REVIEW SUMMARY

CELL BIOLOGY

Stem cells as role models for reprogramming and repair

Magdalena Götz* and Maria-Elena Torres-Padilla*

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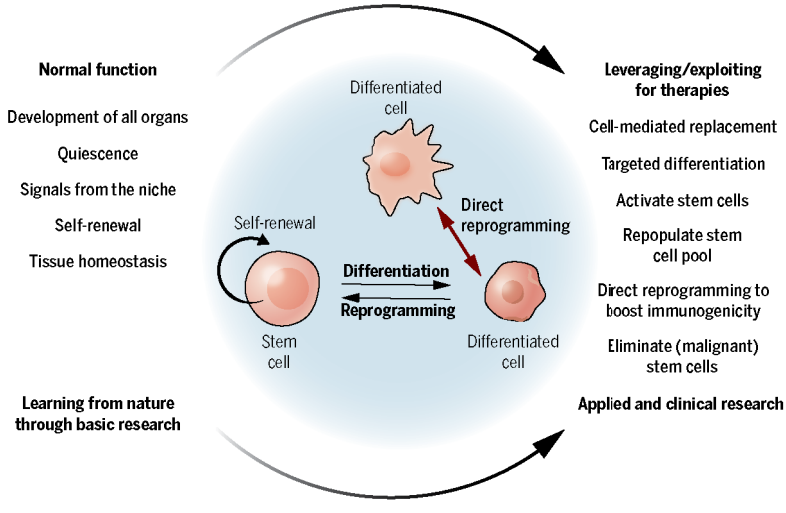
BACKGROUND: Stem cells can generate many different cell types, which makes them useful for understanding developmental mechanisms and as a source to replace cells in disease conditions. Developing stem cell therapies takes time, but there are now many clinical trials in progress. Stem cells start everything off from the very beginning of development as totipotent cells that can generate a complete new being. Later in development, pluripotent stem cells (PSCs) that can generate all cells of the body are produced. During further development, tissue-specific stem cells arise and generate progeny that form tissues and organs. The process of differentiation is governed by the surrounding environment (the niche) and the action of specific transcription factors, which are typically lineage restricted. In the adult organism, some tissues and organs are endowed with adult stem cells, which ensure the natural cycles of tissue turnover and homeostasis seen, e.g., in the skin, intestine, and the hematopoietic system. Such adult stem cells can become activated for tissue repair upon injury or degenerative diseases. However, some adult organs do not have a readily available stem cell pool or the pool changes or becomes exhausted during aging. These organs are typically difficult to repair, but using cellular reprogramming inspired by mechanisms of stem cell differentiation can provide a solution.

ADVANCES: Stem cells inspired direct cellular reprogramming because this approach relies on activating developmental fate determinants from tissue-specific stem cells such as those in the muscle or brain or from PSCs. These potent transcription factors are used to instruct cell fate conversion, and this has arisen as a powerful method to generate cells for repair or disease modeling. A foundational discovery in this area is the reversion of somatic cells into a pluripotent state by the so-called Yamanaka transcription factors, which allow the generation of induced PSCs (iPSCs). This discovery has enabled differentiated somatic cells from patients to be reprogrammed to a pluripotent state. In organs without stem cells, natural dedifferentiation or fate conversion can occur, which can be exploited for cellular replacement approaches. Recently, a plethora of reprogramming paradigms have emerged as approaches to repair, and these are now being used to convert cells across germ layers and cell types across a multitude of organs. These experiments have elucidated the mechanisms of cell fate acquisition, conversion, and maintenance and are an advance toward replacing cells in disease conditions. In addition, direct reprogramming has opened entirely unexpected avenues, such as organismal rejuvenation upon transient expression of some of the pluripotency factors in vivo.

OUTLOOK: The number of clinical trials with stem cells or their derivates has increased tremendously in recent years, with many using iPSCs. These approches can enable the use of the patient's own cells as therapeutics. Remarkable progress has been made in bringing stem cell–based methods and stem cell–inspired reprogramming toward clinical testing with promising outcomes, e.g., in diabetes, macular degeneration, epilepsy, and Parkinson's disease. However, therapeutic approaches have also followed unexpected avenues, such as aiming to reprogram cancer cells into antigen-presenting immune cells. Leveraging the knowledge acquired through decades of basic research on the features and functions that characterize stem cells is now enabling the design of unexpected treatment options. These findings, emerging primarily through our understanding of the developmental trajectories that stem cells follow, have guided the choice of strategies deployed in the use and manipulation of isolated stem cells. We anticipate that reprogramming strategies for repair will open new avenues to generate cell types that have not been accessible or replaceable in disease until now. The inspiration from stem cells will hopefully continue to take us into a bright future to foster understanding and discovery of approaches for treatment. □

*Corresponding author. Email: magdalena.goetz@helmholtz-munich.de (M.G.); torres-padilla@helmholtz-muenchen.de (M.-E.T.-P.) Cite this article as M. Götz and M.-E. Torres-Padilla, *Science* **388**, eadp2959 (2025). DOI: 10.1126/science.adp2959



Uses of stem cells in research. Shown are the properties and uses of stem cells during natural development and tissue turnover and in applied and clinical research.

CELL BIOLOGY

Stem cells as role models for reprogramming and repair

Magdalena Götz[1,2,3]* and Maria-Elena Torres-Padilla[4,5]*

Stem cells are a promising source for cellular therapies across many diseases and tissues. Their inherent ability to differentiate into other cell types has been the focus of investigation over decades. This ability is currently being exploited for therapies using strategies to repair or replace damaged tissues and cells or to alleviate immune rejection. Exploring stem cell function has enabled direct reprogramming approaches, for example, through the production of induced pluripotent stem cells and the generation of tissue-specific stem cells. Understanding stem cell function has emerged as an important strategy for repopulating stem cell pools or generating differentiated cells for therapy. Here, we review general principles of mammalian stem cell biology and cellular reprogramming approaches and their use for current and future therapeutic purposes.

The number of clinical trials using stem cells or their derivatives has substantially increased in the past few years (*1*–*3*). Stem cells are fundamental for the generation of multicellularity, enabling the production of multiple tissues during development. In the adult, tissue-residing stem cells enable the turnover and regeneration of several organs in normal conditions, but also in response to damage or injury. The controlled and appropriate use of stem cells offers a myriad of opportunities to improve human health. Here, we briefly introduce the distinctive properties of stem cells by providing some examples of different tissues and discuss which properties can be leveraged for therapy and which may be unfavorable, e.g., in causing disease. We present current approaches to exploit stem cell reactivation of certain types of tissue-resident stem cells and discuss how stem cells inspire reprogramming strategies to replace lost cells. Finally, we discuss approaches to tissue repair in the framework of currently ongoing stem cell therapies that are already—or soon to be—in the clinic. Although there is extensive and exciting work on stem cells in many metazoans, we will focus primarily on mammalian stem cells.

What makes a cell a stem cell?

Stem cells are generally defined as cells that have the ability to generate different cell types that are more differentiated (Fig. 1). Although self-renewal, the capacity to divide indefinitely, is also a feature of stem cells, not all stem cells have this ability, and some have only a limited capacity to proliferate. For example, cells in the inner cell mass (ICM) of the blastocyst stage embryo do not proliferate indefinitely in vivo. ICM cells only divide one or two times before giving rise to the precursors of the three germ layers (*4*–*6*). The self-renewal capacity of embryonic stem cells (ESCs), which derive from the ICM, is promoted by the presence of specific growth factors in the culture medium (*7*), so their capacity to proliferate indefinitely in vitro does not recapitulate their natural path in vivo.

The first stem cells in our bodies emerge during development and are subject to growth signals that gradually restrict their plasticity as they differentiate to generate all of the cells and tissues of the adult body. As part of the natural developmental process, stem cells are tasked with the goal of building and generating all new tissues and organs (Fig. 1A). Adult tissues also contain stem cells, but some have a limited pool and a limited capacity to self-renew under normal conditions. Each type of tissue-resident stem cell has distinct properties. In organs that undergo constant turnover of cells, such as the hematopoietic system or the skin, stem cells are present all the time. However, during aging or disease, this pool of stem cells can be exhausted, leading to limited tissue regeneration capacity. The existence of stem cells in adult organs is also often a matter of dispute because differentiated cell types can also dedifferentiate toward a stem cell type after injury. Dedifferentiation refers to the phenomenon in which a cell that had performed specific functions in an organ, often a postmitotic cell, acquires features of earlier developmental stages, including the capacity to generate cells of its respective organ.

Stem cells in repair

Organ and tissue regeneration rely on the activation of their stem cell pool, which is typically in a quiescent state. Quiescence refers to the fact that cells that do not divide for a long time, sometimes even years, can resume division and re-enter the cell cycle. To protect from mutations, many adult stem cells divide only rarely, with occasional reactivation (also see below for the role of transient-amplifying progenitors). The balance between tissue homeostasis and quiescence exit is a highly regulated process. For example, quiescence is regulated at multiple levels in the stem cell niche and relies on both cell-intrinsic and cell-extrinsic signaling, including mechanical cues and cell-cell interactions. The stem cell niche refers to the cellular and molecular microenvironment around stem cells (Fig. 1B) and their progeny that promotes stem cell maintenance and regulation. Depending on the tissue, the niche has different cell types and molecules, including fibroblasts, adipocytes, immune and blood cells, extracellular matrix components, and growth factors (*8*). Exit from quiescence typically entails major changes in gene expression, chromatin remodeling, and cellular morphology.

Some adult tissues have an extraordinary capacity to regenerate because they contain stem cells for their natural regeneration during most of our lifetime (Fig. 1C). The intestine and the skin are good examples of this. It is the balance between stem cell quiescence and exit toward differentiation that allows the renewal of the intestinal epithelium, a process that in humans occurs every 3 to 5 days. This process is controlled by WNT (wingless) signaling, in combination with BMP (bone morphogenetic protein) and EGF (epidermal growth factor), which are secreted into the niche, but also involves the function of mechanosensitive signaling and transcriptional networks through the YAP (Yes-associated protein) and TAZ (WW domain containing transcription regulator 1) pathway (*9*). The adult skin is another example of a tissue with high regeneration capacity, where tissue renewal relies on stem cells located in the epidermis, particularly at the basal layer (*10*). The balance between the proliferation of the basal cells and differentiation is driven by signaling and mechanical cues, including through the extracellular matrix and integrins, as well as feedback from the differentiated cells of the higher layers of the epidermis. Differentiating cells arise from asymmetric divisions of the basal stem cells and respond to Notch signaling, again controlled by the niche (*11*). Regeneration of the hair follicle also relies on the activation of differentiation cues that lead to stem cell differentiation, which follows an exquisitely regulated trajectory of quiescence and activation enabled by the niche (*12*).

Stem cells as role models for reprogramming

Stem cells have been the role model for reprogramming. Only a deep understanding of the transcription factors regulating pluripotency in ESCs allowed reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) (*13*). This highlights the typical reprogramming scheme of converting one cell identity into another using transcription factors (Fig. 2A). Reprogramming was initially defined as the

[1]Institute of Stem Cell Research, Helmholtz Center Munich, Munich, Germany. [2]Physiological Genomics, Biomedical Center, Ludwig-Maximilians University, Munich, Germany. [3]SyNergy, Biomedical Center, Ludwig-Maximilians University, Munich, Germany. [4]Institute of Epigenetics and Stem Cells, Helmholtz Center Munich, Munich, Germany. [5]Faculty of Biology, Ludwig-Maximilians University, Munich, Germany. ***Corresponding author. magdalena.goetz@helmholtz-munich.de (M.G.); torres-padilla@helmholtz-muenchen.de (M.-E.T.-P.)**

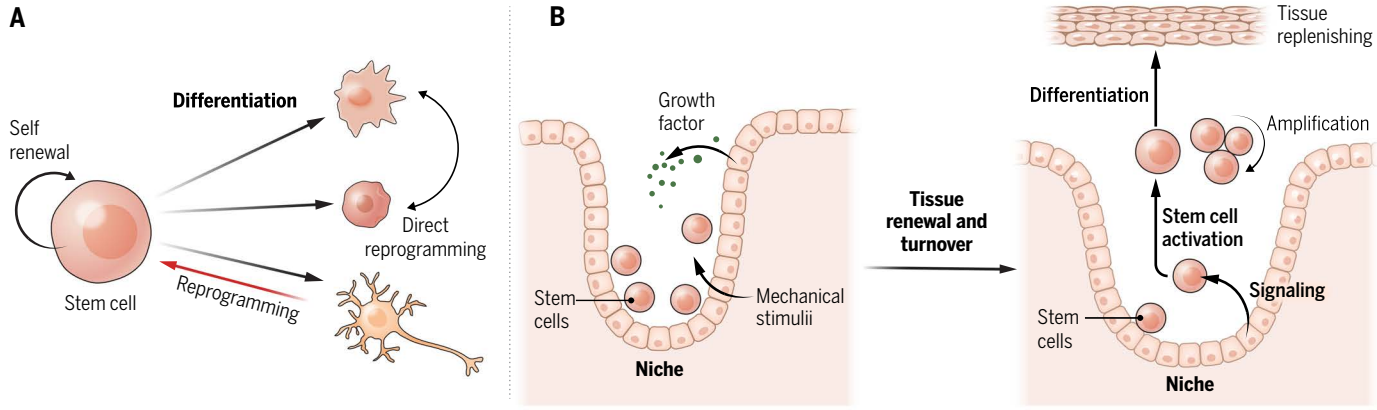


Fig. 1. Stem cell development and niche. (**A**) Stem cells generate different cell types upon differentiation, which then form all of the tissues in the body. The linear arrows from the stem cell pointing right toward the three different cells represent differentiation trajectories. Experimentally, reprogramming can be used to revert to an ESC (bottom red arrow pointing left) or a totipotent-like state, and direct reprogramming allows converting a cell into another cell type. (**B**) Illustration depicting stem cells within their niche, which secretes growth factors and provides mechanical stimuli to ensure quiescence and stem cell homeostasis. This process occurs naturally in organs such as the skin and the blood, ensuring tissue turnover and homeostasis. Under certain conditions, e.g., upon injury, the niche can trigger stem cell activation and differentiation upon signaling. In some cases, generating sufficient cells for tissue replenishing relies on amplification through a TAP cell.

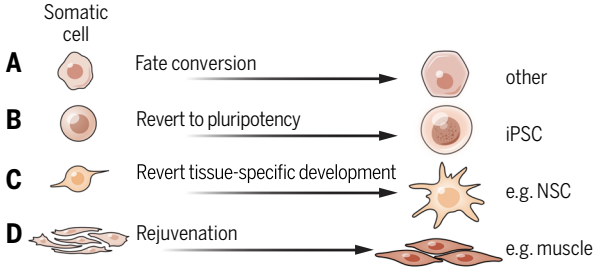


Fig. 2. Schematic depiction of different applications of reprogramming. (**A**) Conversion of somatic cell fate. (**B**) Reversion of development to iPSCs. (**C**) Partial reversion to an organ-specific stem cell fate. (**D**) Reversion of aging hallmarks and rejuvenation of cells.

reversion from a differentiated to a more plastic state (e.g., in iPSCs, in which differentiated cells are "forced" to go back to pluripotency). However, because there are many more examples of turning differentiated cells into another differentiated cell type, the concept of reprogramming is now used in a more general way and refers to a change in cell identity in general. Nevertheless, the tissue of origin from which iPSCs are generated often matters because they are better or more biased to generate progeny of their organ of origin, a phenomenon referred to as "epigenetic memory." Indeed, the pioneering work of converting differentiated *Xenopus* cells to totipotency through somatic cell nuclear transfer, which consists of injecting their nucleus into enucleated oocytes, also revealed that this reprogramming is inefficient. This inefficiency has been linked to deficient reprogramming of ON or OFF memory genes (*14*). This means that genes that are not expressed in the original tissue fail to be activated in the totipotent state (OFF memory genes), whereas genes that have been expressed in the tissue of origin fail to be turned off (ON memory genes). Recent work identified the specific histone marks that are responsible for these phenomena, and their manipulation can improve the reprogramming outcome (*15*). We discuss below further examples of reprogramming in the context of repair and replacement, but it is important to mention that reprogramming also occurs naturally, e.g., after fertilization in mammals, when gametes are reprogrammed into a totipotent embryo (*16*, *17*).

Ensuring stem cell health

A variety of stem cells exist in regenerating tissues in our bodies; others become activated naturally or can be instructed by reprogramming. In all cases, a key factor to enabling the function of repair is stem cell viability and integrity. Often, when cells are induced to dedifferentiate or transdifferentiate, cell death can occur, particularly in cells that fail to exit quiescence or fail to reprogram. For example, both apoptosis and ferroptosis occur as a result of cell competition in the regenerating skin epidermis and during direct neuronal reprogramming (*18*, *19*). Stem cells themselves can also transiently perform phagocytosis of apoptotic corpses for tissue clearance and homeostasis (*20*).

Genome stability must also be ensured for stem and reprogrammed cells to fulfill their function. Cell cycle checkpoint activation, e.g., as a result of genotoxic stress, can threaten genome stability. Moreover, the degree to which stem cells or cells undergoing reprogramming activate, control, or regulate their DNA damage response (DDR) is critical. The DDR can have important implications not only for DNA repair, but also for chromosome stability and replication stress. ESCs are particularly prone to chromosome loss, often of the X chromosome, potentially leading to an unstable karyotype upon passaging (*7*, *21*). Additionally, research has suggested that mouse ESCs have a constitutively active DDR, which is maintained through ATR (ataxia telangiectasia and Rad3 related) activity and can lead to reduced DNA replication fork speed, both of which are considered signs of replication stress (*22*). In fact, expression of the Yamanaka factors for reprogramming iPSCs generates replication stress (*23*). Totipotent cells in both the mouse and the human preimplantation embryo display an even lower fork speed compared with ESCs (*24*, *25*). This feature is also recapitulated in an in vitro system for totipotent-like cells (two-cell-like cells) (*24*). Thus, replication stress and potentially DDR activity differ between differentiated and stem cells. Accordingly, inducing replication stress or experimentally reducing DNA replication fork speed promotes reprogramming in a variety of models, including two-cell-like cells, but also iPSCs and hematopoietic stem cells (HSCs) (*24*, *26*). This highlights how understanding the intrinsic properties of stem cells during their developmental trajectories or natural tissue regeneration cycles can inform the manipulation of cells in vitro to produce bona fide stem cells and ensure their integrity.

Resilience, or adaptability to environmental stimuli, and proliferation are key properties that make stem cells a powerful tool for repair.

However, these characteristics could also potentially lead to deregulated growth, so studies have also focused on understanding and suppressing stem cell tumorigenic capacity. Epidermal skin cells are driven to normal differentiation by WNT signaling, whereby high WNT doses lead to the production of sonic hedgehog (SHH) and cell differentiation (*27*). However, dysregulated SHH signaling leads to tumors such as basal cell carcinoma (*28*). The precise cell of origin of these tumors is not fully established, but lineage-tracing studies have suggested that they derive from long-term resident progenitor cells (*29*). In acute lymphoblastic leukemia, which is associated with highly heterogeneous tumors, a rare subpopulation of cells with HSC features is thought to provide resistance to chemotherapy (*30*). This has been associated with the epigenetic features of stem-like leukemia cells, including reversion of drug resistance and self-renewal capacity, which can endow the tumor with new resistance, thereby inducing patient relapse.

All of this means that stem cell turnover enables tissue regeneration. The niche must be seen as an obligate partner to understanding stem cell potential and regulation. Learning from the developmental cues that stem cells are subject to has been the basis of research leading to repair, but it can also guide research to identify and control potential adverse effects such as unwanted proliferation and tumorigenesis.

Activating stem cells for repair

Stem cell behavior depends crucially on the cell turnover rate in the adult, which differs profoundly between organs and also relates to the capacity for repair. Some organs, such as the skin, blood, and immune system, are entirely exchanged and renewed within days or weeks, whereas others are in a steady state with little to no turnover. Accordingly, the rapidly turning over tissues have quiescent and activated stem cell populations, as discussed above, but most cell production is done by transient-amplifying progenitor (TAP) cell proliferation, with only occasional input from rarely dividing stem cells (Fig. 1B). The TAP cells undergo a number of divisions to expand the progeny of differentiated cells, which enables the generation of a higher number of lineage-differentiated cells while maintaining the stem cells, which may have a lower proliferative capacity (*31*). The passage through a TAP stage avoids the accumulation of mutations that could potentially emerge through many clonal cell divisions. Therefore, if HSCs are needed for repair, such as in the treatment of leukemia with stem cells, HSCs need to be mobilized. Eradication of leukemic cells followed by replacement of the entire blood and immune cell population by the transplanted hematopoietic stem and progenitor cells, was the first stem cell–mediated treatment used in the clinical setting (*32*). It has been further improved by optimizing the mobilization of HSCs by cytokines before collecting blood and purifying typically $CD34^+$ cells for transplantation (*33*, *34*). The $CD34^+$ fraction comprises HSCs and TAP cells, providing a sufficient number of blood cells initially, but the content of the HSCs and their capacity for long-term self-renewal is crucial for long-term replacement and success.

Similarly, skin stem cell–mediated replacements are successful in the clinical setting, e.g., to treat patients with large burns or devastating genetic skin diseases (*35*, *36*). Amplification of the stem cell progeny is also crucial for these treatments, namely by growing larger sheets of skin in the dish before transplantation. In these organs, stem cells need to be activated in larger numbers than usual for successful treatment and ideally should be expanded in vitro to increase numbers without changing their fate. Thus, stem cells are role models for the replacement of lost cells, especially for cell replacement of organs with little or no turnover, such as the brain.

Limitations in stem cell recruitment

An intermediate capacity for cell turnover and repair is encountered in organs containing stem cells that are limited by their capacity to divide and self-renew, which thus become exhausted. This is the case for muscle stem cells that run out of energy when they need to replace more muscle cells than normal, e.g., in muscle dystrophies (*37*, *38*). This shows the down side of "activating stem cells for repair" because it can lead to the depletion of stem cells and thus to an earlier onset of deficiencies in aging, a time when stem cell numbers reduce naturally. This limitation also applies to the few regions where adult neural stem cells (NSCs) reside, namely in different, species-specific niches of the forebrain. Clonal analysis of adult NSCs has shown that they are limited to proliferation for only a few cell cycles before they enter a self-depleting symmetric mode of division generating, e.g., two TAP cells (*39*). However, other specific markers appear to identify subsets of adult NSCs with longer survival and self-renewal capacity (*40*). Indeed, there is notable heterogeneity among adult NSCs, particularly at the level of the transcription factor Ascl1 (achaete scute family of bHLH transcription factor 1) or EGF receptors, which regulate adult NSC activation (*41*, *42*). Although $Ascl1^+$ NSCs are activated and shorter lived, Gli (GLI Family Zinc Finger 1)–, Hopx (Hop homeobox)–, or Troy/Tnfrsf19 (Tumor necrosis factor receptor superfamily, member 19)–expressing NSCs are more quiescent and self-renew for longer (*40*, *43*–*45*). Nevertheless, activation of NSCs after brain injury results in reduced NSC numbers afterward, highlighting their limitation for repair, even in zebrafish, which have lifelong neurogenesis in most brain regions (*46*, *47*).

Even in the mammalian brain, NSCs are activated naturally by injury. For example, after stroke, NSC and TAP proliferation are increased in the adult murine forebrain, and large numbers of young neurons, so-called neuroblasts, are generated and migrate to the lesion side (*48*, *49*). However, these neurons fail to mature and die (*50*). This poststroke increase in neurogenesis goes on for months in rodents, continuously generating abortive neurogenesis (*51*). So why are these neurons dying? It could be because of the adverse environment of the lesion, but transplantation has shown that young neurons can survive and even integrate in such an environment (*52*, *53*). Cell death is thus more likely to occur because of the wrong subtype identity of the newly generated neurons. Adult neurogenesis of the murine brain in this region normally generates specific interneurons of the olfactory bulb in rodents, which sharpen odor discrimination and learning. After stroke, projection neurons of the basal ganglia or the cortex are lost, but the activated adult NSCs have the wrong patterning information to generate these. Thus, in addition to activation in the nervous system, stem cell specification to generate appropriate neuronal subtypes has to be changed, e.g., by the forced expression of reprogramming factors (as discussed below).

In the human brain, there is evidence for neurogenesis after stroke, but it is much more indirect and, like adult human neurogenesis, is also a matter of dispute [for review, see (*54*)]. After stroke and in related pathologies, proteins involved in neurogenesis increase in the cerebrospinal fluid (CSF) or blood (*55*, *56*), and cells in the stem cell niche at the lateral ventricle increase their proliferation (*57*). Also, cells with in vitro NSC potential that can form self-renewing and multipotent neurospheres have been identified after stroke (*58*, *59*) and in pathologies with brain hemorhage (*56*). However, no long-term surviving neurons are generated after stroke in humans (*60*). Thus, whereas the few NSCs present in the human brain react to damage, no long-lasting generation of neurons seems to take place; this is also true in rodent models, in which neuroblasts also die. Therefore, the endogenous activation of NSCs is not sufficient for repair in the human brain and needs further help to achieve repair and restoration of function.

How to repair in the absence of stem cells

A formidable challenge in regenerative medicince is the activation of cells for repair in organs and brain regions where there is no or almost no natural turnover. This includes most regions of the mammalian brain, the pancreas, and also the liver. The liver is particularly interesting because it has a very low turnover rate normally, with hepatocytes having a life span of several hundred days, and even this

is disputed (*61*). Nevertheless, the liver can replace 75% of its volume if necessary. The identity of the exact source of cells achieving this replacement has long been the subject of controversy. Improved animal models and lineage-tracing approaches have shown that both differentiated hepatocytes (*62*) and cholangiocytes (*63*) can dedifferentiate upon challenge and differentiate back to mature cells to repair the organ. This is a prime example of an uncoupling of normal tissue turnover and the capacity for repair, but it is also a rather rare example.

Another organ with little to no turnover of most cell types, namely neurons and most glial cells, is the adult mammalian brain. There are no NSCs in most brain regions (with the exceptions of the few adult NSC niches discussed above), and neurogenesis does not continue after birth. However, after injury, astrocytes, a special type of glial cell, become reactive and assume partial stem cell properties (*64*). This phenomenon is not due to the recruitment of stem cells from their niches when injury occurs, but rather to partial dedifferentiation of resident astrocytes (*64*–*67*). Astrocytes are the closest relatives to the NSCs and both are glial in nature. NSCs are actually radial glial cells with an elongated morphology, whereas astrocytes are star shaped. The radial glial cells generate the nervous system but then disappear in most regions in mammals, whereas they persist in most regions in other vertebrates, such as zebrafish, amphibians, and some reptiles. These nonmammalian species can thus reactivate neurogenesis after injury, even in regions where neurogenesis has stopped, such as the midbrain (*68*). Indeed, such natural or adaptive reprogramming occurs upon irradiation in the cerebellum (*69*). Likewise, glial cells reacquire aspects of NSCs after traumatic or ischemic injury in the mammalian spinal cord or brain and participate in repair by generating oligodendrocytes (spinal cord) or abortive neuroblasts (brain) (*70*–*72*). Similarly, activation of NSCs and neurogenesis genes also occurs in mammalian brain reactive astrocytes (*65*, *67*), but without additional factors, they fail to generate neurons in the gliogenic environment of an adult injured brain. Such dedifferentiation was also observed in human patients with hemorrhage, where astrocytes resumed proliferation in the gliotic regions and their presence was found to be correlated with in vitro stem cell potential, as observed by neurosphere formation (*56*). These partially dedifferentiated astrocytes have the correct regional specification and thus may be ideal cell sources to turn into fully functional adult NSCs. But how could this be achieved?

Instructing stem cell fate for repair

Direct reprogramming converts cells directly to a different cell type by expressing particular transcription factors that are sufficient to induce a different fate (Fig. 2A). Typically, there are several of them and they include a pioneer factor that has the capacity to bind to their DNA target in a nucleosomal context and recruit factors to open chromatin at these sites and activate transcription (*73*, *74*). Such transcription factors are found during development, when the fate of the desired cell type is naturally specified, such as during neurogenesis for NSCs or during myogenesis for muscle cells. This approach was first used to instruct muscle fate from fibroblasts (*75*, *76*) and subsequently to convert astrocytes into neurons (*77*), both fate conversions within the same germ layer. The discovery that differentiated cells can be reverted to iPSCs by the Yamanaka factors (*13*) (Fig. 2B) has enabled the conversion of cells across germ layers, e.g., changing fibroblasts or peripheral blood cells into NSCs (*78*, *79*). Indeed, crossing germ layer origin seems not to have a major influence on the ease of fate conversion (*80*), allowing the choice of the best cell type of origin to be considered for therapeutic needs. For example, endogenous local glia such as astrocytes can be used for neurogenesis because they have the adequate patterning information of the respective brain region, or dermal fibroblasts can be used for lung-like epithelial cells. Expressing neurogenic NSC factors such as Pax6 (Paired-box 6), Sox2 [SRY (sex determining region) 2], or Ngn2 (Neurogenenin 2) in reactive astrocytes converts these directly to young neurons [for review, see (*81*)]. This may actually be desirable for direct conversion within the brain because generating NSCs may risk glioma formation. Initially, reprogramming had been targeted to proliferating reactive glial cells by the use of a MLV (Moloney murine leukemia virus)–based retrovirus (*19*, *64*) that can insert its DNA only in dividing cells because it requires nuclear envelope breakdown. This also ensured that endogenous neurons were not targeted. However, adeno-associated viral vectors elicit less of an immune reaction and less scar formation, but they also target postmitotic neurons, leading to artifactual activation of allegedly glia-specific promoters in endogenous neurons. This is why the claims on reprogramming glia by reducing PTBP1 (Polypyrimidine tract-binding protein 1) levels in various brain regions into just the right neurons turned out to be artifactual [for review, see (*81*)]. These pitfalls highlight the importance of the viral vectors used both experimentally and therapeutically and the need for controls for the former (e.g., genetic fate mapping of the cells of origin and labeling of endogenous neurons) (*81*). However, reliable reactive glia–to–inhibitory neuron reprogramming using MLV-derived retroviral vectors has already achieved beneficial effects in preclinical epilepsy models (*82*), indicating that this approach could be further developed for therapy. This would avoid the need for cell transplantation and immune suppression, because neuronal replacement would come from the patient's own cells.

Although the above-discussed reprogramming generates neurons directly, inducing NSCs has the advantage that they can generate larger numbers of neurons and can be induced from human cells, e.g., from blood or a skin biopsy (Fig. 2C). This approach seems to work best by expressing pluripotency factors transiently (*83*). For example, human fibroblasts can be reprogrammed into expandable NSCs using Oct4 (octamer-binding transcription factor 4), Sox2, Myc (MYC proto-oncogene), and Klf4 (Krüppel-like factor 4) (*84*, *85*). To ensure therapeutic compatibility, tools such as the Sendai virus can be used to deliver these factors because it is inactivated after 2 weeks (*86*). These NSCs are comparable to physiological NSCs, as mapped by single-cell transcriptomics, and can be differentiated into various types of neurons. The same strategy seems to work well with human peripheral blood cells as the origin (*87*), providing further therapeutic accessibility.

Different reprogramming factors have been used to generate endocrine beta–like cells in the pancreas (*88*, *89*), cardiomyocytes in the heart, and epithelial cells in models of lung disease (*90*). In such models, excessive fibrosis can become a burden impairing, e.g., oxygen intake, so reducing scarring under these conditions is essential. Reprogramming of both healthy and chronic obstructive pulmonary disease (COPD) fibroblasts into functional lung epithelial cells by using a combination of the pluripotency Yamanaka factors OSKM, OCT-4, SOX2, KLF4, and MYC with lung lineage–specific factors such as Nkx2-1 (NK2 homeobox 1) has emerged as an alternative for potential treatment (*91*, *92*). In fact, this strategy of combining pluripotency factors with lineage-specific factors has also been used to generate cardiomyocytes, hematopoietic progenitors, and NSCs (*93*–*95*).

Inducing stem or progenitor cell fate for repair (Fig. 2C) also works effectively in other organs. For example, when wound healing in the skin is blocked in conditions of scar or ulcer, mesenchymal cells can be converted into keratinocyte progenitors (which can also be considered unipotent stem cells) in vivo by four transcription factors involved in keratinocyte specification (*96*). These progenitor/stem cells have profound proliferation capacity and can generate skin sheets to cover larger regions of repetitive wounding. Endogenous stem cells are the benchmark to compare the induced stem or progenitor cells. Conversely, identification of gene-regulatory networks followed by reprogramming of somatic cells into a stem cell fate allows the generation of expandable stem cell sources to produce large numbers of specific types of cells needed for repair. However, it is not

always necessary to generate stem cells, because differentiated cells are sufficient for cell replacement. If in vivo conversion works and there are sufficient cell numbers, then converting, e.g., fibroblasts in fibrotic tissue directly into the desired cell type, e.g., hepatocytes (*97*, *98*) or lung epithelial cells (*91*), is likewise a promising avenue to repair. Fibroblasts can be beneficial or harmful in wound healing across organs. More recently, it has become clear that defined subpopulations of fibroblasts have distinctive functions in mediating or exacerbating the fibrosis that leads to scarring (*99*, *100*), thus affecting stem cell–mediated regeneration. Because excessive scarring and fibrosis prevent organ function, fibroblast conversion to functional cells by direct reprogramming can also improve wound healing. The concept of reprogramming scar-forming cells into functional cells has also been proposed for repair strategies of the brain, where reactive glial cells can be converted into neurons [for review, see (*81*)].

Another impressive example of stem cells as role models comes from PSCs. Transient expression of the key pluripotency factors identified in PSCs has revealed several surprising outcomes in reprogramming, with their transient and partial expression instructing or reactivating several stem cell types (Fig. 2C). For example, exhausted muscle stem cells can be reactivated with marked effects by transient expression of the pluripotency factors Oct4, Sox2, cMyc, and Klf4, which activate niche factors to promote muscle stem cell activation (Fig. 2D) (*101*). Such niche effects may also explain the rejuvenation effects that transient expression of pluripotency factors seems to have on organismal aging (*102*, *103*). Thus, understanding the molecular cues specifying and activating stem cells holds multiple avenues for future therapies.

Present and future of stem cell therapies

Much progress has been made in bringing stem cells and reprogramming strategies to the clinic. This is reflected in the large number of clinical trials using stem cell–derived products, as recently reviewed in a comprehensive, up-to-date overview for PSC-derived products (*2*). The process to reach application to patients is lengthy, not only because of the tremendous efforts first needed in basic research, but also because of the regulatory framework needed to ensure quality, robustness, and early identification of undesired side effects. Progress is often achieved by building on research work across several angles from both basic and clinical research, including, e.g., establishing conditions for self-renewal and for organoid formation or cell differentiation, cryopreservation methods, or GMP (Good Manufacturing Practices) production. Additionally, depending on the number of patients enrolled in clinical trials, the trials themselves can also be lengthy.

Current clinical trials often use mesenchymal stem cell–like cells and adult stem cells, but a very active area with multiple ongoing clinical trials is based on the use of human PSC–based derivatives, including human ESCs and iPSCs (*2*, *104*). Examples in this area include trials using human PSC–derived lineages in diabetes, heart attack, eye and CNS diseases, and others, which have been recently comprehensively reviewed (*2*, *105*). So far, most beneficial effects have been achieved by transplanting PSC-derived beta cells (including from chemically reprogrammed iPSCs) (*106*) for focal epilepsy, Parkinson's disease, and age-related macular degeneration. In addition, a nonrandomized trial using human iPSC-derived corneal epithelial cell sheets for transplantation in four patients with a pathological limbal corneal deficiency was just completed (*107*). A 2-year follow-up showed positive results and vision improvement, further highlighting a success story using stem cells for replacement therapy.

Another example of current stem cell therapies focuses on alleviating and/or repairing damage to salivary glands. The standard of care for head and neck cancer is surgery followed by radiotherapy. It is estimated that between 63 and 93% of the patients will have permanent salivary gland damage if the glands are within the field of radiation, leading to several degrees of hyposalivation ranging from mild to very severe (*108*). Recent work describes the successful treatment of the first patient with radiotherapy-induced hyposalivation (www.clinicaltrials.gov identifier NCT04593589) (*109*). The treatment was started much earlier, and a critical step was showing that stem cell–and organoid-derived (xeno)-transplantation into irradiated salivary glands of mice can lead to organ regeneration (*110*–*112*). The current clinical trial for this intervention relies on the use of salivary gland stem cells from the patients themselves, which are biopsied before cancer treatment and undergo expansion into gland organoids before transplantation (www.clinicaltrials.gov identifier NCT04593589).

Direct reprogramming in vivo is also currently at the preclinical exploration stage to treat other types of cancer (*113*). The downregulation of antigen presentation and the major immunohistocompatibility complex is a common strategy used by cancer cells to evade the immune system response. This is in part because antigen-presenting type 2 dendritic cells (referred to as cDC1s) are commonly depleted in tumors (*114*). The quest for a therapeutic source of cDC1s went through several trials and errors, exploiting, e.g., differentiation protocols, which turned out to be largely inefficient. A breakthrough occurred when transcription factors that directly reprogram mouse and human fibroblasts into functional cDC1s were identified (*115*). These transcription factors, PU.1 (SPI-1 Proto-Oncogene), IRF8 (Interferon regulatory factor 8), and BATF3 (basic leucine zipper ATF-like transcription factor 3), are naturally used by the body during the developmental formation of cDC1s, and they are currently used therapeutically to reprogram cancer cells into immunogenic antigen-presenting cancer cells. The goal is to produce cancer cells that actively present cancer-specific antigens, thereby allowing the patient's own immune system to eliminate them (*116*). Although they are still in the early stage, these interventions are extremely promising. As mentioned above, direct reprogramming has a plethora of applications, not least in conditions in which fibrosis interferes with organ function, because fibroblasts seem particularly amenable to reprogramming independently of the germline origin of the target cell type (*80*). Given the power of this approach, cell replacement therapies have now become a feasible option for many organs for which this had seemed absolutely impossible, including the brain.

The use of stem cells, of course, is not limited to cancer treatment. In the nervous system, trials to replace lost neurons in degenerative diseases such as Parkinson's disease and focal epilepsy have been resumed (*1*, *2*, *117*, *118*). Because of years of work and the successful establishment of differentiation protocols, sufficient numbers of young ventral midbrain dopaminergic neurons can now be generated. These cells have undergone extensive quality control and characterization at many levels, including single-cell RNA-sequencing–based comparison with fetal human dopaminergic neurons. Several clinical trials are underway using allogenic (cells from a different donor) or autologous (cells from the patient) transplantation. The latter avoids the need for immune suppression, and this may actually have beneficial effects in disease. Moreover, most past and current clinical trials for transplantation for immune-privileged eye and CNS diseases showed that allogenic cells can survive for years, even when immune suppression was stopped (*1*, *2*).

Stem cells have also been used in patients to reduce rejection responses for kidney replacement (*119*). HSCs from the kidney donor were administered to three patients to achieve lymphoid and myeloid chimerism (e.g., between the donor and the patient) before kidney transplantation (*119*). This led to a reduction in immune rejection and is thus a very promising avenue that further expands the use of stem cells in therapies (*119*). Other interventions include testing the ability of lung progenitor cells to repair lung tissue upon inflammation and fibrosis (www.clinicaltrials.gov identifier NCT06164093). However, many of these interventions remain in the preclinical and/or pilot clinical stage.

Stem cells are now widely used in many therapeutic approaches and have inspired new strategies from unexpected standpoints. Direct reprogramming, with multiple applications before iPSC discovery, has advanced rapidly because of its demonstrated potential for cellular reprogramming. Early reports on direct fate conversion were often met with skepticism based on the argument that a small, nondetectable population of stem cells in the starting population was responsible for generating new fates. The reprogramming of somatic cells into iPSCs, one of the most plastic stem cell types, has revolutionized the view on direct reprogramming, settling long-standing debates in the field. In this context, reprogramming into the only cell type with greater potency, the totipotent cell, holds further promise for treatment options by leveraging the distinct features that characterize these cells, such as slow replication speed (*24*).

Conclusions

Uncovering the strategies that nature uses for generating and maintaining stem cells has improved our understanding of cellular plasticity. This knowledge has enabled engineering cells through direct reprogramming to improve health and organ function. Stem cells will continue to inspire and drive research and clinical applications in the future.

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