Regeneration in humans

Regeneration in humans is the regrowth of lost tissues or organs in response to injury. This is in contrast to wound healing, which involves closing up the injury site with a scar. Some tissues such as skin and large organs including the liver regrow quite readily, while others have been thought to have little or no capacity for regeneration. However ongoing research, particularly in the heart and lungs, suggests that there is hope for a variety of tissues and organs to eventually become regeneration-capable.

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History of human tissue regeneration

In humans with non-injured tissues, the tissue is naturally regenerated over time; by default these tissues have new cells available to replace expended cells. For example, the body regenerates a full bone within 10 years, while non-injured skin tissue is regenerated within two weeks.[1] With injured tissue, the body usually has a different response – this emergency response usually involves building a degree of scar tissue over a time period longer than a regenerative response, as has been proven clinically[2] and via observation.

There are however some human organs and tissues that regenerate rather than simply scar, as a result of injury. These include the liver, fingertips, and endometrium. More information is now known regarding the passive replacement of tissues in the human body, as well as the mechanics of stem cells. Advances in research have enabled the induced regeneration of many more tissues and organs than previously thought possible. The aim for these techniques is to be used in the near future to regenerate any tissue in the human body.

Regeneration with materials

Generally humans, in vivo, can regenerate injured tissues for limited distances. The maximum induced key diffusion distance of regeneration, in 2009, was roughly 1 cm; [1] this regeneration distance standard was achieved, induced and aided by the use of materials that could bridge the wound; this material bridge induced regenerative cells to flow across the wound gap, whereby it then degraded. This technology was first used inside a broken urethra in 1996.[1][3] In 2012, using materials, a full urethra was restored in vivo.[3]

Regeneration by 3d printing

In 2009, the regeneration of hollow organs and tissues with a long diffusion distance, was a little more challenging. Therefore to regenerate hollow organs and tissues with a long diffusion distance, the tissue had to be regenerated inside the lab, via the use of a 3d printer.[1]

With printing tissues, by 2012, there were four accepted standard levels of regenerative complexity that were acknowledged in various academic institutions:

- Level one, *flat tissue* like skin was the simplest to recreate;[3]
- Level two was *tubular structures* such as blood vessels;[3]
- Level three was *hollow non-tubular structures*;[3]
- Level four was *solid organs*, solid organs, which were by far the most complex to recreate due to the vascularity.[3]

Levels			
Level 1	**Level 2**	**Level 3**	**Level 4**
Skin	Blood vessel	Bladder	Heart
Muscle			Liver
			Pancreas
			Penis

In 2012, within 60 days it was possible, inside the lab, to grow tissue the size of half a postage stamp to the size of a football field; and most cell types could be grown and

expanded outside of the body, with the exception of the liver, nerve and pancreas, as these tissue types need stem cell populations.[3]

The first organ ever induced and made in the lab was the bladder, which was created in 1999. In 2014, organs that have been various tissues regenerated by the printer; these tissues include the bladder, muscle, vagina, penis and the thymus.

In 2015 researchers developed a proof of principle biolimb inside a laboratory; they also estimated that it would be a least a decade for any testing of limbs in humans. The limb demonstrated, fully functioning skin, muscles, blood vessels and bones.[4]

Naturally regenerating appendages and organs

Endometrium

The endometrium after the process of breakdown via the menstruation cycle, re-epithelializes swiftly and regenerates.[5] Though tissues with a non-interrupted morphology, like non-injured soft tissue, completely regenerate consistently; the endometrium is the only human tissue that completely regenerates consistently after a disruption and interruption of the morphology.[5]

Fingers

In May 1932, L.H. McKim published a report in *The Canadian Medical Association Journal*, that described the regeneration of an adult digit-tip following amputation. A house surgeon in the Montreal General Hospital underwent amputation of the distal phalanx to stop the spread of an infection. In less than one month following surgery, x-ray analysis showed the regrowth of bone while macroscopic observation showed the regrowth of nail and skin.[6] This is one of the earliest recorded examples of adult human digit-tip regeneration.[7]

Studies in the 1970s showed that children up to the age of 10 or so who lose fingertips in accidents can regrow the tip of the digit within a month provided their wounds are not sealed up with flaps of skin – the de facto treatment in such emergencies. They normally won't have a fingerprint, and if there is any piece of the finger nail left it will grow back as well, usually in a square shape rather than round.[8][9]

In August 2005, Lee Spievack, then in his early sixties, accidentally sliced off the tip of his right middle finger just above the first phalanx. His brother, Dr. Alan Spievack, was researching regeneration and provided him with powdered extracellular matrix, developed by Dr. Stephen Badylak of the McGowan Institute of Regenerative Medicine. Mr. Spievack covered the wound with the powder, and the tip of his finger re-grew in four weeks.[10] The news was released in 2007. Ben Goldacre has described this as "the missing finger that never was", claiming that fingertips regrow and quoted Simon Kay, professor of hand surgery at the University of Leeds, who from the picture provided by Goldacre described the case as seemingly "an ordinary fingertip injury with quite unremarkable healing"[11]

A similar story was reported by CNN. A woman named Deepa Kulkarni lost the tip of her little finger and was initially told by doctors that nothing could be done. Her personal research and consultation with several specialists including Badylak eventually resulted in her undergoing regenerative therapy and regaining her fingertip.[12]

Kidney

Regenerative capacity of the kidney has been recently explored.[13]

The basic functional and structural unit of the kidney is nephron, which is mainly composed of four components: the glomerulus, tubules, the collecting duct and peritubular capillaries. The regenerative capacity of the mammalian kidney is limited compared to that of lower vertebrates.

In the mammalian kidney, the regeneration of the tubular component following an acute injury is well known. Recently regeneration of the glomerulus has also been documented. Following an acute injury, the proximal tubule is damaged more, and the injured epithelial cells slough off the basement membrane of the nephron. The surviving epithelial cells, however, undergo migration, dedifferentiation, proliferation, and redifferentiation to replenish the epithelial lining of the proximal tubule after injury. Recently, the presence and participation of kidney stem cells in the tubular regeneration has been shown. However, the concept of kidney stem cells is currently emerging. In addition to the surviving tubular epithelial cells and kidney stem cells, the bone marrow stem cells have also been shown to participate in regeneration of the proximal tubule, however, the mechanisms remain controversial. Recently, studies examining the capacity of bone marrow stem cells to differentiate into renal cells are emerging.[14]

Like other organs, the kidney is also known to regenerate completely in lower vertebrates such as fish. Some of the known fish that show remarkable capacity of kidney regeneration are goldfish, skates, rays, and sharks. In these fish, the entire nephron regenerates following injury or partial removal of the kidney.

Liver

The human liver is particularly known for its ability to regenerate, and is capable of doing so from only one quarter of its tissue,[15] due chiefly to the unipotency of hepatocytes.[16] Resection of liver can induce the proliferation of the remaining hepatocytes until the lost mass is restored, where the intensity of the liver's response is directly proportional to the mass resected. For almost 80 years surgical resection of the liver in rodents has been a very useful model to the study of cell proliferation.[17][18]

Toes

Toes damaged by gangrene and burns in older people can also regrow with the nail and toe print returning after medical treatment for gangrene.[19]

Induced regeneration in humans

There are now several human tissues that have been successfully or partially induced to regenerate. Many of these examples fall under the topic of regenerative medicine, which includes the methods and research conducted with the aim of regenerating the organs and tissues of humans as a result of injury. The major strategies of regenerative medicine include dedifferentiating injury site cells, transplanting stem cells, implanting lab-grown tissues and organs, and implanting bioartificial tissues.

Bladder

In 1999 the bladder was the first regenerated organ to be given to seven patients; as of 2014, these regenerated bladders are still functioning inside the beneficiaries.[20]

Heart

Cardiovascular diseases are the leading cause of death worldwide, and have increased proportionally from 25.8% of global deaths in 1990, to 31.5% of deaths in 2013.[21] This is true in all areas of the world except Africa.[21][22] In addition, during a typical myocardial infarction or heart attack, an estimated one billion cardiac cells are lost.[23] The scarring that results is then responsible for greatly increasing the risk of life-threatening abnormal heart rhythms or arrhythmias. Therefore, the ability to naturally regenerate the heart would have an enormous impact of modern healthcare. However, while several animals can regenerate heart damage (e.g. the axolotl), mammalian cardiomyocytes (heart muscle cells) cannot proliferate (multiply) and heart damage causes scarring and fibrosis.

Despite the earlier belief that human cardiomyocytes are not generated later in life, a recent study has found that this is not the case. This study took advantage of the nuclear bomb testing during the Cold War, which introduced carbon-14 into the atmosphere and therefore into the cells of nearby inhabitants. [24] They extracted DNA from the myocardium of these research subjects and found that cardiomyocytes do in fact renew at a slowing rate of 1% per year from the age of 25, to 0.45% per year at the age of 75.[24] This amounts to less than half of the original cardiomyocytes being replaced during the average lifespan. However, serious doubts have been placed on the validity of this research, including the appropriateness of the samples as representative of normally aging hearts.[25]

Regardless, further research has been conducted that supports the potential for human cardiac regeneration. Inhibition of p38 MAP kinase was found to induce mitosis in adult mammalian cardiomyocytes.[26] While treatment with FGF1 and p38 MAP kinase inhibitors was found to regenerate the heart, reduce scarring, and improve cardiac function in rats with cardiac injury.[27]

One of the most promising sources of heart regeneration is the use of stem cells. It was demonstrated in mice that there is a resident population of stem cells or cardiac progenitors in the adult heart – this population of stem cells was shown to be reprogrammed to differentiate into cardiomyocytes that replaced those lost during a heart tissue death.[28] In humans specifically, a “cardiac mesenchymal feeder layer” was found in the myocardium that renewed the cells with progenitors that differentiated into mature cardiac cells.[29] What these studies show is that the human heart contains stem cells that could potentially be induced into regenerating the heart when needed, rather than just being used to replace expended cells.

Loss of the myocardium due to disease often leads to heart failure; therefore, it would be useful to be able to take cells from elsewhere in the heart to replenish those lost. This was achieved in 2010 when mature cardiac fibroblasts were reprogrammed directly into cardiomyocyte-like cells. This was done using three transcription factors: GATA4, Mef2c, and Tbx5.[30] Cardiac fibroblasts make up more than half of all heart cells and are usually not able to conduct contractions (are not cardiogenic), but those reprogrammed were able to contract spontaneously.[30] The significance is that fibroblasts from the damaged heart or from elsewhere, may be a source of functional cardiomyocytes for regeneration.

Simply injecting functioning cardiac cells into a damaged heart is only partially effective. In order to achieve more reliable results, structures composed of the cells need to be produced and then transplanted. Masumoto and his team designed a method of producing sheets of cardiomyocytes and vascular cells from human iPSCs. These sheets were then transplanted onto infarcted hearts of rats, leading to significantly improved cardiac function.[31] These sheets were still found to be present four weeks later.[31] Research has also been conducted into the engineering of heart valves. Tissue-engineered heart valves derived from human cells have been created in vitro and transplanted into a non-human primate model. These showed a promising amount of cellular repopulation even after eight weeks, and succeeded in outperforming currently used artificial valves.[32]

Lung

Chronic obstructive pulmonary disease (COPD) is one of the most widespread health threats today. It affects 239 million people worldwide, which makes up nearly 5% of the global population. Having killed over 3 million people in 2012, COPD was the third greatest cause of death.[33] Worse still is that due to increasing smoking rates and the aging populations in many countries, the number of deaths as a result of COPD and other chronic lung diseases is predicted to continue increasing.[34] Therefore, developments in the lung’s capacity for regeneration is in high demand.

It has been shown that bone marrow-derived cells could be the source of progenitor cells of multiple cell lineages, and a 2004 study suggested that one of these cell types was involved in lung regeneration.[35] Therefore, a potential source of cells for lung regeneration has been found; however, due to advances in inducing stem cells and directing their differentiation, major progress in lung regeneration has consistently featured the use of patient-derived iPSCs and bioscaffolds. The extracellular matrix is the key to generating entire organs in vitro. It was found that by carefully removing the cells of an entire lung, a “footprint” is left behind that can guide cellular adhesion and differentiation if a population of lung epithelial cells and chondrocytes are added.[36] This has serious applications in regenerative medicine, particularly as a 2012 study successfully purified a population of lung progenitor cells that were derived from embryonic stem cells. These can then be used to re-cellularise a three-dimensional lung tissue scaffold.[37]

Indeed, in 2008, there was a successful clinical transplantation of a tissue-engineered trachea in a 30 year old woman with end-stage bronchomalacia. An ECM scaffold was created by removing the cells and MHC antigens from a human donated trachea, which was then colonised by epithelial cells and mesenchymal stem cell-derived chondrocytes cultured from cells of the recipient.[38] The graft replaced her left main bronchus, immediately providing a functional airway, and retained its normal appearance and mechanical function after four months.[38] Because the graft was generated from cells cultured from the recipient, no anti-donor antibodies or immunosuppressive drugs were needed – a huge step towards personalised lung regeneration.

A 2010 investigation took this one step further by using the ECM scaffold to produce entire lungs in vitro to be transplanted into living rats. [39] These successfully enabled gas exchange but for short time intervals only.[39] Nevertheless, this was a huge leap towards whole lung regeneration and transplants for humans, which has already taken another step forward with the lung regeneration of a non-human primate.[40]

Cystic fibrosis is another disease of the lungs, which is highly fatal and genetically linked to a mutation in the CFTR gene. Through growing patient-specific lung epithelium in vitro, lung tissue expressing the cystic fibrosis phenotype has been achieved.[41] This is so that modelling and drug testing of the disease pathology can be carried out with the hope of regenerative medical applications.

Penis

The penis has been successfully regenerated in the lab.[20] The penis is a harder organ to regenerate than skin, the bladder and vagina; due to the structural complexity. [20]

Spinal nerves

The nerves in the spine are a tissue that requires a stem cell population to regenerate. In 2012 a Polish fireman Darek Fidyka, with paraplegia of the spinal cord, underwent a procedure, which involved extracting olfactory ensheathing cells (OECs) from Fidyka's olfactory bulbs, and injecting these stem cells, in vivo, into the site of the previous injury. Fidyka eventually gained feeling, movement and sensation in his limbs, especially on the side where the stem cells were injected; he also reported gaining sexual function. Fidyka can now drive and can now walk some distance aided by a frame. He is believed to be the first person in the world to recover sensory function from a complete severing of the spinal nerves.[42][43]

Thymus

Researchers, from University of Edinburgh, have succeeded in regenerating a living organ. Regenerated organ is closely resembled with juvenile thymus in terms of architecture and gene expression profile.[44] The thymus gland is one of the first organs to degenerate in normal healthy individuals. [45]

Vagina

Between the years 2005 and 2008 four women were given regenerated vaginas. Up to eight years after the transplants all organs have normal function and structure.[20]

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External links

Wikisource has the text of a 1920 *Encyclopedia Americana* article about ***Regeneration***.

- UCI Limb Regeneration Lab