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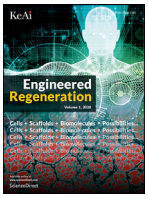

Cellular fluidic-based vascular networks for tissue engineering

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ABSTRACT

Artificial organs are devices implanted into the living body as a substitute for damaged or diseased organs. Current efforts focus on the construction of fully functionalized artificial tissues/organs with vascular networks. Although engineering efforts have been made in creating artificial vessels with simple or complex configurations, building vascular networks with hierarchical architectures approximating native counterparts remains challenging. Herein, we give a perspective of cellular fluidics-based construction of vascular networks for tissue engineering, with inspirations drawn from a novel concept of 3D fluidic control platform based on unit-cell constructs. Through architected design of the unit cells, it enables programmed control over gas-liquid-solid interfaces and fluid flow processes in open-cell structures. This cellular-fluidics concept and the associated platform provide lots of inspirations for constructing artificial vascular networks. We believe that cellular fluidics opens a new avenue for fluid control and deterministic delivery, and would find vast opportunities in tissue engineering.

Artificial organs are highly promising for the replacement of damaged or diseased organs since it exempts from the concerns of donor supply and severe immunoreactions during transplantation [1,2]. Researches in tissue engineering and organoids development are keeping moving towards this goal [3–8]. Although substantial progresses have been made, the construction of fully functionalized artificial tissues/organs is still challenging [9]. One of the major obstacles is the inadequate vascular networks [10,11]. Human organs have extremely rich and intricate vascularized networks with hierarchical structures, which perform the vital functions of oxygen and nutrients supply, waste removal, as well as signal transmission [2,12]. For example, pulmonary circulation relies on the vast vascular network for the exchange of oxygen and carbon dioxide in lung (**Fig. 1a**). A lack of vascular system in current artificial systems results in insufficient substance exchange and eventually accelerates apoptosis and tissue necrosis [13–16]. In view of this, engineering techniques have been employed to fabricate artificial vascular network aiming at fast and efficient vascularization of a variety of tissues and organs (**Fig. 1b**) [1,17]. However, systems approximating the structure and functions of native vascular networks remain elusive, probably due to both manufacturing complexity and the difficulties in fluid control.

Microfluidics is a technique enabling processing of small quantities of fluids in microchannels and precise manipulation of individual fluids and their interfaces [18,19]. Due to this feature, it has been widely used in the synthesis and development of materials with tunable shapes and structures [20,21]. Among them, hollow fibrous materials with well-controlled size and compartments show enormous potential in the construction of artificial vessels [22–25] (**Fig. 1c**). Besides, the derived artificial vessels possess biocompatibility and permeability ideal for gas and nutrients supply, which improves long-term cell viability [26–28]. Moreover, artificial vessels with complex spatial configurations could be generated by folding or waving the fibers, thereby achieving a higher proximity to real vessels [26] (**Fig. 1d**). Although great progress has been achieved, building artificial vascular networks with three-dimensional (3D) topologies (including hierarchical or network architectures) remains difficult. This greatly hinders the further development of vascularized tissues or organoids for regenerative applications. Therefore, it is highly desired to explore novel strategies of hierarchical fluid control imitating the vascular networks in real tissues.

Recently, Dudukovic and colleagues proposed a novel deterministic fluid control concept concept termed as “cellular fluidics” [29]. Inspired by the multiphase transport phenomenon widespread in and living systems (**Fig. 2a**), this work presented a 3D fluidic control platform based on unit-cell constructs. Different from conventional planar and enclosed microfluidics, the platform was made up of small cubic cells fabricated by 3D printing method. Through architected design of the unit cells, it enabled programmed control over gas-liquid-solid interfaces and fluid

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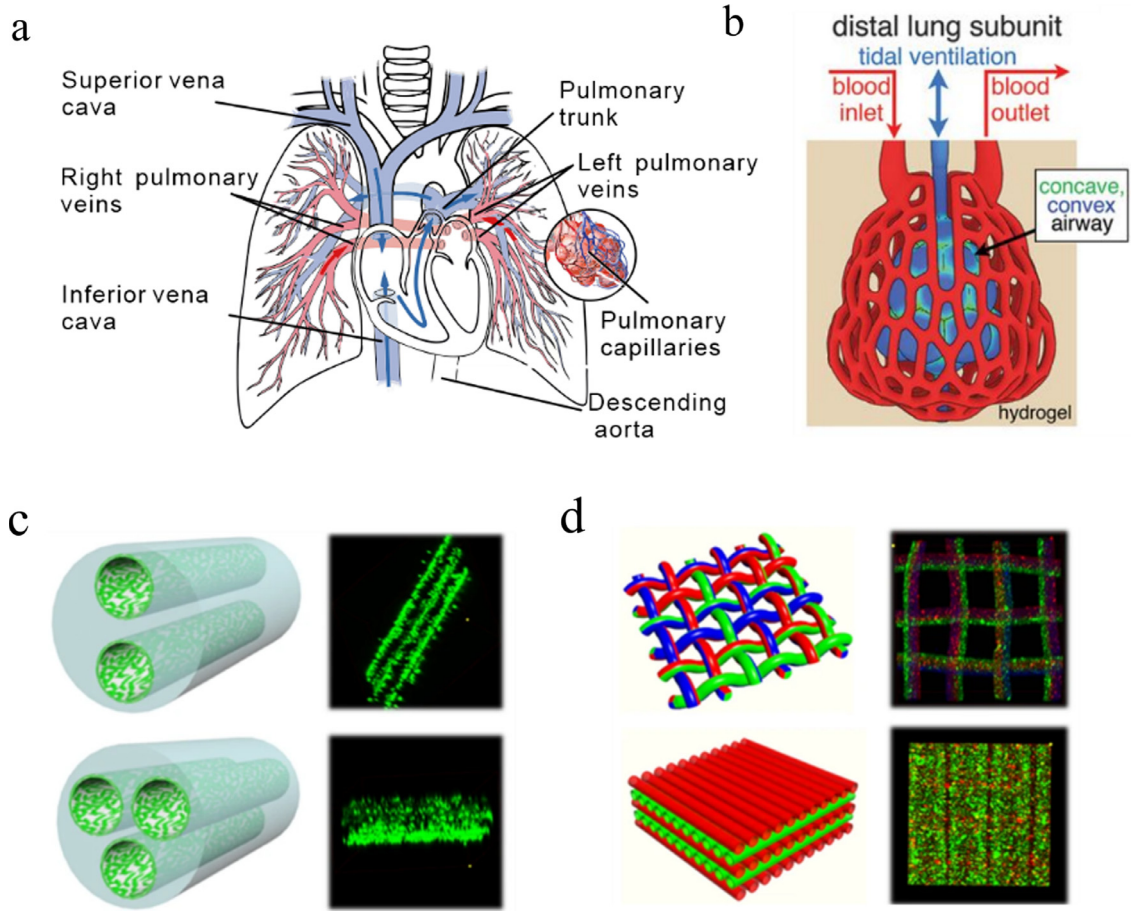

Fig. 1. (a) Schematic diagram of the pulmonary circulation, tree-like capillaries in lung that allows for gas exchange between the inhaled air and tissue; (b) schematic diagram of an example of engineered artificial vascular network; (c, d) schematic illustrations and the corresponding fluorescent images of (c) cell-laden single and (d) woven hollow microfibers. (b) Copyright 2005 The American Association for the Advancement of Science [1]. (c, d) Copyright 2021, Springer Nature [24].

flow processes in open-cell structures. By coupling analytical and numerical data with experimental demonstrations, it successfully achieved deterministic control of gas-liquid transport and flow paths in three dimensions. Besides, cellular-fluidics-based multiphase transport systems were exemplified through modelled transpiration and absorption processes using cellular fluidics with latticed structures. Moreover, potential applications were demonstrated including active continuous flow, preferential fluid pathway, transport across the interface, as well as the generation of multimaterial heterostructures.

Specifically, the design of this novel cellular fluidic system was quite simple. It consisted of lattices of body-centered-cubic cells arranged to form different geometries by microstereolithography. Under steady-state equilibrium conditions, fluid flow was analyzed by predicting the capillary rise in such open-cell system depending on the cell layout, which was further extended to the circumstance of a stacked column of cells (Fig. 2**b**). It was worth noting that the analytical predictions were consistent with the corresponding experimental data. Therefore, novel fluidic performances could be achieved through design of the cell parameters. Apart from that, under non-steady state, numerical simulations were performed to study the fluid dynamics by solving the Navier-Stokes equations. The computations on the ordered cellular fluidics could provide insights on those stochastic porous media systems. These findings suggested that the present cellular fluidics provides lots of inspirations for a broad range of applications involving multiphase processes, such as absorption, transpiration, mixing, extraction, deposition, reaction, etc.

Based on this, two typical multiphase flow processes, i.e., transpiration and absorption were further explored. A lattice cellular fluidic structure was first constructed with a tree-like topology to mimic the continuous transpiration in plants (Fig. 2**c**). It was found that when the lattice was immersed in a reservoir, water could be transported from the "root" to the "branches" and then evaporated, with the highest evaporation flux appearing at the branch tips. This suggested the application value of the branched cellular fluidic system in continuous liquid distribution and the construction of fluid delivery networks. For the modeling of absorption process, lattice structures were built that held liquid sorbent within so that gas could contact the sorbent directly. Benefiting from the high surface-to-volume ratio, such open-interface cellular fluidics could improve the absorption rate comparing to a liquid pool containing the same volume of sorbent. As for the demonstration of applications based on active flow, a series of printed structures were explored. By controlling the relative density and feature size of the cells, design of preferential liquid flow paths could be realized in 1D, 2D, and 3D (Fig. 2**d**) structures. These results showcased, by part, the vast application potentials of the cellular fluidic system, and indicated a lot of previously unobtainable design of fluid phenomena as well as novel materials.

Taken together, this work pioneered a novel, unit-cell-based 3D platform with deterministic multiphase fluidic flow behaviors. It not only provided a fundamental knowledge of capillary rise and fluid dynamics in open-cell structures, but also represented a giant leap forward to the design of complex fluid configurations with implications involving

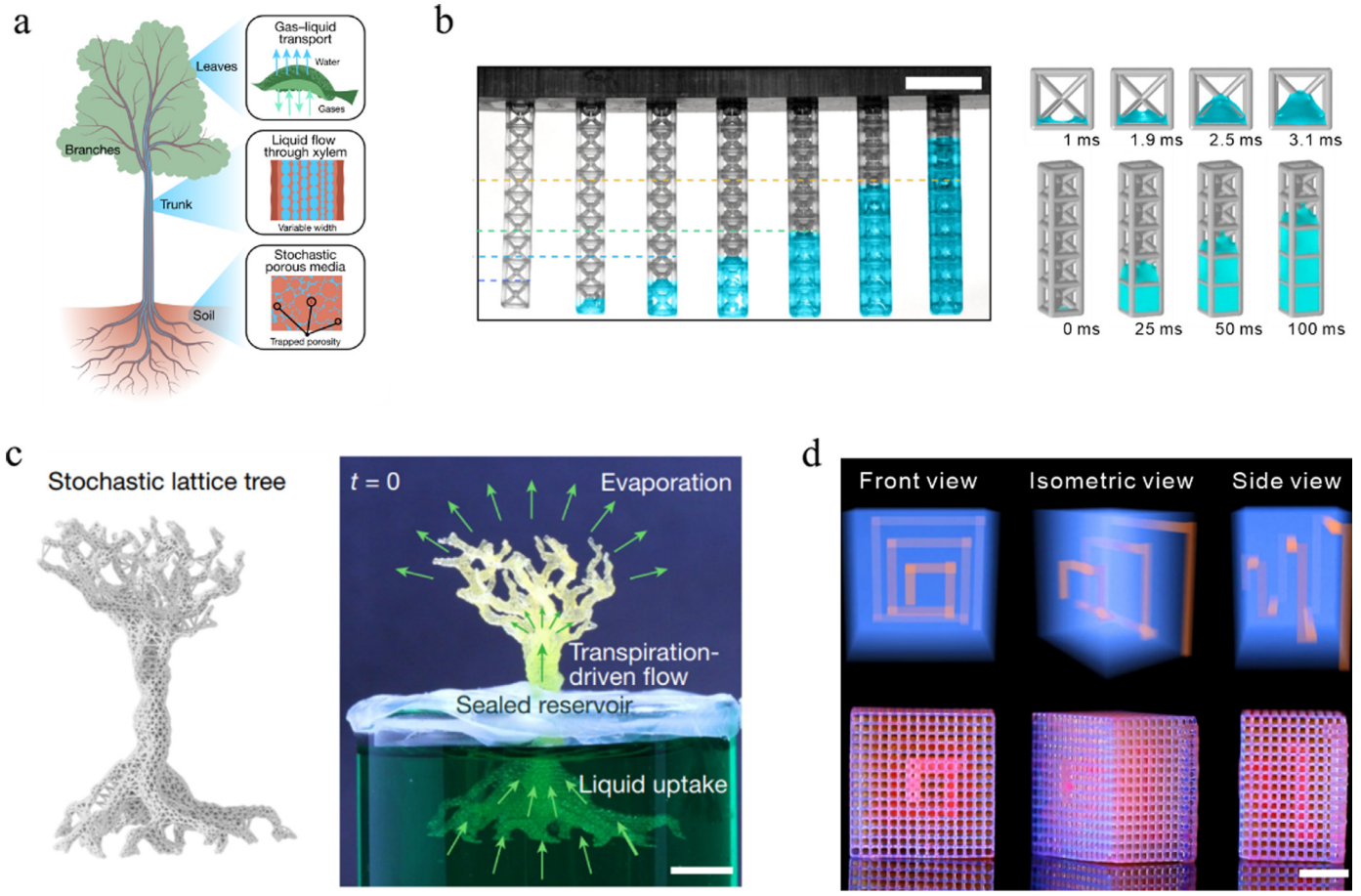

Fig. 2. (a) Water transport in plants; (b) numerical simulations of the (left panel) capillary rise as a function of the strut diameter of the cell and (right panel) dynamic process of the filling stages in single/stacked cells; (c) a branched structure composed of tetrahedral cells immersed in a sealed reservoir modeling transpiration; (d) design of a 3D liquid path achieved by controlling the strut diameter. (a-d) Copyright 2021, Springer Nature [29].

different areas. Of all the application potentials, the construction of artificial vascular networks is one of the most intriguing aspects. It could be anticipated that a branched cellular fluidic system capable of deep tissue penetration and distribution would go beyond the current systems and shed new light on regenerative medicine. As such, future endeavors can be made in developing materials that are not only printable but also have good biocompatibility, such as gelatin methacrylate (GelMa), hyaluronic acid (HA), and chitosan (CS)-based materials [30]. A concomitant question thus comes out concerning possibly different fluidic behaviors, which calls for further analytical and computation work, as well as experimental confirmations. Despite these challenges, we foresee that the concept of cell fluidics would find vast opportunities in biomedical researches. Through the integration of multidisciplinary efforts, construction of artificial organs or living systems could be realized and ultimately serve human healthcare.

Author statement

Luoran Shang conceived the idea; Chaoyu Yang wrote the manuscript; Yunru Yu, Xiaocheng Wang and Qiao Wang attended the scientific discussion.

Conflict of interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.engreg.2021.09.006.

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