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Organ regeneration based on developmental biology: past and future

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In this decade, great progress has been made in the field of organ regeneration by incorporating emerging concepts from the fields of stem cell biology and developmental biology, and this progress has pioneered a new frontier in regenerative medicine. The generation of bioengineered organ germ-utilizing, fate-determined, organ-inductive epithelial and mesenchymal cells has provided evidence for the concept of functional organ regeneration *in vivo*. Organoid studies have verified that nearly all organs can be generated in the form of a mini-organ by recapitulating embryonic body patterning and establishing an organ-forming field among self-organizing pluripotent stem cells by utilizing cytokines that mimic the patterning and positional signals of organogenesis. More recently, the regeneration of an integumentary organ system composed of multiple organs, including hair follicles, has been achieved, demonstrating that regenerative medicine is forthcoming. In this review, we will introduce current research trends aimed at regenerating a functional three-dimensional (3D) organ, and we will discuss the potential use of these recent achievements and future directions needed to realize the next-generation of regenerative therapy for organ replacement.

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Introduction

Organogenesis is a complex process involving tissue self-organization, cell–cell interactions, the regulation of signaling molecules, and cell movement in each organ-forming field according to the embryonic body plan. Nearly all organs arise from organ germs, which are induced by reciprocal interactions between organ-inductive potential stem cells in the embryonic epithelium and mesenchyme within each organ-forming field (Figure 1) [1,2]. The organ germ then develops an organ-specific morphology and function through differentiation and morphogenesis [1,3,4]. During organogenesis, organ-inductive potential stem cells produce a wide variety of cell types and adult tissue-specific stem cells that maintain tissue homeostasis and tissue repair following birth [5]. Thorough these steps, various organs are generated, and with the exception of hair follicles, organogenesis ceases after birth [6–9].

In this review, we will provide an overview of recent studies on organ regeneration from various stem cell populations using strategies inspired by developmental biology and will discuss the future directions of organ regeneration for the next-generation of organ regenerative therapy.

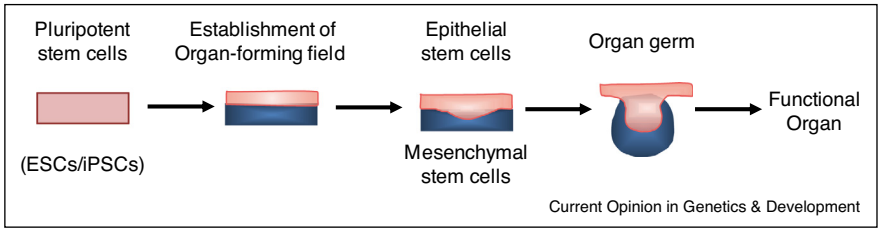
Multiple strategies towards organ regeneration

Organ regeneration has been attempted for decades by combining functional cells, scaffold materials, and physiologically active substances using tissue engineering techniques [10,11]. However, considerable concerns exist in these studies, primarily due to the lack of the incorporation of the concept of stem cells and regenerated organs were incapable of sustain proper cell–cell interaction, which is essential for a functional organ. In this decade, recent advances in developmental biology and stem cell biology have led to breakthroughs in the regeneration of functional organs *in vivo*.

Based on knowledge from developmental biology, a novel method for 3D organ-inductive stem cell manipulation was developed in 2007 that allowed us to generate bioengineered organ germs (Figure 2). This groundbreaking study demonstrated that bioengineered organ germs that were generated by fate-determined epithelial and mesenchymal cells isolated from an organ germ in an embryo can develop *in vitro* [12]. A series of studies using this method demonstrated the regeneration of fully functional organs *in vivo*, proving the concept of functional organ regeneration by mimicking the processes of organogenesis (Figure 2) [12–18].

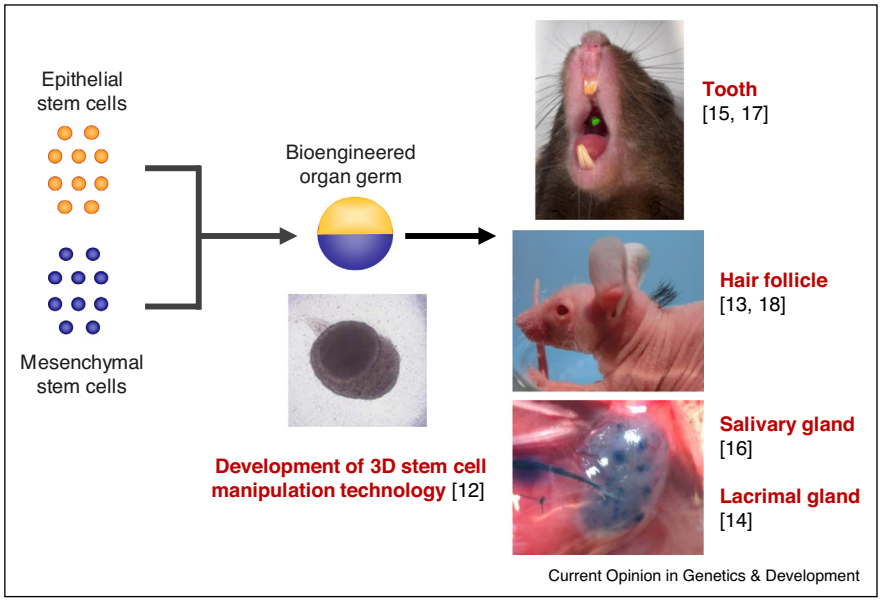
The next breakthrough was the emergence of an organoid as a mini-organ that was generated by inducing body patterning and a subsequent organ-forming field from pluripotent stem cells. The first report appeared in 2008, and it showed the self-organizing formation of

Figure 1



Schematic illustration of organogenesis. Organogenesis occurs through complex signals according to embryonic body patterns. Following the establishment of an organ-forming field, organogenesis begins, and an organ germ is generated via reciprocal interactions between fate-determined and organ-inductive epithelial cells and mesenchymal cells. Through morphogenesis, the organ germ differentiates into individual organs with specific structures and functions.

Figure 2



Proof-of-concept for functional organ regeneration by the organ germ method using organ inductive stem cells. The organ germ method is a new technology to spatially arrange organ-inductive epithelial stem cells and mesenchymal stem cells, allowing them to mimic the process of embryonic organ germ formation through self-assembly, self-organization, and epithelial-mesenchymal interactions. Bioengineered organ germs and immature organs developed *in vitro* from bioengineered organ germs showed functional organ regeneration following orthotopic transplantation.

apico-basally polarized cortical tissues from mouse ES cells [19]. In 2009, another impressive work showed the generation of intestinal crypt-villus units, which included both stem cells and their niche, from a single adult intestinal stem cell in a self-organized manner [20]. To date, many research groups have successfully generated multiple types of organoids, including the retina, pituitary gland, thymus, and lung (Figure 3). These studies verify the concept that a partially functional mini-organ can be generated by inducing body pattern formation from pluripotent stem cells.

The coordinated function of multiple organs, which is called an organ system, such as the central nervous system, circulatory systems, digestive systems, and integumentary organ system (IOS), is vital to sustaining homeostasis in an organism [21]. In 2016, the regeneration of an organ system was achieved using an *in vivo* transplantation model, which can recapitulate nutrient and oxygen supplies for 3D complex organ systems *in vivo*, as an incubator based on the strategy to develop organoids, making great strides toward the realization of regenerative therapy [22••]. This work successfully generated a bioengineered 3D IOS, including appendage organs, such as hair follicles and sebaceous glands (Figure 4). This bioengineered IOS was fully functional *in vivo*, clearly demonstrating the feasibility of regenerating a functional 3D organ system by applying knowledge from embryonic development.