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# Regulation of Oncogenes and Tumor Suppressors to Promote Blastema Formation

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ABSTRACT

While many organisms possess the remarkable ability to regenerate lost body parts, humans have far more limited regenerative capabilities. Harnessing regeneration could revolutionize medicine by serving as a replacement for inaccessible limb transplants or functioning as part of treatments for organ failure from severe illnesses and chronic conditions. Although humans have lost the ability to regenerate through evolution, studies from animal models of regeneration offer insights for potential applications in clinical settings. Studies on zebrafish show that certain pieces of the p53 signaling pathway can suppress blastema formation. Additionally, blastema can't form without the oncogene CK-2 in cockroaches. Short term regulation of these pathways could play a role in developing potential clinical procedures for human regeneration.

## Introduction

Regeneration is widespread across the animal kingdom, though its extent varies greatly between species. Planarians, salamanders, and zebrafish, for instance, exhibit remarkable regenerative capacity, capable of regrowing large anatomical structures including limbs. In contrast, humans demonstrate limited regenerative ability, where the healing process in many cases generates scar tissue instead of restoring lost tissue. In regenerative animals, regeneration consists of two key processes: wound healing and tissue development. At the intersection of these processes lies the blastema, a critical structure that enables regenerative growth.

A blastema is a heterogeneous mass of progenitor cells that forms at an injury site and undergoes morphogenesis (Gerber et al., 2018). Unlike malignant tumors, which are also undifferentiated cell masses, the blastema is defined by its regenerative potential. For a blastema to form, the epidermis first closes over the wound to generate the wound epidermis. The wound epidermis is thinner than normal skin, allowing direct communication between it and the underlying tissues (Seifert and Muneoka, 2019). The extracellular matrix (ECM) shifts to a pro-regenerative state, resembling the composition during embryonic development (Simkin et al., 2015).

In many cases, regeneration is driven by stem cells, which are undifferentiated cells with the ability to self-renew - dividing to create identical copies of themselves - and differentiate into specialized cell types. They are classified based on their potential: totipotent stem cells can develop into any cell type of the animal; pluripotent stem cells can differentiate into any embryonic cell types; multipotent stem cells can produce many different mature cell types; unipotent stem cells are restricted to producing only one type of cell (Kolios and Moodley 2012). While human embryonic stem cells are pluripotent, offering significant regenerative potential, adult stem cells have a much more limited capacity for regeneration.

The cells in blastema are generally limited to replacing their tissue of origin such as muscle, skeleton, or Schwan cells, rather than cells from other areas (Kragl et. al 2009). The lineage-restricted cells seem to be derived from local populations of stem cells and dedifferentiated cells (Zielins et al., 2016). Dedifferentiated cells are cells which go from specialized cells to less differentiated cells in the same lineage, essentially the reverse of the differentiation process. Dedifferentiation allows cells to act like stem cells (Yao and Wang, 2020). Blastema is collectively made up of fibroblasts and periosteal cells, Pax7+ muscle satellite cells, and other undiscovered populations that contribute to blastema function (Leigh et al. 2018). Fibroblasts are a diverse set of stem cells found in bone marrow that play a role in signaling. They provide essential niches, or dynamic environments where stem cells can reside and get activated when needed. They use biochemical cues in the ECM and regulated secretion of soluble mediators, growth factors, and metabolites (Lemos and Duffield, 2018; Plikus et al., 2021).

The typical response to injury in mammals is scarring. It begins with hemostasis, a stopping of the bleeding, followed by inflammation, proliferation and remodeling. Fibroblasts synthesize and maintain the ECM and secrete ECM remodeling enzymes, matrix metalloproteinases and their inhibitors, and tissue inhibitors of

metalloproteinases which remodel the ECM. A complex dialogue exists between fibroblasts and their environment during the scarring process (Darby and Desmoulière, 2020). The annual regeneration of deer antlers is the only example of repeated rounds of mammalian appendage regeneration. They regrow from a blastema into structures of cartilage and bone. Rather than producing a fibrotic scar, wounds on antlers can often go months without healing. Atherogenic periosteum (AP) is a region of the membrane of blood vessels around the bones overlying the frontal bone of deer, and is where antlers are derived from (Hartwig and Schrudde, 1974). Nude mice which were implanted with AP and a small stalk-shaped protuberance, though not antler-like, developed. Wounding was required to generate antler tissue (Li et al., 2001). If blastema can be induced instead of scarring, it is promising for potential human regeneration (Price and Allen, 2004).

## Regeneration Present in Humans

While humans have limited abilities to regenerate large structures like the limbs compared to other regenerative vertebrates, certain tissues, such as the skin and liver, retain high regenerative capabilities. The liver, in particular, can regrow to its normal size even after significant resection (Michalopoulos, 2007). Under normal conditions, liver cells are not highly proliferative. However, in response to acute injury, hepatocytes, the primary cell type of the liver, proliferate to repair the damage (Pu et al., 2016). These cells play essential roles in metabolism, detoxification, and immune cell activation. However, in chronic liver diseases, widespread hepatocyte death can outpace regeneration, leading to progressive organ failure. A key regulator of liver regeneration is catenin signaling, which stimulates cell proliferation by inducing hepatocytes into the G1 phase of the cell cycle, where cells grow and prepare for DNA replication (van Amerongen et al., 2008). Unlike epimorphic regeneration, in which lost anatomical structures are restored through blastema formation, liver regeneration relies on compensatory proliferation, where existing cells expand to restore function rather than regenerate an entirely new liver (Hadjittofi et al., 2021).

Animals that do possess epimorphic regeneration also use compensatory activity for healing. Zebrafish heart regeneration models include a combination of two distinct regenerative processes. The area nearest to the injury consists of a population of cardiac cells that reactivates the expression of embryo-specific sarcomeric proteins and has around ten times the mitotic activity as it normally would have. The undifferentiated cardiomyocytes resemble a blastema-like structure and they integrate with fibrotic tissue through the ECM and mature cardiomyocytes. This is done through the upregulation of connexin 43, a tight junction marker, on the barrier of cells. Along with the blastema, global proliferative activity is important in restoring cardiac function, similar to human liver regeneration. Many cells that aren't near the wound reenter the cell cycle and undergo mitosis. A significant difference between compensatory and epimorphic processes is that in the compensatory mode, the proliferative activity occurs throughout the remaining organ, while in epimorphosis, it is confined to the vicinity of the wound. The compensatory regeneration results in the organ regaining its mass (Sallin, 2015). So while the liver's hepatic tissue enlarges, the original organ doesn't grow back because while the remaining cells divide and proliferate, they can't replace the cells which were lost from injury.

Newborns, unlike adults, can regenerate heart muscle cells within the first week of birth. However, in adults, cardiomyocytes—the contractile muscle cells of the heart—are highly differentiated, often multinucleated with well-aligned sarcomeres. This structural specialization helps maintain heart function but hinders regenerative capacity. Interestingly, cardiomyocyte regeneration has been observed when thyroid hormone pathways and adrenergic receptors—glycoproteins that bind to epinephrine and norepinephrine—are inhibited postnatally. The oxygen rich environment induces cardiomyocyte cell cycle arrest and gives the mammalian heart remarkable regenerative capabilities, but only within a narrow time window before cardiomyocytes become permanently post-mitotic. (Puente et al., 2015).

Typically, aging cells lose proliferative ability and respond poorly to damage. However, during pregnancy, the partially shared maternal-fetal blood system exerts a rejuvenating effect on the mother. In mouse models, pregnant individuals exhibited enhanced muscle regeneration compared to age-matched nonpregnant controls. This effect persisted for two months postpartum, likely due to activation of satellite cells through the Notch signaling pathway, which governs cell fate decisions and tissue homeostasis (Wang et al. 2023). Notably, heart and muscle regeneration occurs without blastema formation; instead, pregnancy-induced systemic factors reactivate dormant muscle progenitor cells, c-Kit positive cardiac cells (Xiao et al., 2013) .

In humans, digit tip regeneration represents a rare example of blastema formation, particularly in young children and, to a lesser extent, in adults. When the distal phalanx (the fingertip) is amputated beyond the nail bed, a blastema-like structure can form, initiating regeneration of bone, connective tissue, and skin. Unlike scarring, this process involves mesenchymal progenitor cells, which aggregate at the wound site and re-enter the cell cycle. The nail bed epithelium plays a crucial role by releasing signals—such as Wnt and FGF pathways—that stimulate the underlying cells to proliferate and differentiate (Simkin, 2015). However, this regenerative capacity is highly limited to injuries that preserve the nail bed; amputations beyond this region result in scarring rather than regeneration. Understanding the mechanisms of blastema formation in digit tip regeneration provides valuable insight into the potential for enhancing regenerative medicine in humans.

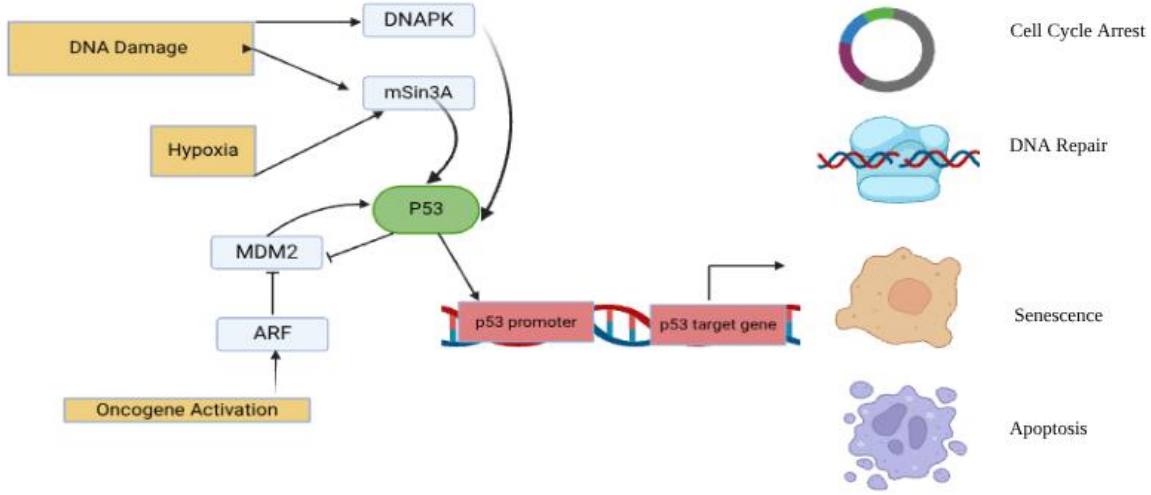
Understanding the signaling pathways that drive blastema formation in regenerative animal models can provide critical insights into the molecular mechanisms underlying human regenerative capacity. Studies in organisms such as salamanders, zebrafish, and mice have identified key pathways that regulate cell proliferation, dedifferentiation, and blastema formation. These signaling pathways are implicated in oncogenesis, and involve the activation of tumor suppressors and oncogenes. While blastema formation in regenerative species is tightly regulated, cancerous growths can hijack these pathways to bypass cell cycle control and apoptosis. Understanding the parallels and differences between these systems in highly regenerative vertebrates and humans can inform the development of new therapies. This review will explore the shared molecular pathways between blastema formation and tumorigenesis, assess their role in regeneration in animal regeneration models, and discuss how these pathways may inform new approaches to increasing regenerative capacity in humans.

## P53 Function and Pathway

Tumor protein p53 is a transcription factor that prevents tumor formation by responding to cellular stresses such as DNA damage (Zhang, 2022). There are several types of DNA damage, including single-strand DNA breaks, double-strand DNA breaks, base mismatches, and DNA-protein crosslinks. DNA-protein crosslinks occur when proteins covalently bond to DNA, interfering with replication, repair, transcription, and recombination (Ruggiano and Ramadan, 2021). Double-strand DNA breaks activate DNA-dependent protein kinase (DNA-PK), which plays a role in transcription regulation and apoptosis (Jackson, 1997). DNA damage alters DNA sequences, disrupting protein formation and function. The accumulation of these errors leads to cancer (Moon et al., 2023).
DNA damage also induces interactions between p53 and the transcriptional activator p300, as well as the transcriptional corepressor mSin3A (Liu and Chen 2005). Another form of cellular stress is oncogene activation. Oncogenes are mutated versions of proto-oncogenes, which normally regulate cell division. When proto-oncogenes become overly active or are duplicated excessively, they can drive normal cells toward cancerous transformation (Liu, 2025).

A common feature of most tumors is hypoxia, a condition characterized by low oxygen levels. Tumor cells divide rapidly, consuming oxygen at an accelerated rate (Muz et al., 2015). Unlike DNA damage, hypoxia interacts with the p53 pathway through mSin3A but not p300. This suggests that distinct cellular pools of p53 modulate transcriptional activity using different coactivators and corepressors (Koumenis et al., 2001).

**Figure 1.** Overview of p-53 pathway. Created with BioRender.com.



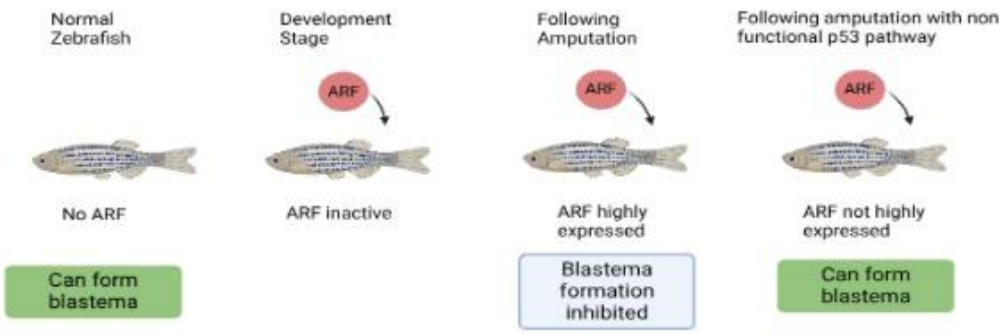

TP53 is the gene that encodes p53, functioning as a guardian of the cell's DNA. p53 induces the hematopoietic zinc finger protein (Hzf), which promotes the expression of p21, a cyclin-dependent kinase inhibitor. p21 helps arrest cell cycle progression and facilitates DNA repair. If the damage is irreparable, apoptosis is triggered, preventing the proliferation and spread of damaged cells.

## ARF Inhibits Regeneration

ARF is a tumor suppressor gene that activates p53, a key regulator of cell division in humans. p53 is frequently inactivated in human cancers and has the ability to induce cell cycle arrest or apoptosis, the process of programmed cell death (Matheu et al., 2008). p53 activity is triggered by various forms of cellular stress, including DNA damage. ARF binds to Mdm2 and suppresses its function, thereby allowing p53 to remain active (Zhang et al., 1998).
To investigate whether ARF inhibits regeneration, researchers introduced it into zebrafish, which naturally exhibit high regenerative capabilities but lack ARF. The introduction of ARF humanized the zebrafish p53 pathway. During developmental stages and in uninjured fins, ARF remained dormant. However, following fin amputation, ARF was highly expressed in the blastema (Hesse et al., 2015).

Regenerative signals induced zebrafish E2f, a family of transcription factors that regulate genes involved in cell proliferation, to bind to ARF. This interaction inhibited epimorphic fin regeneration, a process that occurs normally in zebrafish. ARF could only exert this inhibitory effect if the p53 pathway was functional. When p53 was impaired, ARF did not suppress regeneration, and the zebrafish were able to form a blastema (Hesse et al., 2015).

**Figure 2.** ARF expression in zebrafish and blastema formation. Created with BioRender.com.



Furthermore, ARF specifically inhibits epimorphic regeneration in the zebrafish heart. ARF expression was upregulated during the cardiac regenerative process and slowed the rate of morphological recovery (Lee et al., 2020). The activity of a tumor suppressor during regeneration suggests that ARF identifies blastema formation as a tumor-like process. Furthermore, this finding implies that ARF regulation would be necessary in clinical applications of epimorphic regeneration treatments in humans.

## CK-2 Triggers Blastema Formation in Cockroaches

Other cases where blastema formation has been either clinically induced or repressed include studies on cockroaches. Cockroaches have the ability to regenerate their limbs by forming a blastema at the site of injury, which gives rise to various cell types. These cells then proliferate, and the newly grown tissue establishes proper patterning to restore leg function following the proximal-distal axis (Ren et al., 2024).
Extracellular signal-regulated kinase (ERK)-activated casein kinase 2 (CK-2) is the key trigger for blastema formation in cockroach leg regeneration. However, the role of CK-2 is best documented in cancer. It increases cell proliferation, cell growth, and cell survival. CK-2 functions as an oncogene when overexpressed. (Chua et al., 2017) It is an important phosphorylated and activated target of ERK, a member of the mitogen-activated protein kinase (MAPK) family, which stimulates mitosis. After amputation, CK-2 rapidly undergoes activation through ERK-induced phosphorylation within blastema cells. At five days post-amputation (dpa), phosphorylated ERK (p-ERK) was concentrated in the nuclei of blastema cells (Zhang et al., 2024). p-ERK, which colocalized with CK-2, was rapidly and continuously activated by injury. When amputated groups were compared to an uncut control group, MAPK, forkhead box O (FOXO) transcription factors, and ECM receptor interactions were enriched. MAPK activity continues to increase throughout the regeneration process.

When RNA interference (RNAi), a method that introduces double-stranded RNA to silence a specific gene, was used to knock down CK-2, it impaired blastema formation by repressing cell proliferation (Haiyong, 2018). Cockroaches injected with CK-2 inhibitors lose their regenerative capabilities, demonstrating that CK-2 is essential for cockroach leg regeneration. CK-2 also plays a role in promoting blastema cell proliferation in zebrafish fin regeneration. When p-ERK, which phosphorylates and activates CK-2, was inhibited, regeneration was blocked.

## Discussion

Humans also possess CK-2, which raises the question of why CK-2, which is essential to regeneration in cockroaches, doesn't contribute to regenerative abilities in humans. Inhibiting other MAPKs, such as Jun N-terminal kinases (JNKs), did not have the same effect either. JNK is involved in imaginal regeneration in fruit flies, suggesting that MAPK family members may drive species-specific appendage regeneration (Zhang et al., 2024; Wagner and Nebreda, 2009). It is possible that in a similar manner, CK-2 might not carry as much importance in human blastema formation.

**Figure 3.** Type of MAPK that is the key element in blastema formation for different species

| ERK | Other MAPK |
|---|---|
| ERK needed for blastema formation in cockroaches (Zhang et. al 2024) | JNK needed for the activation of fruit fly regeneration (Santabarbara-Ruiz et. al 2015) |
| ERK activation a key component of salamander regeneration (Yun et al., 2014) | JNK as well as ERK essential to initiate regeneration in fresh water polyp (Tursch et al., 2022) |
| ERK activity controls bone growth in regenerating zebrafish scales (De Simone et al. 2021) | RAS oncogene, part of the RAF/MAPK pathway, promotes wing growth in black cutworm (Xu et al., 2021) |
| ERK crucial for African clawed frog limb blastema formation (Suzuki et al. 2014) | P38 MAPK has a critical role in nerve regeneration in mice (Kato et al., 2013) |

Another explanation could simply be that CK-2 has no opportunity to help form blastema because other factors inhibit blastema in the first place. If CK-2 could play a key role in human regeneration, harnessing it would need to happen in tandem with the inhibition of the barriers to blastema formation, like ARF.

CK-2 is heavily conserved across different species. Meanwhile, the function of ARF stays essentially the same in regards to the cell cycle, however, the gene that encodes the protein is different. Human ARF is made from the Cdkn2A gene. It's the same for mice. However, zebrafish and cockroaches, which are highly regenerative, have different versions of the gene, which could partially account for why ARF doesn't block regeneration in those species (Haraoka et al., 2022; Yuki et al., 2024).

Figure 4. Pathway vs. Model matrix for CK-2 and Cdkn2A

| Experimental Model | CK-2 | Functional role | Cdkn2A | Functional role |
|---|---|---|---|---|
| Zebrafish | Yes | Development and fin regeneration | Has Cdkn2a/b which combines the A and B versions of Cdkn2 | Regulates cell proliferation |
| Human | Yes | Development and wound healing | Yes | Regulates cell proliferation |
| Cockroach | Yes | Development and limb regeneration | Has Cdkn2, an ancestral version | Regulates cell proliferation |
| Mice | Yes | Development and muscle regeneration | Yes | Regulates cell proliferation |

Regulation of ARF could be achieved by controlling transcription factors. E2F1 is a transcription factor that regulates genes involved in cell cycle control and induces ARF transcription by directly interacting with its binding site (DeGregori et al., 1997). Myc, a well-established oncogene, also activates ARF transcription, triggering apoptosis as a protective mechanism (Schmitt, 2003). Other transcription factors that positively regulate ARF

include DMP1, a cyclin D-binding protein, and transforming growth factor-beta 3 (TGF-β3), which can reduce scarring (Inoue et al., 2000; Zheng et al., 2010)

Conversely, several transcription factors repress ARF expression. One example is BMI-1, a polycomb group gene that codes for multiprotein complexes (Ko et al., 2016). BMI-1 suppresses cellular senescence—a state in which a cell ceases to divide but does not undergo apoptosis—by repressing ARF expression (Micco et al., 2020; Parreno, 2022). Another polycomb group gene, CBX7, extends the lifespan of normal human cells by inhibiting ARF expression (Liu et al., 2022).Temporarily repressing ARF using one of these transcriptional repressors could be a crucial step in inducing blastema formation in humans.

It is important to take into account the possible consequences of reducing ARF function. Around 50% of human cancers contain loss of function mutations in p53, and inhibiting ARF would also inhibit p53 (Ozaki and Nakagawara, 2011). Because of its close relation to cancer, long term modulation would be dangerous. While mammalian digit tip regeneration takes about 28 days, larger injuries could take even longer. And clinical treatments using this approach could not be applied to those at risk for developing cancer.

Additionally, repressing the scarring process could be a step needed. Activation of the Wnt/β-catenin pathway, a family of proteins that play critical roles in embryonic development and adult tissue homeostasis could also be helpful (Liu et al., 2022). When the yes-associated protein (YAP) was immediately inhibited with verteporfin in pig wounds, which display the most human-like model of scarring, it was sufficient to prevent scarring and drive wound regeneration in pigs (Mascharak et al., 2025). YAP is an oncoprotein involved in cell proliferation control located in the cytoplasm in an inactive form (Abylkassov and Xie, 2016).

Although there are many additional factors that must be considered in order to effectively induce blastema formation and regeneration in clinical treatments for human diseases, the regulation of the components in the P53 pathway can play a large role in making this happen.

## Conclusion

The human healing process generally involves scarring rather than blastema formation. However, tumor suppressors and oncogenes can act as switches for blastema in certain animals, which leaves the door open to possible medical applications involving their regulation. CK-2, an MAPK whose main role is in cancer, serves as a key component of blastema formation in cockroaches. While humans also possess CK-2, it doesn't have the same effect. This could be because MAPKs have species specific functions. ARF, part of the human p53 tumor suppressor pathway, mistakes blastema for a tumor and interferes with zebrafish fin regeneration. Turning off p53 along with scarring mechanisms might be necessary steps to induce blastema in humans in the future.

## References

Gerber, T., Murawala, P., Knapp, D., Masselink, W., Schuez, M., Hermann, S., Gac-Santel, M., Nowoshilow, S., Kageyama, J., Khattak, S., Currie, J. D., Camp, J. G., Tanaka, E. M., & Treutlein, B. (2018). Single-cell analysis uncovers convergence of cell identities during axolotl limb regeneration. Science (New York, N.Y.), 362(6413), eaaq0681. https://doi.org/10.1126/science.aaq0681

Seifert, A. W., & Muneoka, K. (2018). The blastema and epimorphic regeneration in mammals. Developmental biology, 433(2), 190–199. https://doi.org/10.1016/j.ydbio.2017.08.007

Simkin, J., Sammarco, M. C., Dawson, L. A., Schanes, P. P., Yu, L., & Muneoka, K. (2015). The mammalian blastema: regeneration at our fingertips. Regeneration (Oxford, England), 2(3), 93–105. https://doi.org/10.1002/reg2.36

Kolios, G., & Moodley, Y. (2013). Introduction to stem cells and regenerative medicine. Respiration; international review of thoracic diseases, 85(1), 3–10. https://doi.org/10.1159/000345615

Kragl, M., Knapp, D., Nacu, E., Khattak, S., Maden, M., Epperlein, H. H., & Tanaka, E. M. (2009). Cells keep a memory of their tissue origin during axolotl limb regeneration. Nature, 460(7251), 60–65. https://doi.org/10.1038/nature08152

Zielins, E. R., Ransom, R. C., Leavitt, T. E., Longaker, M. T., & Wan, D. C. (2016). The role of stem cells in limb regeneration. Organogenesis, 12(1), 16–27. https://doi.org/10.1080/15476278.2016.1163463

Yao, Y., & Wang, C. (2020). Dedifferentiation: inspiration for devising engineering strategies for regenerative medicine. NPJ Regenerative medicine, 5, 14. https://doi.org/10.1038/s41536-020-00099-8

Leigh, N. D., Dunlap, G. S., Johnson, K., Mariano, R., Oshiro, R., Wong, A. Y., Bryant, D. M., Miller, B. M., Ratner, A., Chen, A., Ye, W. W., Haas, B. J., & Whited, J. L. (2018). Transcriptomic landscape of the blastema niche in regenerating adult axolotl limbs at single-cell resolution. Nature communications, 9(1), 5153. https://doi.org/10.1038/s41467-018-07604-0

Lemos, D. R., & Duffield, J. S. (2018). Tissue-resident mesenchymal stromal cells: Implications for tissue-specific antifibrotic therapies. Science translational medicine, 10(426), eaan5174. https://doi.org/10.1126/scitranslmed.aan5174

Plikus, M. V., Wang, X., Sinha, S., Forte, E., Thompson, S. M., Herzog, E. L., Driskell, R. R., Rosenthal, N., Biernaskie, J., & Horsley, V. (2021). Fibroblasts: Origins, definitions, and functions in health and disease. Cell, 184(15), 3852–3872. https://doi.org/10.1016/j.cell.2021.06.024

Darby, I.A., Desmoulière, A. (2020). Scar Formation: Cellular Mechanisms. In: Téot, L., Mustoe, T.A., Middelkoop, E., Gauglitz, G.G. (eds) Textbook on Scar Management. Springer, Cham. https://doi.org/10.1007/978-3-030-44766-3_3

Hartwig, H., Schrudde, J. Experimentelle Untersuchungen zur Bildung der primären Stirnauswüchse beim Reh (Capreolus capreolus L.). Zeitschrift für Jagdwissenschaft 20, 1–13 (1974). https://doi.org/10.1007/BF01901843

Li, C., Gao, X., Yang, F., Martin, S. K., Haines, S. R., Deng, X., Schofield, J., & Stanton, J. A. (2009). Development of a nude mouse model for the study of antlerogenesis--mechanism of tissue interactions and ossification pathway. Journal of experimental zoology. Part B, Molecular and developmental evolution, 312(2), 118–135. https://doi.org/10.1002/jez.b.21252

Price, J., & Allen, S. (2004). Exploring the mechanisms regulating regeneration of deer antlers. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 359(1445), 809–822. https://doi.org/10.1098/rstb.2004.1471

Michalopoulos G. K. (2007). Liver regeneration. Journal of cellular physiology, 213(2), 286–300. https://doi.org/10.1002/jcp.21172

Pu, W., Zhang, H., Huang, X., Tian, X., He, L., Wang, Y., Zhang, L., Liu, Q., Li, Y., Li, Y., Zhao, H., Liu, K., Lu, J., Zhou, Y., Huang, P., Nie, Y., Yan, Y., Hui, L., Lui, K. O., & Zhou, B. (2016). Mfsd2a+ hepatocytes repopulate the liver during injury and regeneration. Nature communications, 7, 13369. https://doi.org/10.1038/ncomms13369

van Amerongen, R., Mikels, A., & Nusse, R. (2008). Alternative wnt signaling is initiated by distinct receptors. Science signaling, 1(35), re9. https://doi.org/10.1126/scisignal.135re9

Hadjittofi, C., Feretis, M., Martin, J., Harper, S., & Huguet, E. (2021). Liver regeneration biology: Implications for liver tumour therapies. World journal of clinical oncology, 12(12), 1101–1156. https://doi.org/10.5306/wjco.v12.i12.1101

Sallin, P., de Preux Charles, A. S., Duruz, V., Pfefferli, C., & Jaźwińska, A. (2015). A dual epimorphic and compensatory mode of heart regeneration in zebrafish. Developmental biology, 399(1), 27–40. https://doi.org/10.1016/j.ydbio.2014.12.002

Puente, B. N., Kimura, W., Muralidhar, S. A., Moon, J., Amatruda, J. F., Phelps, K. L., Grinsfelder, D., Rothermel, B. A., Chen, R., Garcia, J. A., Santos, C. X., Thet, S., Mori, E., Kinter, M. T., Rindler, P. M., Zacchigna, S., Mukherjee, S., Chen, D. J., Mahmoud, A. I., Giacca, M., … Sadek, H. A. (2014). The oxygen-rich postnatal environment induces cardiomyocyte cell-cycle arrest through DNA damage response. Cell, 157(3), 565–579. https://doi.org/10.1016/j.cell.2014.03.032

Wang, T., Chen, X., Wang, K., Ju, J., Yu, X., Yu, W., Liu, C., & Wang, Y. (2023). Cardiac regeneration: Pre-existing cardiomyocyte as the hub of novel signaling pathway. Genes & diseases, 11(2), 747–759. https://doi.org/10.1016/j.gendis.2023.01.031

Xiao, J., Li, J., Xu, T., Lv, D., Shen, B., Song, Y., & Xu, J. (2013). Pregnancy-induced physiological hypertrophy protects against cardiac ischemia-reperfusion injury. International journal of clinical and experimental pathology, 7(1), 229–235.

Zhang, S., Carlsen, L., Hernandez Borrero, L., Seyhan, A. A., Tian, X., & El-Deiry, W. S. (2022). Advanced Strategies for Therapeutic Targeting of Wild-Type and Mutant p53 in Cancer. Biomolecules, 12(4), 548. https://doi.org/10.3390/biom12040548

Ruggiano, A., & Ramadan, K. (2021). DNA-protein crosslink proteases in genome stability. Communications biology, 4(1), 11. https://doi.org/10.1038/s42003-020-01539-3

Jackson S. P. (1997). DNA-dependent protein kinase. The international journal of biochemistry & cell biology, 29(7), 935–938. https://doi.org/10.1016/s1357-2725(97)00006-x

Moon, J., Kitty, I., Renata, K., Qin, S., Zhao, F., & Kim, W. (2023). DNA Damage and Its Role in Cancer Therapeutics. International journal of molecular sciences, 24(5), 4741. https://doi.org/10.3390/ijms24054741

Liu, G., & Chen, X. (2006). Regulation of the p53 transcriptional activity. Journal of cellular biochemistry, 97(3), 448–458. https://doi.org/10.1002/jcb.20700

Ozaki, T., & Nakagawara, A. (2011). Role of p53 in Cell Death and Human Cancers. Cancers, 3(1), 994–1013. https://doi.org/10.3390/cancers3010994

Liu, S. V., Nagasaka, M., Atz, J., Solca, F., & Müllauer, L. (2025). Oncogenic gene fusions in cancer: from biology to therapy. Signal transduction and targeted therapy, 10(1), 111. https://doi.org/10.1038/s41392-025-02161-7

Muz, B., de la Puente, P., Azab, F., & Azab, A. K. (2015). The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia (Auckland, N.Z.), 3, 83–92. https://doi.org/10.2147/HP.S93413

Koumenis, C., Alarcon, R., Hammond, E., Sutphin, P., Hoffman, W., Murphy, M., Derr, J., Taya, Y., Lowe, S. W., Kastan, M., & Giaccia, A. (2001). Regulation of p53 by hypoxia: dissociation of transcriptional repression and apoptosis from p53-dependent transactivation. Molecular and cellular biology, 21(4), 1297–1310. https://doi.org/10.1128/MCB.21.4.1297-1310.2001

Matheu, A., Maraver, A., & Serrano, M. (2008). The Arf/p53 pathway in cancer and aging. Cancer research, 68(15), 6031–6034. https://doi.org/10.1158/0008-5472.CAN-07-6851

Zhang, Y., Xiong, Y., & Yarbrough, W. G. (1998). ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. Cell, 92(6), 725–734. https://doi.org/10.1016/s0092-8674(00)81401-4

Hesse, R. G., Kouklis, G. K., Ahituv, N., & Pomerantz, J. H. (2015). The human ARF tumor suppressor senses blastema activity and suppresses epimorphic tissue regeneration. eLife, 4, e07702. https://doi.org/10.7554/eLife.07702

Lee, S., Hesse, R., Tamaki, S., Garland, C., & Pomerantz, J. H. (2020). Human ARF Specifically Inhibits Epimorphic Regeneration in the Zebrafish Heart. Genes, 11(6), 666. https://doi.org/10.3390/genes11060666

Ren, C., Wen, Y., Zheng, S., Zhao, Z., Li, E. Y., Zhao, C., Liao, M., Li, L., Zhang, X., Liu, S., Yuan, D., Luo, K., Wang, W., Fei, J., & Li, S. (2024). Two transcriptional cascades orchestrate cockroach leg regeneration. Cell reports, 43(3), 113889. https://doi.org/10.1016/j.celrep.2024.113889

Chua, M. M., Ortega, C. E., Sheikh, A., Lee, M., Abdul-Rassoul, H., Hartshorn, K. L., & Dominguez, I. (2017). CK2 in Cancer: Cellular and Biochemical Mechanisms and Potential Therapeutic Target. Pharmaceuticals (Basel, Switzerland), 10(1), 18. https://doi.org/10.3390/ph10010018

Zhang, X. S., Wei, L., Zhang, W., Zhang, F. X., Li, L., Li, L., Wen, Y., Zhang, J. H., Liu, S., Yuan, D., Liu, Y., Ren, C., & Li, S. (2024). ERK-activated CK-2 triggers blastema formation during appendage regeneration. Science advances, 10(12), eadk8331. https://doi.org/10.1126/sciadv.adk8331

Han H. (2018). RNA Interference to Knock Down Gene Expression. Methods in molecular biology (Clifton, N.J.), 1706, 293–302. https://doi.org/10.1007/978-1-4939-7471-9_16

Wagner, E. F., & Nebreda, A. R. (2009). Signal integration by JNK and p38 MAPK pathways in cancer development. Nature reviews. Cancer, 9(8), 537–549. https://doi.org/10.1038/nrc2694

Yun, M. H., Gates, P. B., & Brockes, J. P. (2014). Sustained ERK activation underlies reprogramming in regeneration-competent salamander cells and distinguishes them from their mammalian counterparts. Stem cell reports, 3(1), 15–23. https://doi.org/10.1016/j.stemcr.2014.05.009

De Simone, A., Evanitsky, M. N., Hayden, L., Cox, B. D., Wang, J., Tornini, V. A., Ou, J., Chao, A., Poss, K. D., & Di Talia, S. (2021). Control of osteoblast regeneration by a train of Erk activity waves. Nature, 590(7844), 129–133. https://doi.org/10.1038/s41586-020-03085-8

Suzuki, M., Satoh, A., Ide, H., & Tamura, K. (2007). Transgenic Xenopus with prx1 limb enhancer reveals crucial contribution of MEK/ERK and PI3K/AKT pathways in blastema formation during limb regeneration. Developmental biology, 304(2), 675–686. https://doi.org/10.1016/j.ydbio.2007.01.019

Santabárbara-Ruiz, P., López-Santillán, M., Martínez-Rodríguez, I., Binagui-Casas, A., Pérez, L., Milán, M., Corominas, M., & Serras, F. (2015). ROS-Induced JNK and p38 Signaling Is Required for Unpaired Cytokine Activation during Drosophila Regeneration. PLoS genetics, 11(10), e1005595. https://doi.org/10.1371/journal.pgen.1005595

Tursch, A., Bartsch, N., Mercker, M., Schlüter, J., Lommel, M., Marciniak-Czochra, A., Özbek, S., & Holstein, T. W. (2022). Injury-induced MAPK activation triggers body axis formation in Hydra by default Wnt signaling. Proceedings of the National Academy of Sciences of the United States of America, 119(35), e2204122119. https://doi.org/10.1073/pnas.2204122119

Tursch, A., Bartsch, N., Mercker, M., Schlüter, J., Lommel, M., Marciniak-Czochra, A., Özbek, S., & Holstein, T. W. (2022). Injury-induced MAPK activation triggers body axis formation in Hydra by default Wnt signaling. Proceedings of the National Academy of Sciences of the United States of America, 119(35), e2204122119. https://doi.org/10.1073/pnas.2204122119

Xu, Y., Wei, W., Lin, G., Yan, S., Zhang, J., Shen, J., & Wang, D. (2021). The Ras/MAPK pathway is required for regenerative growth of wing discs in the black cutworm Agrotis ypsilon. Insect biochemistry and molecular biology, 131, 103552. https://doi.org/10.1016/j.ibmb.2021.103552

Kato, N., Matsumoto, M., Kogawa, M., Atkins, G. J., Findlay, D. M., Fujikawa, T., Oda, H., & Ogata, M. (2013). Critical role of p38 MAPK for regeneration of the sciatic nerve following crush injury in vivo. Journal of neuroinflammation, 10, 1. https://doi.org/10.1186/1742-2094-10-1

Haraoka, Y., Akieda, Y., Nagai, Y., Mogi, C., & Ishitani, T. (2022). Zebrafish imaging reveals TP53 mutation switching oncogene-induced senescence from suppressor to driver in primary tumorigenesis. Nature communications, 13(1), 1417. https://doi.org/10.1038/s41467-022-29061-6

Yuki, S., Sasaki, S., Yamamoto, Y., Murakami, F., Sakata, K., & Araki, I. (2024). Evolution of the Cdk4/6-Cdkn2 system in invertebrates. Genes to cells : devoted to molecular & cellular mechanisms, 29(11), 1037–1051. https://doi.org/10.1111/gtc.13165

DeGregori, J., Leone, G., Miron, A., Jakoi, L., & Nevins, J. R. (1997). Distinct roles for E2F proteins in cell growth control and apoptosis. Proceedings of the National Academy of Sciences of the United States of America, 94(14), 7245–7250. https://doi.org/10.1073/pnas.94.14.7245

Schmitt C. A. (2003). Senescence, apoptosis and therapy--cutting the lifelines of cancer. Nature reviews. Cancer, 3(4), 286–295. https://doi.org/10.1038/nrc1044

Inoue, K., Wen, R., Rehg, J. E., Adachi, M., Cleveland, J. L., Roussel, M. F., & Sherr, C. J. (2000). Disruption of the ARF transcriptional activator DMP1 facilitates cell immortalization, Ras transformation, and tumorigenesis. Genes & development, 14(14), 1797–1809.

Zheng, Y., Zhao, Y. D., Gibbons, M., Abramova, T., Chu, P. Y., Ash, J. D., Cunningham, J. M., & Skapek, S. X. (2010). Tgfbeta signaling directly induces Arf promoter remodeling by a mechanism involving Smads 2/3 and p38 MAPK. The Journal of biological chemistry, 285(46), 35654–35664. https://doi.org/10.1074/jbc.M110.128959

Ko, A., Han, S. Y., & Song, J. (2016). Dynamics of ARF regulation that control senescence and cancer. BMB reports, 49(11), 598–606. https://doi.org/10.5483/bmbrep.2016.49.11.120

Di Micco, R., Krizhanovsky, V., Baker, D., & d'Adda di Fagagna, F. (2021). Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nature reviews. Molecular cell biology, 22(2), 75–95. https://doi.org/10.1038/s41580-020-00314-w

Parreno, V., Martinez, A. M., & Cavalli, G. (2022). Mechanisms of Polycomb group protein function in cancer. Cell research, 32(3), 231–253. https://doi.org/10.1038/s41422-021-00606-6

Liu, W., Wang, H., Jian, C., Li, W., Ye, K., Ren, J., Zhu, L., Wang, Y., Jin, X., & Yi, L. (2022). The RNF26/CBX7 axis modulates the TNF pathway to promote cell proliferation and regulate sensitivity to TKIs in ccRCC. International journal of biological sciences, 18(5), 2132–2145. https://doi.org/10.7150/ijbs.69325

Liu, J., Xiao, Q., Xiao, J., Niu, C., Li, Y., Zhang, X., Zhou, Z., Shu, G., & Yin, G. (2022). Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal transduction and targeted therapy, 7(1), 3. https://doi.org/10.1038/s41392-021-00762-6

Mascharak, S., Griffin, M., Talbott, H. E., Guo, J. L., Parker, J., Morgan, A. G., Valencia, C., Kuhnert, M. M., Li, D. J., Liang, N. E., Kratofil, R. M., Daccache, J. A., Sidhu, I., Davitt, M. F., Guardino, N., Lu, J. M., Abbas, D. B., Deleon, N. M. D., Lavin, C. V., Adem, S., … Longaker, M. T. (2025). Inhibiting mechanotransduction prevents scarring and yields regeneration in a large animal model. Science translational medicine, 17(786), eadt6387. https://doi.org/10.1126/scitranslmed.adt6387

Abylkassov, R., & Xie, Y. (2016). Role of Yes-associated protein in cancer: An update. Oncology letters, 12(4), 2277–2282. https://doi.org/10.3892/ol.2016.4955