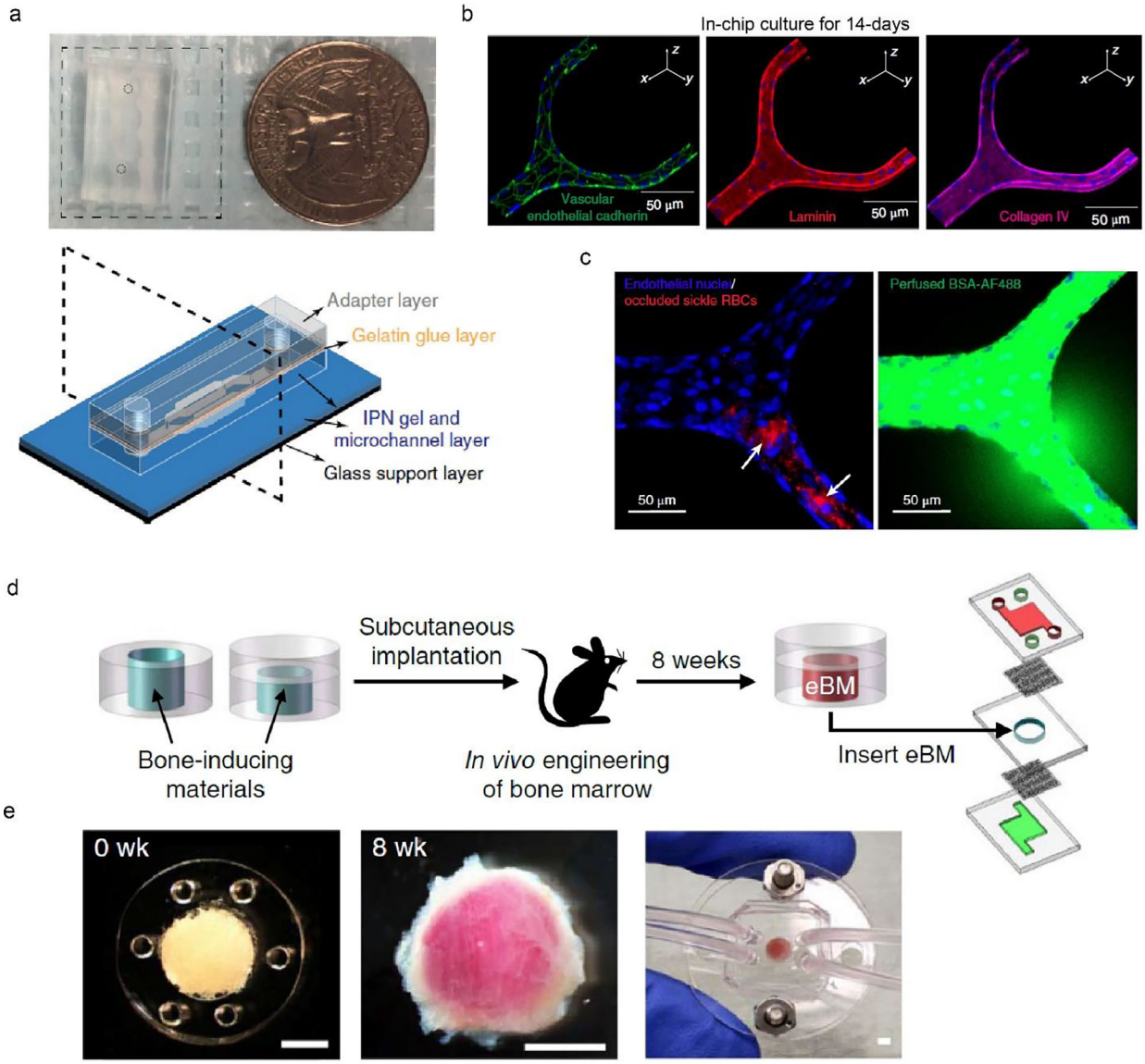

Fig. 2.

Two tissue chips for recapitulating the blood vessel and the bone marrow. **a**. Macroscopic view of a blood vessel chip, the size of which is compared with a quarter. Schematic of the tissue chip design, including glass support layer and several hydrogel layers. **b**. Immunostaining of endothelial cells after 14-day in-chip culture. **c**. Blockage of sickle RBCs in the engineered vessel leads to local leakage. **a-c**, Reproduced with permission (Qiu et al., 2018). Copyright 2018, Springer Nature. **d**. Schematic of a bone marrow chip using subcutaneous implantation for producing engineered bone marrow (eBM). **e**. Bone marrow tissues before (0 week) and after 8 weeks of implantation. The chip enables media perfusion and the delivery of biochemical cues. Scale bars, 2 mm. **d-e**, Reproduced with permission (Torisawa et al., 2014). Copyright 2014, Springer Nature.

Table 1.

Tissue chips for space exploration in the ISS (Tagle, 2022).

#	Targeted tissues & cells	Physiological pathways and diseases	Launch dates	Funding agencies
1	Brain, Liver, and Gut	Brain-liver-gut axis, aging	2022–2025	NASA NIH BARDA FDA
2	Brain	Neurotoxic stress		
3	Neurovasculature	Chronic inflammation and neurodegeneration		
4	Vessel	Atherosclerosis		
5	Multiple tissues	Human tissues to stressors		
6	Multiple tissues	Repair after hypoxia		
7	Heart, vascular tissues	Response to radiation exposure		
8	Kidney	Acute and chronic exposure to drugs and toxins		
9	Myocytes	Muscle wasting	Dec 2020	NCATS
10	Heart	Cardiomyopathy	Dec 2020	
11	Intestine	Bacterial infection	Mar 2020	
12	Cartilage-bone-synovium	Musculoskeletal disease	May 2019; Dec 2020	
13	Lung	Lung host defense	May 2019	
14	Blood-brian barrier	Microgravity effects	May 2019; Dec 2021	
15	Stem cells	Immunological senescence	Dec 2018	
16	Kidney	Proximal and distal tubule functions	May 2019; Jun 2021	
17	Human iPSC, heart	Cardiac dysfunction	Mar 2020	NCATS & NIBIB

NASA, National Aeronautics and Space Administration; NIH, National Institutes of Health; BARDA: Biomedical Advanced Research and Development Authority; FDA, Food and Drug Administration; NCATS, National Center for Advancing Translational Sciences; NIBIB, National Institute for Biomedical Imaging and Bioengineering.