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Review

p53 on the crossroad between regeneration and cancer

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Regeneration and tumorigenesis share common molecular pathways, nevertheless the outcome of regeneration is life, whereas tumorigenesis leads to death. Although the process of regeneration is strictly controlled, malignant transformation is unrestrained. In this review, we discuss the involvement of *TP53*, the major tumor-suppressor gene, in the regeneration process. We point to the role of p53 as coordinator assuring that regeneration will not shift to carcinogenesis. The fluctuation in p53 activity during the regeneration process permits a tight control. On one hand, its inhibition at the initial stages allows massive proliferation, on the other its induction at advanced steps of regeneration is essential for preservation of robustness and fidelity of the regeneration process. A better understanding of the role of p53 in regulation of regeneration may open new opportunities for implementation of *TP53*-based therapies, currently available for cancer patients, in regenerative medicine.
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Facts

- Molecular pathways and gene expression patterns underlying regeneration and tumorigenesis are akin.
- Fluctuations in p53 levels in the regeneration process were observed during salamander limb regeneration, as well as during liver and nerve regeneration in mice.
- Following liver regeneration, *TP53*-deficient mice acquire more chromosomal segregation errors than their p53 wild-type counterparts.
- p53 serves as a regeneration coordinator that blocks the shift from regeneration to carcinogenesis.

Open questions

- Does proper regeneration restrain malignant transformation or may impaired regeneration lead to carcinogenesis?
- What are the roles of tumor suppressors during the regeneration process?
- What is the contribution of liver stem/progenitor cells to liver regeneration process? What is the role of *TP53* in these cells?

The link between regeneration and cancer

Regeneration is a homeostatic process of renewal that comprises well-coordinated restoration of cells, tissues and organs that have been damaged or lost. Hence, regeneration enables maintenance of structural and functional integrity of the tissue/organ. This is manifested by restoration in states of injury and pathology, as well as by cells turnover under normal physiological conditions. At large, tissue regeneration is characterized by three different overlapping stages; inflammation, tissue reconstruction and remodeling.[1] The process of regeneration entails extensive cellular proliferation that is tightly controlled by specific signals, eventually resulting in a finite number of cells. Cellular processes, such as senescence,[1] apoptosis[2] and differentiation,[3] are evoked at different stages of regeneration to ensure controlled expansion. Apoptosis-induced proliferation was also documented in regeneration processes. In this case, damaged or faulty cells undergoing apoptosis are signaling their healthy neighboring cells to proliferate.[4] Finally, once the regeneration process is completed, specific signals are released for the termination of the cell proliferation.

Regeneration may be accomplished by several different mechanisms that vary depending on the given organism species, organ type or cell fate (Table 1). For example, in amphibians such as adult newts, regeneration may be mediated by differentiated post-mitotic cells that re-enter the S-phase of the cell cycle and undergo dedifferentiation.[5,6] In planarians, flatworms, the main regeneration mechanism involves proliferation of resident adult somatic stem cells (SCs).[7,8] Similarly, utilization of dedicated SCs to sustain normal cell turnover is evident in mammalian organs such as skin and intestine, which consist of highly proliferative tissues.[9] Conversely, it was suggested that quiescent tissues such as liver or pancreas, display alternative regenerative mechanisms involving dormant SCs activation, trans-differentiation, metaplasia and compensatory proliferation of mature cells.[10,11] Importantly, one should bear in mind that activation or formation of SCs should be tightly controlled in

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Abbreviations: BECs, biliary epithelial cells; CNS, central nervous system; CSC, cancer stem cells; HCC, hepatocellular carcinoma; HSCs, hepatocyte stellate cells; NASH, nonalcoholic steatohepatitis; NPCs, neuronal progenitor cells; NSCs, neuronal stem cells; PNS, peripheral nervous system; RCC, renal cell carcinoma; RRR, renal regeneration and repair; SCs, stem cells

Table 1 Cellular sources tangled in regeneration processes of different tissues and organisms

Cell type	Process	Regenerating tissue/organism	Reference
Interstitial stem cells	Differentiation to zymogen gland cells	Hydra head	[107]
Zymogen gland cells	Trans-differentiation to granular mucous cells	Hydra head	[108]
Mesenchymal stem cells/neoblasts	Self-renewal and pluripotent differentiation potential	Lethally irradiated planarians	[109, 110]
Liver progenitor cells	Differentiation to hepatocytes	Chronic liver injury in mice	[77,78 111]
Hepatocytes	Proliferation	Partial hepatectomy in mice	[88,89,90 111]
Cardiomyocytes	Proliferation and differentiation	Damaged heart in zebrafish	[112, 113]
Pigmented epithelial cells	Dedifferentiation, proliferation and differentiation to lens cells	Lens regeneration in newt	[114]
Syncytial skeletal myotubes	Dedifferentiation to mononucleate cells that are able to proliferate	Appendage regeneration in urodele	[25, 115]
Skeletal muscle satellite cells	Activation	Limb regeneration in salamander	[116]

One of the essential processes underlying tissue regeneration is production of new cells. These new cells can be derived from distinct origins such as amplification and differentiation of resident stem and progenitor cells, proliferation of mature cells, dedifferentiation of cells to a more stem state or trans-differentiation of one cell type to another cell type.[106] In the table above, the different cell types involved in specific regeneration processes are listed

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Box 1 Cancer stem cells

1. Cancer stem cells (CSCs) are rare quiescent cells within the tumor that possess augmented tumorigenic potential and drug resistance. Alike normal SCs, CSCs are able to self-renew and differentiate. CSCs account for tumor heterogeneity and are able to give rise to a complex tumor bulk following injection into immune-compromised mice. CSCs were found to contribute to various aspects of tumorigenic process including tumor initiation, progression, invasiveness and metastasis.[99]
2. Accumulated data suggested that CSCs may originate from normal SCs that underwent genetic and epigenetic alterations, or alternatively by dedifferetiation of progenitor or mature cells induced by specific signals from the microenvironment.[100]
3. Although wild-type p53 serves as a barrier to CSCs formation regardless of their origin, mutant p53 proteins exhibit their oncogenic gain-of-function by facilitating the acquisition of CSCs phenotype.[44,101]

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order to prevent the acquisition of cancer SCs (CSCs) phenotype (Box 1). SCs and CSCs often share similar regulatory factors that modulate their biological functions.[12] Although the regulation of normal SCs division and differentiation remains under physiological control, in CSCs these processes are unleashed.[13,14] The absence of proper regulation leads to asymmetric and uncontrolled divisions, which give rise to a bulk of tumor cells and a CSC with the capability to initiate new tumors.[15]

Moreover, growing experimental evidence indicates that regeneration and tumorigenesis are related processes, whereby dysregulated regeneration process may lead to tumor development.[16,17] It is well known that chronic inflammation and preceding injuries serve as a precondition for tumorigenesis.[17] This notion was initially postulated in 1863 by Rudolf Virehow.[18] Later, in 1972, Sir Alexander Haddow[19] suggested that 'tumor production is a possible of over healing'. Finally, the association between the term 'wound' and cancer was proposed by Dvorak[20] who stated that tumors are wounds that do not heal. The basis suggested for this statement is that both tissue regeneration restoring wounded organ, as well as carcinogenesis encompass cell proliferation, survival and migration that are regulated by growth factors and cytokines, as well as inflammatory and angiogenic signals. However, in contrast to wound healing, cancer is not self-limiting resulting in uncontrolled cell proliferation, invasion and metastasis.[21] Twenty years later, the statement that regeneration and cancer share common features was corroborated by the study of Riss *et al.,*[22] who compared microarray data from a model of renal regeneration and repair (RRR) with gene expression of renal cell carcinoma

(RCC). The data analysis suggested that the majority (77%) of the genes expressed in RRR and RCC were concordantly regulated, whereas only 23% were discordant (i.e., changed in opposite directions), thus supporting the hypothesis that cancer is an aberrancy of the physiologic processes of wound healing.

Interestingly, it was suggested that the regeneration process may restrain transformation.[23] For example, simultaneous exposure of dorsal and ventral iris of newt to carcinogen showed that the regenerating dorsal iris was persistently resistant to carcinogen, whereas the ventral iris, which cannot regenerate, was more susceptible to tumor induction.[24] Furthermore, it was shown that blastemal cells, which are a mass of cells capable of growth and regeneration into organs, are resistant to tumor formation.[25] Therefore, it is intriguing to understand the mechanisms that assure the high fidelity of regeneration progression.

Cancer is known to be restricted by the action of tumor suppressors.[26] Interestingly, tumor suppressors were proposed to possess 'regeneration suppressor' activities by which they orchestrate major aspects of the regeneration process and ensure its robustness.[21] In this review, we will focus on the role of the pivotal tumor-suppressor *TP53* in the regeneration process at large, and on its contribution to the fidelity of the regeneration process, in particular.

The transcription factor p53 – more than a tumor suppressor

TP53 is one of the most important tumor-suppressor genes that is activated via different stress signals and functions to

determine cell fate. *TP53* is designated as the 'guardian of the genome' because of its ability to protect cells from DNA damage and thus to prevent tumor development.[27] Therefore, it is not surprising that *TP53* is mutated in >50% of human tumors. The majority of *TP53* mutations rise because of missense substitutions.[28] Importantly, most common *TP53* mutations do not only abrogate its tumor-suppressor function, rather they confer it with new oncogenic functions.[29,30]

It is well known that cellular stress such as DNA damage, oncogene activation, hypoxia and telomere shortening can activate p53 and stabilize its protein levels.[31] When activated, the p53 protein functions as a transcriptional regulator, hence initiating a cascade of events that determines the cellular outcome including cell cycle arrest, apoptosis, senescence, DNA repair, development, differentiation and tissue homeostasis.[32] Interestingly, all these cellular activities are part of the regeneration process, pointing to p53 as a potential regeneration coordinator. Notably, besides the full-length p53 protein, different p53 isoforms were identified in multiple human tissues and in various animal models such as *Drosophila*, zebrafish and mouse.[33–37] These p53 isoforms can be generated as a consequence of either alternative splicing, alternative translation initiation or transcription from an alternate promoter.[38] Apparently, p53 isoforms are conserved during evolution and involved in various aspects of cell fate decisions.[36,37,39]

Indeed, full-length p53 and its isoforms often have a regulatory role during normal tissue regeneration following injury. Modulation in p53 levels was observed in different stages of the regeneration process, in a context-dependent manner. For example, in the initial stages of the regeneration process, while mitogenic growth factors promoting cell proliferation were highly expressed, a concomitant suppression of p53 was evident. Whereas, at the late stages of healing, at the remission of the regeneration process, the suppression of mitogenic growth factors was accompanied by strong induction of p53 expression, which served to down-regulate cellular growth.[40] Variations in p53 levels were also found during salamander limb regeneration. It was shown that at first p53 activity decreased, thus allowing both the formation of the blastema and the cell cycle reentry of post-mitotic differentiated cells. Then, p53 level returned to baseline allowing the re-differentiation to muscle. The authors suggested that the regulation of p53 activity is a pivotal mechanism that controls the plasticity of the differentiated

state during regeneration.[41] The role of *TP53* in regeneration-related processes such as proliferation and differentiation is conserved through evolution in additional multicellular organisms such as planarians and *Drosophila*[42,43] (Box 2).

Taken together, it is conceivable to assume that p53 may function as a coordinator of the regeneration process assuring the quality and quantity of the SCs nourishing the regenerative site, as well as the differentiated cells, at the end of the process. This is in line with the notion that p53 functions as the barrier to CSCs formation,[44] by governing the quantity and quality of various SCs, by restricting either expansion or dedifferentiation processes of SCs.

The role of p53 in nerve regeneration

Accomplishing successful regeneration and functional recovery following neural damage, because of either physical injury or pathological conditions, is one of the biggest challenges of neuroscientists and clinicians. Identification of the molecular factors and understanding the molecular pathways is a major step toward achievement of such a goal. The nervous system comprises the peripheral nervous system (PNS) and the central nervous system (CNS) possessing different regenerative capacities. Although the PNS neurons successfully regenerate after damage, the CNS has limited regeneration potential because of the presence of glial inhibitory environment and suppressive intrinsic molecular networks.[45–47]

It should be emphasized that impaired tissue regeneration is often associated with aging, carcinogenesis and augmented degenerative disease.[48] p53 and its isoforms are associated with development of neurodegenerative diseases such as Parkinson's and Alzheimer's because of its induction of cell death in response to stress and interaction with distinct cellular factors that have the ability to facilitate the development of these diseases.[49–52]

Recent accumulating data suggest that p53 has a role in regulation of PNS regeneration. Di Giovanni *et al.*[53] have shown that *TP53* null mice exhibited limited nerve regeneration and suggested that this is due to the transcriptional activity mediated by p53, which activates the axon regenerating genes *Coronin 1b* and *Rab13*. p53 exhibited dual activity that may lead to diverse outcomes depending on the different stages of the regeneration process. Indeed, it was demonstrated that following neurons injury p53 exerted its pro-apoptotic effect via transactivation of *noxa*,[54,55] as well as

promoted cell cycle arrest by the MAPK, JNK and p38 signaling pathways.[56–58] However, it was found that p53 enhanced proliferation and axonal outgrowth that are required for axonal regeneration following injury, through other mechanisms.[59,60] Furthermore, ample data indicate that post-translational modifications affect p53 pro-regenerative activity. For instance, acetylation of p53 by CBP/p300 enables its regulation of GAP-43, which expression is essential for axonal outgrowth and regeneration.[61–63]

Although the regeneration capacity of the injured CNS is restricted, in some cases it may be mediated via modulation of the neuronal intrinsic potential of neuronal stem/progenitor cell (NSCs/NPCs) populations.[64] p53 was suggested to have a role in maintaining self-renewal and differentiation of NSCs under homeostatic conditions. In the absence of p53, the number of differentiated neurons increases.[60] Moreover, p53 was also suggested to be critical for the CNS regeneration upon damage.[65] Following brain injury, p53 was shown to inhibit Rho kinase activity leading to axonal growth and motility, eventually resulting in axonal regeneration.[66] In addition, it was reported that regeneration and axonal sprouting can be attenuated by the MDM4/2-p53-IGF1 signaling complex. Accordingly, inhibition of the triad or one of its components promoted functional recovery after spinal cord injury.[67]

Taking together, it seems that p53 has a role in both PNS and CNS regeneration upon nerve damage. p53 acts beyond its pro-apoptotic regulation activity and facilitates axonal proliferation and regeneration. Yet, to date, the underlying mechanisms are not fully deciphered and more research is needed to uncover the specific molecular networks. With our growing understanding and the emergence of novel findings, it is conceivable to hope that in the future pharmacological reagents modulating p53 activity, which are currently applied for cancer treatment, may be also implemented in neurodegenerative therapy.

The role of p53 in liver regeneration

One of the primary characteristics of the liver is its ability to regenerate.[68] As the liver is the main site of drug detoxification, being constantly subjected to a myriad of toxic chemicals that may induce injury, its remarkable regeneration capacity is of great importance. Moreover, high hepatic regeneration potential permits the use of surgery as a major strategy for treatment of liver diseases including hepatocellular carcinoma (HCC) and liver fibrosis.[69] The liver structure is composed of many sub-units named the 'hepatic lobules'. These well-organized structures contain diverse cell types that reside in different compartments of the lobules. The central part comprises the central veins and contains mainly hepatocytes. The peripheral part named 'canal of Hering' contains the portal tracts and is primarily populated with the biliary epithelial cells (BECs). In addition, other cells types found in the lobules are fibroblasts, endothelial cells and the macrophage-like cells (Kupper cells).[70,71]

Apparently, mechanisms underlying the liver regeneration process vary according to different conditions: the regeneration mechanisms upon normal homeostasis are different from regeneration upon chronic or acute injury.[71]

The liver is characterized by slow turnover rate and the mechanisms underlying its normal homeostasis maintenance are still debatable. Until recently, the accepted hypothesis has been the 'streaming liver', proposing that the entire lobule is eventually replaced by sub-population of hepatocytes, which reside near the portal tracts and possess the ability to regenerate and to stream along the lobule.[72] However, many studies have refuted this hypothesis as lineage tracing methods have failed to prove it.[73,74] Currently, the prevalent assumption is that normal liver turnover is maintained by pre-existing hepatocytes cells.[70] Interestingly, recently Wang *et al.*[75] have identified a small population of cells expressing Axin2+ that possess self-renewal ability as well as the capacity to differentiate into hepatocytes.[75] Therefore, this population of cells was suggested to be referred as hepatocyte SCs, which participate in maintaining the normal liver homeostasis.

Importantly, in addition to preservation of normal homeostasis, the liver has the capacity to regenerate following damage. Different regeneration mechanisms are executed upon acute or chronic injury of the liver. Chronic disease of the liver can be triggered by several agents including viral infections, alcohol abuse and nonalcoholic steatohepatitis (NASH). These agents can cause long-term damage that may lead to liver fibrosis and even to liver cirrhosis, which eventually may result in HCC.[76] Chronic injuries lead to reduction of hepatocytes proliferative capacity, inducing them to undergo senescence, mediated by p53. Under these conditions, the vast majority of the liver is replaced by hepatic progenitor cells.[77,78] For example, it was demonstrated that upon chronic injury induced by CCl_4 treatment, the quiescent hepatocyte stellate cells (HSCs) become activated and regenerate the fibrotic scar. p53 was found to attenuate fibrosis by inducing HSC senescence in non-cell autonomous mechanism. Thus, p53 regulates the fibrosis response and may prevent the deterioration to HCC.[77,79]

To date, many studies have been addressing the question whether there are specific SCs in the liver.[80] The most prevalent hypothesis refers to the ovals cells as the facultative SCs of the liver.[71] It was suggested that these cells arise upon injury and have common characteristics of both hepatocytes and BECs.[81] The oval cells reside in a niche inside the canal of Hering in the liver lobule.[82] Nevertheless, several reports claimed that the oval cells cannot be regarded as liver SCs as they are incapable of undergoing terminal differentiation into hepatocytes.[71,83] Moreover, it was shown that the oval cells may promote the progression of HCC.[84] Considering the profound role of p53 in the life of normal SCs and CSC,[44] it is not surprising that oval cells that were isolated from *TP53* null mice and maintained in culture, gave rise to HCC *in vivo*.[85]

Accumulating experimental evidence indicate that besides oval cells, other cellular sub-population may also contribute to liver regeneration upon chronic injury. One example is a sub-population of liver cells expressing the Lgr5 marker. These cells, unlike the oval cells, can differentiate to hepatocytes or BECs after *in vitro* cultivation.[86] Another example is the hybrid hepatocytes residing at the periportal region of the lobule that are capable to regenerate after chronic injury without promoting HCC.[87] However, the role of p53 in these diverged sub-populations of cells is still unknown and requires further investigation.

Following acute damage such as hepatectomy, the liver is able to restore up to 70% of the tissue resection. The main source of cells that renovate the liver are mature hepatocytes. This process comprises three major phases. Priming – adult hepatocytes re-enter the cell cycle and undergo transition from G0 to the G1 phase. Progression – the cells complete the mitosis process. Termination – the cells return to the G0 phase and the liver retains its original size.[88–90]

Numerous proteins are implicated in the regulation of these phases, among them is p53. Of note, at first glance it seemed as if p53 activity is not crucial for liver regeneration following partial hepatectomy, as *TP53* null mice exhibited complete liver regeneration.[91,92] Strikingly, it was later discovered that p53 function is essential for controlling the robustness of the regeneration process and its fidelity.[93] Similar to the regeneration process in the nerves, modulation in p53 levels was also documented in liver regeneration. In the priming phase, p53 activity is repressed by c-JUN to enable the hepatocytes re-enter the cell cycle.[94] Ample data suggest that following liver regeneration hepatocytes are tolerant to nuclear ploidy without gaining tumorigenic potential.[95,96] This phenomenon may be attributed to the presence of functional p53, which is known to protect genome stability.[97] Indeed, it was recently demonstrated that *TP53*-deficient mice acquire more chromosome segregation errors following liver regeneration than their *TP53*-expressing counterparts. Moreover, it was reported that p53 is involved in controlling the levels of hepatic ploidy by direct regulation of specific target genes, such as Foxm1, Plk2/4, Lats2 and Aurka, at the different phases of the cell cycle.[93,98] Thus, the activity of p53 during the regeneration process following acute damage of the liver is context and time dependent. Despite the inhibition of p53 activity in the initial stage of the regeneration, its function in more advanced steps is essential for keeping the robustness and assuring the fidelity of the process.

All in all, liver regeneration is a complex process that is so far not completely elucidated. It may involve mature hepatocytes as suggested for regeneration upon partial hepatectomy as well as vast sub-population of SCs following other injuries and normal homeostasis turnover. Collectively, it seems that preservation of DNA fidelity and tumor-suppressor activities are crucial to ensure proper regeneration and prevent HCC development.

Concluding remarks

Regeneration and tumorigenesis have been proposed to be related processes and yet the former is a well-orchestrated and controlled process, while the latter is an unrestrained one. As p53 is a major tumor suppressor, it is tempting to speculate that p53 has a key role in regulation of the regeneration process, blocking the shift toward tumorigenesis. p53 activity is fluctuated during regeneration. Although p53 is inhibited during the initial proliferative steps, it is upregulated toward the final stage, when preservation of fidelity and integrity of the regeneration process is of great importance. Activated p53 may induce a variety of signaling pathways such as DNA repair, apoptosis, senescence and others that contribute to the elimination of faulty cells in order to prevent the drifting from regeneration to malignancy. Thus, induction of p53 activity may serve as the quality control checkpoint in the regeneration process, thereby preventing carcinogenesis (Figure 1).

Bearing in mind the great opportunities offered by regenerative medicine to repair pathologic tissues, a better understanding of the regulatory landscape fundamental for p53 function as a coordinator of regeneration may pave the way for overcoming the current challenges.

Conflict of Interest
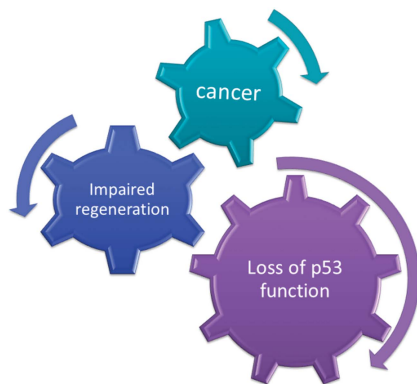
The authors declare no conflict of interest.

Figure 1 p53 coordinates proper regeneration process to prevent cancer development. p53 serves as a quality control protein that assures the integrity of the regeneration process. When p53 function is lost, the regeneration process is impaired leading to cancer development

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