Review

p53 on the crossroad between regeneration and cancer

Meital Charni1,2, Ronit Aloni-Grinstein1,2, Alina Molchadska1 and Varda Rotter1*

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 apoptosis2 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...
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. Although the regulation of normal SCs division and differentiation remains under physiological control, in CSCs these processes are unleashed. 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.

Moreover, growing experimental evidence indicates that regeneration and tumorigenesis are related processes, whereby dysregulated regeneration process may lead to tumor development. It is well known that chronic inflammation and preceding injuries serve as a precondition for tumorigenesis. This notion was initially postulated in 1863 by Rudolf Virchow. Later, in 1972, Sir Alexander Haddow suggested that regeneration and cancer share common features.

### 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|
| 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. In the table above, the different cell types involved in specific regeneration processes are listed.

### 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. Unlike 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.

2. Accumulated data suggested that CSCs may originate from normal SCs that underwent genetic and epigenetic alterations, or alternatively by dedifferentiation of progenitor or mature cells induced by specific signals from the microenvironment.

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.

### 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...
**Box 2** The p53 duality: p53 can differentially regulate numerous molecular pathways dependent on the cell fate and cellular surroundings

- p53 is termed the ‘guardian of the genome’ because of its profound role in preservation of cell genomic fidelity. Following exposure to cellular insults, p53 activity may lead to dual outcomes, such as cell cycle arrest or cell death dependent on various circumstances.
- p53 has a dual role in cancer and aging. Although p53 activation blocks cancer development, it promotes aging by and may restrict normal tissue turnover and regeneration.  
- p53 was found to control autophagy by two opposing mechanisms, depending on its cellular localization: the nuclear p53 induces autophagy whereas, the cytoplasmic p53 may repress it.  
- p53 in the liver is activated following tissue damage and acts as two-edged sword. In the short term, p53 activity prevents carcinogenesis, however, in the long term, same p53 activities may contribute to progress of liver disease, which may eventually lead to cancer development.  
- *Drosophila*p53 exhibits dual roles in cells death and cell differentiation. On one hand, p53 induces apoptosis via the hid gene, on the other it attenuates the differentiation of the photoreceptor neurons and cone cells in the eye, independently of cell death induction.

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**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.

It should be emphasized that impaired tissue regeneration is often associated with aging, carcinogenesis and augmented degenerative disease. 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.

Recent accumulating data suggest that p53 has a role in regulation of PNS regeneration. Di Giovanni et al. 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*, as well as state during regeneration.
promoted cell cycle arrest by the MAPK, JNK and p38 signaling pathways. However, it was found that p53 enhanced proliferation and axonal outgrowth that are required for axonal regeneration following injury, through other mechanisms. 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.

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. 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. Moreover, p53 was also suggested to be critical for the CNS regeneration upon damage. Following brain injury, p53 was shown to inhibit Rho kinase activity leading to axonal growth and motility, eventually resulting in axonal regeneration. 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.

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. 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. 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 (Kupffer cells).

Apparentl, 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. 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. However, many studies have refuted this hypothesis as lineage tracing methods have failed to prove it. Currently, the prevalent assumption is that normal liver turnover is maintained by pre-existing hepatocytes. Interestingly, recently Wang et al. have identified a small population of cells expressing Axin2+ that possess self-renewal ability as well as the capacity to differentiate into hepatocytes. 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. 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. For example, it was demonstrated that upon chronic injury induced by CCl4 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.

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

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. 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. 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 TP53expressing 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.

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