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REVIEW

Organ Repair and Regeneration: An Overview

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A number of organs have the intrinsic ability to regenerate, a distinctive feature that varies among organisms. Organ regeneration is a process not fully yet understood. However, when its underlying mechanisms are unraveled, it holds tremendous therapeutic potential for humans. In this review, we chose to summarize the repair and regenerative potential of the following organs and organ systems: thymus, adrenal gland, thyroid gland, intestine, lungs, heart, liver, blood vessels, germ cells, nervous system, eye tissues, hair cells, kidney and bladder, skin, hair follicles, pancreas, bone, and cartilage. For each organ, a review of the following is presented: (a) factors, pathways, and cells that are involved in the organ's intrinsic regenerative ability, (b) contribution of exogenous cells – such as progenitor cells, embryonic stem cells, induced pluripotent stem cells, and bone marrow-, adipose- and umbilical cord blood-derived stem cells – in repairing and regenerating organs in the absence of an innate intrinsic regenerative capability, (c) and the progress made in engineering bio-artificial scaffolds, tissues, and organs. Organ regeneration is a promising therapy that can alleviate humans from diseases that have not been yet cured. It is also superior to already existing treatments that utilize exogenous sources to substitute for the organ's lost structure and/or function(s). **Birth Defects Research (Part C) 96:1–29, 2012.** © 2012 Wiley Periodicals, Inc.

Key words: organ repair; organ regeneration

INTRODUCTION

In this review, we present the regenerative and reparative capabilities of different organs. To help us distinguish between the two processes, we have set up specific guidelines. In order for a tissue ''recovery'' process to be classified as regeneration, the following requirements need to be met: (a) first, the experiment needs to demonstrate that the organ is significantly damaged (e.g., agents, diseases), or partially or completely removed (e.g., surgery), (b) the study needs to show that the organ is completely regenerated – in the sense that at least most of the organ's original cell types have been renewed and have successfully regained their function – using markers for cell proliferation and differentiation, tracking techniques (e.g., transgenic using cre-loxP system), and physiological tests (e.g., gas/nutrient transport), and (c) studies that make use of induced pluripotent stem cells (iPSC), embryonic stem cells (ESC), and mesenchymal stem cells need to further show that tumors do not appear following the completion of the experiment (the reason for that being that homeostasis signals that promote repair have been shown to induce the formation of a tumor from these cells). When these criteria are met, then the damaged organ has regenerated. As for organ repair, it is characterized by: (a) epithelial proliferation, and restitution of the injury site, and (b) fibrosis and extracellular matrix deposition. In many of the studies we have reviewed, we noted that the authors have not made it clear whether the regenerated/repaired organ is fully functional, or whether all the cell types have been indeed regenerated/renewed – two missing important criteria that were reflected in our decision to treat the study as either a case of organ regeneration or repair. In these regards, we have chosen a number of major organs that play key roles in physiology and homeostasis of the human body (e.g., lung, heart), glands that secrete hormones that affect gene expression throughout the body (e.g., thyroid), and large body parts in which the process of pattern formation is recapitulated (e.g., limbs).

In addition to studying the intrinsic regenerative and repair capabilities of organs, we also aim to introduce the readers to novel therapeutic strategies and tissue engineering techniques that are currently being tested/used to aid the organs in their recovery process following injury. Furthermore, a brief overview of clinical trials, if any, is presented in each of the organ's section. In the end, we hope to have addressed a great deal of the most current studies on this topic, as well as some of the excellent reviews, and we do apologize for not being

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able to take into account the entirety of the publications on organ regeneration and repair.

THYMUS

Thymus is part of the lymphoid system and its function is directly related to the immune system. It is composed of the external capsule, the cortex, and medulla. Immature T cells migrate from the bone marrow (BM) to the thymus where they differentiate into naive T cells that play a key role in immunity. The differentiation process involves a series of selections via dendritic and mesenchymal cells. Thymus has the ability to regenerate. However, thymus loses its structure, function, and regenerative capability with age, resulting in atrophy. In addition, diseases, chemicals, clinical treatments, and radiation can play a role in the involution of this organ. When the thymus and/or BM seize to function properly, they result in a weakened immune system which mostly affects elderly people. Similarly, a weakened immune system is observed in BM transplant receivers. These patients are susceptible to serious diseases – including virus infections of the cytomegalovirus and Epstein–Barr virus – during a period of 6 months post-transplantation, the time required for immature T cells to mature. In these regards, a review on thymus can take on two pathways: one that focuses on the potential of thymus regeneration and the other on the potential of mature T cells production (Taub and Longo, 2005; Zhang et al., 2007; Gordon and Manley, 2011).

Young animal models have shown great regenerative potential of the thymus. Thus, the thymus of young animals has been adopted as a model for ex vivo production of mature T cells. Moreover, experiments in beef cattle have shown that the thymus is regenerated following a treatment with a chemical that damages it. However, this regenerative potential, as well as the organ's function, are lost with age (Cannizzo et al., 2010). Partial repair of the damaged parts of the thymus can be achieved by progenitor cells from the cortex and the medulla, or by the intrinsic ability of the epithelial cells of the thymus to proliferate (Gill et al., 2002; Rossi et al., 2006). Studies show that one thymic progenitor cell can reconstruct a functional thymus in mice (Bleul et al., 2006). Additional studies in animals have demonstrated that a functional thymus can be regenerated after transplantation of thymic parts (Hong et al., 1979; Waer et al., 1990; Barry et al., 1991; Kamano et al., 2004). Thymus transplantation has also been attempted in infants with DiGeorge Syndrome (Markert et al., 2003). Another interesting aspect is the effect of sex steroids in damaging thymus and/or BM. Experiments have shown that when sex steroids are inhibited (by gonadectomy or other inhibitors), thymus' function is improved (Greenstein et al., 1986; Greenstein et al., 1992; Goldberg et al., 2005; Heng et al., 2005; Sutherland et al., 2005). Conversely, treatment with testosterone inhibits thymus' repair (Greenstein et al., 1986).

Numerous studies in this field focus on the second aspect – T cell reconstitution in blood (Barthlott et al., 2007; Chidgey et al., 2007). In this respect, researchers have tried the following: induction of T cell production with different molecules (Alpdogan et al., 2001; Chadwick et al., 2003; Lu et al., 2005), in vitro models, ex vivo thymus-xenografts (Schmitt and Zuniga-Pflucker, 2002), and T cell transferring (Zakrzewski et al., 2006) [for reviews see, van den Brink et al. (2004), Taub and Longo (2005), and Legrand et al. (2007)]. In vitro cultures and ex vivo xenografts of humanized models, which have been extensively studied, use mostly fetal mice thymus. These models, although expensive, are widely used to coax T cells into maturation (Legrand et al., 2007).

ADRENAL GLAND

The adrenal gland is comprised of two areas: the cortex and the medulla. The cortex is composed of four different zones (from capsule to medulla: zona glomerulosa, zona intermedia, zona fasciculata, and zona reticularis) which serve different functions mainly by synthesizing different hormones. The secreted hormones can influence various responses, mostly stress-related. In response to stress, the hypothalamus regulates the secretion of aldosterone (zona glomerulosa) and corticosterone (zona fasciculata and zona reticularis) from the cortex. In parallel, the medulla secretes epinephrine and norepinephrine. It is, therefore, crucial that regeneration restores both the structure and function of the adrenal gland following injury.

Although the medulla does not have the intrinsic ability to regenerate, the cortex can regenerate after injury. Cortex regeneration is achieved by the dedifferentiation, proliferation, and redifferentiation of the remaining cells in the cortex and/or from the stem cells present in the zona glumerolosa (Taki and Nickerson, 1985; Engeland et al., 1996; Mitani et al., 2003). Adrenocorticotropic hormone and pro-gamma-melanocyte-stimulating hormone seem to play a crucial role in adrenal cortex regeneration. After complete removal of one of the two adrenal glands, the remaining gland grows through interactions with the ventromedial hypothalamus to compensate for the lost gland. This process, called compensatory adrenal growth, is mediated by steroidogenic factor-1 (SF-1), a transcriptional factor that is related to the proliferation of residual progenitor cells (Ikeda et al., 1995; Dellovade et al., 2000; Beuschlein et al., 2002). Studies have shown that pro-gamma-melanocyte-stimulating hormone can be involved in the regulation of compensatory adrenal growth (Lowry et al., 1983), and could be controlled by SF-1 (Bland et al., 2003).

Many peptides and neuropeptides have been found to control the growth and regeneration of the adrenal cortex. Neuromedin-U can aid regeneration after adrenalectomy (Trejter et al., 2008). Also,

beacon (Ziolkowska et al., 2006), galanin (Hochol et al., 2000), orexin (Spinazzi et al., 2006), and arginine–vasopressin (Trejter et al., 2005) can positively control growth through stimulation of proliferation of residual cells in the adrenal gland. Conversely, leptin (Markowska et al., 2004) and enkephalin (Malendowicz et al., 2005) can negatively control growth.

Mutations in *SF-1* (Achermann et al., 1999) and *Dax1* are commonly related to problems associated with the adrenal gland. Dysregulation of the adrenocorticotropic hormone can lead to problems in hormone production and secretion (Babu et al., 2002). Patients that have dysfunctional adrenal cortex are treated with exogenous glucocorticoids. ESC expressing *SF-1* have also been used in an attempt to regenerate the adrenal gland in experimental models, with promising results for human trials (Yanase et al., 2003). In addition, transplantation studies have proved promising in regards to the regeneration of a fully functional adrenal gland (Allende et al., 2001).

THYROID GLAND

The thyroid gland consists of follicles and specialized cells called thyrocytes. Thyrocytes have a basal-lumen (apical) polarity which aids in their function of transporting hormones in and out of the gland. The thyroid gland secretes thyroid hormones for homeostatic regulation, such as the regulation of blood pressure, metabolic activities, and development. The thyroid stimulating hormone secreted by the anterior pituitary gland regulates the secretion of the thyroid hormones triiodothyronine and thyroxine. Disruption of this hormone balance can lead to Graves and goiter diseases that result in hyperthyroidism and hypothyroidism, respectively.

One model used for studying thyroid folliculogenesis in vitro is three-dimensional (3D) cultures using collagen (Toda et al., 2001). This model has been used to test for different factors and the role they play in thyroid regeneration. Subacute thyroiditis is a human disease that destroys follicles. Follicles regenerate continuously, thus, making subacute thyroiditis a suitable model for studying thyroid folliculogenesis. Factors identified from biopsies of human patients with subacute thyroiditis have been evaluated using the 3D collagen culture model. A number of growth factors [vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β 1, epidermal growth factor (EGF), hepatocyte growth factor (HGF)] (Westermark et al., 1991; Nilsson et al., 1995; Toda et al., 1997, 1999) and other factors that contribute to apoptosis (Koga et al., 1999) have been identified to play a role in folliculogenesis.

Regeneration of the thyroid has been reported with the contribution of the following cells: stem cells, ESC, and bone marrow-derived mesenchymal stem cells (BMMSC). Recently, stem cells residing in the thyroid (Thomas et al., 2006; Hoshi et al., 2007; Lan et al., 2007) have been coaxed to acquire a thyroid fate to contribute to thyroid regeneration (Lan et al., 2007). In addition, in vivo studies have shown that CD24 is essential for thyroid regeneration in autoimmune thyroiditis (Chen et al., 2009a). Furthermore, ESC were used and their fate committed to becoming thyrocytes (Lin et al., 2003). It is important to note, though, that thyroid stem cells have been associated in some cases with cancer formation in the thyroid (Gibelli et al., 2009). Finally, through the use of green fluorescent protein mice grafts to wild type, BMMSC were found to contribute to thyroid regeneration (Mikhailov et al., 2011).

INTESTINE

The intestine is the organ through which various nutrients and other solutes are transported to the rest of the body. To serve this role, the intestine is comprised of epithelial cells and subepithelial myofibroblasts. Epithelial cells are of two types – the mature epithelial cells present in the villi in contact with the gastrointestinal tract and are responsible for nutrient transport and defense, and the stem cells residing in the crypt. Subepithelial myofibroblasts can interact with various processes of the overlaying epithelial cells. The acquisition of nutrients requires that the gastrointestinal tract be in contact with the external environment. The intestine is, therefore, exposed to various pathological agents from which the organ ought to protect itself and the organism. Two of the intestine defense mechanisms include a tight epithelial barrier, and the secretion of large amounts of glycoproteins that form the mucin.

The intestine possesses a very high turnover rate which aids in the organ's regenerative capability following injury (Podolsky, 1999). Stem cells, located in a stem cell niche inside the crypt, have the ability to rapidly proliferate and can differentiate into all the cell types of the intestine wall. These differentiated cells include different types of epithelial cells (columnar, mucin-secreting, endocrine, and Paneth) and myofibroblasts. Following injury, the epithelial cells that are near the injury site restitute and form a barrier (Feil et al., 1989). Subsequently, signaling pathways including those involving fibroblast growth factor (FGF) (Itoh et al., 2000), Wnt (Pinto et al., 2003; Kuhnert et al., 2004), bone morphogenetic protein (BMP) (Haramis et al., 2004; He et al., 2004; Ishizuya-Oka and Hasebe, 2008), and Sonic Hedgehog (Shh) and Indian Hedgehog (Ishizuya-Oka and Hasebe, 2008; van Dop et al., 2010) are enabled to stimulate the proliferation and differentiation of the intestine stem cells of the crypt.

A number of studies have reported gene regulation as well as the effect of different molecules on the regeneration and repair of the intestine. These include repair roles of bombesin, neurotensin

(Alexandris et al., 2004), and lecopene (Saada et al., 2010) in oxidative stress protection, tadalafil in iscemic anastomosis (Kaya et al., 2010), interleukin-11 in necrotizing enterocolitis animal models (Dickinson et al., 2000), carnitine in reperfusion (Hosgorler et al., 2010), bael (aegle marmelos, AME) after irradiation (Jagetia et al., 2006), and anabolic steroids (Ishihara et al., 2011). In addition, BMMSC can repopulate the intestine. Studies in humans with sex-mismatched BM transplants show that BMMSC are found in the intestine and contribute to the turnover and/or repair of the organ (Brittan et al., 2002; Okamoto et al., 2002; Matsumoto et al., 2005). Recently, human pluripotent stem cells have been successfully differentiated into the intestine's major cell types in vitro composing an intestine tissue (Spence et al., 2011).

Transplantation studies and tissue engineering pursuits hold great promise for the intestine regeneration and the de novo reconstruction of the intestinal wall. Scaffold-free cells (Hori et al., 2001) and scaffolds seeded with intestinal epithelial cells (Choi et al., 1998), Mesenchymal Stem Cells (MSC) (Hori et al., 2002), and smooth muscle cells (Nakase et al., 2007) have been designed to simulate the balanced cellular environment of the intestine. In pigs, Sala et al. (2009) were able to utilize a biodegradable scaffold and autologous organoid units to construct an intestine.

LUNGS

The lung is the organ responsible for gas exchange. Incoming air from the trachea passes through the bronchi and bronchioles to the alveoli, where gas exchange occurs. This branching results in the very large surface area of the lungs which enables the effective exchange of gas. Lungs are made of different types of cells that play critical roles in scaffolding, defense against microbes, damage repair, and certainly in gas exchange.

Many studies today focus mostly on stem and progenitor cell research. These studies have identified several areas of cells with proliferating capabilities. The first evidence for the presence of progenitor cells in lungs emerged as the result of a study in which rats were exposed to nitric oxide or ozone, and proliferating cells were labeled with tritiated thymidine. These labeled cells, the nonciliated Clara cells, were later identified as precursor progenitor cells of ciliated cells (Evans et al., 1976). In the years following this study, novel tracing methods, and methods to induce and simulate lung injury have been improved. These techniques allowed the identification of specific sites in different areas of the lungs as stem cell niches. These sites are capable of regenerating parts of the damaged lungs. Treatment with naphthalene has led to the depletion of Clara cells which helped detect new sources of progenitor cells. In lungs, neuroepithelial bodies function as progenitor cells capable of regenerating proximal bronchiolar epithelium (Reynolds et al., 2000) containing Clara cell secretory-expressing cells (Hong et al., 2001). Progenitor cells from the bronchoalveolar duct junction, also called bronchioalveolar stem cells (Kim et al., 2005a), contribute to the terminal bronchiolar regeneration of the epithelium (Giangreco et al., 2002). Today, several studies aim to identify which stem cells contribute to the regeneration of which tissue, and more specifically to which cell type of the tissue. In these regards, Clara cells expressing the Scgb1a1 marker were found to contribute to bronchioli repair, but not to alveoli repair (Rawlins et al., 2009). However, recent studies have demonstrated that bronchioalveolar stem cells slightly contributed to alveoli epithelial cell repair (Nolen-Walston et al., 2008), that p63+ Krt5+ basal-like cells can regenerate alveoli structures (Kumar et al., 2011), and that cytokeratin14-expressing basal cells are capable of restoring bronchiole epithelium (Hong et al., 2004). Other factors have also been found to play a role in lung repair; these include Wnt pathway through Gata6 (Zhang et al., 2008b), matrix metalloprotease14 expression and EGF, VEGF signaling (Ding et al., 2011), HGF through Smad7 (Shukla et al., 2009), and extracellular matrix (Hoffman et al., 2010), including tenascin C (Snyder et al., 2009). More recently, additional molecules and signaling pathways have been extensively reviewed (Crosby and Waters, 2010).

BMMSC and umbilical cord blood-derived mesenchymal stem cells (UCBMSC) also contribute to lung repair. Green fluorescent protein, lacZ, or sex-mismatched BM transplants or injections of BM cells have been commonly used for tracing. BMMSC contribute to lung epithelial (Theise et al., 2002; Kleeberger et al., 2003; Suratt et al., 2003; Mattsson et al., 2004; Kahler et al., 2007) and endothelial cells (Yan et al., 2007b) repair, by regenerating a variety of cell types including the alveoli type II epithelial cells, also known as alveoli progenitor cells (Yan et al., 2007a). The engraftment of BMMSC can be mediated by CXCL12 (Gomperts et al., 2006). Improved colonization of BMMSC to the lung can be achieved with all-trans retinoic acid, and granulocyte colony-stimulating factor (G-CSF) (Aliotta et al., 2006; Ishizawa et al., 2004). BMMSC have also been used to improve survival of animal models after *Escherichia coli* endotoxin treatment, by reducing inflammation (Gupta et al., 2007) and restoring fluid balance in the lungs (Lee et al., 2009). Furthermore, BMMSC contributed to lung repair after *E. coli* (Serikov et al., 2008) and *Streptococcus pneumoniae*- (Suzuki et al., 2008a) induced pneumonia, and also to the improvement of hyperoxia or bronchopulmonary dysplasia (Aslam et al., 2009; van Haaften et al., 2009), allergic reactions by inhibiting Th2 pathway (Goodwin et al., 2011), pulmonary emphysema induced by papain (Zhen et al., 2008), and lipopolysaccharide-induced injury by components of bacterial wall (Yamada et al., 2004). BMMSC also contribute to the repair of bleomycin-induced injury (inflammation and fibrosis) (Kotton et al., 2001) by reducing fibrosis (Ortiz et al., 2003), increasing G-CSF and granulocyte-macrophage colony-stimulating factor

(Rojas et al., 2005), reducing nitric oxide (Lee et al., 2010), and reducing inflammation cytokines (Lee et al., 2010; Rojas et al., 2005). The ability of BMMSC to incorporate into the lungs has been recently used as a tool for gene therapy. BMMSC transfected with cystic fibrosis transmembrane conductance regulator can help on cystic fibrosis (Wang et al., 2005), and those transfected with angiopoietin-1 can help on lipopolysaccharide-induced injury (Mei et al., 2007; Xu et al., 2008a). As for human UCBMSC, they have been used in animal models to help on hyperoxia (Chang et al., 2009) and repair of the lung epithelium (Sueblinvong et al., 2008). In one case, a patient with systemic lupus erythematosus had her condition improved after transplantation of UCBMSC (Liang et al., 2010). ESC have also been used in lung repair and have been differentiated to alveoli type I (Rippon et al., 2004) and type II epithelial cells, and nonciliated secretory Clara cells (Coraux et al., 2005). In addition, the use of ESC resulted in increased survival (Wang et al., 2010a) and reduced fibrosis (Moodley et al., 2009) in bleomycin-induced lung injury animal models.

Using biomaterial scaffolds, scientists have also successfully created lung tissue in vitro (Mondrinos et al., 2007), alveolar tissues both in vitro and in vivo (Cortiella et al., 2006), bronchioles (Miller et al., 2010), and lungs (Ott et al., 2010; Petersen et al., 2010; Beronja and Fuchs, 2011) that were both transiently functional in vivo. These scaffolds, in addition to FGF2, improved vascularization in vivo (Mondrinos et al., 2008). In humans, transplantation of matrix with trachea donor cells have successfully replaced the left bronchus (Macchiarini et al., 2008). Tissue engineering is promising for trachea regeneration. Patients in need of a trachea resection can have their trachea reconstructed using Marlex mesh scaffold with collagen sponge (Omori et al., 2005; Omori et al., 2008). In addition, different types of scaffolds seeded with different types of cells have been used in animal models to efficiently engineer a functional trachea. Scaffolds seeded with epithelial cells (Nomoto et al., 2006), adipose-derived stem cells (Suzuki et al., 2008b) with gingival fibroblasts (Kobayashi et al., 2010), MSC co-cultured with lung tissue (Le Visage et al., 2004), BMMSC (Liu et al., 2010), chondrocytes with b-FGF (Komura et al., 2008) or fibrin and hyaluronic acid (Kim et al., 2010), or epithelial and mesenchymal-derived stem cells (Go et al., 2010), as well as scaffold-free autologous or auricular chondrocytes (Gilpin et al., 2010; Weidenbecher et al., 2008) have all been used for the regeneration of the trachea.

HEART

The heart is the organ responsible for the body's blood and oxygen supply. The human heart is divided into four chambers and is contained in a fluid filled sac, called the pericardium, within the chest cavity. Together with the circulatory system, the heart forms the cardiovascular system. The cardiac muscular tissue is composed of specialized cells called cardiac myocytes or cardiomyocytes (CMs). A deficiency in CMs typically results in heart failure, a major cause of death worldwide every year. Two to four billion CMs constitute the human left ventricle: some are slowly killed over the years by hypertension and cardiac overload disorders, 25% are usually destroyed in the few hours following a myocardial infarction, and about 20 million per year are lost due to ageing [as reviewed by Laflamme and Murry (2011)].

Being one of the least regenerative organs, the heart with its innate ability to regenerate has been extensively reported in amphibians (Oberpriller and Oberpriller, 1974) and fish, and only recently in developing mammals (Laflamme and Murry, 2011). Experimentally, heart response to injury has been reported following induced injury to the organ using mechanical, chemical, and biological means from stabbing and snipping to toxin injection and infection. Typically, mammalian hearts respond to injury by scarring, whereby the damaged cardiac muscle is replaced by fibrotic scar tissue. Nonetheless, regeneration of the heart is possible, and the zebrafish is one example of particular importance due to the animal's ability to regenerate approximately 20% of its resected ventricular mass 2 months following heart injury (Poss et al., 2002; Laflamme and Murry, 2011). Initially, a population of progenitor cells was thought to be solely responsible for heart regeneration in zebrafsh by contributing CMs with increased mitotic capability (Lepilina et al., 2006). However, two subsequent studies using genetic fate-mapping techniques demonstrated that pre-existing committed CMs are the major contributors to cardiac regeneration in zebrafish (Jopling et al., 2010; Kikuchi et al., 2010). Furthermore, these studies established the critical role of the embryonic cardiogenesis gene, *gata4* (Kikuchi et al., 2010), and the cell cycle regulator, polo-like kinase (*plk1*) (Jopling et al., 2010), during heart regeneration in zebrafish. This innate ability to regenerate injured or lost cardiac tissue does not, however, seem to occur in mammals. Studies have shown that mammalian CMs rapidly proliferate during fetal life, as well as in one-day-old neonatal mice (Porrello et al., 2011), but noticeably decrease their proliferation activity after birth. Thus far, extremely low levels of CM activity have been reported in postnatal mammalian hearts during normal ageing and disease without any meaningful regeneration of cardiac tissue (Soonpaa and Field, 1997, 1998). Similarly with humans, heart regeneration at the macroscopic level has not been detected yet, and only limited to very slow CMs replacement has been reported in human hearts after birth (Macmahon, 1937; Beltrami et al., 2001). Most human CMs seem to undergo DNA synthesis without nuclear division (Bergmann et al., 2009; Kajstura et al.; 2010; Bergmann et al., 2011). Therefore, and

as previously mentioned, injured human hearts respond to injury by scar formation and fibrotic deposition (Mummery and Passier, 2011).

Efforts to overcome the restricted proliferation of adult CMs include the over-expression of cell cycle activators and mitogens (such as neuregulin1, FGFs, cyclin D2, and periostins) (Pasumarthi et al., 2005; Engel et al., 2006; Kuhn et al., 2007; Hassink et al., 2008; Bersell et al., 2009; Lorts et al., 2009) [for a comprehensive review see Ahuja et al. (2007)]. To date, only a few proteins have also been shown to induce sustained ventricular CM cell cycle activity when expressed in adult transgenic animals. These include simian virus 40 Large T antigen (Katz et al., 1992), an inducible form of c-myc (Xiao et al., 2001), cyclin-dependent kinase 2 (Liao et al., 2001), tuberous sclerosis complex 2 (Pasumarthi et al., 2000), p53 and p193 (Nakajima et al., 2004), cyclin A2 (Chaudhry et al., 2004), insulin-like growth factor (IGF)-1 (Reiss et al., 1996), and bcl-2 (Limana et al., 2002).

Apart from studying CM proliferation and renewal from pre-existing CMs, recent studies have focused on CMs derived from progenitor cells (Hsieh et al., 2007). C-kit-positive CD45-negative cardiac progenitor cells have been shown to contribute to the formation of new myocardium and vessels following cardiac injury (Bearzi et al., 2007; Kubo et al., 2008; Tallini et al., 2009; Sandstedt et al., 2010; Tang et al., 2010). Numerous studies argue about the potential of transplanted cardiosphere-derived cells (Smith et al., 2007) to contribute to the enhanced cardiac function following infarction (Messina et al., 2004; Andersen et al., 2009; Chimenti et al., 2010). Additionally, bone marrow-derived cells were shown to play a role in cardiac repair, both directly (Orlic et al., 2001a, b, c; Toma et al., 2002; Chen et al., 2004; Hare et al., 2009; Maltais et al.; 2011) and indirectly through signals and molecules (Balsam et al., 2004; Murry et al., 2004; Mirotsou et al., 2007; Hatzistergos et al., 2010). Furthermore, CMs derived from human iPSC (Laflamme et al., 2007; Xu et al., 2008b; Yang et al., 2008; Zhang et al., 2009; Zwi et al., 2009; Zhu et al., 2010) and ESC (Laflamme et al., 2007; Xu et al., 2008b; Yang et al., 2008; Zhang et al., 2009; Zwi et al., 2009; Zhu et al., 2010) have been reported to improve myocardial performance following cardiac injury (Caspi et al., 2007a; Fernandes et al., 2010), but in some cases to be incapable of restoring heart function (Caspi et al., 2007a; Fernandes et al., 2010). Cellular reprogramming has also been adopted as an alternative avenue for cardiac repair. Reprogramming of mouse embryonic fibroblasts to CMs has been performed by Efe and coworkers (Efe et al., 2011).

Finally, tissue engineered scaffolds for cardiac therapy has emerged as a rapidly growing field. In an attempt to build in vitro tissue models for in vivo regenerative cardiac therapy, biodegradable scaffolds and biomaterials have been widely adopted (Ratner and Bryant, 2004; Madden et al., 2010). Non-vascularized (Stevens et al., 2009) and vascularized (Reinecke et al., 1999; Radisic et al., 2004; Zimmermann et al., 2006; Caspi et al., 2007b; Dvir et al., 2009; Stevens et al., 2009; Zakharova et al., 2010) scaffold-free cardiac tissue patches derived from human ESC have been designed to overcome a lack of suitable sources of human CMs. Furthermore, scaffold-free cardiac progenitor and stromal cells were shown to promote cardiogenesis after transplantation onto injured myocardium (Reinecke et al., 1999; Radisic et al., 2004; Zimmermann et al., 2006; Caspi et al., 2007b; Dvir et al., 2009; Stevens et al., 2009; Zakharova et al., 2010). In addition, the construction of scaffolds with neonatal cardiac cells (Reinecke et al., 1999; Radisic et al., 2004; Zimmermann et al., 2006; Caspi et al., 2007b; Dvir et al., 2009; Stevens et al., 2009; Zakharova et al., 2010), combined with angiogenic factors (Reinecke et al., 1999; Radisic et al., 2004; Zimmermann et al., 2006; Caspi et al., 2007b; Dvir et al., 2009; Stevens et al., 2009; Zakharova et al., 2010), have been successfully used for studying their contribution during heart repair.

LIVER

Liver is a lobed organ in the abdominal cavity. Some of its major functions are toxic agent detoxification, energy storing in the form of glycogen, and lipid catabolism via enzymes. Liver can regenerate even when 70% of the organ tissue has been removed. The organ evolved with this intrinsic regenerative ability because of the fundamental roles it plays in the organism, especially in cleaning the blood from hazardous substances to which it is also exposed.

In rodents, partial hepatectomy, toxic agents (e.g., CCl4, allyl alcohol) and viruses (Hepatitis A/B/C) can affect the liver and damage it. After surgical resection of 70% of the liver, hepatocytes begin to gradually proliferate starting from the peri-portal and ending near the central vein. In response to various signals, Kupffer cells, stellate cells, vascular and biliary endothelial cells interact with hepatocytes and also proliferate following hepatectomy. After 10 days, the liver is regenerated by compensatory growth of the remaining liver tissue, rather than recreating an exact copy of the lost lobes (Higgins and Anderson, 1931). Liver regeneration has been extensively studied and excellent reviews clearly document the underlying process mechanisms. Some commonly studied factors are HGF, FGF1, FGF2, stem cell factor, epidermal patterning factor, interferon gamma tumor necrosis factor, and interleukin-6 (Michalopoulos and DeFrances, 1997; Fausto, 2000; Michalopoulos and DeFrances, 2005; Fausto et al., 2006; Michalopoulos, 2007). During liver regeneration, the expression and function of chemokines and chemokine-related receptors in hepatocytes, as well as toll-like receptors, have been recently reviewed (Van Sweringen et al., 2011). Furthermore, the role of and potential treatments

with connective tissue growth factor, IGF binding protein 3, somatostatin, stromal cell derived factor-1, G-CSF, and TGF-β (Shupe and Petersen, 2011), as well as the role of the Wnt pathway and β-catenin (Nejak-Bowen and Monga, 2011), extracellular matrix and matrix metalloproteinases (Kollet et al., 2003; Lorenzini et al., 2010), transcriptional factor hierarchies (Kurinna and Barton, 2011), and reactive oxygen species and inflammation (Jaeschke, 2011) have all been studied and well-reviewed. Complement component C5 has also been shown to play a role in liver regeneration (Mastellos et al., 2001). The extensive study of liver regeneration brings to light many other factors that play a role in the process, as well as potential mechanisms and pathways which are discussed in recent reviews (Fujiyoshi and Ozaki, 2011; Riehle et al., 2011).

Progenitor cells are present in the liver (Farber, 1956) in the Canals of Hering (Theise et al., 1999; Zhang et al., 2008a) and they can contribute to regeneration if proliferation of the hepatocytes is blocked by the following treatments: N-2-acetylaminofluorene, choline deficient and ethionine diets, 3,5 – diethoxycarbonyl-1,4-dihydrocollidine (Sell et al., 1981), or dipin (Factor et al., 1994). Progenitor cells express cytokeratin 19, γ-glutamyl transpeptidase, and α-fetoprotein (Petersen et al., 1998). Other progenitor cells express epithelial cell adhesion molecule, cytokeratin 19, CD44, but not α-fetoprotein (Schmelzer et al., 2007; Dan and Yeoh, 2008; Inada et al., 2008; Yovchev et al., 2008). A recent study suggests that there are four potential stem cell niches in the liver: Canals of Hering, intraductular, peribiliary non-hepatocytes non-biliary, and peribiliary hepatocytes (Kuwahara et al., 2008). These progenitor cells can give rise to the two main hepatic cell types: hepatocytes and cholangiocytes (Fausto and Campbell, 2003). In humans, progenitor cells contribute to liver regeneration during viral hepatitis (Libbrecht et al., 2000) and cirrhosis (Xiao et al., 2004), and the progenitor cell number is correlated to the severity of the hepatic chronic disease (Lowes et al., 1999). However, liver progenitor/stem cells have been associated with the formation of fibrosis via myofibroblast formation (Greenbaum and Wells, 2011).

The introduction of target inactive gene in in vitro culture of isolated hepatocytes followed by the autologous transplantation to the liver is one way of gene therapy. Hepatocyte transplantation in animal models is being studied by transplanting normal hepatocytes to animals that do not express fumaryl acetoacetate hydrolase and are treated with 2(2-nitro-4 trifluoromethylbenzoyl)-1,3 cyclohexane dione, a drug that leads to the proliferation of the implanted cells (Overturf et al., 1998). In humans, transplantation of hepatocytes (Strom et al., 1999), fetal hepatocytes (Habibullah et al., 1994), and bone marrow stem cells (am Esch et al., 2005; Houlihan and Newsome, 2008) have been used to treat liver problems. Also, the transplantation of hepatocytes have been used in clinical trials to treat Crigler–Najjar syndrome type I (hyperbilirubinemia) (Fox et al., 1998), glycogenosis type Ia (Muraca et al., 2002), arginosuccinate lyase deficiency (Stephenne et al., 2006), fulminant liver failure (Habibullah et al., 1994), terminal liver failure (Strom et al., 1997), acute liver failure (Bilir et al., 2000), and postresectional liver failure (Ezzat et al., 2011).

Bone marrow-derived cells can be found in the liver only following injury, and can improve metabolic disorders such as Gunn (Muraca et al., 2007). BMMSC can contribute to the progenitor pool of oval cells in the liver (Petersen et al., 1999). Studies also suggest that BMMSC fuse with already existing hepatocytes in the liver (Wang et al., 2003), a process that can be traced by sex-mismatched transplants. Clinical trials include treatments for drug-induced toxicity (Gasbarrini et al., 2007) and cirrhosis (Pai et al., 2008). The contribution of extra-hepatic cells to liver regeneration and cell therapy has been extensively reviewed (Duncan et al., 2009; Kisseleva et al., 2010; Li et al., 2011; Muraca, 2011). Conversely, other studies suggest that the engraftment of BMMSC in the liver is insufficient and can not play a substantial role in liver regeneration (Cantz et al., 2004; Menthena et al., 2004).

Bioengineering a liver is a very promising method for treating liver failures (Fukumitsu et al., 2011). Clinical trials of bioartificial livers have had modest success (Ellis et al., 1996; Demetriou et al., 2004). Newer methods that make use of scaffolds of decellularized liver tissue, seeded with hepatocytes or progenitor cells have been shown to possess potential clinical applications (Linke et al., 2007). Finally, methods developed by Shupe and Petersen (2011), as well as Uygun et al. (2010) have shown great potential for liver regeneration.

BLOOD VESSELS

Blood vessels extend throughout the body and mediate gas exchange, nutrient and waste transport, and immune defense. The blood vessels consist of endothelial cells that are in contact with the blood, vascular smooth muscle cells that cover the endothelial cells, and fibroblasts and matrix that form the vessels' outer layer. These layers of cells play a role in repair, remodeling, and blood vessels maintenance following injury. All these cell types have been involved in cardiovascular diseases (Wilcox and Scott, 1996; Parizek et al., 2011). The role of blood vessels is crucial; when they deliver insufficient blood to a tissue, ischemia occurs, and when they deliver excessive blood, other diseases may result. To maintain a balance in blood delivery, endothelial cells respond to certain signals (VEGF, oxygen, low blood flow) by creating more blood vessels or by decreasing the branching in already existing blood vessels (Potente et al., 2011).

The vascular endothelium can be repaired by the mature vessel

wall-resident endothelial cells that migrate to the injured area. Using pigs and in vitro cultured cells of damaged and normal endothelial cells, it has been shown that regeneration of the endothelium can occur but that the regenerate is not fully functional. The mechanisms of this process involve G-coupled proteins and nitric oxide [reviewed by Vanhoutte (2010)]. Platelets and hematopoietic cells can also contribute to the endothelium repair process. Furthermore, mature circulating endothelial cells, endothelial progenitor cells, and/or vascular-resident progenitor cells have all been shown to play a role in blood vessel repair (Becher et al., 2010). Studies using ischemia models show that circulating endothelial progenitor cells seem to contribute to angiogenesis (Kalka et al., 2000; Hur et al., 2004; Yoon et al., 2005). Nonetheless, endothelial progenitor cells have controversial origins and this issue has been reflected on the markers used in identification and isolation methods. In this respect, some progenitor cells have hematopoietic origin while expressing endothelial progenitor marker (Case et al., 2007). More thoughts on this topic, as well as factors that play a role in angiogenesis and repair of blood vessels, are discussed by Watt et al. (2010). Only endothelial colony forming cells (also termed endothelial outgrowth cells – cells that possess high proliferation capabilities) have been shown to form de novo blood vessels in vitro that can be used with matrix in vivo (Yoder et al., 2007). Transplantation of human skin substitutes with keratinocytes and endothelial colony-forming cells in mice have demonstrated that blood vessels can be incorporated in the circulatory system (Kung et al., 2008; Shepherd et al., 2006). Other cells, such as pericytes/mullar cells have also been reviewed for their role in vascular repair (Corselli et al., 2010).

Human BMMSC, UCBMSC, and adipose stromal cells can aid in stabilizing blood vessel formation from endothelial colony-forming cells with appropriate matrix in vivo (Au et al., 2008; Critser et al., 2011; Melero-Martin-Martin et al., 2008; Traktuev et al., 2009). Chew and Low (2011) and Ravi and Chaikof (2010) have recently reviewed novel ways to differentiate and tissue-engineer cardiovascular tissues using matrix-based biomaterials. These elaborate studies show that more research is required in order to fully simulate the cell microenvironment in vitro for de novo reconstruction of blood cells. As previously mentioned, smooth muscle cells have been associated with various cardiovascular diseases, including stenosis. Scaffolds seeded with vascular smooth muscle cells in a suitable environment were found to be essential for tissue engineered blood vessels [reviewed by Parizek et al. (2011)].

The role and therapeutic potential of ESC and iPSC in human vascular repair is discussed by Iacobas et al. (2010). In addition, Kane et al. (2011) discuss in a very informative review the differentiation of pluripotent cells to vascular cells in association with factors and pathways involved in this process. Nonetheless, studies involving pluripotent cells have not been yet tested for vascular regeneration in large animals in vivo.

GERM CELLS

Germ cells are derived from primordial germ cells. Oogenesis in females and spermatogenesis in males are enabled by the migration of germ cells to the genital ridge. In females, oogenesis is completed upon birth so that the starting number of oocytes can not be increased throughout life. Conversely, spermatogenesis continues until death in males, producing a large number of sperm via the self-renewal capability and differentiation of spermatogonia. Germ cells are considered the ''fourth'' embryonic layer. Pluripotent stem-like cells need to contribute to this fourth embryonic layer in order for them to be used for transgenic method purposes. In the last couple of years, the mechanisms underlying the self-renewal capability of spermatogonia, ways to ''regenerate'' oocytes after birth, and the differentiation of germ cells to other types of tissues have been studied.

Two factors (germ cell nuclear factor and Plzf) have been found to play a role in spermatogonia's ability for self-renewal. Germ cell nuclear factor is a marker for germ cells that can directly repress Oct4 pluripotency factor (Fuhrmann et al., 2001). Plzf has been found to be essential for the stem cell self-renewal of the germline and has been found to be coexpressed with the germ cell nuclear factor (Buaas et al., 2004).

ESC have been used to create oocyte-like cells with follicles that express lineage specific markers and estrogen (Hubner et al., 2003). In vitro cultured Mvh-positive human ESC-derived cells with BMP4 and BMP8b primodial germ-specific inducers have been found able to participate in spermatogenesis (Toyooka et al., 2003). Interestingly, stem cells from skin were also found to make oocyte-like cells in vitro (Dyce et al., 2006). Recently, studies show that oogenesis after birth can be possible using ''putative'' germ cells from BM and the peripheral blood (Johnson et al., 2005; Lee et al., 2007). Furthermore, hematopoietic progenitor cells have been shown to express germline markers (Pessac et al., 2011). A recent review discusses the data supporting, or not, these findings (Oktem and Oktay, 2009). More recently, ESC and iPSC were used to successfully produce primodial germ cell-like cells through interaction with the epiplast-like cells. These newly formed cells also contributed to gametogenesis and offspring production in mice (Hayashi et al., 2011).

Germ cells have also been exploited for their stem cell-like capabilities. They have been used to create other cell types of all three embryonic layers (Simon

et al., 2009), such as muscle cells (Kim et al., 2005b), neurons (Pan et al., 2005), and mature oocytes (Qing et al., 2008). They have also been used to aid in the regeneration of other body parts, such as the mouse distal digit (Rinkevich et al., 2011). In these regards, attempts have been made to simulate the stem cell-like environment in vitro for propagation and differentiation studies, and of course for studying the different aspects of potential therapies (Chu et al., 2009).

NERVOUS SYSTEM

The nervous system is an organ system composed of two main types of cells: neurons and glial cells. Neurons are of three types: sensory neurons that transport signals from sensory receptors to the central nervous system (CNS), motor neurons that carry signals from the CNS to muscles and glands, and the interneurons of the CNS that transmit impulses between neurons. Statistics have shown that peripheral nerve injury affects more than 67,000 people in the Unites States per year (Taylor et al., 2008). Nerve injury rapidly generates a cascade of events that lead to the degeneration of the axon stump and the myelin sheath distal to the lesion. Following axotomy, the mature peripheral nervous system of adult mammals possesses the intrinsic ability to regenerate (Wood et al., 2011). A cDNA array hybridization study has allowed the identification of 192 genes, 91 of which (that is 47%) are detected after nerve-injury as well as during development, suggesting that regeneration only partially recapitulates development (Bosse et al., 2006). As it has been previously demonstrated, regeneration best occurs immediately following injury when the environment of the peripheral nerves best supports nerve regeneration and reinnervation (Tessier-Lavigne and Goodman, 1996; Fu and Gordon, 1997; Burnett and Zager, 2004).

Despite the peripheral nervous system's ability for regeneration, nerve recovery is far from normal. It is often the case that whenever a nerve injury involves the destruction of the basal lamina and Schwann cells, a nonpermissive fibroblastic scar tissue forms that traps the outgrowing axon and compromises regeneration (Morgenstern et al., 2003). Another cause of axon regeneration impairment is axon misalignment at the site of injury that causes the axon to re-grow to the wrong target (Brown and Hopkins, 1981). Additionally, chronic axotomy and denervation often result in the impairment of the underlying regenerative mechanisms of the nerve cells (Wood et al., 2011). Therefore, efforts have focused on promoting axon regeneration by using neurotrophic factors [such as brain-derived neurotrophic factors and glial-derived neurotrophic factor] through osmotic pumps, microspheres, or gene therapy (Young et al., 2001; Tannemaat et al., 2009; Zacchigna and Giacca, 2009; de Boer et al., 2010). Similarly, axon regeneration can be promoted through the activation of atrophic dormant Schwann cells with cytokine TGF-β (Midha et al., 2005), transplantation of Schwann cells, or skin derived Schwann cell precursors (or progenitor cells) (Walsh and Midha, 2009; Walsh et al., 2010), use of artificial biodegradable nerve guides (Schmidt and Leach, 2003), use of photodynamic therapy (Rochkind et al., 2009), and the short-term electrical stimulation of the injured nerve (Al-Majed et al., 2000; Gordon et al., 2007, 2008, 2009, 2010; Pfister et al., 2011). Furthermore, improved nerve healing has been promoted using techniques such as microtechnology, electrokinetic axonal manipulation, and cell fusion (Sretavan et al., 2005). Currently, surgical intervention aims at coapting the proximal and distal end of the injured nerve, either directly or through the insertion of autografts or allografts (Evans et al., 1991; Weber et al., 2000; Whitlock et al., 2009; Isaacs, 2010; Ray and Mackinnon, 2010).

Alternatively, the regeneration and repair of the axon and nerve have been improved using a variety of artificial implants, such as degradable nerve conduits, scaffolds, and electrodes that overcome the limitations associated with autografts (Smith, 1966a, b; Meek and Coert, 2002; Moore et al., 2009; Siemionow and Brzezicki, 2009; Whitlock et al., 2009). Generally, conduits act to localize Schwann cells, allow the accumulation of trophic factors, and guide the regenerating nerve toward the disconnected distal nerve (Evans, 2001; Meek and Coert, 2002; Belkas et al., 2004; Moore et al., 2009). Scaffolds often comprise cells (such as glial cells, Schwann cells, and stem cells), and factors (such as laminin-1, neural growth factor, brain-derived neurotrophic factors, and bFGF) (Dubey et al., 1999; Hudson et al., 1999; Rosner et al., 2003; Bellamkonda, 2006; Dodla and Bellamkonda, 2008; Kemp et al., 2008; Dahlin et al., 2009; de Ruiter et al., 2009; Yan et al., 2009). The application of nanotubes and nanofibers to promote nerve repair has also been studied and, with proper training and a biocompatible design, these materials could direct axonal growth and promote nerve healing [for a review see Olakowska et al. (2010)].

As for the CNS, it was long believed that adult mammalian brain and spinal cord do not regenerate following injury. Typically, injury of the axons in the CNS is often accompanied by inflammation and glial scar formation, both of which inhibit the regenerative response of the CNS. Nevertheless, several recent studies have shown that neurogenesis is possible in several regions of the CNS, such as hypothalamus, neocortex, cerebellum, striatum, amygdala, and substantia nigra [for a review see Gould (2007) and Martino et al. (2011)]. It is thought that neural stem/progenitor cells residing in the CNS are capable of undergoing proliferation and differentiation and could, thus, promote repair of the CNS. Cell therapy using BMMSC [for

review see Wright et al. (2011)] and neural stem cells [for review see Martino et al. (2011)] into the spinal cord has been performed in an attempt to enhance axonal regeneration in the CNS.

Some amphibian and especially urodeles have nevertheless remarkable regenerative ability of spinal cord and the brain. Spinal cord regenerates perfectly after transaction of the tail, most likely from ependymal cells. Ependymal cells seem to be the source of regeneration of parts of the brain. In a recent study, a whole optic tectum was removed from newts to result in complete regeneration within 8 months (Okamoto et al., 2007).

The ongoing search for novel strategies to promote neural regeneration and repair has generated substantial progress so far. However, there remains a need to design scaffolds and tissue-like constructs that can repair lengthy axonal injuries and can match the advantages offered by autografts.

EYE – LENS AND RETINA

Lens and retina are two organs inside the eye cup that perform the basic function of vision. Lens is transparent mostly due to soluble proteins such as crystallins and denucleated fibers. The lens comprises a monolayer of epithelial cells that resides in the anterior side. These cells continuously proliferate and differentiate into fibers toward the posterior side of the lens. The lens capsule, that covers the lens on the outside, consists of extracellular matrix. Light passes through the lens and is focused on the retina. Retina converts light into signals, and this process is mediated by a family of proteins, called opsins. The light signals are then transmitted through the optic nerve to the brain to enable vision. Retina consists of a number of cell types: Müller cells, cones, rods, ganglion cells, horizontal cells, bipolar cells, amacrine cells, and pigment epithelial cells.

Mammalian lens can not regenerate. Opacification of the lens or cataract is a common eye disease that can lead to blindness in humans. Depending on the cause and the affected position of the lens, cataract can be of a number of types: age-related nuclear cataract (Truscott, 2005), anterior subcapsular cataract, posterior capsule opacification, posterior subcapsular cataract, and Sparc-related cataract (Hejtmancik, 2008; Martinez and de Iongh, 2010). Today, the standard treatment for lens opacification is cataract surgery that consists in removing the lens fibers and leaving the lens capsule behind. The residual epithelial cells remaining in the capsular bag can then proliferate and differentiate to form new fibers. However, cataract surgery might lead to secondary cataract through epithelial to mesenchymal transition (EMT). This process is regulated by TGF-β that mediates differentiation of epithelial cells to elongated myofibroblast cells expressing α-smooth muscle protein. It has been recently shown that a C5R antagonist can delay the formation of secondary cataract (Suetsugu-Maki et al., 2011).

Lens regeneration can, however, occur in lower vertebrates such as newts that can regenerate the lens even as adults, and frog tadpoles. In newts, iris pigmented epithelial cells from the dorsal side of the eye transdifferentiate to lens epithelial cells that eventually regenerate the lens. This process has been shown to involve Pax6 (Del Rio-Tsonis et al., 1995; Madhavan et al., 2006), Prox1 (Del Rio-Tsonis et al., 1999), FGF (Del Rio-Tsonis et al., 1997), Wnt (Hayashi et al., 2006), Shh (Tsonis et al., 2004), BMP, Six3 (Grogg et al., 2005), and retinoic acid (Tsonis et al., 2000). In frog tadpoles, lens regeneration occurs through transdifferentiation of the cornea. This process involves transcriptional factors Otx2, Pax6, Sox3, and Prox1 (Schaefer et al., 1999; Henry et al., 2002). Signaling pathways involved in amphibian lens regeneration have been recently reviewed (Henry and Tsonis, 2010).

Retina does not regenerate in mammals after injury. Studies of embryonic stages of animal models have revealed only a limited number of stem cell-like cells in the eye. Experiments with mammalian models have shown that Müller glia cells respond to damage, and that pigmented progenitor cells can transdifferentiate to neuronal progenitor-like cells. Attempts have also been made to increase the efficiency of retina regeneration by manipulating putative proliferation pathways, including Wnt and FGF (Karl and Reh, 2010). As for amphibians, fishes and pre-, post-hatch chicks have been the dominant models for retina regeneration. During regeneration of the amphibian retina, the retina pigmented epithelium recapitulates retinal normal development by transdifferentiation. Retina regeneration in fish is achieved by the differentiation of residual progenitor cells to rod photoreceptors (Raymond et al., 1988), and the dedifferentiation of Müller glia to a progenitor-like state to regenerate rods and other neuronal cell types (Bernardos et al., 2007). Other potential sources of cells that contribute to retina regeneration in fish reside in the circumferential germinal zone and the ciliary marginal zone, both of which are well-known for containing stem-like cells (Stenkamp et al., 2001; Hitchcock et al., 2004). For a review on the genetic aspect of zebrafish retina regeneration, see Brockerhoff and Fadool (2011). Furthermore, embryonic chicks have the ability to regenerate retina upon treatment with growth factors (Park and Hollenberg, 1991). Essential pathways have been identified to play a role in this process, and these pathways include FGF, BMP, and Shh (Spence et al., 2004; Haynes et al., 2007; Spence et al., 2007). Müller glia of post-hatch chicks have been shown to possess limited regenerative ability when it comes to retina regeneration. Nonetheless, alternative potential sources of cells are present in the circumferential germinal zone, the ciliary marginal zone, and the par

plana of the ciliary zone (Fischer and Reh, 2003), [for review see (Fischer and Bongini (2010) and Bermingham-McDonogh and Reh (2011)]. Factors and processes that play a role in transdifferentiation of retinal pigmented epithelium to retinal cells in various animal models have been extensively studied [for a review see Wang et al. (2010b)].

Studies on the differentiation of bone marrow-derived stem cells to retinal cells have been reported with low efficiencies (Chen et al., 2006). Mesenchymal cells have been used extensively for regeneration purposes in other organs, and their potential therapeutic use in the context of ocular diseases is discussed in a review by Joe and Gregory-Evans (2010). ESC and iPSC have also been studied for their contribution to retinal regeneration in vivo through their differentiation into retinal neurons (Lamba et al., 2009, 2010) [for a review on iPSC role in retina regeneration see Osakada et al. (2010)]. Tissue engineering methods have also been applied for eye tissues [and their potential therapeutic aspects are reviewed by Silva et al. (2011)].

HAIR CELLS

Hair cells are found in the inner ear (Cochlear) with the fundamental role of converting the sound waves to nerve signals that get sent to the brain. Mammalian cochlear hair cells can not regenerate following injury or when lost with age. Birds, amphibians, and fishes have been extensively studied for their ability to regenerate and restore cochlear hair cells throughout their life. In chicks, supporting non-hair cells transdifferentiate to hair cells. Supporting cells also proliferate to maintain the progenitor reservoir. Atoh1 and Notch signaling are potential mechanisms for the transdifferentiation or proliferation of the supporting cells. Notch signaling keeps a reservoir of progenitor cells by inhibiting their differentiation, whereas Atoh1 promotes their differentiation [for review see Cotanche and Kaiser (2010)].

As mammalian supporting cochlear hair cells are present but do not transdifferentiate, studies have focused on using several growth factors to induce mitosis. Alternatively, downregulation of proliferation inhibitors, such as the protein $p27^{kip1}$, have also been attempted (Lowenheim et al., 1999). Furthermore, activating Atoh1 pathway in big animal models has led to promising results. For a review on hair cell regeneration and the pathways involved in mammalian and non-mammalian regeneration models, see Bermingham-McDonogh and Reh (2011)].

KIDNEY AND BLADDER

Kidney is the organ that cleans the blood from unwanted substances, and regulates osmotic pressure and salt concentration. It is composed of the cortex on the outside and the medulla on the inner side. Glomeruli are the site in the kidney where filtration occurs. Filtrate then flows through proximal tubules (close to glomeruli), Henle's loop, and distal tubules to end up in the collecting tube. Reabsorption of certain molecules across this network occurs. Mammalian kidneys do not have regeneration capabilities. In addition, they possess a slow turnover rate which is reflected on the low number of stem cell-like cells or inactive stem cell-like cells. Following injury (ischemic- or toxic-related), mammalian kidneys restore filtrate flow and repair the tubular epithelium by the action of renal residual epithelial cells, progenitor cells, and/or extra-renal cells. Factors and processes that play a role in repair following acute kidney injury include angiogenesis, inflammation/immune responses/chemokines, apoptosis, and oxidative stress, and they have been recently reviewed by El Sabbahy and Vaidya (2011). Also in a recent review, Guo and Cantley (2010) discuss kidney maintenance, turnover rate, and regeneration. Gene therapy for acute kidney injury involves downregulation of NF-kB (Cao et al., 2004), intercellular adhesion molecule 1 (Dragun et al., 1998), Complement component 3, and caspase 3 (Zheng et al., 2006) using antisense oligodesoxynucleotides or siRNA. Using viruses or electroporation, increased levels of Bcl-2 (Chien et al., 2005) and HGF (Herrero-Fresneda et al., 2006) have also been achieved and shown great potential for kidney regeneration in animal models.

TGF-β, a major molecule for EMT, leads to kidney fibrosis by inducing myofibroblasts formation (Carew et al., 2012). Aldosterone effect on kidney fibrosis has been recently reviewed, along with EMT and inflammation processes (Brem et al., 2011). EMT is a major cause of chronic kidney disease, and treatments for factors associated with EMT and its related pathways have been attempted and shown to lead to positive results in animal models. An interesting aspect of kidney repair is compensatory mammalian kidney hypertrophy (Hayslett, 1979). Today, the most effective therapeutic strategy for kidney failure is transplantation, with a less effective treatment through dialysis tubing. Patients can delay death from kidney failure through treatments with drugs (such as ramipril) that inhibit the synthesis of angiotensin, and treat diabetes. The aforementioned show that kidney diseases are related to organs that play a role in regulating the concentration of blood components and blood circulation. Other organisms such as fish (Reimschuessel, 2001) have the ability to regenerate the kidney via neonephropoieisis, a process by which new nephrons are generated throughout the organ. In these organisms, new nephrons are also regenerated following injury (Reimschuessel et al., 1990). A review by Davidson (2011) discusses kidney repair and the regenerative capabilities of fish versus mammals in response to injury.

Tubular epithelial cells can repair kidney damage after ischaemic reperfusion injury by dedifferentiating and proliferating (Humphreys et al., 2008). Other potential sources of progenitor cells that have been shown to participate in kidney

repair or were able to differentiate to various cell types in vitro are distal tubular cells (Gobe and Johnson, 2007), cells residing in the renal cortex near the tubules (Bussolati et al., 2005), cells in Bowman's capsules (Sagrinati et al., 2006), glomerular parietal epithelial cells (Swetha et al., 2011), metanephric mesenchymal cells (Oliver et al., 2002), and cells in the papilla (Oliver et al., 2004).

BMMSC have been the main type of cells used for treating acute kidney injury and chronic kidney diseases (Choi et al., 2009; Togel et al., 2009). These cells have been shown to aid in the repair process of various injured kidney parts. They can differentiate to tubular epithelial cells in human bone marrow recipients with sex-mismatch bone marrow transplant (Poulsom et al., 2001). In animal models, they have also been shown to differentiate to podocytes, glomerular, endothelial, and mesangial cells. Mesenchymal cells release factors that have anti-inflammatory action, can stimulate the residing kidney stem cells, and can reduce fibrosis (Bussolati et al., 2008). The different animal models used with MSC have been reviewed in Asanuma et al. (2010).

Membranes for dialysis have been engineered using scaffolds and renal cells (Aebischer et al., 1987; Ip and Aebischer, 1989; Dankers et al., 2011a). Functional analysis of solute transport across such membranes shows their great potential for future usage (Fujita et al., 2002; Sato et al., 2005). Human cell-seeded bioartificial kidneys have also been used in vivo (Humes et al., 2002) and human clinical trials have been performed (Humes et al., 2004). Wearable kidneys have been recently engineered for dialysis (Ronco and Fecondini, 2007; Gura et al., 2009; Rambod et al., 2010). In addition, decellularized kidneys seeded with pluripotent stem cells have been recently used to engineer a kidney in vitro (Ross et al., 2009; Nakayama et al., 2010).

Dankers et al. (2011b) and Perin et al. (2011) have recently reviewed the field of kidney regeneration and repair.

The bladder is the organ responsible for the storage of urine made in the kidneys and the voluntary control of urination. The organ's function can be compromised due to loss of bladder tissue (as a result of injury, disease, inflammation, etc.), a condition that has been generally treated with reconstructive surgery (e.g., autoaugmentation, ureterocystoplasty). However, and to overcome the complications associated with surgical procedures, tissue engineered bladder tissues have been designed using non-seeded or cell-seeded scaffolds, with the latter demonstrating a higher tissue engineering efficiency. Synthetic materials (e.g., silicone) have been mostly used to construct artificial bladders, whereas biomaterials (e.g., collagen, alginate) have been widely applied for regenerative medicine purposes. Bioreactors are currently being constructed for bladder development in vitro, and used to simulate the mechanical environment in which the bioartificial bladder is to be implanted. Furthermore, nanoscaffolds have been designed for bladder repair or replacement. Transplantation of cells (e.g., native cells, amniotic fluid and BM-derived stem cells, ESC) for the reconstruction of functional bladder segments has also been attempted. Clinical trials were also conducted in which patients received either collagen or PGA-collagen seeded scaffolds for bladder replacement. For a detailed review on this topic, see Atala (2011).

SKIN

Skin is the body's largest organ with an epithelium that comes in direct contact with the external environment. The skin plays four key functions: (1) protection against radiation, and physical, biological and chemical agents, (2) regulation of body temperature, (3) production of vitamin D, and (4) sensory. In addition, the skin serves as an ''embedding'' scaffold for tissues and organs, such as hair follicles. Following skin injury, thrombin cleaves fibrinogen to fibrin. This latter combined with platelets, blood cells, and other matrices (such as fibronectin) form a clot that serves as a scaffold for infiltration of other cells. Also in response to injury, keratinocytes release interleukin-1 and tumor necrosis factor-α. Macrophages, neutrophils, T cells, and platelets populate the area, and along with residual cell population produce growth factors essential for wound closure. Some of the growth factors include EGF, TGF-β, PDGF, and various inflammatory cytokines. Finally, re-epithelialization is enabled by the proliferation of keratinocytes. In some instances, complete regeneration of the skin might require the regeneration of additional epidermis components that might have also been injured or damaged. Endothelial and fibroblastic cells often help in this regenerative process [an excellent review on the pathway of skin regeneration following injury in regards to the role of macrophages by (Mahdavian Delavary et al., 2011). For a detailed review on the molecules that play a role in skin repair and disease, also see Kondo and Ishida (2010)]. $\gamma\delta$ T cells residing in the skin have been shown to play a variety of roles, including infection, malignancy, inflammation, maintenance of the epithelium, and repair (Nestle et al., 2009). A subpopulation of cells in the epidermis of the skin, called the dendritic epidermal T cells, that express a single T-cell antigen receptor, show wound healing specific roles (Jameson and Havran, 2007) by potentially recognizing a specific antigen from the residing keratinocytes. Subsequently, $\gamma\delta$ T cells synthesize keratinocyte growth factor for keratinocyte proliferation. In addition, $\gamma\delta$ T cells signal $\alpha\beta$ T cells and macrophages to invade the injured area. Humans possess $\alpha\beta$ T cells and $\gamma\delta$ T cells, both of which reside in the epidermis [for more detail on the epidermal T cells see Havran and Jameson, (2010)]).

Bone marrow-derived stem cells have been shown to contribute to epithelial repair following injury.

These cells are recruited by cytokines synthesized near the injury site (Wu et al., 2007; Sasaki et al., 2008). Similarly, mesenchymal-derived fibrocytes from peripheral blood have been shown to contribute to epithelial repair (Chesney and Bucala, 2000) by differentiating into myofibroblasts and reducing fibrosis. More recently, fibrocytes were also identified to participate in skin repair (Ishida et al., 2009).

Bioartificial dermal substitutes are widely used for treating severely damaged skin. Scaffolds made from different matrix layers serve for guiding the proliferation and differentiation of cells present near the injury site, resulting in the regeneration of the missing skin parts. Furthermore, scaffolds seeded with a mixture of different types of cells and factors are extensively studied for their efficiency and effect on wound closure (Helgeson et al., 2007; Jeng et al., 2007). Substitutes as such have been used for treating foot and ankle deep soft war injuries (Baechler et al., 2010).

HAIR FOLLICLES

Hair follicles are the organs that serve sensory and homeostatic functions in the body. Their movement is enabled by a muscle, called arrector pili. Nerve fibers transmit signals from the hair follicles to the nervous system. Progenitor cells residing in these follicles produce keratinocytes (during anagen phase) that differentiate (during catagen phase) to make terminally differentiated "dead" keratinized cells (during telogen phase). From the epidermal- and dermal-originating cells, dermal cells show the highest proliferation capability. The part of the hair follicle located in the dermal layer is composed of the dermal papilla at the base and the dermal sheath near the bulge. The dermal sheath contains collagen and fibroblasts whose origin is partially from neural crest cells (Fernandes et al., 2004). Cells in the dermal sheath have been shown to regenerate the dermal papilla (Horne and Jahoda, 1992), a process that involves thrombin signaling (Feutz et al., 2008). Hair follicle pluripotent stem cells have been identified to be positive for nestin, and have been found to contribute to hair production. Furthermore, differentiation studies have shown that hair follicle pluripotent stem cells are capable of differentiating into a number of nerve lineage cell types. These cells, even when from human origin, can contribute to peripheral nerve repair [reviewed by Amoh et al. (2010)]. Hair follicles can also be regenerated from extra-hair follicle epithelial progenitor cells (Taylor et al., 2000). Recent reviews have discussed the molecular mechanisms underlying hair follicle regeneration (Fuchs, 2009), as well as the markers for epithelial and hair regeneration by residual progenitor cells (Jaks et al., 2010). In addition, a number of studies have focused on determining the appropriate conditions for the different hair follicle parts to maintain their regenerative capabilities and generate a hair follicle in vitro (Amoh et al., 2010; Yang and Cotsarelis, 2010). BMP (Rendl et al., 2008) and Wnt pathways (Kishimoto et al., 2000) have both been found essential for prolonged dermal papilla cell inducibility. Dermal inductive signature molecules are alkaline phosphatase, α-smooth muscle actin, versican, corin, and CD133. A recent review discusses the role of these molecules in the dermal compartment of the hair follicles in regards to regeneration (Yang and Cotsarelis, 2010).

PANCREAS

The pancreas is an organ of two compartments: exocrine and endocrine. The exocrine tissue, which forms the majority of the pancreas, is composed of acinar cells. It secretes digestive enzymes that are used in the stomach. The endocrine tissue is composed of various types of cells including α, β, δ, ε, and PP cells, assembled in regions known as the islet of Langerhans. These cells secrete hormones and other pancreatic peptides. Diabetes type I is a pancreatic disorder caused by a disruption in the secretion of insulin by β-cells. The majority of the studies focus on β-cell replenishment as a way to treat diabetes in the absence of any exogenous source of insulin.

Models for pancreas regeneration include partial pancreatectomy, partial duct ligation, chemicals or genetic manipulation. Pancreatic acinar cells have the ability to regenerate (Jensen et al., 2005; Desai et al., 2007) and this process involves Shh and Indian Hedgehog pathways (Cano and Hebrok, 2008; Fendrich et al., 2008). In contrast, islets have limited regeneration ability following injury or other conditions that promote diabetes. As a result, patients either receive islet transplants (Shapiro et al., 2000; Ryan et al., 2005; Shapiro et al., 2006) or prolonged treatment with exogenous insulin. Studies have shown that insulin-secreting β-cells can be replenished by proliferation of existing β-cells or from progenitor cells (Gonez and Knight, 2010). IGF-1 has been shown to play a role in proliferation of existing β-cells (Agudo et al., 2008). Studies using BrdU or Ki-67 show that β-cells are able to proliferate in mice, and to a lesser extent in humans (Dor, 2006; Teta et al., 2007). However, this ability is reduced with age (Teta et al., 2005; Salpeter et al., 2010). Using fate mapping techniques, it has been shown that β-cells can be regenerated by progenitors residing in the pancreatic duct (Bonner-Weir et al., 2010), by transdifferentiation of α-cells (Chung and Levine, 2010; Chung et al., 2010; Collombat et al., 2010; Thorel et al., 2010; Gianani, 2011), or from bone marrow-derived stem cells in vivo (Chamson-Reig et al., 2010). Furthermore, in vitro and in vivo functional studies have identified the antiapoptotic and chaperone protein clusterin to play a crucial role in regeneration of pancreatic islets and the formation of β-cells (Lee et al., 2011).

BMMSC, adipose tissue-derived MSC, umbilical cord mononuclear cells, placenta-derived adherent

cells, and Wharton's jelly derived MSC have been used in vitro to produce insulin-secreting cells [for an excellent review on this topic, that also includes an elaborate literature search on methods, markers, and results, see Anzalone et al. (2011)]. Moreover, ESC have been differentiated into insulin-secreting cells and have been used in functional studies in vivo to produce insulin-secreting cells (Soria et al., 2000). Studies that make use of ESC and iPSC to make pancreatic cells have been reviewed by Baiu et al. (2011). Two signaling pathways that have been exploited for their role in ESC and iPSC differentiation are FGF and BMP, both of which are also essential for pancreatic lineage. In addition, Wnt and retinoic acid, and the inhibition of EGF and TGF-β have been studied in differentiation studies.

The field of tissue engineering has focused on the development of biomaterials (such as silicone-based chambers) that can be seeded with different types of cells (β-cells or progenitor cells) in an attempt to construct a bioartificial pancreas. A vascularized silicone chamber (Cronin et al., 2004) seeded with islets combined with extracellular matrix has shown great potential for glucose regulation in mice (Hussey et al., 2009). A recent review discusses the construction of bioartificial devices that can simulate insulin secretion (Silva et al., 2006).

BONE AND CARTILAGE

Bone cells, also known as osteocytes, are differentiated specialized cells capable of responding to mechanical stimuli by either increasing or reducing bone apposition (Lemaire et al., 2004). Throughout adult life, bone possesses the intrinsic ability to regenerate during skeletal development and to promote normal fracture healing (Einhorn, 1998; Ferguson et al., 1999; Dimitriou et al., 2011). Natural bone remodeling involves the participation of two types of cells: osteoblasts (derived from MSC) and osteoclasts (derived from hematopoietic cells), both of which are responsible for maintaining a dynamic equilibrium between bone formation and bone resorption (Dalle Carbonare et al., 2011). A number of circulant factors and pathways, including interleukin-11, Wnt, notch, BMP, and SMAD signaling (Lin and Hankenson, 2011; Matsumoto et al., 2012), are known for being capable of controlling the differentiation of osteoblasts (Karsenty, 1999). When pre-osteoblasts differentiate into active mature osteoblasts, they undergo phenotypic changes that lead to the secretion of bone matrix proteins that are necessary for the cells' terminal differentiation to osteocytes (Dalle Carbonare et al., 2011).

One master gene that plays a key role in the osteogenic differentiation process from mesenchymal precursors is *Runx2*, also known as *Cbfa1* or *Aml3* (Otto et al., 2003; Lian et al., 2004; Ylonen et al., 2005; Cohen, 2009; Hu et al., 2011). *Runx2* has 2 isoforms: type I and type II (Enomoto et al., 2000; Banerjee et al., 2001; Park et al., 2001; Prince et al., 2001), and has been shown to regulate the expression of bone alkaline phosphatase and osteocalcin (Lian et al., 2004). The activity of *Runx2* can be regulated by histone deacetylase 7 (Jensen et al., 2008), twist proteins (Howard et al., 1997; Bialek et al., 2004), activator protein 1, and activating transcription factor 4 (Cohen, 2009). The induction of *Runx2* in human BMMSC has been shown to induce the expression of specific osteoblastic markers, such as collagen type I, bone alkaline phosphatase, and osteocalcin during osteoblastic maturation (Cohen, 2009). For all of its roles, *Runx2* has been a material of interest for novel therapeutic approaches aimed at enhancing bone regeneration and repair. Jeon et al. (2006) have succeeded in preventing the process of Runx2 ubiquination and subsequent degradation by inhibiting histone deacetylase 4. Furthermore, *Runx2* expression was successfully induced in bone marrow stromal cells as a mean to increase osteogenic expression (Gillissen et al., 1997; Byers et al., 2004; Donna et al., 2006).

However, as the number of diseases due to the loss of large bone quantities as a result of trauma, neoplasia, reconstructive surgery, congenital defects, or periodontal diseases increases, so does the need for the development of novel therapeutic approaches to aid in the compromised regenerative process. Today, a number of different strategies are used to augment large bone defects. These include autologous bone graft (Younger and Chapman, 1989; Ahlmann et al., 2002; St John et al., 2003; Knothe Tate et al., 2011), allograft implantation (Finkemeier, 2002), bone-graft substitutes with growth factors (Giannoudis et al., 2005; Giannoudis and Einhorn, 2009; Dimitriou et al., 2011), distraction osteogenesis, bone transport (Green et al., 1992; Aronson, 1997; Dimitriou et al., 2011), and the use of osteoconductive scaffolds for proliferation and differentiation of bone cells. More conventional strategies for correcting and repairing lengthy bone deformities include external fixators and the Ilizarov technique (Green et al., 1992; Aronson, 1997), intramedullary nails combined with external monorail distraction devices (Raschke et al., 1993), or intramedullary lengthening devices (Cole et al., 2001). An alternative technique used for reconstructing long-bone defects is a two-step procedure known as the Masquelet technique (Giannoudis et al., 2011). At the molecular level, BMP2 and BMP7 have been extensively studied for their osteo-inductive properties in the induction of bone regeneration (Blokhuis, 2009; Giannoudis and Einhorn, 2009; Nauth et al., 2011). Other growth factors studied for their implication in bone repair processes include but are not limited to PDGF, TGF-β, IGF-1, VEGF, and FGF (Dimitriou et al., 2005; Chen et al., 2009b; Nauth et al., 2010). Additionally, MSC have been exploited for their application in bone repair through local injection, systemic application, recombinant gene technology, and tissue engineering

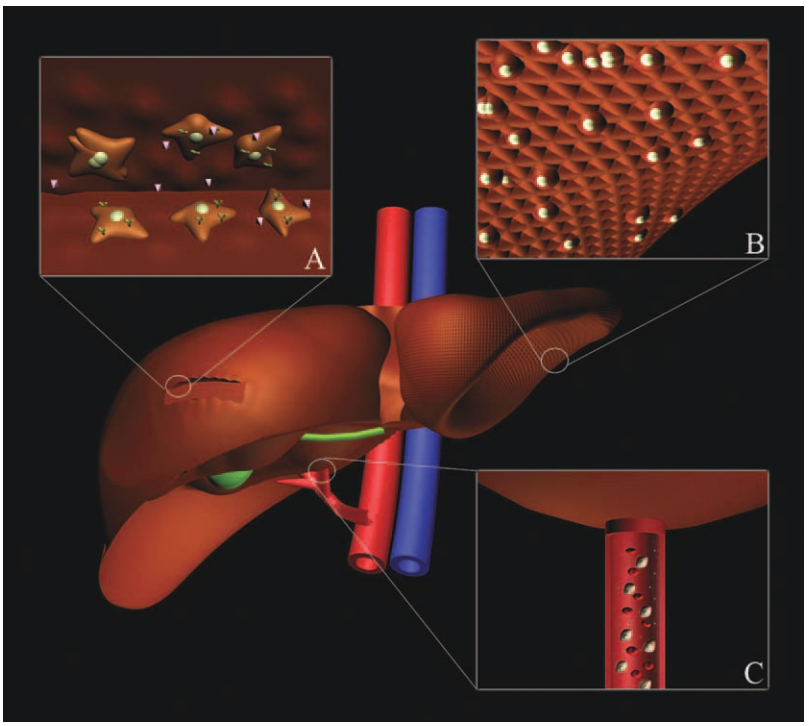

Figure 1. An illustration depicting artistically the different concepts of regeneration using as a template the liver. (**A**) Local cells (either differentiated hepatocytes or tissue specific-stem cells) proliferate and repopulate the injured area, providing as well important factors for growth. This concept can be applied to dedifferentiation of cells at the injured site as well. (**B**) An artificial scaffold is seeded with cells to repopulate and reconstruct the lost part of the organ. (**C**) Cells from bone marrow can be brought via blood vessels to the injured area and contribute to the repair or regeneration.

(D'Ippolito et al., 1999; Huibregtse et al., 2000; Hernigou et al., 2005; Pountos et al., 2010; Aicher et al., 2011; Jager et al., 2011; Jones and Yang, 2011). Alternatively, MSC have been first expanded in vitro before their implantation due to the large number of cells that can be generated from in vitro cultures (Bianchi et al., 2003; D'Ippolito et al., 2004; McGonagle et al., 2007). Also under study are other sources of cells that could play a role in bone regeneration; those include peripheral blood (Matsumoto et al., 2006), mesenchymal progenitor cells from fat (Zuk et al., 2001; Im et al., 2005; Niemeyer et al., 2010; Monaco et al., 2011), and cells from traumatized muscle tissue (Jackson et al., 2009).

As with every case where regeneration or repair has been compromised, tissue engineered scaffolds come into play to promote healing. A large number of synthetic bone substitutes are widely in use (Finkemeier, 2002; Giannoudis et al., 2005; Lew et al., 2011). However, synthetic bone grafts often trigger negative host reaction. Thus, more recently, therapeutic approaches use gene (e.g. expressing BMP and parathyroid hormone) and cell-based therapies to design biocompatible, biodegradable, and osteogenic bone tissue grafts and biomaterials (Fang et al., 1996; Laurencin et al., 1999). Viral and nonviral vectors have also been used for gene transfer in osteogenic precursors and stem cells (Franceschi, 2005; Evans, 2011), and for gene factor-mediated delivery (Ishihara et al., 2010, 2011). Furthermore, 3D biodegradable scaffolds for cell proliferation and matrix formation have been designed and are currently being tested for biocompatibility (Ishaug-Riley et al., 1998; Cartmell et al., 2003; Czarnecki et al., 2008; Buckley and O'Kelly; 2010; Akkouch et al., 2011; Tampieri et al., 2011). Even injectable scaffolds are currently under study for their reduced invasiveness and easy application (Laschke et al., 2007). Alternatively, biomaterials made from a combination of natural or synthetic matrices and micro- or nano-particles have been tested for mechanical properties and bone formation efficacy (Giannoudis et al., 2005; Cai et al., 2009; Jose et al., 2009; Shekaran and Garcia, 2010). Moreover, a recent review by Habibovic and Barralet (2011) shed light on the potential use of bioinorganics to promote bone regeneration. Particulate grafts have also proven effective in repairing localized defects (Aloy-Prosper et al., 2011). Tissue-like structures are also being designed in which cells, such as MSC, are being seeded onto 3D scaffolds and combined with growth factors to generate and maintain bone (Rose and Oreffo, 2002; Salgado et al., 2004).

Cartilage is a tough but flexible connective tissue that covers the end of the bones, generally at the joint site. Osteochondral defects result in mechanical instability that constitutes a challenge for the regenerating bone tissue and could lead to disfiguration in the case where the cartilage of the ear or nose is destroyed. Today, cartilage reconstruction is one of the most pursued fields in tissue repair and regeneration. Cartilage repair is achieved using biodegradable synthetic polymers in combination with cells and proteins to promote cell adhesion and proliferation [for a detailed review see Panseri et al. (2011)]. Ear reconstruction was one of the earliest models of cartilage repair achieved in nude mice (Cao et al., 1997). In contrast to auricular cartilage, articular cartilage does not require very sophisticated design fabrication. Mesenchymal stem cell therapy has been one general approach used to repair articular defects (Brittberg et al., 2003; Wakitani et al., 2007; Nejadnik et al., 2010; Wakitani et al., 2011). In one study, the injection of a suspension of BMMSC in hyaluronic acid scaffold has led to the regeneration of the meniscus and the retardation of the degeneration of the cartilage (Murphy et al., 2003). Bone marrow stem cells have also been

seeded on biomaterial scaffolds and implanted to lead to fully repaired articular osteochondral defects (Zhou et al., 2006). Chondrocyte-engineered scaffolds are another alternative that have been successfully used to repair cartilage defects (Wakitani et al., 1989; Brittberg et al., 1994; van Susante et al., 1998; Liu et al., 2002). These constructs have repaired defective tracheal cartilage in a rabbit model as reported in Macchiarini et al. (2008), Luo et al. (2009), and Sun et al., 2011.

Current clinical strategies for enhancing bone and cartilage regeneration and repair have generated relatively satisfactory results. Nonetheless, no currently available synthetic bone substitute possesses superior if not similar biological or mechanical properties when compared with bone. It, therefore, remains a necessity to engineer scaffolds that are biocompatible and mechanically stable, as well as tissue constructs that are cost-effective and capable of promoting short-term healing, and to exploit growth factors that can be administered at safe optimum dosages and can still induce vascular ingrowth and bone- or cartilage-tissue formation.

FUTURE DIRECTIONS

In this review, we have attempted to present an overview of organ repair and regeneration with a main emphasis in mammals. Occasionally, and when appropriate, information has been provided from lower vertebrates, such as amphibian and fish. Undoubtedly, mammals do not match the regenerative capabilities of amphibian, where body parts, such as limbs and tails, can regenerate perfectly even in the adult (Tsonis, 1996), or even invertebrates where whole animals can be regenerated from small pieces (Sanchez Alvarado and Tsonis, 2006). However, the main take-home message here is that every animal, including mammals, have devised strategies that allow in one way or another repair and regeneration. Will we ever be able to regenerate human organs and parts the way that the newt does? Are stem cells able to reconstruct a whole damaged tissue or organ? While an answer at this point is premature, the news for the future in our opinion is good when all possible strategies will be at use. What is, for example, the relationship of stem cells as we know them in mammals to the dedifferentiating newt cells that create the source of regenerating tissues? Are there similarities and, if yes, can we learn from them. Indeed, newt cells do express factors that characterize stem cells (Maki et al., 2009, 2010). Can we learn how cells create these progenitor cells and guide them via scaffolds to build tissues and organs? These three concepts (classical animal regeneration, stem cells, and tissue engineering) can provide the necessary raw materials to materialize the final goals of regenerative biology and medicine. These general ideas of the different ways to regeneration are depicted in Figure 1.

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