Dedifferentiation and *in vivo* reprogramming of committed cells in wound repair (Review)

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Abstract. Accumulating evidence has shown that cell dedifferentiation or reprogramming is a pivotal procedure for animals to deal with injury and promote endogenous tissue repair. Tissue damage is a critical factor that triggers cell dedifferentiation or reprogramming *in vivo*. By contrast, microenvironmental changes, including the loss of stem cells, hypoxia, cell senescence, inflammation and immunity, caused by tissue damage can return cells to an unstable state. If the wound persists in the long-term due to chronic damage, then dedifferentiation or reprogramming of the surrounding cells may lead to carcinogenesis. In recent years, extensive research has been performed investigating cell dedifferentiation or reprogramming *in vivo*, which can have significant implications for wound repair, treatment and prevention of cancer in the future. The current review summarizes the molecular events that are known to drive cell dedifferentiation directly following tissue injury and the effects of epigenetic modification on dedifferentiation or reprogramming *in vivo*. In addition, the present review explores the intracellular mechanism of endogenous tissue repair and its relationship with cancer, which is essential for balancing the risk between tissue repair and malignant transformation after injury.

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1. Introduction

A fundamental change in the cellular characteristics of differentiated cells *in vivo* provides the necessary pathway for the recovery of a wide variety of mammalian tissues following injury or other stress challenges. Previous studies investigating cell reprogramming have demonstrated that, even in mature tissues, the characteristics of differentiated cells are not fixed and maintain a certain degree of plasticity (1-3). Cell plasticity was first discovered through nuclear transfer experiments (4). However, with the advent of higher throughput studies came the discovery that fibroblast cell lines can be transformed into muscle cells by the induced expression of the transcription factor myoblast determination protein 1 (5). At present, a number of studies have shown that the ectopic expression of key transcription factors, microRNAs (miRNAs) or even treatment using small molecule compounds, can be used to induce intercellular conversion (6,7). This suggests that cell plasticity may be a universal feature, where as long as the correct extrinsic signal and intracellular conditions are present, cell type switching may occur. Therefore, cell identity can also be changed physiologically in a manner dependent on the internal changes of the cell, signals received by the cell or the environment surrounding the cell (8). Tissue damage is one of these driving factors, where transformation of cell phenotype constitutes a key physiological healing mechanism in the body after injury (9). Cell dedifferentiation and reprogramming are the two main methods of phenotype switching in response to injury, both of which serve a critical role in tissue homeostasis and repair (8). Their importance is underlined by the observations that they are also highly conserved throughout the animal kingdom (10-13).

The present review summarizes the key factors leading to dedifferentiation and *in vivo* reprogramming during the process of injury repair, in addition to summarizing the relationship between cell plasticity caused by injury and tumorigenesis. Clarifying these processes at both molecular and cellular levels will deepen understanding into the repair mechanism after injury and diseases involving cell plasticity. This information can then be used for the potential use of *in vivo* cell dedifferentiation and reprogramming in clinical treatment.

2. Tissue damage and microenvironmental change

Dedifferentiation and reprogramming are common physiological responses to injury or cell ablation across various tissues in a wide range of organisms (13-15). Therefore, dedifferentiation and reprogramming may be a general characteristic of terminally differentiated cells after injury. However, this event appears to only occur after environmental perturbations around the cell but not under conditions of homeostasis, tissue damage being one of the main causes of these environmental disturbances. Previous studies have shown that during the regeneration of *Ambystoma mexicanum* tissues, including the jaw, lens, retina, large region of heart, limbs and tail, cell identity changes occurred within a 100 μm radius of the tissue resection site (16). In addition, the dedifferentiation pattern of GATA6-positive cells during wound repair in the epidermis suggests that dedifferentiation is more likely to occur in close proximity to the wound (17). Therefore, tissue damage most likely exposes cells to new stimuli that lead to dedifferentiation or reprogramming, or cells are relieved of inhibitory signals that suppress any phenotypic changes, ultimately promoting dedifferentiation and reprogramming. These signals involving cellular autonomic and non-autonomic factors altogether constitute a regulatory mechanism for cell identity changes after tissue injury.

Tissue damage caused stem cell loss. Dedifferentiation or reprogramming of committed cells occurs only after disturbances in the surrounding environment of the cells; however, this does not occur under homeostatic conditions (18,19). This suggests that committed cells are inhibited by signals under homeostatic conditions, rendering them unable to change phenotypically. This maintains the equilibrium between stem cells and their differentiated counterparts. This balance allows each cell type to have a clearly defined function. Previous studies have shown that signals that maintain intercellular balance may come from stem cells themselves (15,20-22).

Drosophila melanogaster serves as an effective model to illustrate the inhibitory role of stem cells on the dedifferentiation of neighboring committed cells. In the fly testis, germline stem cells (GSCs) are sustained by signal transducer and activator of transcription (STAT) signaling, which serves as the central signaling niche known as the 'hub' (23,24). Once the STAT signal is removed the GSCs cannot be maintained; however, new functional GSCs will arise to restore STAT signaling and return the entire system to homeostasis (10). The new functional GSCs are derived from the dedifferentiation of gonialblasts and spermatogonia (10). The aforementioned process also occurs after the forced differentiation of GSCs by the ectopic expression of the differentiation factor Bam, suggesting that elimination of the GSC pool is responsible for cell dedifferentiation, rather than STAT signaling (25). In addition, this process appears to be conserved in mammals, since there are reports that differentiated mouse secretory cells can be converted into stable and functional airway basal stem cells *in vivo* (15). However, this dedifferentiation process can be prevented by even only one single basal stem cell being in direct contact with the secretory cells (15). Similarly, studies in gastric and intestinal epithelium have shown that when stem cells are ablated, other cell types dedifferentiate into stem cells (20-22). This suggests that the presence of stem cells will strongly inhibit the dedifferentiation of committed cells. Furthermore, this inhibition will be lifted only when the stem cells are completely ablated. Otherwise, the repair of damaged tissues would be more inclined to rely on existing stem cells instead of the dedifferentiation of committed cells.

It should be noted that this mixed population of cells appears to exist under a hierarchical structure. In this structure, stem cells serve as 'the leader', where under their 'rule', cells form a strict hierarchy that is difficult to break. However, once the leader is lost, new members will fill the vacancy to stabilize the normal order of this hierarchy. The loss of stem cells caused by tissue injury is one of the key factors that releases the inhibition of committed cells and triggers dedifferentiation or reprogramming (15,20-22) (Fig. 1).

Hypoxia and metabolic change. After tissue damage, the loss of the epidermal barrier can lead to a sudden influx of extracellular oxygen, which is quickly consumed by metabolically active cells or converted into reactive oxygen species (26). At the same time, blood flow is interrupted due to vascular injury and constriction, reducing oxygen delivery to the wound. At this time, the wound site is in a state of local tissue hypoxia, where hypoxia-inducible factor (HIF), which is normally degraded under normoxic conditions, becomes stabilized in the hypoxic wound site (27). Therefore, injury results in the disturbance of the cell microenvironment at the wound site, creating a hypoxic niche that embryonic stem cells (ESCs) and adult stem cells rely on for self-renewal (28). Previous studies have shown that hypoxic conditions can promote the self-renewal and maintenance of pluripotency in embryonic and other types of stem cells (29-31). Under hypoxia, human ESCs control HIF2α through glycolytic flux, thereby upregulating the expression of C-terminal binding proteins 1 and 2 to sustain self-renewal (29). In addition, HIF2α is closely associated with the pluripotency regulatory network of genes, such that HIF2α knockdown leads to the downregulation of octamer-binding transcription factors 3 and 4 (OCT3/4), sex determining region Y-box 2 (SOX2) and NANOG (30). *In vitro* reprogramming experiments have also revealed that hypoxia can promote the expression of pluripotent factors, such as OCT3, OCT4, SOX2, NANOG and Krüppel-like factor 4 (KLF4), to increase the efficiency of reprogramming, and can reduce the number of transcription factors required for reprogramming (31). Therefore, it is not surprising that hypoxia signaling serves a key role in wound healing and tissue repair, largely by inducing cell dedifferentiation or reprogramming at the wound site. In the zebrafish model, myocardial hypoxia induced by ventricular amputation has been shown to serve

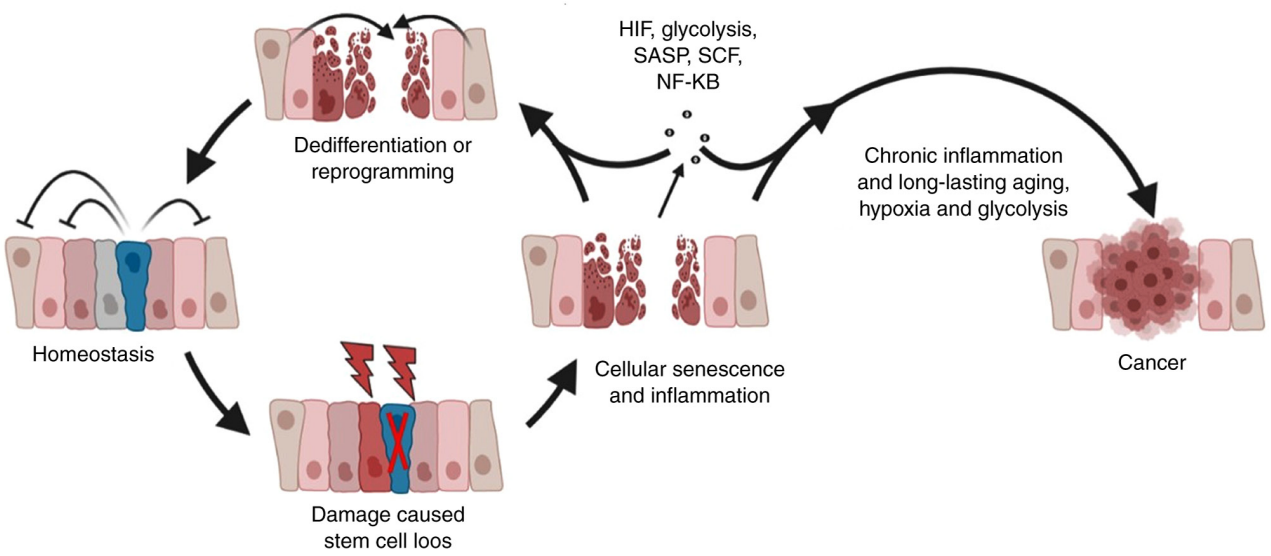

Figure 1. Dedifferentiation or reprogramming process after tissue damage. During homeostasis, signals from stem cells (blue) inhibit dedifferentiation of neighboring cells. The loss of stem cells caused by tissue injury is one of the key factors that relieves the inhibition of committed cells and triggers dedifferentiation or reprogramming. In some cases, differentiation or reprogramming could be inhibited in the presence of individual stem cells. Reprogramming and regeneration could be more efficiently modulated when tissue damage combined with hypoxia, glycolysis, cell senescence and inflammation. Appropriate levels of hypoxia, glycolysis, inflammation and cellular senescence could induce cell dedifferentiation to promote tissue repair. Dedifferentiation or reprogramming will still occur; however, in chronic inflammatory and long-lasting aging, hypoxia and glycolysis responses, this may be a cause of cancer.

a positive role in myocardial regeneration, whilst hyperoxic conditions or the overexpression of HIF1α can strongly prevent the regeneration process after ventricular amputation (32). After culturing *in vitro*, it has been revealed that the dedifferentiation of cardiomyocytes is significantly promoted under hypoxic conditions compared with that under normoxia, whilst the number of dedifferentiated cardiomyocytes is significantly decreased following hyperoxic treatment (32). In addition, there is evidence that hypoxia can induce the reprogramming of resident muscle cells post-injury so that they exhibit the characteristics of pluripotent cells known as injury-induced muscle-derived stem cells (33-35). A similar phenomenon has also been observed in the brain tissues of patients with ischemic stroke (36). It is noteworthy that hypoxia has been found to induce dedifferentiation in a wide variety of cell types, such as adipocytes, renal cells and astrocytes (37-39).

A significant effect of hypoxia on cells is the change to their metabolic state. Under hypoxia, the majority of eukaryotic cells can switch their primary metabolic strategy from mitochondrial respiration to glycolysis to maintain ATP levels (40). Multiple previous studies have shown that high levels of glycolysis can maintain the self-renewal properties of stem cells (41-45). Mitochondrial function has been found to be reduced in the inner cell mass (46), whereas ESCs obtained *in vitro* also showed higher glycolytic rates (41). In addition, induced pluripotent stem cells exhibit metabolic reprogramming from oxidative phosphorylation to glycolysis (42). Similarly, in adult stem cells, hematopoietic stem cells (HSCs) typically show more hypoxic states with higher levels of HIF1α expression. These cells rely heavily on anaerobic glycolysis and suppressed mitochondrial respiration, which allows them to sustain their self-renewal characteristics (43-45). Similar to HSCs, bone marrow stem cells also rely on glycolysis for energy. When these cells are transferred from hypoxic to normoxic conditions, their stem cell properties become impaired and they differentiate (47,48). Metabolic conversion from oxidative phosphorylation to aerobic glycolysis therefore likely serves a key role in regeneration. Studies have previously shown that metabolic transformation to glycolysis is an inevitable initial event during blastema formation and tail regeneration in zebrafish after amputation (49,50). During this process, cells undergo epithelial-mesenchymal transition and dedifferentiation. Inhibiting glycolysis leads to the failure of tail regeneration (49,50). In a zebrafish cardiac regeneration model, glycolysis transfer has been found to be concentrated in the vicinity of damaged tissues (51). Following treatment with 2-deoxy-D-glucose or when glycolysis is inhibited by affecting pyruvate kinase M2 function, the dedifferentiation levels of cardiomyocytes are decreased significantly (51). The importance of glycolytic transfer on cell dedifferentiation after tissue damage is also evident in mammals. Compared with normal mice, the Murphy Roths Large (MRL) strain of mice exhibit higher glycolysis levels, which enable MRL mice to retain the ability of forming blastema, resulting in superior regenerative capabilities compared with normal mice (52). A further study has demonstrated that the HIF-1α pathway is key in understanding the regenerative abilities of MRL mice. The expression level of HIF-1α in MRL mice has been found to be significantly increased after tissue injury, where the tissue regeneration abilities of MRL mice are severely damaged after the downregulation of HIF-1α expression (53). In normal mice, injection of HIF-1α degradation inhibitors after ear perforation injury has been found to promote perforation closure and healing, cartilage regeneration and hair follicle formation (54). In addition, a number of studies have shown that *in vitro* mammalian cell dedifferentiation requires glycolysis transfer (42,55,56). Therefore,

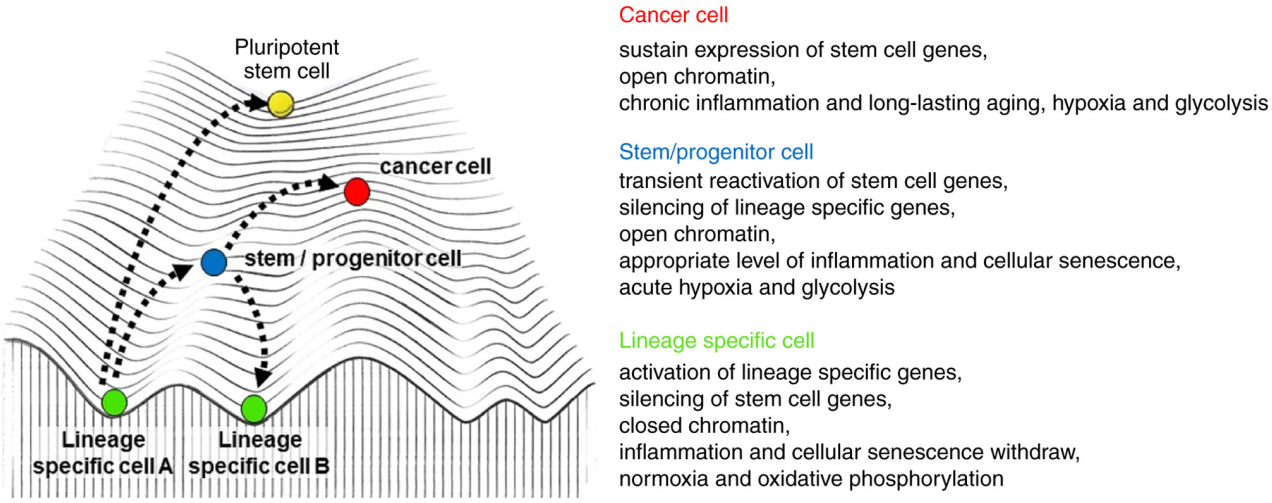

Figure 2. States of cells at different stages of dedifferentiation or reprogramming in Waddington's epigenetic landscape. Dashed arrows indicate state changes. Colored circles correspond to different cell states (yellow, pluripotent; blue, stem/progenitor; red, cancer; green, lineage specific). Acute hypoxia, glycolysis, inflammation, senescence and chromatin remodeling create a relaxed environment for cells that promotes reprogramming and facilitates cell type conversion. However, these events need to be maintained at appropriate levels and withdrawn at appropriate times after the initiation of repair of damaged or diseased tissue. Otherwise, these conditions will become factors that induce cancer.

hypoxia and consequent transformation into glycolysis have been shown to provide a favorable condition at the site of the damaged tissue, allowing the susceptible cells to re-enter pluripotency. However, there is also a risk that if hypoxia and glycolysis are not switched off at the early stages, specifically after the initiation of dedifferentiation and during healing, then their persistence will lead to chronic wound formation and the continued activation of proinflammatory factor transcription (57-60). This accelerates cell senescence and tissue damage. Such conditions, namely hypoxia, high glycolytic rates, chronic inflammation and continuous aging of cells, provides a favorable environment the promotion of carcinogenesis (61-64) (Fig. 2).

Cellular senescence. Cellular senescence, whether it is physiological or pathological, is characterized by the secretion of inflammatory cytokines and the inability to proliferate (65-68). It can be triggered by tissue injury or increased with aging to prevent the unwarranted proliferation of cells, through the induction of cell cycle arrest (69-71). Accumulating evidence shows that cell plasticity is closely associated with senescence (72-74). Recent studies have shown that transient senescence can stimulate regeneration in the heart, whilst the elimination of senescent cells can prevent regeneration (75,76). Senescence can regulate reprogramming and regeneration through a range of extracellular mechanisms *in vivo* (72,73,77,78). Previous studies have shown that when combined with injury, it can more effectively induce reprogramming in the liver and pancreas *in vivo* (77,78). Similarly, in another previous study, only after treatment with the DNA damaging agent bleomycin can NANOG-positive cell clusters be observed in the lungs (73). During the regeneration process of the skeletal muscle, reprogrammed cells can only be observed in the injured area, where they appear in the vicinity of senescent cells (72). Similarly, compared with younger mice, older mice show a higher degree of reprogramming and teratoma formation, as does a progeria mouse model that is characterized by a premature aging phenotype (72,73). In addition, after senescent cells are inoculated into the livers of mice, expression of stemness-related genes can be detected (78).

Although they are no longer proliferative, senescent cells remain metabolically and transcriptionally active and are capable of a wide range of secretory activities. These secretory proteins are capable of inducing cell cycle arrest and senescence in a paracrine manner, in a process known as senescence-associated secretory phenotype (SASP) (68,79,80). However, previous studies show that the beneficial roles of senescence are mainly mediated through SASP (79,80). SASP has been shown to promote the regenerative response by inducing cell dedifferentiation in a time-dependent manner. After being transiently exposed to SASP, mouse keratinocytes can dedifferentiate into hair follicle stem cells and regenerate the skin after transplantation (78). However, prolonged exposure to SASP causes subsequent cell-intrinsic senescence that inhibits continuous regenerative stimulation (78). Interleukin-6, which is the most prominent cytokine released during SASP, has been identified to be a critical mediator for creating a permissive tissue environment for factor-mediated *in vivo* reprogramming (72,73). A similar event may occur under physiological conditions, where tissue injury-induced senescence can promote tissue repair by inducing cell dedifferentiation (Fig. 1). Therefore, understanding the beneficial paracrine effects of injury-induced senescence would be instructive for the development of novel tissue repair strategies.

Inflammation and immunity. Wound or tissue damage can trigger a series of events in multicellular animals, such as acute inflammation and the activation of local or systemic adaptive immunity, in response to microorganism infection and the appearance of necrotic cells (81). In addition to effectively protecting the organism from foreign pathogens, another key function of these early events involving inflammation and immunity is to stimulate tissue repair in the damaged area, even if the repair is typically defective and

incomplete (31). During the process of response following injury, cell reprogramming caused by tissue regeneration is closely associated with inflammation and immunity (82-84). This involves a complex network of associated growth factors, signal transduction pathways and cytokines (85,86).

Stem cell factor (SCF) is one of the cytokines that is accumulated during inflammation. Schmitt *et al* (87) has previously showed that a large number of Leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5+) stem cells are lost and the expression of SCF is enhanced after acute inflammation of the small intestine in mice. For restoration, Paneth cells are induced to dedifferentiate and their secretory phenotype is lost. This dedifferentiation process has been revealed to be triggered by the SCF/c-Kit signaling pathway, which eventually leads to glycogen synthase kinase 3β inhibition and Wnt activation in Paneth cells.

Nuclear factor κB (NF-κB) is another key transcription factor that is activated in the inflammatory and immunity microenvironment. It has been shown to serve as a key link between inflammation and cellular plasticity (65,72,88,89). In the brain, activation of the NF-κB pathway by tumor necrosis factor has been shown to induce the dedifferentiation of mature astrocytes into neural progenitor cell phenotypes, which are capable of proliferating and differentiating into neurons or astrocytes (90). In the intestine, coactivation of Wnt/β-catenin and NF-κB signaling can induce the dedifferentiation of villus cells (91). In the pancreas, previous investigation has reported that NF-κB downstream of inflammation can trigger the dedifferentiation of β-cells and acinar cells (92). Accumulating evidence has confirmed that activation of inflammatory signals cause global changes in the expression and activity of several chromatin modifying enzymes, such as the downregulation of histone deacetylases and histone methyltransferases (with disruptor of telomeric silencing 1-like being one of the examples) and the upregulation of histone acetyltransferases, which can promote epigenetic cell plasticity (82,83,93).

The notion that an inflammatory environment triggers or promotes cell reprogramming remains controversial. However, an appropriate level of inflammation appears to be critical for tissue repair (94,95). A previous study into inflammatory responses during amphibian limb regeneration has revealed that potent, chronic inflammation induced by beryllium can inhibit limb patterning by suppressing the expression of sonic hedgehog, T-box transcription factor 3 and spalt-like transcription factor (Sall) 1; however, this had no effect on the expression of Sall4, a genetic reprogramming marker (96). This suggests that under high levels of inflammation, cellular reprogramming and dedifferentiation can still occur locally; however, the developmental mechanisms of limb regeneration cannot be replicated. Although acute inflammation can trigger tissue repair or regeneration, it will hinder the establishment of normal cell-cell interactions and signaling gradients that promote limb patterning if it is not released at appropriate times (96). Acute inflammatory responses provide cells with a more plastic epigenetic state for repairing tissue injury (97). However, if the acute inflammatory response is not eliminated in time and becomes a chronic inflammatory response, the cells then cannot be effectively reprogrammed to initiate repair of the injury, thereby hindering tissue regeneration (97). During chronic inflammatory responses, dedifferentiation or reprogramming can still occur, which may be one of the main causes of carcinogenesis (Fig. 1) (98-100).

3. Epigenetic modification

Epigenetic modifications, such as DNA methylation, histone acetylation and methylation and non-coding RNAs, are the main methods of structural chromatin remodeling. Changes in the chromatin structure affects DNA accessibility, leading to either enhanced or decreased gene expression, or even gene silencing (101). It is widely considered that chromatin remodeling and epigenetic modification are critical processes for controlling cell fate due to the unique epigenetic features that exist for these two processes (102,103). The effect of epigenetic modification on cell dedifferentiation or reprogramming after tissue injury remain poorly understood. The present review summarized the epigenetic mechanism underlying cell dedifferentiation on a macroscopic level.

Procedural dynamic changes in global epigenetic modification. Dedifferentiation or reprogramming during damage repair is a process of dramatic changes in cell identity that involves a gradual but global remodeling of the epigenetic signatures, resulting in generally more open chromatin. The newt lens regeneration process involves the dedifferentiation of dorsal pigment epithelial cells (PEC). Analysis of the global histone modifications revealed that PEC dedifferentiation is accompanied by an increase in trimethylated histone H3 lysine 4 (H3K4) and acetylated histone H4 with a corresponding decrease in acetylated histone H3 lysine 9 (H3K9) (104). Significant epigenetic modifications were also observed during reprogramming triggered by NF-κB and acute inflammation, including a decrease in H3K9 methylation and an increase in H3K4 methylation in the promoter regions of endogenous pluripotency factors (83,93). In addition, activation of acute inflammatory signals can cause changes in the expression of enzymes involved in chromosomal modification, such as upregulation of histone acetyltransferases, downregulation of histone deacetylases and downregulation of histone methyltransferases, which enhance the plasticity of the cells to facilitate dedifferentiation or reprogramming (83,93). Successful tissue repair processes should be accompanied by procedural dynamic changes in epigenetic modification, such as early demethylation followed by *de novo* methylation. Regeneration of the zebrafish retina provides a good example (105). Müller cell dedifferentiation into retinal progenitor cells occurs during zebrafish retina regeneration (105). Studies into DNA methylation in Müller cells have shown that methylation levels will typically undergo an early reduction followed by a later increase (105). This coincides with the dedifferentiation of Müller cells into retinal progenitor cells during retinal regeneration and then redifferentiation into retinal cells. This early reduction in DNA methylation facilitates the dedifferentiation of Müller cells into retinal progenitor cells and efficient progenitor cell proliferation. Subsequently, the increase in DNA methylation during the later stages causes the retinal progenitor cells to redifferentiate into retinal cells (105). This suggest that whilst epigenetic modification can occur to complete tissue repair and regeneration by regulating cell dedifferentiation, it can also regulate subsequent redifferentiation.

Regulating the expression of stemness and lineage-related genes. The expression of stemness-related genes is one of the most intuitive markers of cell dedifferentiation. Epigenetic mechanisms regulate the effective expression and maintenance of stemness-related genes, which determine the outcome of cell dedifferentiation and subsequent regeneration (106). Compared with zebrafish, the regenerative abilities of mammals after retinal injury are severely limited (107,108). After N-methyl-D-aspartate-induced retinal injury in mice, the expression levels of pluripotent factors and progenitor cell-specific transcription factors, such as OCT4, NANOG, KLF4 and paired box protein (PAX) 6, increase rapidly during the early stages of injury, suggesting that cells are undergoing dedifferentiation (108). However, this change is transient, where the expression of all the aforementioned genes are greatly reduced or even become undetectable 18 to 24 h post-injury (hpi) (108).

By contrast, the high expression of pluripotent factors, such as OCT4, in damaged retinal cells can persist for up to a week after injury in zebrafish (107). Detection of the expression of methylation-related genes has revealed that the expression of pluripotency genes is positively associated with growth arrest and DNA damage inducible β whilst being negatively associated with DNA methyltransferase (dnmt) 3β. Correspondingly, the methylation level of OCT4 is decreased during the early stages of injury, which is recovered 24 hpi (108). Therefore, the rapid methylation of stemness-related genes after tissue injury prevents successful Müller glia (MG) dedifferentiation and their potential regeneration in mammals (107,108).

In the intestinal epithelium, secretory cells can dedifferentiate into Lgr5+ intestinal stem cells (ISCs) in response to the ablation of native ISCs. Analysis of chromosomal status has revealed the presence of thousands of transposase-accessible genomic loci in the secretory cells controlling the expression of lineage-restricted genes (109). However, these sites are inaccessible in ISCs. When the secretory cells dedifferentiate into ISCs after ISC ablation, the accessibility signature dynamically converts into that of Lgr5+ ISCs (109). In the liver, AT-rich interactive domain-containing protein 1A (Arid1a), a key component of the switch/sucrose non-fermentable chromatin remodeling complex, can regulate the expression of injury-induced liver progenitor-like cell (LPLC)-related genes to promote liver regeneration. Arid1a can establish an accessible state on LPLC-enriched genes by regulating the accessibility of chromatin (110). By contrast, Arid1a can promote the Hippo-dependent transcriptional activation of yes-associated protein/transcriptional enhanced associate domain at the LPLC-enriched gene loci (110). Therefore, in response to tissue damage, cells can turn on specific enhancers of stemness-related genes whilst turning off specific enhancers of lineage restriction genes by regulating chromatin accessibility to complete the transformation of cell identity.

miRNA also serves a role in regulating the expression of stemness and lineage-related genes (107,111). During the injury response in the peripheral nervous system (PNS), a specific set of miRNAs have been found to control myelination by silencing the positive and negative regulators of Schwann cell dedifferentiation. Specifically, miRNA-138 and miRNA-709 can directly target early growth response 2 (Egr2), c-Jun and SOX2, which are the major gene regulators of dedifferentiation after PNS injury (111). During retinal regeneration, lethal-7 miRNA is able to prevent MG dedifferentiation by inhibiting the expression of regeneration-related genes, such as achaete-scute homolog 1, heat shock protein family D member 1, lin-28, OCT4, PAX6b and c-myc (107).

Derepression of dedifferentiation-related signals by regulating tumor suppressor genes. In addition to regulating the dedifferentiation process of cells after tissue injury by directly regulating the expression of stemness and lineage-related genes, the reversal of dedifferentiation-associated signals through the expression of tumor suppressor genes may provide another potential mechanism. The tumor suppressor gene, especially the tumor protein p53 (TP53) gene, is one of the major obstacles to the cellular dedifferentiation process after tissue injury. As the blastema forms after amputation, p53 expression decreases but is then absent in completely dedifferentiated stem cells. However, p53 expression is typically increased as the limb begins to regenerate (112). Studies into reprogramming in mammalian cells *in vitro* also suggests that loss of p53 function leads to more efficient cell dedifferentiation (113).

In the liver, biliary epithelial cells (BECs) dedifferentiate into bipotential progenitor cells (BPPCs) to complete liver regeneration after injury. He *et al* (114) found that the significant upregulation of the dnmt1 gene in BECs is able to methylate the TP53 locus during this process, thereby inhibiting the expression of TP53, which then reverses the inhibition of mammalian target of rapamycin complex 1 signaling to activate the dedifferentiation of BECs to BPPCs. By contrast, early DNA methylation inhibition using 5-azacytidine (5azaC) significantly reduces the methylation level of the TP53 locus, where BEC dedifferentiation is dramatically reduced and liver regeneration is blocked (114). In smooth muscle cells (SMCs), the loss of phosphatase and tensin homolog (PTEN) is associated with the dedifferentiation of SMCs (115), where a transcriptional blockade of PTEN is observed during the dedifferentiation of SMCs induced by platelet-derived growth factor (PDGF). However, 5azaC, an inhibitor of dnmt1, is able to upregulate PTEN expression by decreasing the methylation level whilst increasing the expression of genes associated with the differentiated SMCs phenotype. Thus, blocking PDGF-mediated SMC dedifferentiation (116).

Compensatory effects among epigenetic mechanisms. After tissue injury, it can be hypothesized that the effects of epigenetic modifications on cell dedifferentiation are not achieved by a single pathway. In response to tissue injury, genome-wide DNA methylation does not appear to affect gene expression indiscriminately, such that other epigenetic mechanisms will cooperate to maintain the silencing or activation of specific DNA regions, showing compensatory effects among epigenetic mechanisms (117,118). After deleting ubiquitin-like with PHD and ring finger domains 1 expression, a protein that maintains DNA methylation in the liver, Wang *et al* (117) found that this leads to genome-wide DNA hypomethylation and the activation of regenerative genes in hepatocytes, thereby promoting regeneration after partial hepatectomy. However, genome-wide DNA hypomethylation does not induce the expression of transposable elements, the re-mobilization of which can lead to genome instability and cell death (118).

Hypomethylated transposons are repressed by the repositioning of the repressive histone marker, trimethylated histone H3 lysine 27 (H3K27me3), whilst reduced H3K27me3 expression can lead to activation of the regenerative genes (117). After PNS injury, miRNA-709 is able to form epigenetic silencing complexes together with H3K27me3 and Agonaute-1 on the Egr2 promoter, a key regulator of Schwann cell dedifferentiation, thereby regulating the process of dedifferentiation and affecting myelination (111). Cell dedifferentiation after tissue injury appears to be the result of a combinatorial action of multiple epigenetic mechanisms.

4. Wound repair and tumorigenesis

Cellular plasticity may be the key to regeneration after severe injury, which is the functional replacement of tissue-specific stem cells lost due to injury by the transient reprogramming of mature committed cells (119-121). However, elevated plasticity of the tissue can also have potentially adverse consequences, such as cancer (119-121). On a cellular level, as a reaction to the signals released during tissue injury and inflammation, the gene expression profile and chromatin structure of the cells can undergo dramatic changes, which forms the basis of cellular plasticity (83,93). These processes are normally tightly controlled, because these same changes in the chromatin structure and gene expression profile underlying cell plasticity may also lead to oncogene expression or the inhibition of tumor suppressors (112,114,115).

Indeed, dysregulation of plasticity has been reported to be responsible for disrupting tissue stability and is a key etiological factor in cancer. There is accumulating evidence showing that several of the same signals that induce cell reprogramming may also be carcinogenic, where cancer cells can arise from somatic stem cells (90,91,122-126). NF-κB signaling has been reported to induce the differentiation of mature astrocytes into neural progenitor cells in the brain, whereas NF-κB signaling in the intestines can induce non-stem cell dedifferentiation to promote carcinogenesis (90,91). Similarly, the NOTCH signaling pathway can induce hepatocyte transdifferentiation into biliary cells, whereas activation of NOTCH in hepatocytes can lead to hepatocellular carcinoma with biliary features or intrahepatic cholangiocarcinomas (122,123). To explore the source of tumor cells, Cobaleda *et al* (124) used the PAX5 conditional knockout system to demonstrate that lymphoma can occur by the dedifferentiation of mature B cells into a progenitor cell state. A similar phenomenon of cancer caused by the dedifferentiation of committed cells has also been found in gliomas (125,126). These findings suggest that signals that cause committed cells to change their phenotype may increase the risk of malignant transformation. This may be driven by two factors. Firstly, directly by epigenetic alterations. Genetic mutations are generally considered to be the main cause of cancer and numerous types of cancer cells do have mutations in multiple genes (127). However, genetic mutations do not appear to be the only factor contributing to cancer. Driver gene mutations are rarely found in childhood tumors, including Wilms' tumor, medulloblastoma, neuroblastoma and rhabdoid tumor. These tumors may be mainly due to epigenetic disruption triggered by dedifferentiation (128-131). During *in vivo* reprogramming in mice, it was also found that tumors distinct from teratomas were detected in mice when Dox was withdrawn to induce incomplete reprogramming (132). DNA methylation patterns in these cancer cells exhibited partial reprogramming and no mutations in cancer-related genes were detected in these cells (132). Thus, epigenetic alterations can directly drive the development of cancer. Secondly, the synergistic drive of epigenetic alterations on the basis of genetic mutation. Dedifferentiation exhibits strong perturbations of epigenetic modifications and in some cases these epigenetic alterations play a key boost to cancer development on the basis of genetic variation. The findings in the Apc min/+ mouse model indicated that mutations in the Apc gene, the driver gene of intestinal neoplasms, were responsible for the initial colon adenomas but were insufficient to trigger the overall tumor progression (133-136). Thus, DNA methylation is a key factor in the development of colon tumor (137-140). Understanding the idea that epigenetic alterations drive cancer could allow us to develop anti-cancer strategies that differ from genetic damage. For example, epigenome reprogramming of human pancreatic ductal adenocarcinoma can significantly reduce its tumorigenicity and along this line, aberrant epigenetic modifications that drive cancer may be new therapeutic targets (141). Increased risk of malignant transformation during cell dedifferentiation meaning that cell plasticity comes at a price that requires a trade-off between maximizing tissue repair and minimizing the risk of malignant cell transformation. This may explain why some tissues initiate a process of dedifferentiation or reprogramming only after the stem cell population has been completely ablated, whereas differentiation or reprogramming is inhibited in the presence of homeostasis or individual stem cells (15). Compared with dedifferentiation or cell reprogramming, stem cell differentiation can control the change of cell identity in a more accurate manner, phenotypically, to reduce the frequency of identity changes. This serves to reduce the risk of malignant transformation during tissue repair. It is only when the stem cells are completely eliminated or signals that allow normal differentiation are hindered, that dedifferentiation and reprogramming can be used to maintain homeostasis or tissue regeneration as the preferred mechanism.

Similarly, maintaining a balance between maximizing tissue repair and minimizing the risk of malignant cell transformation also requires a moderate level of tissue inflammation, cellular senescence and hypoxia after injury. Acute inflammatory responses and transient cellular senescence can induce dedifferentiation or reprogramming of cells by repairing damaged or diseased tissues by providing the cells with a more plastic epigenetic state (78,97). However, inflammation and cellular senescence need to be maintained at an appropriate level and can be withdrawn at appropriate times after the initiation of damaged or diseased tissue repair, represented by decreased levels of NF-κB and SASP-related factors. Dedifferentiated or reprogrammed cells being redirected to differentiate and the plasticity of the cells is then reduced to return to homeostasis. Once cells are transformed into a chronic inflammatory and a long-lasting aging status, represented by elevated levels and persistent expression of NF-κB and SASP-associated factors, they will more likely exhibit a persistently hyperplastic state in which dedifferentiated or reprogrammed cells are unable to re-differentiate, resulting in malignant transformation (Fig. 2). Although SASP can induce

stemness-related gene expression and promote cell dedifferentiation, long-term SASP exposure can activate cell senescence arrest and lead to the formation of papilloma *in vivo* (78). This is why long-term use of non-steroidal anti-inflammatory drugs, such as aspirin, can prevent the formation of tumors and dramatically reduce the incidence of solid tumors, including colorectal cancer (142-144).

5. Prospects

The purpose of regenerative medicine is to restore the physiological functions of organs and tissues that are typically not easily repaired after injury, to promote changes in cell characteristics and to enhance endogenous regeneration. Dedifferentiation or reprogramming is a key method for tissue repair after injury, where the local microenvironment serves a crucial role. Hypoxia, inflammation and cellular senescence in injury-induced local microenvironmental changes are key parameters that can influence reprogramming. Hypoxia, inflammation and senescence create a relaxed environment for cells that typically promote reprogramming through a number of factors, such as HIF, NF-κB and SASP (78,88,90).

The link between *in vivo* reprogramming, hypoxia, inflammation and senescence will most likely be dependent on the presence of endogenous mechanisms that promote damage-dependent tissue repair in mammals. However, transient hypoxia, moderate levels of inflammation and senescence are critical for maintaining the balance between maximizing tissue repair whilst minimizing the risk of malignant transformation. Therefore, exploring the link between *in vivo* reprogramming, hypoxia, inflammation and senescence would enable researchers to understand the response of mammalian tissues to injury for designing treatment strategies to enhance their repair capabilities.

There is increasing evidence that certain cell types can be dedifferentiated by specific signals and therapeutic stimuli. Injury-induced dedifferentiation of MG in the mammalian retina can be promoted by treatment with insulin, epidermal growth factor and Wnt3a (145-148). However, the majority of *in vivo* reprogramming studies use viral delivery to allow key transcription factors to be overexpressed in cells, where the process of using transcription factor-induced reprogramming typically activates endogenous pluripotency programs (149-151). This means that cells can maintain their stem-state but also increase the risk of tumorigenesis, which greatly limits the potential of clinical applications. In addition, small molecules can be used to eliminate epigenetic barriers and promote changes in cell characteristics. For example, SGI-1027, a DNA-methyltransferase inhibitor, is used to block DNA methylation and maintain OCT4 expression after retinal injury (108). 5-aza-2'-deoxycytidine (5-aza-dC) or trichostatin A, the DNA demethylation agent, have been used to increase stem cell numbers at the amputation site and enhance digital regeneration (152). Therefore, establishment of small molecule-mediated *in vivo* reprogramming has become a promising new strategy (153-156). In addition, because they are generally more cost-effective, more stable, less immunogenic and can be more easily synthesized and standardized, small molecules offer a more attractive alternative to transcription factor-mediated *in vivo* reprogramming. Local microenvironments that promote dedifferentiation or reprogramming are generally specific for certain cell types, such that a specific combination of small molecules can be designed to repair particular tissue injury. Similarly, the local microenvironment that promotes tissue repair can be maintained by adjusting the concentration of small molecules. The present study hypothesized that the cells could maintain moderate levels of inflammation and senescence by adjusting the combination and concentration of small molecules, thus achieving the goal of maximizing tissue repair and minimizing the risk of malignant cell transformation (Fig. 3).

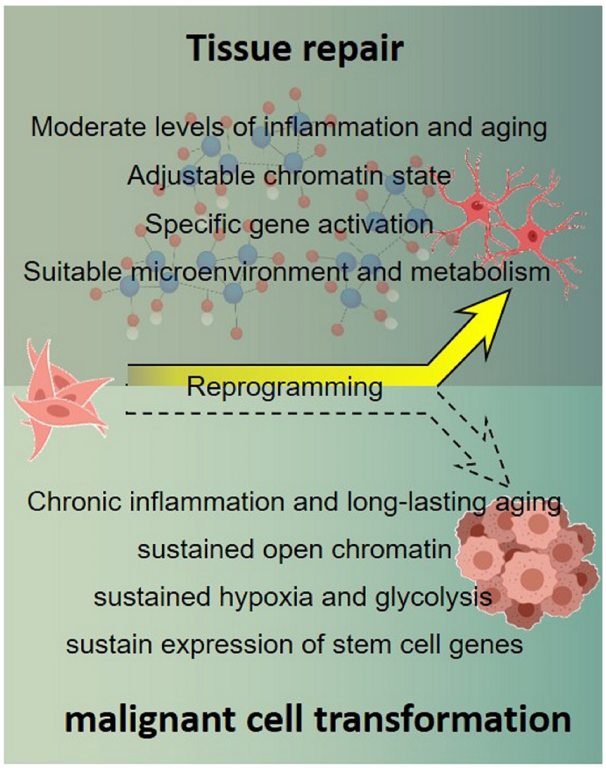

Figure 3. Prospects of small chemical molecules for *in vivo* cell reprogramming. Specific combinations of small molecules can be designed to provide optimal local microenvironments and metabolic states, moderate levels of inflammation and aging, adjustable chromatin state and specific gene activation, so as to maximize tissue repair and minimize the risk of malignant cell transformation.

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Authors' contributions

YG, XY and XF conceptualized the study. YG, WW, XY and XF wrote the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Del Rio-Tsonis K and Tsonis PA: Eye regeneration at the molecular age. Dev Dyn 226: 211-224, 2003.
2. Gurdon JB: The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. J Embryol Exp Morphol 10: 622-640, 1962.
3. Worley MI, Setiawan L and Hariharan IK: Regeneration and transdetermination in Drosophila imaginal discs. Annu Rev Genet 46: 289-310, 2012.
4. Gurdon JB: Adult frogs derived from the nuclei of single somatic cells. Dev Biol 4: 256-273, 1962.
5. Davis RL, Weintraub H and Lassar AB: Expression of a single transfected cDNA converts fibroblasts to myoblasts. Cell 51: 987-1000, 1987.
6. Yamanaka S and Blau HM: Nuclear reprogramming to a pluripotent state by three approaches. Nature 465: 704-712, 2010.
7. Sisakhtnezhad S and Matin MM: Transdifferentiation: A cell and molecular reprogramming process. Cell Tissue Res 348: 379-396, 2012.
8. Jopling C, Boue S and Izpisua Belmonte JC: Dedifferentiation, transdifferentiation and reprogramming: Three routes to regeneration. Nat Rev Mol Cell Biol 12: 79-89, 2011.
9. Yao and Wang C: Dedifferentiation: Inspiration for devising engineering strategies for regenerative medicine. NPJ Regen Med 5: 14, 2020.
10. Brawley C and Matunis E: Regeneration of male germline stem cells by spermatogonial dedifferentiation in vivo. Science 304: 1331-1334, 2004.
11. Kai T and Spradling A: Differentiating germ cells can revert into functional stem cells in Drosophila melanogaster ovaries. Nature 428: 564-569, 2004.
12. Kragl M, Knapp D, Nacu E, Khattak S, Maden M, Epperlein HH and Tanaka EM: Cells keep a memory of their tissue origin during axolotl limb regeneration. Nature 460: 60-65, 2009.
13. Blanpain C and Fuchs E: Stem cell plasticity. Plasticity of epithelial stem cells in tissue regeneration. Science 344: 1242281, 2014.
14. van Es JH, Sato T, van de Wetering M, Lyubimova A, Yee Nee AN, Gregorieff A, Sasaki N, Zeinstra L, van den Born M, Korving J, *et al*: Dll1+ secretory progenitor cells revert to stem cells upon crypt damage. Nat Cell Biol 14: 1099-1104, 2012.
15. Tata PR, Mou H, Pardo-Saganta A, Zhao R, Prabhu M, Law BM, Vinarsky V, Cho JL, Breton S, Sahay A, *et al*: Dedifferentiation of committed epithelial cells into stem cells in vivo. Nature 503: 218-223, 2013.
16. Brockes JP and Kumar A: Plasticity and reprogramming of differentiated cells in amphibian regeneration. Nat Rev Mol Cell Biol 3: 566-574, 2002.
17. Donati G, Rognoni E, Hiratsuka T, Liakath-Ali K, Hoste E, Kar G, Kayikci M, Russell R, Kretzschmar K, Mulder KW, *et al*: Wounding induces dedifferentiation of epidermal Gata6$^+$ cells and acquisition of stem cell properties. Nat Cell Biol 19: 603-613, 2017.
18. Stange DE, Koo BK, Huch M, Sibbel G, Basak O, Lyubimova A, Kujala P, Bartfeld S, Koster J, Geahlen JH, *et al*: Differentiated Troy+ chief cells act as reserve stem cells to generate all lineages of the stomach epithelium. Cell 155: 357-368, 2013.
19. Painter MW, Brosius Lutz A, Cheng YC, Latremoliere A, Duong K, Miller CM, Posada S, Cobos EJ, Zhang AX, Wagers AJ, *et al*: Diminished Schwann cell repair responses underlie age-associated impaired axonal regeneration. Neuron 83: 331-343, 2014.
20. Buczacki SJ, Zecchini HI, Nicholson AM, Russell R, Vermeulen L, Kemp R and Winton DJ: Intestinal label-retaining cells are secretory precursors expressing Lgr5. Nature 495: 65-69, 2013.
21. Tian H, Biehs B, Warming S, Leong KG, Rangell L, Klein OD and de Sauvage FJ: A reserve stem cell population in small intestine renders Lgr5-positive cells dispensable. Nature 478: 255-259, 2011.
22. Leushacke M, Tan SH, Wong A, Swathi Y, Hajamohideen A, Tan LT, Goh J, Wong E, Denil SLIJ, Murakami K and Barker N: Lgr5-expressing chief cells drive epithelial regeneration and cancer in the oxyntic stomach. Nat Cell Biol 19: 774-786, 2017.
23. Tulina N and Matunis E: Control of stem cell self-renewal in Drosophila spermatogenesis by JAK-STAT signaling. Science 294: 2546-2549, 2001.
24. Kiger AA, Jones DL, Schulz C, Rogers MB and Fuller MT: Stem cell self-renewal specified by JAK-STAT activation in response to a support cell cue. Science 294: 2542-2545, 2001.
25. Sheng XR, Brawley CM and Matunis EL: Dedifferentiating spermatogonia outcompete somatic stem cells for niche occupancy in the Drosophila testis. Cell Stem Cell 5: 191-203, 2009.
26. Hameed LS, Berg DA, Belnoue L, Jensen LD, Cao Y and Simon A: Environmental changes in oxygen tension reveal ROS-dependent neurogenesis and regeneration in the adult newt brain. Elife 4: e08422, 2015.
27. D'Ignazio L, Batie M and Rocha S: Hypoxia and Inflammation in Cancer, Focus on HIF and NF-κB. Biomedicines 5: 21, 2017.
28. Mohyeldin A, Garzon-Muvdi T and Quinones-Hinojosa A: Oxygen in stem cell biology: A critical component of the stem cell niche. Cell Stem Cell 7: 150-161, 2010.
29. Arthur SA, Blaydes JP and Houghton FD: Glycolysis regulates human embryonic stem cell self-renewal under hypoxia through HIF-2α and the glycolytic sensors CTBPs. Stem Cell Reports 12: 728-742, 2019.
30. Forristal CE, Wright KL, Hanley NA, Oreffo RO and Houghton FD: Hypoxia inducible factors regulate pluripotency and proliferation in human embryonic stem cells cultured at reduced oxygen tensions. Reproduction 139: 85-97, 2010.
31. Yoshida Y, Takahashi K, Okita K, Ichisaka T and Yamanaka S: Hypoxia enhances the generation of induced pluripotent stem cells. Cell Stem Cell 5: 237-241, 2009.
32. Jopling C, Sune G, Faucherre A, Fabregat C and Izpisua Belmonte JC: Hypoxia induces myocardial regeneration in zebrafish. Circulation 126: 3017-3027, 2012.
33. Mu X, Xiang G, Rathbone CR, Pan H, Bellayr IH, Walters TJ and Li Y: Slow-adhering stem cells derived from injured skeletal muscle have improved regenerative capacity. Am J Pathol 179: 931-941, 2011.
34. Vojnits K, Pan H, Mu X and Li Y: Characterization of an injury induced population of muscle-derived stem cell-like cells. Sci Rep 5: 17355, 2015.
35. Vojnits K, Pan H, Dai X, Sun H, Tong Q, Darabi R, Huard J and Li Y: Functional neuronal differentiation of injury-induced muscle-derived stem cell-like cells with therapeutic implications. Sci Rep 7: 1177, 2017.
36. Tatebayashi K, Tanaka Y, Nakano-Doi A, Sakuma R, Kamachi S, Shirakawa M, Uchida K, Kageyama H, Takagi T, Yoshimura S, *et al*: Identification of multipotent stem cells in human brain tissue following stroke. Stem Cells Dev 26: 787-797, 2017.
37. Liao YJ, Gao JH, Jiang P and Lu F: Effect of hypoxia on dedifferentiation of mature adipocytes: An experimental study. Nan Fang Yi Ke Da Xue Xue Bao 28: 339-342, 2008 (In Chinese).
38. Schmidt-Ott KM, Xu AD, Tuschick S, Liefeldt L, Kresse W, Verkhratsky A, Kettenmann H and Paul M: Hypoxia reverses dibutyryl-cAMP-induced stellation of cultured astrocytes via activation of the endothelin system. FASEB J 15: 1227-1229, 2001.
39. Sahai A, Mei C, Schrier RW and Tannen RL: Mechanisms of chronic hypoxia-induced renal cell growth. Kidney Int 56: 1277-1281, 1999.

40. Kierans SJ and Taylor CT: Regulation of glycolysis by the hypoxia-inducible factor (HIF): Implications for cellular physiology. J Physiol 599: 23-37, 2021.
41. Kondoh H, Lleonart ME, Nakashima Y, Yokode M, Tanaka M, Bernard D, Gil J and Beach D: A high glycolytic flux supports the proliferative potential of murine embryonic stem cells. Antioxid Redox Signal 9: 293-299, 2007.
42. Folmes CD, Nelson TJ, Martinez-Fernandez A, Arrell DK, Lindor JZ, Dzeja PP, Ikeda Y, Perez-Terzic C and Terzic A: Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. Cell Metab 14: 264-271, 2011.
43. Nombela-Arrieta C, Pivarnik G, Winkel B, Canty KJ, Harley B, Mahoney JE, Park SY, Lu J, Protopopov A and Silberstein LE: Quantitative imaging of haematopoietic stem and progenitor cell localization and hypoxic status in the bone marrow microenvironment. Nat Cell Biol 15: 533-543, 2013.
44. Takubo K, Nagamatsu G, Kobayashi CI, Nakamura-Ishizu A, Kobayashi H, Ikeda E, Goda N, Rahimi Y, Johnson RS, Soga T, *et al*: Regulation of glycolysis by Pdk functions as a metabolic checkpoint for cell cycle quiescence in hematopoietic stem cells. Cell Stem Cell 12: 49-61, 2013.
45. Warr MR and Passegue E: Metabolic makeover for HSCs. Cell Stem Cell 12: 1-3, 2013.
46. Lima A, Burgstaller J, Sanchez-Nieto JM and Rodriguez TA: The mitochondria and the regulation of cell fitness during early mammalian development. Curr Top Dev Biol 128: 339-363, 2018.
47. Chen CT, Shih YR, Kuo TK, Lee OK and Wei YH: Coordinated changes of mitochondrial biogenesis and antioxidant enzymes during osteogenic differentiation of human mesenchymal stem cells. Stem Cells 26: 960-968, 2008.
48. Pattappa G, Thorpe SD, Jegard NC, Heywood HK, de Bruijn JD and Lee DA: Continuous and uninterrupted oxygen tension influences the colony formation and oxidative metabolism of human mesenchymal stem cells. Tissue Eng Part C Methods 19: 68-79, 2013.
49. Scott CA, Carney TJ and Amaya E: Aerobic glycolysis is important for zebrafish larval wound closure and tail regeneration. Wound Repair Regen: Sep 23, 2022 (Epub ahead of print).
50. Sinclair JW, Hoying DR, Bresciani E, Nogare DD, Needle CD, Wu W, Bishop K, Elkahloun AG, Chitnis AB, Liu PP, *et al*: A metabolic shift to glycolysis promotes zebrafish tail regeneration through TGF-β dependent dedifferentiation of notochord cells to form the blastema. bioRxiv: Mar 20, 2020 (Epub ahead of print).
51. Fukuda R, Marin-Juez R, El-Sammak H, Beisaw A, Ramadass R, Kuenne C, Guenther S, Konzer A, Bhagwat AM, Graumann J and Stainier DY: Stimulation of glycolysis promotes cardiomyocyte proliferation after injury in adult zebrafish. EMBO Rep 21: e49752, 2020.
52. Naviaux RK, Le TP, Bedelbaeva K, Leferovich J, Gourevitch D, Sachadyn P, Zhang XM, Clark L and Heber-Katz E: Retained features of embryonic metabolism in the adult MRL mouse. Mol Genet Metab 96: 133-144, 2009.
53. Sinha KM, Tseng C, Guo P, Lu A, Pan H, Gao X, Andrews R, Eltzschig H and Huard J: Hypoxia-inducible factor 1α (HIF-1α) is a major determinant in the enhanced function of muscle-derived progenitors from MRL/MpJ mice. FASEB J 33: 8321-8334, 2019.
54. Zhang Y, Strehin I, Bedelbaeva K, Gourevitch D, Clark L, Leferovich J, Messersmith PB and Heber-Katz E: Drug-induced regeneration in adult mice. Sci Transl Med 7: 290ra292, 2015.
55. Pennock R, Bray E, Pryor P, James S, McKeegan P, Sturmey R and Genever P: Human cell dedifferentiation in mesenchymal condensates through controlled autophagy. Sci Rep 5: 13113, 2015.
56. Varum S, Rodrigues AS, Moura MB, Momcilovic O, Easley CA IV, Ramalho-Santos J, Van Houten B and Schatten G: Energy metabolism in human pluripotent stem cells and their differentiated counterparts. PLoS One 6: e20914, 2011.
57. Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M and Babilas P: Oxygen in acute and chronic wound healing. Br J Dermatol 163: 257-268, 2010.
58. Hong WX, Hu MS, Esquivel M, Liang GY, Rennert RC, McArdle A, Paik KJ, Duscher D, Gurtner GC, Lorenz HP and Longaker MT: The role of hypoxia-inducible factor in wound healing. Adv Wound Care (New Rochelle) 3: 390-399, 2014.
59. Baatar D, Jones MK, Tsugawa K, Pai R, Moon WS, Koh GY, Kim I, Kitano S and Tarnawski AS: Esophageal ulceration triggers expression of hypoxia-inducible factor-1 alpha and activates vascular endothelial growth factor gene: Implications for angiogenesis and ulcer healing. Am J Pathol 161: 1449-1457, 2002.
60. Elson DA, Ryan HE, Snow JW, Johnson R and Arbeit JM: Coordinate up-regulation of hypoxia inducible factor (HIF)-1alpha and HIF-1 target genes during multi-stage epidermal carcinogenesis and wound healing. Cancer Res 60: 6189-6195, 2000.
61. Coussens LM and Werb Z: Inflammation and cancer. Nature 420: 860-867, 2002.
62. Muz B, de la Puente P, Azab F and Azab AK: The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia (Auckl) 3: 83-92, 2015.
63. Jiang B: Aerobic glycolysis and high level of lactate in cancer metabolism and microenvironment. Genes Dis 4: 25-27, 2017.
64. Wyld L, Bellantuono I, Tchkonia T, Morgan J, Turner O, Foss F, George J, Danson S and Kirkland JL: Senescence and cancer: A review of clinical implications of senescence and senotherapies. Cancers (Basel) 12: 2134, 2020.
65. Lasry A and Ben-Neriah Y: Senescence-associated inflammatory responses: Aging and cancer perspectives. Trends Immunol 36: 217-228, 2015.
66. Munoz-Espin D and Serrano M: Cellular senescence: From physiology to pathology. Nat Rev Mol Cell Biol 15: 482-496, 2014.
67. Tchkonia T, Zhu Y, van Deursen J, Campisi J and Kirkland JL: Cellular senescence and the senescent secretory phenotype: Therapeutic opportunities. J Clin Invest 123: 966-972, 2013.
68. Watanabe S, Kawamoto S, Ohtani N and Hara E: Impact of senescence-associated secretory phenotype and its potential as a therapeutic target for senescence-associated diseases. Cancer Sci 108: 563-569, 2017.
69. Schmitt CA, Fridman JS, Yang M, Lee S, Baranov E, Hoffman RM and Lowe SW: A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. Cell 109: 335-346, 2002.
70. Coppe JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez PY and Campisi J: Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6: 2853-2868, 2008.
71. Campisi J: Aging, cellular senescence, and cancer. Annu Rev Physiol 75: 685-705, 2013.
72. Chiche A, Le Roux I, von Joest M, Sakai H, Aguín SB, Cazin C, Salam R, Fiette L, Alegria O, Flamant P, *et al*: Injury-Induced senescence enables in vivo reprogramming in skeletal muscle. Cell Stem Cell 20: 407-414 e4, 2017.
73. Mosteiro L, Pantoja C, Alcazar N, Marión RM, Chondronasiou D, Rovira M, Fernandez-Marcos PJ, Muñoz-Martin M, Blanco-Aparicio C, Pastor J, *et al*: Tissue damage and senescence provide critical signals for cellular reprogramming in vivo. Science 354: aaf4445, 2016.
74. Taguchi J and Yamada Y: Unveiling the role of senescence-induced cellular plasticity. Cell Stem Cell 20: 293-294, 2017.
75. Feng T, Meng J, Kou S, Jiang Z, Huang X, Lu Z, Zhao H, Lau LF, Zhou B and Zhang H: CCN1-Induced cellular senescence promotes heart regeneration. Circulation 139: 2495-2498, 2019.
76. Sarig R, Rimmer R, Bassat E, Zhang L, Umansky KB, Lendengolts D, Perlmoter G, Yaniv K and Tzahor E: Transient p53-mediated regenerative senescence in the injured heart. Circulation 139: 2491-2494, 2019.
77. Heinrich C, Spagnoli FM and Berninger B: In vivo reprogramming for tissue repair. Nat Cell Biol 17: 204-211, 2015.
78. Ritschka B, Storer M, Mas A, Heinzmann F, Ortells MC, Morton JP, Sansom OJ, Zender L and Keyes WM: The senescence-associated secretory phenotype induces cellular plasticity and tissue regeneration. Genes Dev 31: 172-183, 2017.
79. Munoz-Espin D, Canamero M, Maraver A, Gómez-López G, Contreras J, Murillo-Cuesta S, Rodríguez-Baeza A, Varela-Nieto I, Ruberte J, Collado M and Serrano M: Programmed cell senescence during mammalian embryonic development. Cell 155: 1104-1118, 2013.
80. Storer M, Mas A, Robert-Moreno A, Pecoraro M, Ortells MC, Di Giacomo V, Yosef R, Pilpel N, Krizhanovsky V, Sharpe J and Keyes WM: Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell 155: 1119-1130, 2013.
81. Hanna J, Guerra-Moreno A, Ang J and Micoogullari Y: Protein degradation and the pathologic basis of disease. Am J Pathol 189: 94-103, 2019.
82. Cooke JP, Sayed N, Lee J and Wong WT: Innate immunity and epigenetic plasticity in cellular reprogramming. Curr Opin Genet Dev 28: 89-91, 2014.

83. Lee J, Sayed N, Hunter A, Au KF, Wong WH, Mocarski ES, Pera RR, Yakubov E and Cooke JP: Activation of innate immunity is required for efficient nuclear reprogramming. Cell 151: 547-558, 2012.
84. King MW, Neff AW and Mescher AL: The developing Xenopus limb as a model for studies on the balance between inflammation and regeneration. Anat Rec (Hoboken) 295: 1552-1561, 2012.
85. Cavaillon JM: Pro-versus anti-inflammatory cytokines: Myth or reality. Cell Mol Biol (Noisy-le-grand) 47: 695-702, 2001.
86. Lennartsson J and Ronnstrand L: Stem cell factor receptor/c-Kit: From basic science to clinical implications. Physiol Rev 92: 1619-1649, 2012.
87. Schmitt M, Schewe M, Sacchetti A, Feijtel D, van de Geer WS, Teeuwssen M, Sleddens HF, Joosten R, van Royen ME, van de Werken HJG, *et al*: Paneth cells respond to inflammation and contribute to tissue regeneration by acquiring stem-like features through SCF/c-Kit Signaling. Cell Rep 24: 2312-2328 e7, 2018.
88. Soria-Valles C, Osorio FG, Gutierrez-Fernandez A, De Los Angeles A, Bueno C, Menéndez P, Martín-Subero JI, Daley GQ, Freije JM and López-Otín C: NF-κB activation impairs somatic cell reprogramming in ageing. Nat Cell Biol 17: 1004-1013, 2015.
89. Soria-Valles C, Osorio FG and Lopez-Otin C: Reprogramming aging through DOT1L inhibition. Cell Cycle 14: 3345-3346, 2015.
90. Gabel S, Koncina E, Dorban G, Heurtaux T, Birck C, Glaab E, Michelucci A, Heuschling P and Grandbarbe L: Inflammation promotes a conversion of astrocytes into neural progenitor cells via NF-κB activation. Mol Neurobiol 53: 5041-5055, 2016.
91. Schwitalla S, Fingerle AA, Cammareri P, Nebelsiek T, Göktuna SI, Ziegler PK, Canli O, Heijmans J, Huels DJ, Moreaux G, *et al*: Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties. Cell 152: 25-38, 2013.
92. Murtaugh LC and Keefe MD: Regeneration and repair of the exocrine pancreas. Annu Rev Physiol 77: 229-249, 2015.
93. O'Neill LA: 'Transflammation': When innate immunity meets induced pluripotency. Cell 151: 471-473, 2012.
94. Jiang B and Liao R: The paradoxical role of inflammation in cardiac repair and regeneration. J Cardiovasc Transl Res 3: 410-416, 2010.
95. Cooke JP: Inflammation and its role in regeneration and repair. Circ Res 124: 1166-1168, 2019.
96. Mescher AL, Neff AW and King MW: Changes in the inflammatory response to injury and its resolution during the loss of regenerative capacity in developing Xenopus limbs. PLoS One 8: e80477, 2013.
97. Pietras EM, Mirantes-Barbeito C, Fong S, Loeffler D, Kovtonyuk LV, Zhang S, Lakshminarasimhan R, Chin CP, Techner JM, Will B, *et al*: Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal. Nat Cell Biol 18: 607-618, 2016.
98. Grivennikov SI, Greten FR and Karin M: Immunity, inflammation, and cancer. Cell 140: 883-899, 2010.
99. Ben-Neriah Y and Karin M: Inflammation meets cancer, with NF-κB as the matchmaker. Nat Immunol 12: 715-723, 2011.
100. Balkwill FR and Mantovani A: Cancer-related inflammation: Common themes and therapeutic opportunities. Semin Cancer Biol 22: 33-40, 2012.
101. Fedorova E and Zink D: Nuclear architecture and gene regulation. Biochim Biophys Acta 1783: 2174-2184, 2008.
102. Boland MJ, Nazor KL and Loring JF: Epigenetic regulation of pluripotency and differentiation. Circ Res 115: 311-324, 2014.
103. Wu H and Sun YE: Epigenetic regulation of stem cell differentiation. Pediatr Res 59: 21R-25R, 2006.
104. Nakamura K, Maki N, Trinh A, Trask HW, Gui J, Tomlinson CR and Tsonis PA: miRNAs in newt lens regeneration: Specific control of proliferation and evidence for miRNA networking. PLoS One 5: e12058, 2010.
105. Powell C, Grant AR, Cornblath E and Goldman D: Analysis of DNA methylation reveals a partial reprogramming of the Muller glia genome during retina regeneration. Proc Natl Acad Sci USA 110: 19814-19819, 2013.
106. Oliveri RS: Epigenetic dedifferentiation of somatic cells into pluripotency: Cellular alchemy in the age of regenerative medicine? Regen Med 2: 795-816, 2007.
107. Ramachandran R, Fausett BV and Goldman D: Ascl1a regulates Muller glia dedifferentiation and retinal regeneration through a Lin-28-dependent, let-7 microRNA signalling pathway. Nat Cell Biol 12: 1101-1107, 2010.
108. Reyes-Aguirre LI and Lamas M: Oct4 Methylation-Mediated silencing as an epigenetic barrier preventing muller glia dedifferentiation in a murine model of retinal injury. Front Neurosci 10: 523, 2016.
109. Jadhav U, Saxena M, O'Neill NK, Saadatpour A, Yuan GC, Herbert Z, Murata K and Shivdasani RA: Dynamic reorganization of chromatin accessibility signatures during dedifferentiation of secretory precursors into Lgr5+ Intestinal stem cells. Cell Stem Cell 21: 65-77 e5, 2017.
110. Li W, Yang L, He Q, Hu C, Zhu L, Ma X, Ma X, Bao S, Li L, Chen Y, *et al*: A homeostatic arid1a-dependent permissive chromatin state licenses hepatocyte responsiveness to liver-injury-associated YAP signaling. Cell Stem Cell 25: 54-68 e55, 2019.
111. Adilakshmi T, Sudol I and Tapinos N: Combinatorial action of miRNAs regulates transcriptional and post-transcriptional gene silencing following in vivo PNS injury. PLoS One 7: e39674, 2012.
112. Yun MH, Gates PB and Brockes JP: Regulation of p53 is critical for vertebrate limb regeneration. Proc Natl Acad Sci USA 110: 17392-17397, 2013.
113. Yi L, Lu C, Hu W, Sun Y and Levine AJ: Multiple roles of p53-related pathways in somatic cell reprogramming and stem cell differentiation. Cancer Res 72: 5635-5645, 2012.
114. He J, Zhou Y, Qian C, Wang D, Yang Z, Huang Z, Sun J, Ni R, Yang Q, Chen J and Luo L: DNA methylation maintenance at the p53 locus initiates biliary-mediated liver regeneration. NPJ Regen Med 7: 21, 2022.
115. Nemenoff RA, Simpson PA, Furgeson SB, Kaplan-Albuquerque N, Crossno J, Garl PJ, Cooper J and Weiser-Evans MC: Targeted deletion of PTEN in smooth muscle cells results in vascular remodeling and recruitment of progenitor cells through induction of stromal cell-derived factor-1alpha. Circ Res 102: 1036-1045, 2008.
116. Strand KA, Lu S, Mutryn MF, Li L, Zhou Q, Enyart BT, Jolly AJ, Dubner AM, Moulton KS, Nemenoff RA, *et al*: High throughput screen identifies the DNMT1 (DNA Methyltransferase-1) Inhibitor, 5-Azacytidine, as a potent inducer of PTEN (Phosphatase and Tensin Homolog): Central role for PTEN in 5-Azacytidine protection against pathological vascular remodeling. Arterioscler Thromb Vasc Biol 40: 1854-1869, 2020.
117. Wang S, Zhang C, Hasson D, Desai A, SenBanerjee S, Magnani E, Ukomadu C, Lujambio A, Bernstein E and Sadler KC: Epigenetic compensation promotes liver regeneration. Dev Cell 50: 43-56 e6, 2019.
118. Chuong EB, Elde NC and Feschotte C: Regulatory activities of transposable elements: From conflicts to benefits. Nat Rev Genet 18: 71-86, 2017.
119. Tosh D and Slack JM: How cells change their phenotype. Nat Rev Mol Cell Biol 3: 187-194, 2002.
120. Corbett JL and Tosh D: Conversion of one cell type into another: Implications for understanding organ development, pathogenesis of cancer and generating cells for therapy. Biochem Soc Trans 42: 609-616, 2014.
121. Abollo-Jimenez F, Jimenez R and Cobaleda C: Physiological cellular reprogramming and cancer. Semin Cancer Biol 20: 98-106, 2010.
122. Villanueva A, Alsinet C, Yanger K, Hoshida Y, Zong Y, Toffanin S, Rodriguez-Carunchio L, Solé M, Thung S, Stanger BZ and Llovet JM: Notch signaling is activated in human hepatocellular carcinoma and induces tumor formation in mice. Gastroenterology 143: 1660-1669 e7, 2012.
123. Fan B, Malato Y, Calvisi DF, Naqvi S, Razumilava N, Ribback S, Gores GJ, Dombrowski F, Evert M, Chen X and Willenbring H: Cholangiocarcinomas can originate from hepatocytes in mice. J Clin Invest 122: 2911-2915, 2012.
124. Cobaleda C, Jochum W and Busslinger M: Conversion of mature B cells into T cells by dedifferentiation to uncommitted progenitors. Nature 449: 473-477, 2007.
125. Liu C, Sage JC, Miller MR, Verhaak RG, Hippenmeyer S, Vogel H, Foreman O, Bronson RT, Nishiyama A, Luo L and Zong H: Mosaic analysis with double markers reveals tumor cell of origin in glioma. Cell 146: 209-221, 2011.
126. Friedmann-Morvinski D, Bushong EA, Ke E, Soda Y, Marumoto T, Singer O, Ellisman MH and Verma IM: Dedifferentiation of neurons and astrocytes by oncogenes can induce gliomas in mice. Science 338: 1080-1084, 2012.

127. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, Xie M, Zhang Q, McMichael JF, Wyczalkowski MA, *et al*: Mutational landscape and significance across 12 major cancer types. Nature 502: 333-339, 2013.
128. Yamada Y, Haga H and Yamada Y: Concise review: Dedifferentiation meets cancer development: Proof of concept for epigenetic cancer. Stem Cells Transl Med 3: 1182-1187, 2014.
129. Rausch T, Jones DT, Zapatka M, Stütz AM, Zichner T, Weischenfeldt J, Jäger N, Remke M, Shih D, Northcott PA, *et al*: Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with TP53 mutations. Cell 148: 59-71, 2012.
130. Molenaar JJ, Koster J, Zwijnenburg DA, van Sluis P, Valentijn LJ, van der Ploeg I, Hamdi M, van Nes J, Westerman BA, van Arkel J, *et al*: Sequencing of neuroblastoma identifies chromothripsis and defects in neuritogenesis genes. Nature 483: 589-593, 2012.
131. Lee RS, Stewart C, Carter SL, Ambrogio L, Cibulskis K, Sougnez C, Lawrence MS, Auclair D, Mora J, Golub TR, *et al*: A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. J Clin Invest 122: 2983-2988, 2012.
132. Yamada Y and Yamada Y: The causal relationship between epigenetic abnormality and cancer development: In vivo reprogramming and its future application. Proc Jpn Acad Ser B Phys Biol Sci 94: 235-247, 2018.
133. Rao CV, Cooma I, Rodriguez JG, Simi B, El-Bayoumy K and Reddy BS: Chemoprevention of familial adenomatous polyposis development in the APC(min) mouse model by 1,4-phenylene bis(methylene)selenocyanate. Carcinogenesis 21: 617-621, 2000.
134. Yamada Y, Hata K, Hirose Y, Hara A, Sugie S, Kuno T, Yoshimi N, Tanaka T and Mori H: Microadenomatous lesions involving loss of Apc heterozygosity in the colon of adult Apc(Min/+) mice. Cancer Res 62: 6367-6370, 2002.
135. Yamada Y and Mori H: Pre-cancerous lesions for colorectal cancers in rodents: A new concept. Carcinogenesis 24: 1015-1019, 2003.
136. Moser AR, Pitot HC and Dove WF: A dominant mutation that predisposes to multiple intestinal neoplasia in the mouse. Science 247: 322-324, 1990.
137. Yamada Y, Jackson-Grusby L, Linhart H, Meissner A, Eden A, Lin H and Jaenisch R: Opposing effects of DNA hypomethylation on intestinal and liver carcinogenesis. Proc Natl Acad Sci USA 102: 13580-13585, 2005.
138. Lin H, Yamada Y, Nguyen S, Linhart H, Jackson-Grusby L, Meissner A, Meletis K, Lo G and Jaenisch R: Suppression of intestinal neoplasia by deletion of Dnmt3b. Mol Cell Biol 26: 2976-2983, 2006.
139. Linhart HG, Lin H, Yamada Y, Moran E, Steine EJ, Gokhale S, Lo G, Cantu E, Ehrich M, He T, *et al*: Dnmt3b promotes tumorigenesis in vivo by gene-specific de novo methylation and transcriptional silencing. Genes Dev 21: 3110-3122, 2007.
140. Hatano Y, Semi K, Hashimoto K, Lee MS, Hirata A, Tomita H, Kuno T, Takamatsu M, Aoki K, Taketo MM, *et al*: Reducing DNA methylation suppresses colon carcinogenesis by inducing tumor cell differentiation. Carcinogenesis 36: 719-729, 2015.
141. Khoshchehreh R, Totonchi M, Carlos Ramirez J, Torres R, Baharvand H, Aicher A, Ebrahimi M and Heeschen C: Epigenetic reprogramming of primary pancreatic cancer cells counteracts their in vivo tumourigenicity. Oncogene 38: 6226-6239, 2019.
142. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP and Meade TW: Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomised trials. Lancet 377: 31-41, 2011.
143. Fraser DM, Sullivan FM, Thompson AM and McCowan C: Aspirin use and survival after the diagnosis of breast cancer: A population-based cohort study. Br J Cancer 111: 623-627, 2014.
144. Streicher SA, Yu H, Lu L, Kidd MS and Risch HA: Case-control study of aspirin use and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 23: 1254-1263, 2014.
145. Close JL, Liu J, Gumuscu B and Reh TA: Epidermal growth factor receptor expression regulates proliferation in the postnatal rat retina. Glia 54: 94-104, 2006.
146. Karl MO, Hayes S, Nelson BR, Tan K, Buckingham B and Reh TA: Stimulation of neural regeneration in the mouse retina. Proc Natl Acad Sci USA 105: 19508-19513, 2008.
147. Takeda M, Takamiya A, Jiao JW, Cho KS, Trevino SG, Matsuda T and Chen DF: alpha-Aminoadipate induces progenitor cell properties of Muller glia in adult mice. Invest Ophthalmol Vis Sci 49: 1142-1150, 2008.
148. Osakada F, Ooto S, Akagi T, Mandai M, Akaike A and Takahashi M: Wnt signaling promotes regeneration in the retina of adult mammals. J Neurosci 27: 4210-4219, 2007.
149. Zhou Q, Brown J, Kanarek A, Rajagopal J and Melton DA: In vivo reprogramming of adult pancreatic exocrine cells to beta-cells. Nature 455: 627-632, 2008.
150. Qian L, Huang Y, Spencer CI, Foley A, Vedantham V, Liu L, Conway SJ, Fu JD and Srivastava D: In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes. Nature 485: 593-598, 2012.
151. Kurita M, Araoka T, Hishida T, O'Keefe DD, Takahashi Y, Sakamoto A, Sakurai M, Suzuki K, Wu J, Yamamoto M, *et al*: In vivo reprogramming of wound-resident cells generates skin epithelial tissue. Nature 561: 243-247, 2018.
152. Wang G, Badylak SF, Heber-Katz E, Braunhut SJ and Gudas LJ: The effects of DNA methyltransferase inhibitors and histone deacetylase inhibitors on digit regeneration in mice. Regen Med 5: 201-220, 2010.
153. Ma X, Kong L and Zhu S: Reprogramming cell fates by small molecules. Protein Cell 8: 328-348, 2017.
154. Tang Y and Cheng L: Cocktail of chemical compounds robustly promoting cell reprogramming protects liver against acute injury. Protein Cell 8: 273-283, 2017.
155. Niu W, Zang T, Zou Y, Fang S, Smith DK, Bachoo R and Zhang CL: In vivo reprogramming of astrocytes to neuroblasts in the adult brain. Nat Cell Biol 15: 1164-1175, 2013.
156. Guan J, Wang G, Wang J, Zhang J, Fu Y, Cheng L, Meng G, Lyu Y, Zhu J, Li Y, *et al*: Chemical reprogramming of human somatic cells to pluripotent stem cells. Nature 605: 325-331, 2022.