Seminars in Cell and Developmental Biology 169 (2025) 103605

Contents lists available at ScienceDirect

Seminars in Cell and Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Cell death in regeneration and cell turnover: Lessons from planarians and *Drosophila*

Teresa Adell *, Francesc Cebrià, Josep F. Abril, Sofia J. Araújo, Montserrat Corominas, Marta Morey, Florenci Serras, Cristina González-Estévez *

Department of Genetics, Microbiology and Statistics, School of Biology and Institute of Biomedicine of the University of Barcelona (IBUB), University of Barcelona, Av. Diagonal 643, Edifici Prevosti 1st floor, Barcelona 08028, Spain

ARTICLE INFO

Keywords:
Planarian
Drosophila
Regeneration
Homeostasis
Apoptosis
Cell death
Autophagy
Stem cell

ABSTRACT

Programmed cell death plays a crucial role during tissue turnover in all animal species, and it is also essential during regeneration, serving as a key signalling mechanism to promote tissue repair and regrowth. In freshwater planarians, remarkable regenerative abilities are supported by neoblasts, a population of adult stem cells, which enable high somatic cell turnover. Cell death in planarians occurs continuously during regeneration and adult homeostasis, underscoring its critical role in tissue remodeling and repair. However, the exact mechanisms regulating cell death in these organisms remain elusive. In contrast, *Drosophila melanogaster* serves as a powerful model for studying programmed cell death in development, metamorphosis, and adult tissue maintenance, leveraging advanced genetic tools and visualization techniques. In *Drosophila*, cell death sculpts tissues, eliminates larval structures during metamorphosis, and supports homeostasis in adulthood. Despite limited regenerative capacity compared to planarians, *Drosophila* provides unique insights into cell death's regulatory mechanisms. Comparative analysis of these two systems highlights both conserved and divergent roles of programmed cell death in tissue renewal and regeneration. This review synthesizes the latest knowledge of programmed cell death in planarians and *Drosophila*, aiming to illuminate shared principles and system-specific adaptations, with relevance to tissue repair across biological systems.

1. Introduction

Programmed cell death plays a crucial role during tissue turnover in all animal species, and it is also essential during regeneration, serving as a key signalling mechanism to promote tissue repair and regrowth. Apoptosis is a form of programmed cell death essential for maintaining tissue health and regeneration by systematically dismantling damaged or unnecessary cells while avoiding harm to neighboring tissues. This process ensures proper development, eliminates potentially harmful cells, and contributes to tissue remodeling. In addition to apoptosis, other forms of cell death, such as autophagy-dependent cell death, support regeneration and homeostasis by clearing cellular debris and recycling components for energy and repair. With ongoing research, scientists continue to uncover new types of cell death, revealing a complex landscape of mechanisms that contribute to cellular balance and organismal health.

In this study we compare cell death processes occurring in two animal species that show essentially different live cycle and regenerative abilities, such as planarians and *Drosophila.* Freshwater planarians show a striking plasticity in their adult stage. They are able to regenerate any body part, including an entire head, within just a few days. They also continuously adjust their body size in response to nutritional availability [1–3]. These abilities rely on the presence of an abundant population of adult stem cells, known as neoblasts, which are distributed throughout the planarian body and can replace any cell type. Neoblasts are the only proliferative cell type in planarians and are responsible for giving rise to all the various cell types within the planarian body [4,5]. As a result, planarians experience a high rate of somatic cell turnover throughout their life, offering a unique opportunity to study the mechanisms and regulation of cell turnover in adult tissues. There are evidences that cell death is present during the entire regeneration process indicating its continuous role in tissue remodeling and repair [6–8]. Regeneration and tissue homeostasis rely on a delicate balance between cell proliferation and cell death, but, despite conservation of molecular pathways,

* Corresponding authors.
E-mail addresses: tadellc@ub.edu (T. Adell), crisgonzalez@ub.edu (C. González-Estévez).

https://doi.org/10.1016/j.semcdb.2025.103605
Received 29 November 2024; Received in revised form 27 February 2025; Accepted 9 March 2025
Available online 25 March 2025

mechanisms responsible for cell death in planarians have remained elusive [9].

Drosophila melanogaster does not possess the extensive regenerative abilities observed in some other species, but certain developing and adult tissues are capable of regeneration [10]. *Drosophila* is also a valuable model due to its powerful genetic tools, well-understood developmental biology and the ability to visualize cell death at specific lifecycle stages, advantages not yet possible in planarians [10,11]. In *Drosophila*, cell death is essential for development, metamorphosis, and maintaining adulthood homeostasis. During development, programmed cell death removes unnecessary or misplaced cells, shaping tissues and organ structures. In metamorphosis, apoptosis and autophagy eliminate larval tissues that are not retained in the adult, making room for new structures. After metamorphosis, cell death in specific tissues, like the brain and muscles, helps complete maturation [12]. In adulthood, cell death is limited to tissue maintenance rather than large-scale remodeling.

The role of cell death in regeneration and tissue turnover extends

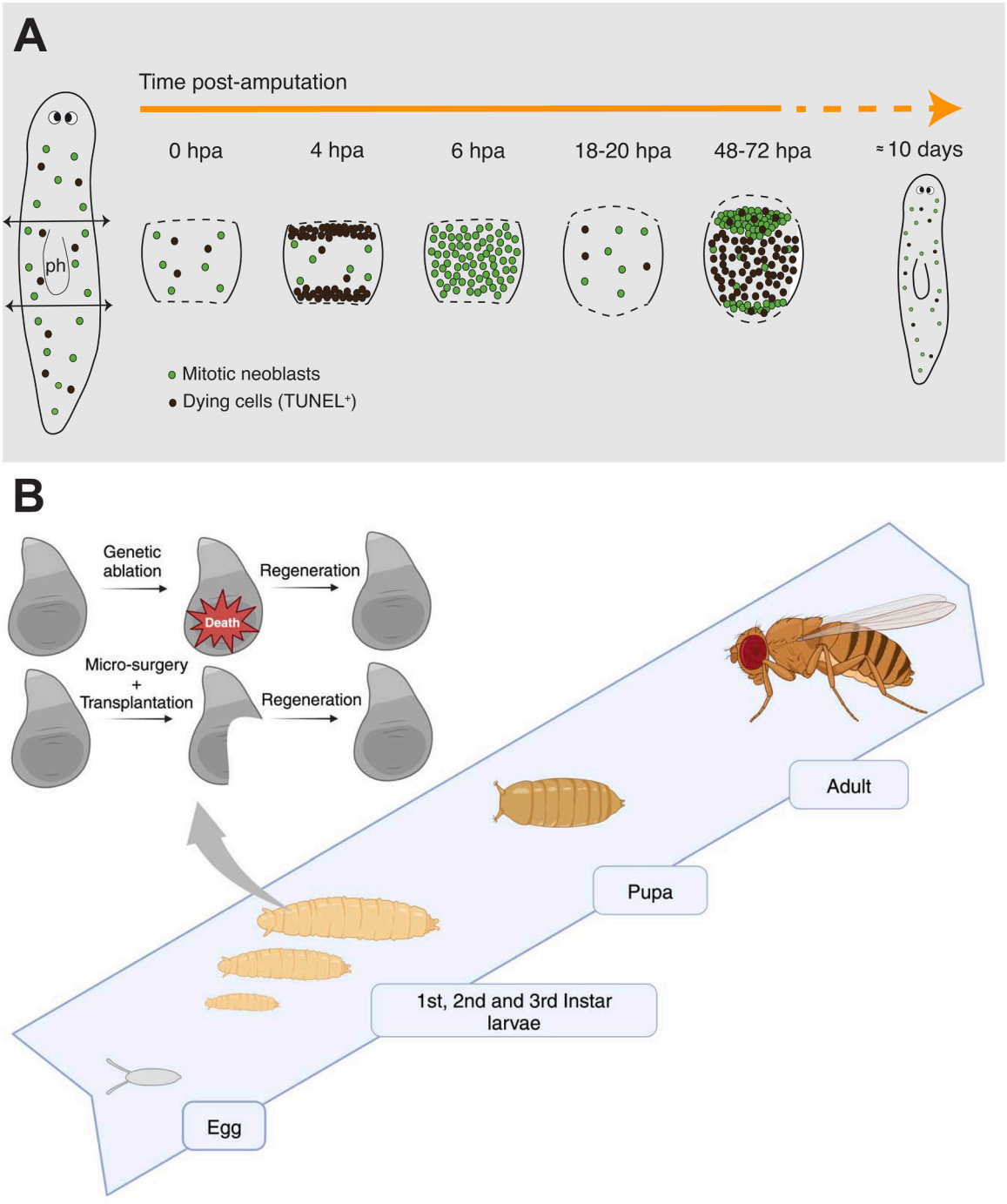

Fig. 1. Regeneration in planarian and *Drosophila*. A. Planarians can regenerate almost any part of their bodies. The illustration follows the regeneration process of a trunk fragment (the double-arrows display the two levels of amputation). A wound-localized increase in cell death at 4hR and a systemic increase at 72 hR is observed. A generalized increase in mitosis at 6hR (first mitotic peak) and a wound-localized increase at 48–72 hR (second mitotic peak) are observed. hpa, hours post-amputation; ph, pharynx. **B.** The *Drosophila* life-cycle is illustrated. While *Drosophila* itself lacks the ability to regenerate, imaginal discs taken from third-instar larvae can regenerate completely and are commonly utilized in regeneration studies. Researchers typically employ two primary methods to induce damage: genetic ablation and microsurgery with transplantation. Panel B was created in BioRender. Gonzalez Estevez, C. (2024) https://BioRender.com/d80t268.

beyond planarians and *Drosophila* and has been well-documented in other sources, which we recommend to the reader. For example, similar mechanisms are observed in other organisms, such as zebrafish [13], *Hydra* [14], *Xenopus* tadpoles [15] or some mammalian organs, including skin, gut, kidney, and muscle [16]. Also, much information of cell death processes and regeneration is available for other insect orders such as Lepidoptera, Orthoptera, and Coleoptera [17].

This review explores the types of cell death involved in cell renewal and regeneration in planarians and *Drosophila*, highlighting the similarities and differences in their roles. It also examines the signalling pathways that play a key role, such as the JNK and PI3K/Akt pathways, both of which are shared between these two species. Our goal is to provide an overview of the current understanding of this process, highlighting key topics from these two model systems and considering their potential implications for other organisms and tissues.

2. Cell death during regeneration

2.1. Cell death as an inducer of regeneration

Planarians exhibit an astonishing capacity for rapid regeneration. Following amputation, planarians can regrow lost body parts in just 10 days (Fig. 1A). This regeneration relies on the formation of new tissue, known as the blastema. As the blastema expands, it establishes the identity and position of new structures, and cells within the blastema differentiate into specific types. Meanwhile, existing tissues undergo remodeling and reshaping. This coordinated effort ensures that all organ systems are restored to their proper proportions and symmetry. Within about two weeks, the planarian emerges not only fully regenerated but also perfectly scaled to its new size (reviewed in [1,18,19]).

In planarians, amputation triggers two waves of cell death (described by TUNEL staining and cleaved-caspase-3 detection), an early and localized response near the wound site that peaks 1–4 h after injury and a late and systemic response that peaks at 3 days after amputation [6,7] (Fig. 1A). The second response varies in magnitude influenced by two key factors, the extent of the amputation and the specific type of fragment under examination; it is particularly pronounced in smaller fragments that miss multiple tissues and need to regenerate more complex structures, such as the head or the pharynx. It has been shown that the location of the amputation along the planarian body significantly impacts the rate of cell death in the pharynx, even though this organ was not directly affected by the cut [7]. This finding suggests that the widespread increase in cell death observed around 3 days post-amputation is linked to the process of tissue remodeling. This systemic response highlights the intricate and coordinated nature of planarian regeneration, where localized injury triggers body-wide changes to facilitate the reconstruction and rescaling of the organism. The number of dying cells during both the early and late waves of cell death after amputation remains unchanged even after irradiation, a process known to eliminate all stem cells (neoblasts) in planarians [7]. This suggests that these cell death responses occur predominantly in differentiated cells, and their initiation does not require stem cells. In planarians, evidence suggests that autophagy-dependent cell death also plays a role in regeneration, particularly in tissue remodeling [6,20–22], indicating that the cell death processes involve at least two distinct mechanisms: one primarily apoptotic and the other dependent on autophagy [23].

Several signalling pathways with a role in regeneration and cell death in *Drosophila,* as presented below*,* have been involved in the activation of the cell death response in planarians, although only the broad effects—such as whether these pathways inhibit or induce cell death—are known. The specific details of these mechanisms, including the exact cell types undergoing death in most cases, remain unclear. One such pathway is the JNK signalling pathway, which is involved in cell differentiation, proliferation and its function as a pro-apoptotic factor is evolutionary conserved [24]. In planarians it is described to be important for the induction of cell death in both regenerative and remodeling responses [25]. The Hippo signalling pathway and its effector Yki also play crucial roles in regulating apoptosis in other organisms [26]. During planarian regeneration and tissue remodeling, inhibition of Yki results in decreased cell death, which negatively impacts the regenerative process and proper organ scaling [27]. Several other factors contribute to the regulation of cell death during planarian regeneration. For example, inhibition of PARylation, a widespread post-translational modification at DNA lesions, by PARP-3 RNAi reduces the initial wave of cell death response in anterior wounds and impairs anterior blastema formation [28]. Also, molecular chaperones and chaperonins, which play an important role in cytoprotection and anti-apoptosis in many organisms [29], seem to be important in stem cells to inhibit cell death and to protect them from ER stress during the regenerative responses [30–32].

In the context of regeneration, apoptotic cells are known to generate ROS in many organisms [33]. The ROS released by apoptotic cells can act as signaling molecules that affect neighboring cells and stimulate protective mechanisms or inflammatory responses in surrounding healthy cells [34]. It is also increasingly accepted that ROS-induced post-translational modifications in proteins play a physiological role in cell signalling [34]. ROS production following apoptosis has been extensively studied in *Drosophila* imaginal disc regeneration [35–41] (Fig. 1B). When apoptosis is activated, it results in a burst of ROS that spreads from apoptotic cells to neighboring healthy cells. This triggers the activation of the MAP3 kinase ASK1, which is part of the MAPK pathway, subsequently activating the JNK and p38 pathways [41,42] (Fig. 2). These kinases promote regenerative growth by acting upstream of Wnt signalling and IL-6 cytokines [41,43,44]. ASK1 not only facilitates apoptosis but also functions as a survival signal, promoting p38-dependent regeneration [36,40]. This dual role depends on the nutrient-driven activation of the ROS-sensitive insulin/Pi3K/Akt pathway, which phosphorylates ASK1 to shift its function toward p38-dependent survival and growth [36] (Fig. 2). Additionally, the ROS-sensitive Tumor Necrosis Factor receptor (TNFR) Wengen recruits adaptor proteins that interact with ASK1, enhancing cell protection and stimulating regeneration [45]. The controlled activation of ASK1 by apoptosis-induced ROS generates a specific transcriptional signature that supports regeneration by promoting survival, proliferation, and differentiation of newly formed tissue [42,46–48] (Fig. 2).

In planarians, ROS also regulates the ERK/MAPK pathway (Fig. 2), suggesting an interconnected signalling mechanism [49]. A burst of ROS occurs within minutes after amputation, accompanied by a marked upregulation of ERK and other components of the MAPK pathway [50–52] (Fig. 2). However, although each wave of cell death in planarians is followed by a peak of proliferation [5,53,54] (Fig. 1A), it remains unknown whether ROS originates from apoptotic cells and whether ROS or cell death contribute to stem cell proliferation or early regenerative responses. Instead, it has been shown a role of ROS in regulating cell differentiation approximately 48–72 h post-amputation [52]. In accordance, down-regulation of *mek1*, a component of the MAPK pathway, affects only the second wave of cell death [55]. Likewise, in agreement with a role of ROS in cell differentiation, ERK signalling is involved in cell differentiation [56] and acts as an inducer of the second proliferative and cell death responses, which are associated with body remodeling [51]. As in *Drosophila*, the analysis of ROS-dependent upstream MAP3 kinases could elucidate the molecular mechanism that links ROS with ERK and the triggering of early regenerative responses.

2.2. Ionizing radiation induced cell death

Ionizing radiation (IR) is commonly used to treat various human cancers by inducing apoptosis and cell cycle arrest. However, it also promotes the proliferation of surviving cells, potentially leading to tumor repopulation and resistance to radiation therapy.

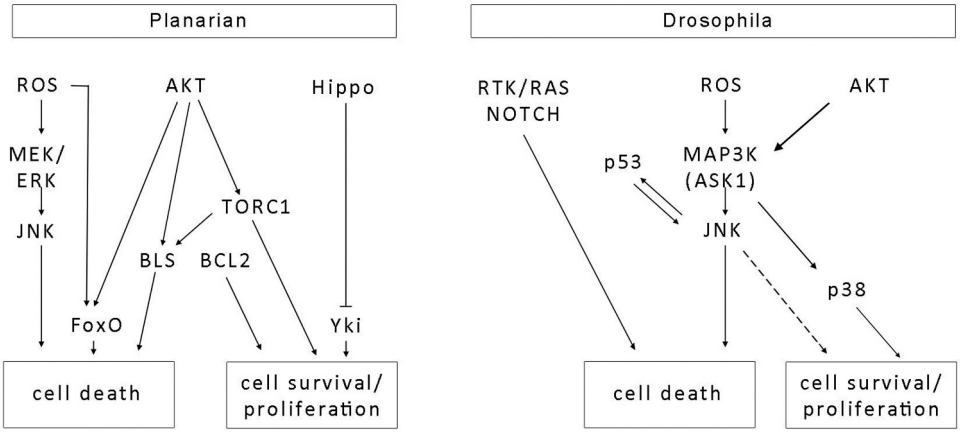

Fig. 2. Main signalling pathways involved in cell death and cell survival/proliferation in planarians and *Drosophila*. The scheme focuses in the signalling molecules presented in this review. The ROS-MAPK-JNK pathway and the AKT axis appear as conserved signals promoting cell death in planarians and *Drosophila*. The arrows do not necessarily indicate direct relationships.

IR can induce cell death in insects, although the extent and mechanisms may vary significantly across different species, and developmental stages or tissues and organs. Bryant and Haynie's 1977 seminal study on *Drosophila* revealed that X-ray irradiation induced compensatory proliferation in imaginal wing discs [57]. They found that even low radiation doses caused immediate cell death, with higher doses reducing cell survival significantly (40–60 %). Surviving cells, however, were stimulated to proliferate, restoring normal wing size and pattern despite severe cellular damage. This research highlighted the wing disc's ability to maintain structural integrity through compensatory proliferation, offering insights into cellular resilience and regeneration in response to ionizing radiation [57].

In *Drosophila*, IR triggers cell death through multiple pathways, primarily mediated by DNA damage activating p53-dependent signalling. This induces pro-apoptotic genes such as *reaper* (*rpr)*, *head involution defective* (*hid*), and *grim* (reviewed in [58] that inhibit *Drosophila* inhibitor of apoptosis protein 1 (Diap1), activating caspases like Dronc, Drice, and Dcp1. The JNK signalling pathway also plays a crucial role in IR-induced cell death, with p53 necessary for JNK activation [59,60]. Interestingly, some wing disc regions resist IR-induced cell death due to anti-apoptotic microRNA bantam and receptor tyrosine kinase Tie [61]. Additionally, regions like the dorsal part of the future wing hinge exhibit intrinsic resistance to IR-induced apoptosis, possibly due to high Wingless (Wg) and STAT92E signalling levels [62]. This highlights the complex regulation of cell death in response to ionizing radiation in *Drosophila*.

In a pioneering work, Barden and Baetjer [63] found that IR disrupts the regenerative capacity of planarians by inducing cell death in stem cells, leading to their elimination at lethal doses (30 Gy or higher). Despite sublethal doses (20 Gy or lower) causing also a rapid decline in the majority of stem cells, a subset manages to survive and repopulate the organism, allowing some planarians to recover [64]. The mechanisms behind stem cell survival and repopulation after sublethal IR remain unclear, as does the reason for some stem cells' resistance to apoptosis. These studies parallel the previously discussed IR experiments in *Drosophila* wing imaginal discs, where surviving cells were induced to proliferate. In planarians, however, cell death influences stem cells differently—not by triggering their proliferation, as in *Drosophila*, but by increasing the number of stem cells that persist after IR [65]. When irradiated planarians are decapitated shortly after IR exposure, a typical cell death burst occurs at the wound site, retaining neoblasts in an ERK-dependent manner. This suggests that ERK, and possibly also ROS, are important regulators of stem cells very early post-amputation. The bigger the amputated piece, the higher the cell death burst and the number of persistent neoblasts. The extent of cell death correlates with the number of retained neoblasts, meaning that the amount of retained stem cells is related to the strength of the cell death burst [65]. Indeed, the apoptosis induced by cycloheximide treatment in adult unirradiated planarians increases the number of retained neoblasts. The study concluded that the cell death induced by injury -which happens in differentiated cells- can delay the IR induced cell death of stem cells by preventing stem cells from entering mitosis, presumably to enable DNA damage repair and survival.

Planarian stem cells continuously cycle during normal homeostasis and regeneration, exhibiting remarkable functionality and resilience. They are often considered "immortal". They have a low incidence of spontaneous tumor formation, although tumors can be induced through chemical treatments or by inhibiting tumor suppressors [66–69]. Nevertheless, planarians, like other organisms, face environmental challenges that increase mutation risks with each cell division. Their apparent immortality might be attributed to enhanced DNA repair mechanisms, as happens with some long-lived animals [70] and/or efficient removal of damaged cells. Despite having conserved DNA Damage Response (DDR) pathways [71], RNA interference (RNAi) targeting components of homologous recombination (HR) (*atr*, *atm*, *brca2*, *rad51*, and *fancJ*) and non-homologous end-joining (NHEJ) (*parp1*, *parp2*, and *parp3*) pathways generally do not affect planarian regeneration or homeostasis, with the exception of *rad51,* suggesting redundancy or lack of necessity in these contexts [72,73]. However, under sub-lethal IR, RNAi of ATM, ATR, and MRN complex components allows stem cells to persist and successfully regenerate. Those cells can proceed into the S and G2 phase of the cell cycle, re-enter the cell cycle and successfully induce regeneration and repair [74]. While ATM promotes HR-mediated repair in *Drosophila* and mammals, its downregulation in planarians appears to facilitate stem cell recovery through HR-mediated repair. This suggests that, in planarians, eliminating damaged stem cells may be a more efficient strategy than attempting their repair [74], highlighting species-specific differences in DNA damage response mechanisms.

In summary, IR induces apoptosis through complex pathways and mechanisms. While IR effectively triggers apoptosis, it also activates survival mechanisms, particularly in certain cell populations, complicating therapeutic outcomes. Understanding these pathways is crucial for improving cancer radiotherapy and radiation protection. The intricate balance between apoptotic and survival signals underscores the sophisticated cellular responses to radiation damage, offering insights into potential therapeutic targets and regenerative processes and highlighting the value of *Drosophila* and planarians.

3. Cell death in adult tissues

3.1. Cell death during planarian adult homeostasis

Planarians are very plastic organisms that constantly adjust their body size depending on food availability [2]. Under nutrient restriction conditions they degrow by reducing their overall mass and when food is plentiful, they regrow again (Fig. 3A). It is known that the decrease in size is not due to changes in cell size, but rather to cell number [75–77]. This reduction in cell number during nutrient restriction is linked to an increase in TUNEL-positive cells among differentiated cells [7] and possibly among some stem and progenitor cells, since basal levels of stem cell death have been reported in homeostatic planarians [65,78,79].

The type of cell death observed during planarian degrowth likely involves a combination of apoptosis and autophagy-dependent cell death. Autophagy-dependent cell death has been observed in starved planarians, including in the gonads of starved sexual planarians, which regress during starvation [6,20,23]. This process is thought to help fuel the remaining cells in the planarian body, facilitating survival during nutrient scarcity [2].

The balance between cell proliferation and death is crucial for planarian growth and de-growth, and several signalling pathways are implicated in maintaining it. For instance, in starved *jnk* RNAi planarians, there are fewer TUNEL-positive cells compared to controls, indicating reduced cell death and inability to remodel during degrowth [25]. This suggests that JNK-dependent apoptotic cell death is essential for maintaining a balance between cell proliferation and death, ensuring proper tissue renewal and remodeling to maintain proportionate body size (Fig. 2).

Mammalian target of rapamycin (mTOR) regulates cell proliferation, autophagy, and apoptosis in response to nutrient availability [80]. In planarians, inhibiting mTOR in nutrient-rich conditions leads to increased cell death (TUNEL-positive cells) without compensatory stem cell proliferation [81,82] (Fig. 2). This suggests that *tor* RNAi planarian cells are not able to sense their nutritional status, leading to shrinkage and death. The *tor* RNAi phenotype is replicated by *raptor* RNAi or rapamycin treatment, which means that it is the TORC1 complex but not TORC2 the one implicated in cell balance regulation in planarians [66,81,82].

The Akt-mTOR pathway plays a crucial role in planarian growth regulation. On the one hand, Akt activates mTOR in nutrient-rich environments [83]. In this context *akt* RNAi decreases stem cells and increases cell death, similar to *tor* RNAi. Activation of the insulin receptor by nutrients also triggers Akt-dependent phosphorylation of FoxO, and its retention in the cytoplasm. On the other hand, during starvation, unphosphorylated FoxO enters the nucleus, regulating energy, stress, proliferation, and cell death [84]. There is a single ortholog of *foxO*, which is also regulated by Akt, and has a conserved role as pro-apoptotic signal in planarians [85] (Fig. 2). Its inhibition causes unpigmented zones and accumulation of disorganized epidermal cells, suggesting that the proper activation of cell death is crucial for maintaining the differentiated fate. This is the same result observed after inhibition of the Hippo pathway in planarians [69]. The Hippo pathway controls cell proliferation, differentiation and cell death in response to mechanical stimulus and its dysregulation is a hallmark of solid tumors [86]. Inhibition of *hippo* during homeostatic cell renewal in starved planarians produces overgrowths and the appearance of undifferentiated regions, similar to the ones observed in *foxO* RNAi animals [69]. In planarians, Hippo is required to maintain the differentiated state, and its dysregulation leads to aberrant dedifferentiation, which is coupled by a decrease in apoptosis and thus the inability to eliminate damaged cells [69]. It is interesting to compare the *hippo* and *foxO* RNAi phenotypes with the previously presented *jnk* RNAi phenotype. In both cases there is a decrease in apoptosis. While in *jnk* RNAi animals it leads to the inability to remodel and to an increase in cell density, in *hippo* or *foxO* RNAi animals it leads to a tumoral-like process. This result agrees with the current view in the field of cancer, in which oncogenic mutations are not enough to lead to tumorigenesis but they require further environmental alterations to become malignant.

The last mechanism described in planarians to control cellular balance in response to nutrients is a planarian-specific gene family, consisting of *de novo* and taxonomically restricted genes called *blitzschnell* (*bls*) [87]. During homeostasis, *bls* silencing promotes an increase in cell

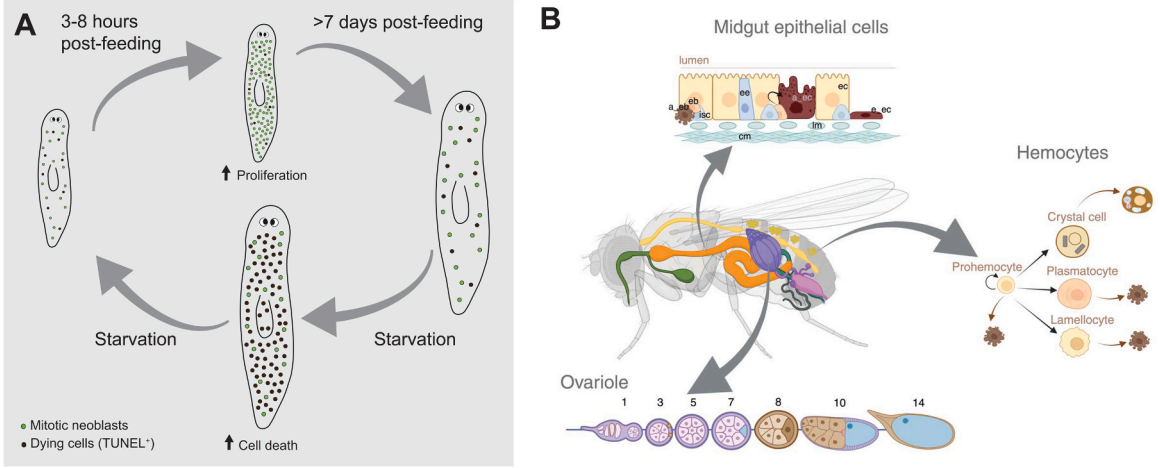

Fig. 3. Homeostasis in adult planarian and *Drosophila*. A. Planarians grow and degrow continuously depending on food availability. After feeding planarians grow. Mitoses increase 3–8 h post-feeding and go back to baseline levels around 7 days post-feeding. During starvation planarians degrow by increasing cell death. **B.** Illustration of adult *Drosophila* displaying tissues with high turnover: in orange the midgut, in violet the ovary and in yellow the heart and hematopoietic hubs of the open circulatory system (the hemocoel is in grey). The grey arrows display cellular details on those organs indicating cell death events in brown. In the midgut epithelial cells, adjustment of differentiated cell production is regulated by intestinal progenitor cell apoptosis (apoptotic enteroblast; a_eb). Enterocytes undergo apoptosis (a_ec) as part of the normal cell turnover (the arrow indicates turnover). Enterocytes can also undergo erebosis (erebotic enterocytes; e_ec). eb, enteroblast; ec, enterocyte; ee, enteroendocrine cell; isc, intestinal stem cell; cm, circular visceral muscle; lm, longitudinal visceral muscle. In the hemocytes, pro-hemocytes, plasmatocytes and lamellocytes can undergo apoptosis and crystal cells can undergo autophagy-dependent cell death. In the ovariole, cell death occurs at stage 1 at the germarium as a combination of apoptosis and autophagic cell death, at stage 3 apoptosis occurs in superfluous polar cells. From stages 2–8 apoptosis can occur in stalk cells. At stage 8 the whole egg chamber can be destroyed if the conditions are not adequate. During stage 10, nurse cells undergo phagocytic-dependent cell death and during stage 14, the nurse cell remnants are removed. Panel B was created in BioRender. Gonzalez Estevez, C. (2024) https://BioRender.com/h84f518.

number by reducing apoptosis and enhancing mitosis under both nutrient-rich and starved conditions. In nutrient-rich environments, this results in a larger body size, whereas in starved planarians, body size remains unchanged, leading instead to localized overgrowths. *bls* expression depends on the insulin/Akt/mTOR pathway, being upregulated during starvation and down-regulated after feeding (Fig. 2). Overall, it was suggested that the *bls* family evolved in planarians as a mechanism to restrict cell number in fluctuating nutrient environments.

3.2. Cell death in Drosophila high-turnover tissues

In contrast to the embryonic and larval-pupal stages, where programmed cell death refines and removes obsolete tissues to make way for adult structures [88], in adult *Drosophila*, cell death is less widespread, but vital for maintaining high-turnover cell populations such as the germline, hemocytes, and the gut (Fig. 3B).

In the germline, cell death is crucial for oocyte development, ensuring that only viable cells contribute to maturation [89] (Fig. 3B). During embryogenesis, primordial germ cells undergo programmed cell death, while adult germline cells follow varied pathways depending on their role in oogenesis. At mid-oogenesis, germline cells are sensitive to nutrient levels and may undergo apoptosis during nutrient scarcity [88, 90], acting as a checkpoint for viable oocyte development and ultimately conserving resources for future reproduction. In later oogenesis stages, nurse cells are eliminated through a non-apoptotic process, transferring nutrients to the developing oocyte. Thus, by releasing their cytoplasmic contents, these nurse cells transfer nutrients and resources to the developing oocyte. This tightly regulated process is essential for reproductive success [88,89], and misregulation can lead to reduced fertility or tumorigenesis.

Similarly, cell death in *Drosophila* hemocytes plays a crucial role in maintaining immune homeostasis and overall health [91] (Fig. 3B). As the primary immune cells, hemocytes respond to environmental stressors and DNA damage. Their regulated elimination through apoptosis prevents the accumulation of dysfunctional cells that could compromise tissue integrity. Hemocytes cell death is influenced by multiple signalling pathways, including the RTK/RAS network and Notch signalling (Fig. 2), which dictate whether a hemocyte undergoes apoptosis or survives based on situational needs [92,93]. Notch activation in circulating hemocytes was found to induce caspase-independent and non-autophagic cell death [93]. Interestingly, apoptotic hemocytes do more than simply exit the immune system; they can actively signal to other immune cells, thereby modulating immune responses during infections or oxidative stress [94]. This dual role as both active defenders and regulatory elements, illustrates the adaptability of *Drosophila* hemocytes in maintaining organismal health.

The *Drosophila* digestive system also serves as a key model for studying the balance between cell proliferation and death during homeostasis (Fig. 3B). Intestinal stem cells (ISC) constantly renew the gut epithelium by producing progenitor cells or enteroblasts, which differentiate respectively into the most abundant absorptive enterocytes (90 %) or enteroendocrine cells (10 %) [95]. The turnover rate ranges from 4 days to 3 weeks [96–98], influenced by environmental factors like pathogens and toxins. How stem cells perform and adapt to respond to different renewal demands is a fundamental question. To address this issue, a study compared ISC behavior in high and low renewal demand scenarios [98] where ISCs divide slowly but continually [99]. Under low demand, ISCs generated more progenitor cells than necessary, with the excess being eliminated through caspase-mediated cell death, regulated by signals from ISCs and the niche [98]. The survival of these progenitor cells is believed to be regulated by a delicate balance of life and death signals. ISCs emit death signals via Delta protein, activating Notch signalling in the enteroblasts [98]. Conversely, survival signals in the form of epidermal growth factor (EGF) are provided by the surrounding niche or dying enterocytes [96]). This overproduction of progenitor cells may serve as an adaptive mechanism, enabling the gut to respond swiftly to environmental changes or acute damage. Another study [96] proposes a feedback mechanism for maintaining intestinal homeostasis, challenging the idea of constitutively cycling stem cells. This mechanism couples enterocyte death to ISC division, resulting in a balanced zero-sum turnover over time. Key aspects of this feedback mechanism include E-cadherin (E-cad) loss in dying enterocytes, which trigger expression of an EGF maturation factor (*rhomboid*), which in turn activates EGFR in nearby ISCs, providing a mitogenic signal. Inhibiting enterocyte apoptosis leads to fewer ISC divisions, suggesting that E-cad expression in healthy ECs maintains stem cell quiescence. This localized cell-cell communication contributes to tissue-level homeostasis by ensuring that ISC divisions are triggered only when necessary to replace dying enterocytes.

The role of apoptosis in enterocytes remains debated, with some studies showing fewer ISC divisions upon its inhibition—suggesting its involvement in tissue renewal—while others report no significant effects, questioning whether aging enterocytes undergo apoptosis at all [96,100,101]. Notably, a novel cell death mechanism, erebosis, has been identified as a key player in homeostatic turnover under low renewal demand conditions [101]. Unlike apoptosis, erebotic cells exhibit a progressive degradation of organelles and proteins while maintaining barrier function—a feature reminiscent of keratinizing skin cells. This mechanism ensures tissue integrity while enabling renewal, highlighting its potential physiological significance. Unlike traditional cell death pathways, erebosis progresses through distinct stages, with nuclear fragmentation detectable only in late phases, and remains unaffected by mutations in apoptosis, autophagy, or necrosis genes [102]. Further research is crucial to fully uncover the regulatory mechanisms and physiological relevance of this emerging homeostatic cell elimination process.

4. Clearance of dead cells

The removal of dead cells is crucial for maintaining homeostasis. This process, known as efferocytosis, involves the phagocytosis of dead and dying cells by macrophages or other cell types [103,104]. During *Drosophila* metamorphosis, macrophages remove dying adipocytes [105]; also, epithelial follicular cells clear dead germline cells during oogenesis [106]. During *Drosophila* embryonic development, particularly in the central nervous system, apoptotic cells are cleared by phagocytic glia and dispersing ventral hemocytes (macrophages) [107]. The use of genetically encoded fluorescent reporters, such as CharON, has enabled real-time tracking of apoptotic cells and their clearance in *Drosophila* embryos [107]. It has been revealed that macrophages exhibit heterogeneity as they may have no, low (1–3 corpses), medium (4–6 corpses) or high (> 7 corpses) burden, ensuring rapid clearance of extensive apoptosis during development [107]. However, macrophages with high corpse burdens show impaired ability to engulf necrotic debris at wound sites, indicating a trade-off between developmental and inflammatory efferocytosis. The *Drosophila* embryo model has demonstrated that efferocytosis is a complex process, affecting cells dying by different mechanisms, and different types of phagocytes, and multiple engulfment mechanisms [108]. This complexity ensures efficient clearance of corpses throughout the organism. Overall, research using *Drosophila* has significantly contributed to our understanding of efferocytosis, revealing its dynamic nature and importance in maintaining tissue homeostasis during development and in response to tissue damage.

Recent studies have highlighted the importance of phagocytes in clearing dead cells in planarians [109,110]. Ablation of sub-epidermal pigment cells by exposure to intense light produces the accumulation of pigment granules that are engulfed by gut phagocytes and expelled through the pharynx [110]. This engulfment of dead pigment cells by phagocytes is mediated by the conserved pathway CED-12/ELMO [111, 112]. Nevertheless, it is not yet clear how the pigment cells travel from their sub-epidermal localization to the gut to be engulfed by the

phagocytes [110]. It remains to be determined whether this clearance mechanism also occurs during normal homeostatic cell renewal of planarian pigment cells.

In a recent study on planarians, Lee et al. [109] analyzed epidermal cell turnover taking advantage of some dyes that label epidermal cells. They showed that ventral epidermal cells have a half-life of 4.5 days, while dorsal cells have a half-life of 20 days. Moreover, the authors found that dead epidermal cells are cleared through basal extrusion and internalization by the phagocytes located in the gut epithelium, which may also serve as a means of energy recovery through self-catabolism [109].

The role of the planarian phagocytes to eliminate dead cells might explain some previous results in which defects in the regeneration and the maintenance of the digestive system has been associated to an increase of apoptotic cells in the mesenchyme. Thus, the silencing of *egfr-1* (an epidermal growth factor receptor homologue) leads to the failure of both regeneration and renewal of the digestive system, as gut progenitors fail to fully differentiate [113]. Interestingly, this phenotype correlates with a significant increase of TUNEL^{+} cells in the mesenchyme around the gut [113]. Based on the role of the planarian gut to clear dead cells [109,110], it seems plausible to hypothesize that the increase of apoptotic cells after silencing *egfr-1* could be a consequence of the loss of a functional gastrodermis that, consequently, might impair the internalization and posterior clearance of those dead cells.

Further research should investigate whether planarian phagocytes universally eliminate dead cells across all cell types during normal homeostasis and regeneration. Understanding this process could provide insights into how tissue homeostasis is maintained and how disruptions can lead to increased cell death and regeneration defects.

5. Concluding remarks

Cell death plays a crucial role in maintaining tissue homeostasis and during regeneration by eliminating damaged, dysfunctional, or unnecessary cells, thereby preserving tissue integrity and facilitating repair. Programmed cell death also acts as a catalyst for regeneration by creating an environment that promotes cell renewal and proliferation. In homeostasis, cell death ensures a balance between cell loss and cell replacement, preventing excessive accumulation or depletion of cells. Despite significant progress, further research is needed to unravel the complex signalling pathways and interactions linking cell death and regeneration. The activation of cell death upon damage and its requirement for mounting the regenerative response has been reported in several organisms such as zebrafish, *Hydra*, *Xenopus*, and even in mammalian organs [13–16]. However, the mechanisms that link cell death with the activation of the regenerative signals are not well understood, since the knowledge resulting from each model is still fragmentary. Comparing different animals like planarians and *Drosophila* provides a novel view and highlight cellular and molecular mechanisms which appear conserved in the regulation of cell death, such as the ROS-MAPK-JNK axis, and others which are species-specific, such as BLS in planarians. Thus, comparative studies in different animal models can help uncover conserved mechanisms, essential molecular players, and the interplay between cell death and regenerative signalling occurring in all species. Understanding how different types of cell death influence specific regenerative contexts and how their dysregulation contributes to human diseases such as cancer or degenerative disorders remains a significant challenge. Insights from a variety of animal species displaying different life cycles and cellular dynamics could open avenues for therapeutic strategies to enhance tissue repair and restore equilibrium in human pathological conditions.

Declaration of Competing Interest

As required for publishing at Seminars in Cell and Developmental Biology,

we declare that:

- the work described has not been published previously.
- the article is not under consideration for publication elsewhere.
- the article's publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.
- if accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder.

We, the authors, have nothing else to declare.

Acknowledgments

This work was supported by Agència de Gestió d'Ajuts Universitaris i de Recerca de la Generalitat de Catalunya (Grant no.: 2021SGR00293 to MC); Consolidación Investigadora MICIU/AEI/10.13039/501100011033 and European Union NextGenerationEU/PRTR (Grant no.: CNS2023-144759 to CGE); Ministerio de Ciencia, Innovación y Universidades (Grant nos.: PID2023-149733NB-I00 to TA and CGE; PID2021-123300NB-I00 to MC and FS; PID2021-126958NB-I00 to FC; PID2021-125860NB-I00 to SJA) financed by MICIU/AEI/10.13039/501100011033 and by FEDER, UE.; Ministerio de Ciencia e Innovación (Grant nos.: PID2019-107340GB-I00 to MM; FU2020-116372GB-I00 to TA). CGE is a Professor Serra Húnter (Generalitat de Catalunya).

References

[1] P.W. Reddien, The cellular and molecular basis for planarian regeneration, Cell 175 (2) (2018) 327–345.
[2] D.A. Felix, Ó. Gutiérrez-Gutiérrez, L. Espada, A. Thems, C. González-Estévez, It is not all about regeneration: planarians striking power to stand starvation, Semin. Cell Dev. Biol. 87 (2019) 169–181.
[3] J. Pellettieri, Regenerative tissue remodeling in planarians – the mysteries of morphallaxis, Semin. Cell Dev. Biol. 87 (2019) 13–21.
[4] J. Baguñà, Mitosis in the intact and regenerating planarian *Dugesia mediterranea* n. sp. I. Mitotic studies during growth, feeding and starvation, J. Exp. Zool. 195 (1976) 53–64.
[5] J. Baguñà, Mitosis in the intact and regenerating planarian *Dugesia mediterranea* n. sp. II. Mitotic studies during regeneration and a possible mechanism of blastema formation, J. Exp. Zool. 195 (1976) 65–80.
[6] C. González-Estévez, D.A. Felix, A.A. Aboobaker, E. Saló, Gtdap-1 promotes autophagy and is required for planarian remodeling during regeneration and starvation, Proc. Natl. Acad. Sci. USA 104 (33) (2007) 13373–13378.
[7] J. Pellettieri, P. Fitzgerald, S. Watanabe, J. Mancuso, D.R. Green, A. Sánchez Alvarado, Cell death and tissue remodeling in planarian regeneration, Dev. Biol. 338 (1) (2010) 76–85.
[8] J.S. Hwang, C. Kobayashi, K. Agata, K. Ikeo, T. Gojobori, Detection of apoptosis during planarian regeneration by the expression of apoptosis-related genes and TUNEL assay, Gene 333 (2004) 15–25.
[9] C.E. Bender, P. Fitzgerald, S.W. Tait, F. Llambi, G.P. McStay, D.O. Tupper, J. Pellettieri, A. Sánchez Alvarado, G.S. Salvesen, D.R. Green, Mitochondrial pathway of apoptosis is ancestral in metazoans, Proc. Natl. Acad. Sci. USA 109 (13) (2012) 4904–4909.
[10] D.T. Fox, E. Cohen, R. Smith-Bolton, Model systems for regeneration: Drosophila, Development 147 (7) (2020).
[11] F. Serras, The sooner, the better: ROS, kinases and nutrients at the onset of the damage response in Drosophila, Front. Cell Dev. Biol. 10 (2022) 1047823.
[12] M. Suzanne, H. Steller, Shaping organisms with apoptosis, Cell Death Differ. 20 (5) (2013) 669–675.
[13] C. Gauron, C. Rampon, M. Bouzaffour, E. Ipendey, J. Teillon, M. Volovitch, S. Vriz, Sustained production of ROS triggers compensatory proliferation and is required for regeneration to proceed, Sci. Rep. 3 (2013) 2084.
[14] S. Vriz, S. Reiter, B. Galliot, Cell death: a program to regenerate, Curr. Top. Dev. Biol. 108 (2014) 121–151.
[15] A.S. Tseng, D.S. Adams, D. Qiu, P. Koustubhan, M. Levin, Apoptosis is required during early stages of tail regeneration in Xenopus laevis, Dev. Biol. 301 (1) (2007) 62–69.
[16] A. Bergmann, H. Steller, Apoptosis, stem cells, and tissue regeneration, Sci. Signal. 3 (145) (2010) re8.
[17] S. Pandita, S. Singh, S.K. Bajpai, G. Mishra, G. Saxena, P.C. Verma, Molecular aspects of regeneration in insects, Dev. Biol. 507 (2024) 64–72.
[18] F. Cebrià, T. Adell, E. Saló, Rebuilding a planarian: from early signaling to final shape, Int. J. Dev. Biol. 62 (6–8) (2018) 537–550.
[19] M. Sureda-Gomez, T. Adell, Planarian organizers, Semin. Cell Dev. Biol. 87 (2019) 95–104.

[20] C. González-Estévez, D.A. Felix, A.A. Aboobaker, E. Saló, Gtdap-1 and the role of autophagy during planarian regeneration and starvation, Autophagy 3 (6) (2007) 640–642.
[21] J. Kang, Z. Dong, J. Wang, G. Chen, D. Liu, Autophagy-related Djatg8 is required for remodeling in planarian Dugesia japonica, Biol. Open 8 (12) (2019).
[22] B. Jin, J. Ren, J. Chen, Z. Dong, G. Chen, D. Liu, Autophagy-related DjAtg1-1 plays critical role in planarian regeneration by regulating proliferation and cell death, Cell Tissue Res. 388 (2) (2022) 273–286.
[23] C. González-Estévez, E. Saló, Autophagy and apoptosis in planarians, Apoptosis 15 (3) (2010) 279–292.
[24] G. Nadel, G. Maik-Rachline, R. Seger, JNK cascade-induced apoptosis–a unique role in GqPCR signaling, Int. J. Mol. Sci. 24 (17) (2023).
[25] M. Almuedo-Castillo, X. Crespo-Yanez, F. Seebeck, K. Bartscherer, E. Salò, T. Adell, JNK controls the onset of mitosis in planarian stem cells and triggers apoptotic cell death required for regeneration and remodeling, PLoS Genet. 10 (6) (2014) e1004400.
[26] N. Furth, Y. Aylon, M. Oren, p53 shades of hippo, Cell Death Differ. 25 (1) (2018) 81–92.
[27] A.Y.T. Lin, B.J. Pearson, Yorkie is required to restrict the injury responses in planarians, PLoS Genet. 13 (7) (2017) e1006874.
[28] P.G. Barghouth, P. Karabinis, A. Venegas, N.J. Oviedo, Poly(ADP-ribose) polymerase-3 regulates regeneration in planarians, Int. J. Mol. Sci. 21 (3) (2020).
[29] J.M. Storey, K.B. Storey, Chaperone proteins: universal roles in surviving environmental stress, Cell Stress Chaperon. 28 (5) (2023) 455–466.
[30] Q. Wang, L. Xie, Y. Wang, B. Jin, J. Ren, Z. Dong, G. Chen, D. Liu, Djhsp70s, especially Djhsp70c, play a key role in planarian regeneration and tissue homeostasis by regulating cell proliferation and apoptosis, Gene 820 (2022) 146215.
[31] M. Conte, M.E. Isolani, P. Deri, L. Mannini, R. Batistoni, Expression of hsp90 mediates cytoprotective effects in the gastrodermis of planarians, Cell Stress Chaperon. 16 (1) (2011) 33–39.
[32] Ó. Gutiérrez-Gutiérrez, D.A. Felix, A. Salvetti, E.M. Amro, A. Thems, S. Pietsch, A. Koeberle, K.L. Rudolph, C. González-Estévez, Regeneration in starved planarians depends on TRiC/CCT subunits modulating the unfolded protein response, EMBO Rep. 22 (8) (2021) e52905.
[33] X. An, W. Yu, J. Liu, D. Tang, L. Yang, X. Chen, Oxidative cell death in cancer: mechanisms and therapeutic opportunities, Cell Death Dis. 15 (8) (2024) 556.
[34] T. Finkel, Signal transduction by reactive oxygen species, J. Cell Biol. 194 (1) (2011) 7–15.
[35] N. Diwanji, A. Bergmann, An unexpected friend – ROS in apoptosis-induced compensatory proliferation: implications for regeneration and cancer, Semin. Cell Dev. Biol. 80 (2018) 74–82.
[36] J. Esteban-Collado, M. Corominas, F. Serras, Nutrition and PI3K/Akt signaling are required for p38-dependent regeneration, Development 148 (8) (2021).
[37] C.E. Fogarty, N. Diwanji, J.L. Lindblad, M. Tare, A. Amcheslavsky, K. Makhijani, K. Brückner, Y. Fan, A. Bergmann, Extracellular reactive oxygen species drive apoptosis-induced proliferation via Drosophila macrophages, Curr. Biol. 26 (5) (2016) 575–584.
[38] J.S. Jaszczak, J.B. Wolpe, A.Q. Dao, A. Halme, Nitric oxide synthase regulates growth coordination during Drosophila melanogaster imaginal disc regeneration, Genetics 200 (4) (2015) 1219–1228.
[39] S.J. Khan, S.N.F. Abidi, A. Skinner, Y. Tian, R.K. Smith-Bolton, The Drosophila duox maturation factor is a key component of a positive feedback loop that sustains regeneration signaling, PLoS Genet. 13 (7) (2017) e1006937.
[40] P. Santabárbara-Ruiz, J. Esteban-Collado, L. Pérez, G. Viola, J.F. Abril, M. Milán, M. Corominas, F. Serras, Ask1 and Akt act synergistically to promote ROS-dependent regeneration in Drosophila, PLoS Genet. 15 (1) (2019) e1007926.
[41] P. Santabárbara-Ruiz, M. López-Santillán, I. Martínez-Rodríguez, A. Binagui-Casas, L. Pérez, M. Milán, M. Corominas, F. Serras, ROS-induced JNK and p38 signaling is required for unpaired cytokine activation during Drosophila regeneration, PLoS Genet. 11 (10) (2015) e1005595.
[42] C. Camilleri-Robles, P. Climent-Cantó, P. Llorens-Giralt, C.C. Klein, F. Serras, M. Corominas, A shift in chromatin binding of phosphorylated p38 precedes transcriptional changes upon oxidative stress, FEBS Lett. (2024).
[43] J.E. La Marca, H.E. Richardson, Two-faced: roles of JNK signalling during tumourigenesis in the Drosophila model, Front. Cell Dev. Biol. 8 (2020) 42.
[44] R.K. Smith-Bolton, M.I. Worley, H. Kanda, I.K. Hariharan, Regenerative growth in Drosophila imaginal discs is regulated by Wingless and Myc, Dev. Cell 16 (6) (2009) 797–809.
[45] J. Esteban-Collado, M. Fernández-Mañas, M. Fernández-Moreno, I. Maeso, M. Corominas, F. Serras, Reactive oxygen species activate the Drosophila TNF receptor Wengen for damage-induced regeneration, Embo J. 43 (17) (2024) 3604–3626.
[46] C. Camilleri-Robles, F. Serras, M. Corominas, Role of D-GADD45 in JNK-dependent apoptosis and regeneration in Drosophila, Genes 10 (5) (2019).
[47] R.E. Harris, L. Setiawan, J. Saul, I.K. Hariharan, Localized epigenetic silencing of a damage-activated WNT enhancer limits regeneration in mature Drosophila imaginal discs, Elife 5 (2016).
[48] E. Vizcaya-Molina, C.C. Klein, F. Serras, R.K. Mishra, R. Guigó, M. Corominas, Damage-responsive elements in Drosophila regeneration, Genome Res. 28 (12) (2018) 1852–1866.
[49] V. Jaenen, S. Fraguas, K. Bijnens, M. Heleven, T. Artois, R. Romero, K. Smeets, F. Cebrià, Reactive oxygen species rescue regeneration after silencing the MAPK-ERK signaling pathway in Schmidtea mediterranea, Sci. Rep. 11 (1) (2021) 881.
[50] J. Yuan, Z. Wang, D. Zou, Q. Peng, R. Peng, F. Zou, Expression profiling of planarians shed light on a dual role of programmed cell death during the regeneration, J. Cell. Biochem. 119 (7) (2018) 5875–5884.
[51] S. Owlarn, F. Klenner, D. Schmidt, F. Rabert, A. Tomasso, H. Reuter, M.A. Mulaw, S. Moritz, L. Gentile, G. Weidinger, K. Bartscherer, Generic wound signals initiate regeneration in missing-tissue contexts, Nat. Commun. 8 (1) (2017) 2282.
[52] N. Pirotte, A.S. Stevens, S. Fraguas, M. Plusquin, A. Van Roten, F. Van Belleghem, R. Paesen, M. Ameloot, F. Cebrià, T. Artois, K. Smeets, Reactive oxygen species in planarian regeneration: an upstream necessity for correct patterning and brain formation, Oxid. Med. Cell. Longev. 2015 (2015) 392476.
[53] E. Saló, J. Baguñà, Regeneration and pattern formation in planarians. I. The pattern of mitosis in anterior and posterior regeneration in *Dugesia* (G) *tigrina*, and a new proposal for blastema formation, J. Embryol. Exp. Morphol. 83 (1984) 63–80.
[54] D. Wenemoser, P.W. Reddien, Planarian regeneration involves distinct stem cell responses to wounds and tissue absence, Dev. Biol. 344 (2) (2010) 979–991.
[55] Q. Wang, Y. Liu, B. Jin, Z. Dong, G. Chen, D. Liu, Djmek is involved in planarian regeneration by regulation of cell proliferation and apoptosis, Biochem. Biophys. Res. Commun. 532 (3) (2020) 355–361.
[56] J. Tasaki, N. Shibata, O. Nishimura, K. Itomi, Y. Tabata, F. Son, N. Suzuki, R. Araki, M. Abe, K. Agata, Y. Umesono, ERK signaling controls blastema cell differentiation during planarian regeneration, Development 138 (12) (2011) 2417–2427.
[57] J.L. Haynie, P.J. Bryant, The effects of X-rays on the proliferation dynamics of cells in the imaginal wing disc ofDrosophila melanogaster, Wilehm Roux Arch. Dev. Biol. 183 (2) (1977) 85–100.
[58] A. Baonza, S. Tur-Gracia, M. Pérez-Aguilera, C. Estella, Regulation and coordination of the different DNA damage responses in Drosophila, Front. Cell Dev. Biol. 10 (2022) 993257.
[59] E. Shlevkov, G. Morata, A dp53/JNK-dependant feedback amplification loop is essential for the apoptotic response to stress in Drosophila, Cell Death Differ. 19 (3) (2012) 451–460.
[60] B.S. Wells, E. Yoshida, L.A. Johnston, Compensatory proliferation in Drosophila imaginal discs requires Dronc-dependent p53 activity, Curr. Biol. 16 (16) (2006) 1606–1615.
[61] A. Bilak, L. Uyetake, T.T. Su, Dying cells protect survivors from radiation-induced cell death in Drosophila, PLoS Genet. 10 (3) (2014) e1004220.
[62] S. Verghese, T.T. Su, Ionizing radiation induces stem cell-like properties in a caspase-dependent manner in Drosophila, PLoS Genet. 14 (11) (2018) e1007659.
[63] C. Bardeen, F. Baetjer, The inhibitive action of the Roentgen rays on regeneration in planarians, J. Exp. Zool. 1 (1904) 191–195.
[64] D.E. Wagner, I.E. Wang, P.W. Reddien, Clonogenic neoblasts are pluripotent adult stem cells that underlie planarian regeneration, Science 332 (6031) (2011) 811–816.
[65] D.A. Shiroor, T.E. Bohr, C.E. Adler, Injury delays stem cell apoptosis after radiation in planarians, Curr. Biol. 30 (11) (2020) 2166–2174.e3.
[66] C. González-Estévez, D.A. Felix, M.D. Smith, J. Paps, S.J. Morley, V. James, T. V. Sharp, A.A. Aboobaker, SMG-1 and mTORC1 act antagonistically to regulate response to injury and growth in planarians, PLoS Genet. 8 (3) (2012) e1002619.
[67] B.J. Pearson, A. Sánchez Alvarado, A planarian p53 homolog regulates proliferation and self-renewal in adult stem cell lineages, Development 137 (2) (2010) 213–221.
[68] A. Van Roten, A.Z.A. Barakat, A. Wouters, T.A. Tran, S. Mouton, J.P. Noben, L. Gentile, K. Smeets, A carcinogenic trigger to study the function of tumor suppressor genes in Schmidtea mediterranea, Dis. Model. Mech. 11 (9) (2018).
[69] N. de Sousa, G. Rodríguez-Esteban, J.I. Rojo-Laguna, E. Saló, T. Adell, Hippo signaling controls cell cycle and restricts cell plasticity in planarians, PLoS Biol. 16 (1) (2018) e2002399.
[70] A. Evdokimov, M. Kutuzov, I. Petruseva, N. Lukjanchikova, E. Kashina, E. Kolova, T. Zemerova, S. Romanenko, P. Perelman, D. Prokopov, A. Seluanov, V. Gorbunova, A. Graphodatsky, V. Trifonov, S. Khodyreva, O. Lavrik, Naked mole rat cells display more efficient excision repair than mouse cells, Aging 10 (6) (2018) 1454–1473.
[71] P.G. Barghouth, M. Thiruvalluvan, M. LeGro, N.J. Oviedo, DNA damage and tissue repair: what we can learn from planaria, Semin. Cell Dev. Biol. 87 (2019) 145–159.
[72] T.H. Peiris, D. Ramirez, P.G. Barghouth, U. Ofoha, D. Davidian, F. Weckerle, N. J. Oviedo, Regional signals in the planarian body guide stem cell fate in the presence of genomic instability, Development 143 (10) (2016) 1697–1709.
[73] S. Sahu, D. Sridhar, P. Abnave, N. Kosaka, A. Dattani, J.M. Thompson, M.A. Hill, A. Aboobaker, Ongoing repair of migration-coupled DNA damage allows planarian adult stem cells to reach wound sites, Elife 10 (2021).
[74] D.A. Shiroor, K.T. Wang, B.D. Sanketi, J.K. Tapper, C.E. Adler, Inhibition of ATM kinase rescues planarian regeneration after lethal radiation, EMBO Rep. 24 (5) (2023) e56112.
[75] C. González-Estévez, D.A. Felix, G. Rodríguez-Esteban, A.A. Aboobaker, Decreased neoblast progeny and increased cell death during starvation-induced planarian degrowth, Int. J. Dev. Biol. 56 (1-3) (2012) 83–91.
[76] J. Baguñà, R. Romero, E. Saló, J. Collet, C. Auladell, M. Ribas, M. Riutort, J. Garcia-Fernàndez, F. Burgaya, D. Bueno, Growth, degrowth and regeneration as developmental phenomena in adult freshwater planarians, in: H.-J. Marthy (Ed.), Experimental Embryology in Aquatic Plants and animals, Plenum Publishing Corp., New York, 1990, pp. 129–162.
[77] J. Baguñà, R. Romero, Quantitative analysis of cell types during growth, degrowth and regeneration in the planarians *Dugesia mediterranea* and *Dugesia tigrina*, Hydrobiologia 84 (1981) 181–194.

[78] S.J. Zhu, B.J. Pearson, The Retinoblastoma pathway regulates stem cell proliferation in freshwater planarians, Dev. Biol. 373 (2) (2013) 442–452.
[79] A. Karge, N.A. Bonar, S. Wood, C.P. Petersen, tec-1 kinase negatively regulates regenerative neurogenesis in planarians, Elife 9 (2020).
[80] J. Kim, K.L. Guan, mTOR as a central hub of nutrient signalling and cell growth, Nat. Cell Biol. 21 (1) (2019) 63–71.
[81] K.C. Tu, B.J. Pearson, A. Sánchez Alvarado, TORC1 is required to balance cell proliferation and cell death in planarians, Dev. Biol. 365 (2) (2012) 458–469.
[82] T.H. Peiris, F. Weckerle, E. Ozamoto, D. Ramirez, D. Davidian, M.E. García-Ojeda, N.J. Oviedo, TOR signaling regulates planarian stem cells and controls localized and organismal growth, J. Cell Sci. 125 (Pt 7) (2012) 1657–1665.
[83] T.H. Peiris, D. Ramirez, P.G. Barghouth, N.J. Oviedo, The Akt signaling pathway is required for tissue maintenance and regeneration in planarians, BMC Dev. Biol. 16 (2016) 7.
[84] A.K. Brown, A.E. Webb, Regulation of FOXO factors in mammalian cells, Curr. Top. Dev. Biol. 127 (2018) 165–192.
[85] E. Pascual-Carreras, C. Herrera-Úbeda, M. Rosselló, P. Coronel-Córdoba, J. Garcia-Fernàndez, E. Saló, T. Adell, Analysis of Fox genes in Schmidtea mediterranea reveals new families and a conserved role of Smed-foxO in controlling cell death, Sci. Rep. 11 (1) (2021) 2947.
[86] S. Piccolo, T. Panciera, P. Contessotto, M. Cordenonsi, YAP/TAZ as master regulators in cancer: modulation, function and therapeutic approaches, Nat. Cancer 4 (1) (2023) 9–26.
[87] E. Pascual-Carreras, M. Marin-Barba, C. Herrera-Úbeda, D. Font-Martín, K. Eckelt, N. de Sousa, J. García-Fernández, E. Saló, T. Adell, Planarian cell number depends on blitzschnell, a novel gene family that balances cell proliferation and cell death, Development 147 (7) (2020).
[88] J.C. Rusconi, R. Hays, R.L. Cagan, Programmed cell death and patterning in Drosophila, Cell Death Differ. 7 (11) (2000) 1063–1070.
[89] J.S. Peterson, A.K. Timmons, A.A. Mondragon, K. McCall, The end of the beginning: cell death in the germline, Curr. Top. Dev. Biol. 114 (2015) 93–119.
[90] D. Drummond-Barbosa, A.C. Spradling, Stem cells and their progeny respond to nutritional changes during Drosophila oogenesis, Dev. Biol. 231 (1) (2001) 265–278.
[91] A. Mase, J. Augsburger, K. Brückner, Macrophages and their organ locations shape each other in development and homeostasis – a Drosophila perspective, Front. Cell Dev. Biol. 9 (2021) 630272.
[92] C. Gafuik, H. Steller, A gain-of-function germline mutation in Drosophila ras1 affects apoptosis and cell fate during development, PLoS One 6 (8) (2011) e23535.
[93] F. Luo, C. Zhang, Z. Shi, T. Mao, L.H. Jin, Notch signaling promotes differentiation, cell death and autophagy in Drosophila hematopoietic system, Insect Biochem. Mol. Biol. 173 (2024) 104176.
[94] S. Ghosh, A. Singh, S. Mandal, L. Mandal, Active hematopoietic hubs in Drosophila adults generate hemocytes and contribute to immune response, Dev. Cell 33 (4) (2015) 478–488.
[95] X. Zeng, S.X. Hou, Enteroendocrine cells are generated from stem cells through a distinct progenitor in the adult Drosophila posterior midgut, Development 142 (4) (2015) 644–653.
[96] J. Liang, S. Balachandra, S. Ngo, L.E. O'Brien, Feedback regulation of steady-state epithelial turnover and organ size, Nature 548 (7669) (2017) 588–591.
[97] H. Jiang, P.H. Patel, A. Kohlmaier, M.O. Grenley, D.G. McEwen, B.A. Edgar, Cytokine/Jak/Stat signaling mediates regeneration and homeostasis in the Drosophila midgut, Cell 137 (7) (2009) 1343–1355.
[98] T. Reiff, Z.A. Antonello, E. Ballesta-Illán, L. Mira, S. Sala, M. Navarro, L. M. Martinez, M. Dominguez, Notch and EGFR regulate apoptosis in progenitor cells to ensure gut homeostasis in Drosophila, Embo J. 38 (21) (2019) e101346.
[99] Z.A. Antonello, T. Reiff, E. Ballesta-Illan, M. Dominguez, Robust intestinal homeostasis relies on cellular plasticity in enteroblasts mediated by miR-8-Escargot switch, Embo J. 34 (15) (2015) 2025–2041.
[100] A. Takeishi, E. Kuranaga, A. Tonoki, K. Misaki, S. Yonemura, H. Kanuka, M. Miura, Homeostatic epithelial renewal in the gut is required for dampening a fatal systemic wound response in Drosophila, Cell Rep. 3 (3) (2013) 919–930.
[101] H.M. Ciesielski, H. Nishida, T. Takano, A. Fukuhara, T. Otani, Y. Ikegawa, M. Okada, T. Nishimura, M. Furuse, S.K. Yoo, Erebosis, a new cell death mechanism during homeostatic turnover of gut enterocytes, PLoS Biol. 20 (4) (2022) e3001586.
[102] A. Bergmann, Erebosis is a new type of cell death for tissue homeostasis in the Drosophila intestine, PLoS Biol. 20 (4) (2022) e3001614.
[103] E. Boada-Romero, J. Martinez, B.L. Heckmann, D.R. Green, The clearance of dead cells by efferocytosis, Nat. Rev. Mol. Cell Biol. 21 (7) (2020) 398–414.
[104] P.M. Henson, Cell removal: efferocytosis, Annu. Rev. Cell Dev. Biol. 33 (2017) 127–144.
[105] G. Krejčová, A. Danielová, H. Sehadová, F. Dyčka, J. Kubásek, M. Moos, A. Bajgar, Macrophages play a nutritive role in post-metamorphic maturation in Drosophila, Development 151 (7) (2024).
[106] S.B. Serizier, K. McCall, Scrambled eggs: apoptotic cell clearance by non-professional phagocytes in the Drosophila ovary, Front. Immunol. 8 (2017) 1642.
[107] M.H. Raymond, A.J. Davidson, Y. Shen, D.R. Tudor, C.D. Lucas, S. Morioka, J.S. A. Perry, J. Krapivkina, D. Perrais, L.J. Schumacher, R.E. Campbell, W. Wood, K. S. Ravichandran, Live cell tracking of macrophage efferocytosis during Drosophila embryo development in vivo, Science 375 (6585) (2022) 1182–1187.
[108] R. Heron, C. Amato, W. Wood, A.J. Davidson, Understanding the diversity and dynamics of in vivo efferocytosis: Insights from the fly embryo, Immunol. Rev. 319 (1) (2023) 27–44.
[109] J.R. Lee, T. Boothe, C. Mauksch, A. Thommen, J.C. Rink, Epidermal turnover in the planarian Schmidtea mediterranea involves basal cell extrusion and intestinal digestion, Cell Rep. 43 (7) (2024) 114305.
[110] N. Lindsay-Mosher, S. Lusk, B.J. Pearson, Planarians require ced-12/elmo-1 to clear dead cells by excretion through the gut, Cell Rep. 43 (1) (2024) 113621.
[111] Z. Zhou, E. Hartwieg, H.R. Horvitz, CED-1 is a transmembrane receptor that mediates cell corpse engulfment in C. elegans, Cell 104 (1) (2001) 43–56.
[112] T. Awasaki, R. Tatsumi, K. Takahashi, K. Arai, Y. Nakanishi, R. Ueda, K. Ito, Essential role of the apoptotic cell engulfment genes draper and ced-6 in programmed axon pruning during Drosophila metamorphosis, Neuron 50 (6) (2006) 855–867.
[113] S. Barberán, S. Fraguas, F. Cebrià, The EGFR signaling pathway controls gut progenitor differentiation during planarian regeneration and homeostasis, Development 143 (12) (2016) 2089–2102.