

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

YANJIE GUO<sup>1</sup>, WEINI WU<sup>1</sup>, XUEYI YANG<sup>1</sup> and XIAOBING FU<sup>2-4</sup>

<sup>1</sup>Life Science College, Luoyang Normal University, Luoyang, Henan 471934; <sup>2</sup>Research Center for Tissue Repair and Regeneration Affiliated to The Medical Innovation Research Department, PLA General Hospital; <sup>3</sup>PLA Key Laboratory of Tissue Repair and Regenerative Medicine and Beijing Key Research Laboratory of Skin Injury, Repair and Regeneration, Chinese PLA General Hospital and PLA Medical College; <sup>4</sup>Research Unit of Trauma Care, Tissue Repair and Regeneration, Chinese Academy of Medical Sciences, Beijing 100048, P.R. China

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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).

**Correspondence to:** Professor Xueyi Yang, Life Science College, Luoyang Normal University, 6 Jiqing Road, Luoyang, Henan 471934, P.R. China

E-mail: yangxueyi2002@163.com

Professor Xiaobing Fu, PLA Key Laboratory of Tissue Repair and Regenerative Medicine and Beijing Key Research Laboratory of Skin Injury, Repair and Regeneration, Chinese PLA General Hospital and PLA Medical College, 51 Fucheng Road, Beijing 100048, P.R. China  
E-mail: fuxiaobing@vip.sina.com

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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  $\mu\text{m}$  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 HIF2 $\alpha$  through glycolytic flux, thereby upregulating the expression of C-terminal binding proteins 1 and 2 to sustain self-renewal (29). In addition, HIF2 $\alpha$  is closely associated with the pluripotency regulatory network of genes, such that HIF2 $\alpha$  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

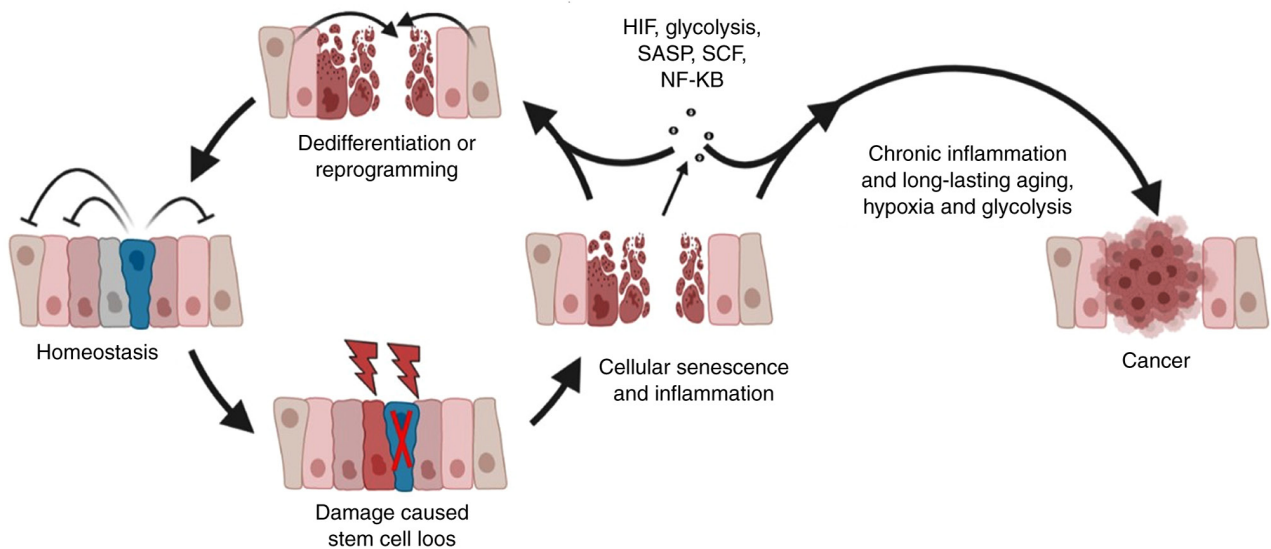


Figure 1. Dedifferentiation or reprogramming process after tissue damage. During homeostasis, signals from stem cells (blue) inhibit dedifferentiation of neighboring cells. The loss of stem cells caused by tissue injury is one of the key factors that relieves the inhibition of committed cells and triggers 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 HIF1 $\alpha$  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 HIF1 $\alpha$  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-1 $\alpha$  pathway is key in understanding the regenerative abilities of MRL mice. The expression level of HIF-1 $\alpha$  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-1 $\alpha$  expression (53). In normal mice, injection of HIF-1 $\alpha$  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,

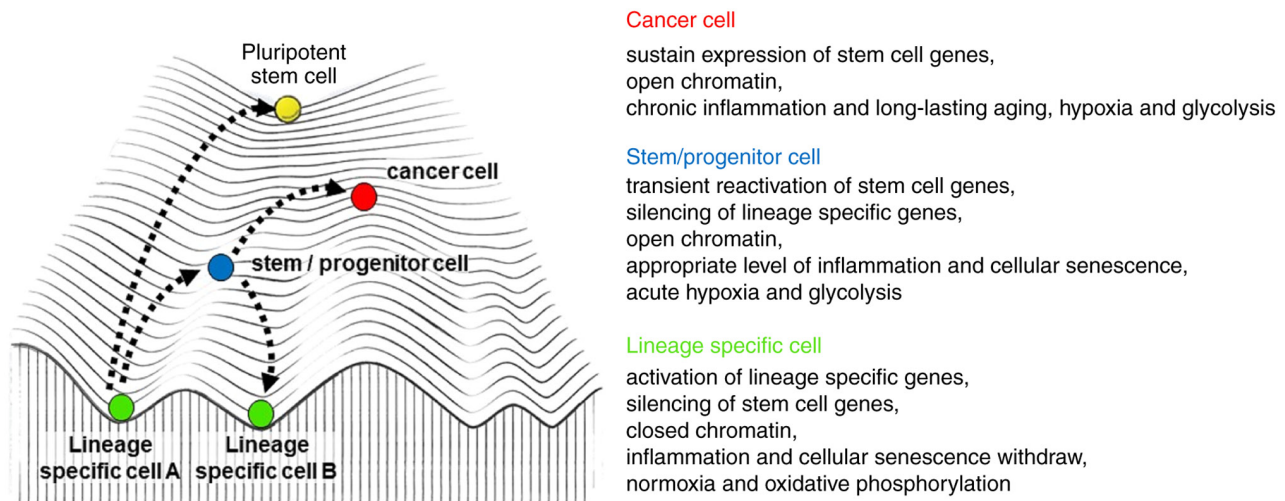


Figure 2. States of cells at different stages of dedifferentiation or reprogramming in Waddington's epigenetic landscape. Dashed arrows indicate state changes. Colored circles correspond to different cell states (yellow, pluripotent; blue, stem/progenitor; red, cancer; green, lineage specific). Acute 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 3 $\beta$  inhibition and Wnt activation in Paneth cells.

Nuclear factor  $\kappa$ B (NF- $\kappa$ B) 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- $\kappa$ B 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/ $\beta$ -catenin and NF- $\kappa$ B signaling can induce the dedifferentiation of villus cells (91). In the pancreas, previous investigation has reported that NF- $\kappa$ B downstream of inflammation can trigger the dedifferentiation of  $\beta$ -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- $\kappa$ B 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  $\beta$  whilst being negatively associated with DNA methyltransferase (dnmt) 3 $\beta$ . 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 Ago2 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- $\kappa$ B signaling has been reported to induce the differentiation of mature astrocytes into neural progenitor cells in the brain, whereas NF- $\kappa$ B 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- $\kappa$ B 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- $\kappa$ B 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- $\kappa$ B 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

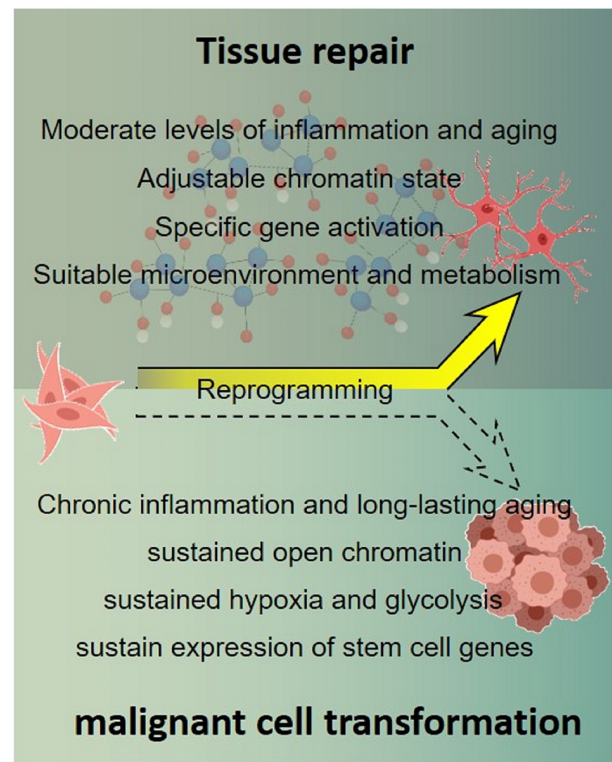


Figure 3. Prospects of small chemical molecules for *in vivo* cell reprogramming. Specific combinations of small molecules can be designed to provide optimal local microenvironments and metabolic states, moderate levels of inflammation and aging, adjustable chromatin state and specific gene activation,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

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).

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## Availability of data and materials

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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.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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