Review

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Review

Are Axolotls Resistant to Cancer? Possible Explanations

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Abstract

The axolotl (*Ambystoma mexicanum*), a neotenic salamander native to the lakes and wetlands of southern Mexico, is renowned for its remarkable regenerative capacity. Beyond regeneration, increasing evidence suggests that axolotls may also display resistance to cancer, making them a valuable model for exploring mechanisms of tumor suppression. This review provides an updated overview of molecular and physiological traits potentially underlying this resistance. Central aspects include their permanent larval state, high cellular plasticity, and tightly regulated cell proliferation during regeneration, all of which may limit malignant transformation. Additional mechanisms considered are their low metabolic rate, reduced thyroid hormone levels, decreased insulin sensitivity, presence of natural antitumor compounds, distinctive genomic and epigenetic features, and a robust innate immune system. Particular emphasis is placed on how these mechanisms may counteract established cancer hallmarks. Studying these features not only deepens understanding of axolotl biology but may also inspire novel strategies for cancer prevention and therapy in humans.

Keywords: regeneration; metamorphosis; resistance to cancer development; molecular mechanisms

1. Introduction

The axolotl, a species of salamander belonging to the genus *Ambystoma* (commonly known as the mole salamander) and specifically the species *Ambystoma mexicanum*, is native to the lakes and wetlands of southern Mexico [1]. Recognizable by their feathery external gills and perpetual "smile", axolotls have become popular around the world. Their extraordinary ability to regenerate complex body parts, such as limbs, eyes, heart, spinal cord and even parts of the brain, has made them the subject of intense scientific and genetic research [2]. Notably, this dual status has created a conservation paradox: while axolotls abound in laboratories and aquariums around the world, their wild populations have plummeted due to severe habitat degradation, leaving the species critically endangered in the wild [3].

On the other hand, cancer represents a major global challenge, with profound societal, public health, and economic impacts. It accounts for nearly one in six deaths worldwide (16.8%) and approximately one in four deaths (22.8%) caused by noncommunicable diseases (NCDs) [4]. Cancer is characterized by the abnormal growth of cells that expand beyond their normal boundaries. These uncontrolled cells can invade nearby tissues and have the potential to spread to distant organs through a process known as metastasis [5,6].

Carcinogenesis is a gradual, multistep process driven by the accumulation of genetic alterations that disrupt normal cellular regulation and endow malignant cells with specific traits collectively known as the hallmarks of cancer [7]. Core hallmarks include the ability to sustain proliferative signaling by generating continuous growth cues, evade growth suppressors that normally act as brakes on cell division, and resist programmed cell death, ensuring survival despite damage or stress. Cancer cells also achieve replicative immortality by maintaining telomeres and bypassing senescence, induce or co-opt angiogenesis to secure oxygen and nutrients, and activate invasion and metastasis, spreading from their tissue of origin to distant organs. At the metabolic level, cancer cells reprogram energy pathways to fuel rapid growth even under adverse conditions, while simultaneously evading immune destruction, allowing them to persist despite immune surveillance. Beyond these established features, additional mechanisms are increasingly recognized. Cancer cell plasticity is increasingly appreciated as a key factor, supported by mechanisms such as non-mutational epigenetic reprogramming and variations in organ- or tissue-specific microbiomes, which may serve as novel enablers of hallmark capabilities. Moreover, tumor-promoting inflammation emerges as a critical process that cooperates with genetic mutations and other oncogenic alterations to sustain malignant progression. Finally, senescent cells of diverse origins, including both tumor cells and stromal cells, have been identified as functional contributors to cancer development and progression [7].

Several animal species in nature have demonstrated remarkable resistance to cancer, a disease often considered an inevitable consequence of complex life [8]. Notable examples include the naked mole rat [9], the blind mole rat [10], bats [11], whales [12], and elephants [13], all of which exhibit unique biological traits that seem to protect them against tumor development.

However, what about axolotls? The idea that these amphibians might also be resistant to cancer has circulated for many years (since 1971, it was suggested) [14]. However, scientific evidence to support this claim is limited. In fact, as more researchers begin studying salamanders—including axolotls—reports of cancer cases in these animals are increasing. Furthermore, axolotls are rarely subjected to systematic cancer monitoring, and most individuals kept in laboratories are only observed until around 3 to 4 years of age. In the wild, axolotls generally live 5 to 6 years but can live up to 21 years in captivity [15]. As a result, many potential cancer cases may go undetected, especially those that develop later in life.

Particularly intriguing are the biological factors that may contribute to this resilience (Table 1). Among these, the species' ability to retain a larval state throughout life —a form of "perpetual youth"—without showing the typical decline associated with aging could play a key role [16]. This is accompanied by a high degree of cellular plasticity, allowing its cells to adapt and reprogram in response to external stimuli [17]. Another remarkable characteristic of the axolotl is its extraordinary capacity to regenerate complex tissues and organs without developing tumors. This regenerative capacity requires precise control over cell proliferation and mechanisms that prevent uncontrolled growth, as well as early suppression of potentially cancerous cells [18].

With this in mind, the aim of this review was to compile current knowledge and provide an overview of the molecular mechanisms that may underlie resistance of the axolotl to cancer (Figure 1). Key factors under analysis include the axolotl's neoteny (retention of juvenile characteristics in a sexually mature adult animal), its remarkable cellular plasticity, and the tightly regulated cell proliferation observed during regeneration. Other factors not previously considered are their low metabolic rate, their reduced thyroid hormone levels, their lower insulin sensitivity, the presence of natural antitumor compounds, their unique genomic and epigenetic traits, and the characteristics of their innate immune system.

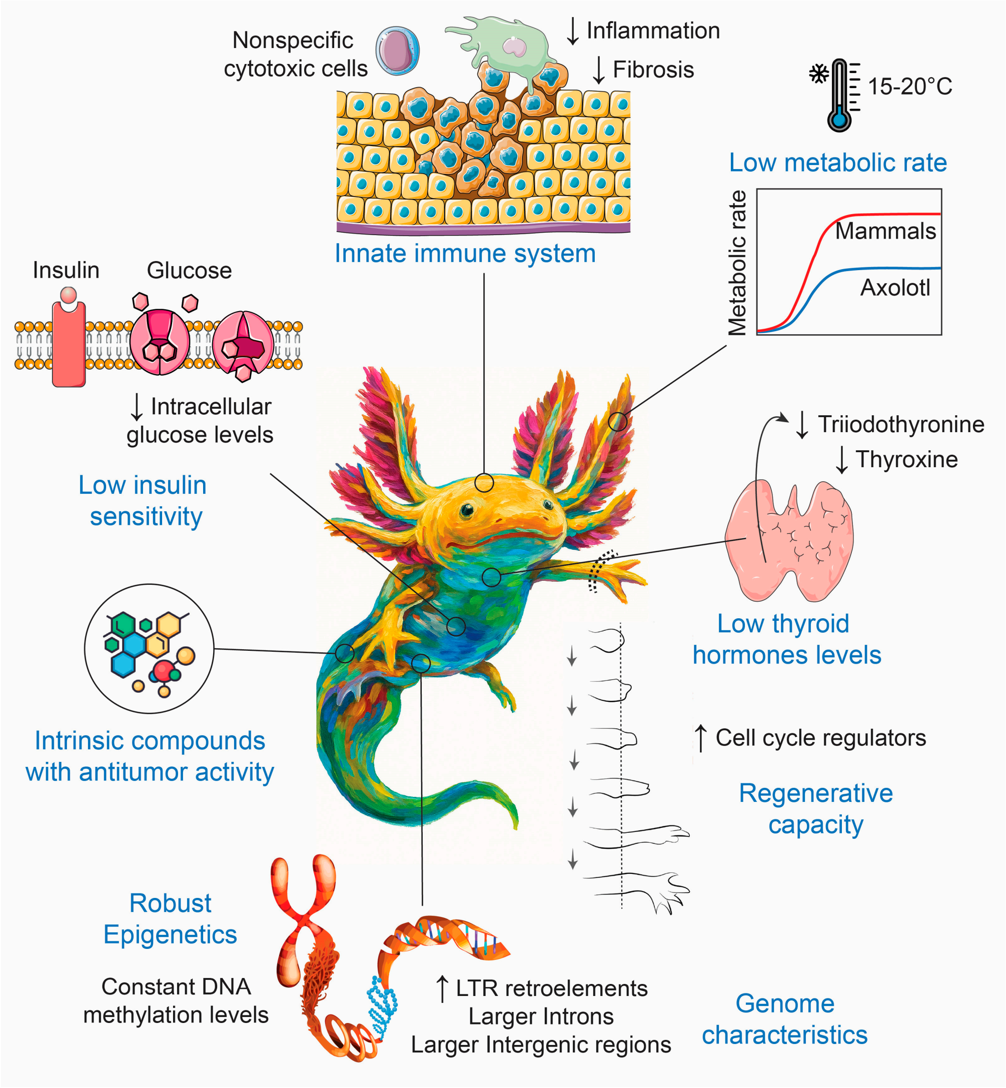

Figure 1. Key mechanisms identified in the axolotl that could contribute to cancer resistance.

Table 1. Comparative analysis of key aspects relevant to cancer across axolotls, zebrafish, mice, and humans.

	Organism			
Feature	**Axolotl**	**Zebrafish**	**Mice**	**Human**
Maximum longevity [15]	21 years (captivity)	5.5 years (captivity)	4 years (captivity)	122.5 years
Basal metabolic rate [15]	~0.025 W	~0.00056 W	0.2710 W	82.7800 W
Body mass [15]	~60–150 g (lab-bred individuals)	~0.3–0.9 g (lab-reared adults)	18.0 g	70,000.0 g
Typical body temperature [15]	~16–20 °C (laboratory)	~28 °C (laboratory)	36.9 °C	37.0 °C
Cancer incidence	Rare (suggested)	Moderate	High	Moderate
Regenerative capacity	Very high	High (embryos) Moderate (adults)	Limited	Very limited
Genome size [19]	~32 Gb	~1.5 Gb	~2.7 Gb	~3.2 Gb
Chromosomes [19]	56	50	40	46
Protein-coding genes [19]	23,251	26,206	21,529	19,435
Median intron length [19]	22,759 bp	~1350 bp	1469 bp	1750 bp

LTR retroelements [19]	High	Low	Moderate	Moderate
Innate immune system	Robust and active	Functional and efficient	Functional and balanced	Functional and balanced
Adaptive immune system	Limited	Limited	Diversified and efficient	Highly diversified and efficient

2. Tumor Cases in Axolotls

Few cases of spontaneous tumors have been described in the axolotl, and a relatively small proportion of them have been identified as malignant. Early and most commonly described cases include cutaneous and subcutaneous melanomas [20,21]. This could be explained by the fact that axolotls, particularly wild-type strains, possess a large number of pigment-producing cells called melanophores [22]. These cells are especially sensitive to mutagenic changes due to their high metabolic activity and the generation of reactive oxygen species (ROS) during melanin production [23]. As a result, melanophores are more susceptible to malignant transformation. Interestingly, in one group of animals, melanoma growth was observed to occur in parallel with tissue regeneration. However, the infiltration of melanotic tissue into the regeneration zone was limited and temporary, so it did not interfere with the process and resulted in the formation of normal tissue [24]. A case of chromatophoroma (a tumor also arising from pigment-producing cells) was reported in the tail of a 3-year-old female axolotl [25]. Another report documented a teratoma arising in the dorsal muscles of the proximal tail in a 2.5-year-old animal [26]. In addition, spontaneous mastocytomas have been observed in older members (11–17 years old) of an inbred laboratory colony [27]. Similarly, a case series reported ten instances of spontaneous myeloid leukemia in genetically related adult axolotls that were housed together in a zoo [28]. Another reported case described the development of a malignant abdominal tumor, identified as either lymphangiosarcoma or lymphosarcoma [29]. Two cases of olfactory neuroblastoma have been described in the axolotl, presenting as masses in the oral and nasal cavities [30,31]. Over a 27-year period, 16 cases of testicular tumors were reported within a laboratory axolotl colony in which all individuals were genetically related [32].

An important consideration is that human influence may have played a role in increasing cancer susceptibility in some of the reported cases. Observations from some laboratory colonies suggest a familial link (inbred) in cases where tumors such as mastocytomas [27], testicular tumors [32], melanoma [24], and acute myeloid leukemia [28] have occurred. It is possible that a small founder population in these colonies caused inbreeding and reduced genetic diversity, thus increasing the susceptibility of these individuals to develop tumors and cancer.

On the other hand, experimental induction of tumors in axolotls has also shown signs of resistance to cancer development. When exposed to polycyclic hydrocarbons such as dibenzanthracene and methylcholanthrene, the animals showed a low incidence of papilloma tumors (28.83%). The occurrence of malignant tumors was even lower (1.8%) and required a long latency period of 2 to 3 years to develop [14]. A case of lymphosarcoma was observed in an axolotl during experiments with allogeneic skin transplants. The cancer emerged after the third round of transplants and could only be transmitted through viable tumor cells to individuals that were both immunodeficient and genetically compatible. Interestingly, very young individuals of allogeneic strains acted as “regressors”, allowing transient tumor growth followed by regression, whereas adults of these same strains were “rejecters” and did not develop tumors at all [33].

3. Possible Molecular Mechanisms Involved in the Reduction of Cancer Incidence in Axolotls

3.1. Habitat and Low Metabolic Rate

Tumor growth has been reported to slow under low-temperature conditions [34]. Axolotls, which naturally inhabit cool environments (15–20 °C), could benefit from this factor as part of their arsenal against cancer development. Low temperatures reduce the metabolic rate in axolotls, and a lower basal metabolic rate may contribute to a decreased risk of cancer [35]. Axolotls exhibit a lower metabolic rate compared to mammals (Table 1) [36,37], which may create an unfavorable environment for cancer cells whose reprogrammed metabolism must sustain rapid proliferation—a well-recognized hallmark of cancer (Table 2). Similarly, exposure to cold can reduce inflammation [38], including tumor-promoting inflammation, representing inhibition of another established hallmark of cancer (Table 2).

Table 2. Hallmarks of cancer and potential mechanisms by which axolotls counteract it. The hallmarks of cancer framework serves as a powerful heuristic tool to distill the extraordinary complexity of cancer phenotypes and genotypes into a defined set of underlying biological principles [7]. In this context, axolotls display traits that may counteract cancer hallmarks, suggesting mechanisms that could underlie their resistance to cancer. Section 3 provides a more detailed explanation of the axolotl's mechanisms.

Hallmark of Cancer	**Hallmark Description**	**Axolotl Mechanisms That May Counteract the Hallmark Trait**
Sustaining proliferative signaling	Cancer cells maintain chronic growth-promoting signals that drive uncontrolled proliferation.	- Low levels of thyroid hormones - Low insulin sensitivity - Genomic stability
Evading growth suppressors	Cancer cells inactivate tumor suppressor pathways that normally restrict cell division.	- Genomic stability - Action of tumor suppressor genes
Resisting cell death	Malignant cells circumvent apoptosis and other programmed cell death mechanisms.	- Low levels of thyroid hormones - Low insulin sensitivity
Enabling replicative immortality	Telomere maintenance and bypassing senescence mechanisms permit unlimited cellular replication.	- Genomic stability
Inducing or accessing vasculature	Tumors promote angiogenesis or exploit existing blood vessels to secure oxygen and nutrients.	- Low levels of thyroid hormones - Low insulin sensitivity
Activating invasion and metastasis	Cancer cells acquire abilities to invade tissues and colonize distant organs.	- Low levels of thyroid hormones - Low insulin sensitivity - Genomic stability
Reprogramming cellular metabolism	Tumor cells adapt metabolic pathways to support growth, survival, and biosynthesis.	- Cool environment - Low levels of thyroid hormones - Low insulin sensitivity - Genomic stability
Avoiding immune destruction	Cancer cells evade recognition and elimination by the host immune system.	- Nonspecific cytotoxic cells - Thymus regeneration
Non-mutational epigenetic reprogramming	Epigenetic changes, such as DNA methylation or histone modification, alter gene expression without changing the DNA sequence, allowing cancer cells to adapt and progress more rapidly.	- Robust epigenetic characteristics
Polymorphic microbiomes	Variations in host-associated microbiota influence tumor initiation, progression, and therapeutic response.	---
Tumor-promoting inflammation	Inflammatory mediators and cells create a microenvironment that supports tumor progression.	- Cool environment - Attenuated adaptive immune response

Senescent cells	Senescent cells have been identified as functional contributors to cancer development and progression	---

Interestingly, the axolotl tumor protein p53 (TP53) harbors several amino acid substitutions, including changes at residues T155 and V157, which, in humans, are associated with reduced tumor suppressor activity. Notably, some of these changes may have been selected to maintain TP53 activity at the low physiological temperatures of this amphibian [39]. TP53 is known as the "guardian of the genome" because it preserves DNA integrity by monitoring cellular stress and genetic damage. When such damage is detected, TP53 acts as a master regulator of cell fate by halting cell-cycle progression to allow DNA repair or, if the damage is irreparable, by inducing programmed cell death (apoptosis). Through these mechanisms, TP53 prevents the propagation of genetically unstable cells and plays a central role in cancer suppression [40].

3.2. Low Levels of Thyroid Hormones

Although axolotls typically exhibit lifelong neoteny both in the wild and in captivity, metamorphosis can be experimentally triggered by the administration of thyroid hormones [41]. It is well established that neoteny in axolotls is a consequence of the low activity of the hypothalamo-pituitary-thyroid (HPT) axis [42]. In this context, thyroid hormones play a central role in regulating metabolism, growth, and numerous other physiological processes [43]. Some evidence indicates that both subclinical and clinical hyperthyroidism are associated with an increased risk of various solid tumors. Conversely, hypothyroidism has been linked to reduced tumor aggressiveness and, in some cases, a delayed onset of cancer [44]. In particular, thyroid hormones regulate key processes associated with cancer hallmarks, including metabolism, angiogenesis, cell proliferation, and survival (Table 2) [45]. In axolotls, low thyroid hormone levels may dampen growth signaling, restrict angiogenesis, prevent metabolic reprogramming, and increase susceptibility to apoptosis [46]. In this context, the naturally low levels of thyroid hormones in axolotls may play a role in their apparent resistance to cancer. However, it remains unclear whether cancer incidence is significantly higher in terrestrial salamanders that have undergone metamorphosis triggered by thyroid hormones, as comparative data are limited. The naked mole rat, another organism with exceptional resistance to cancer, also exhibits low levels of thyroid hormones [9,47].

3.3. Low Insulin Sensitivity

Hyperinsulinemia is associated with an increased risk of various types of cancer and increased mortality from cancer [48]. Unlike mammals, axolotls display lower blood glucose levels and are also less sensitive to insulin, resulting in slow blood glucose regulation [36]. Since most cancer cells rely heavily on glycolysis to support their rapid growth, invasion, and metastasis [49], the combination of low body temperature, reduced metabolic activity, and impaired glucose-insulin responsiveness in axolotls may create a physiological environment that is less conducive (or even hostile) to cancer cell proliferation and metastasis (Table 2). In addition, the insulin and insulin-like growth factor (IGF-1) pathways act as potent mitogenic and anti-apoptotic signals (Figure 2) [48]. Therefore, reduced activation of these pathways can impair uncontrolled cell proliferation and resistance to cell death, both of which represent central hallmarks of cancer (Table 2).

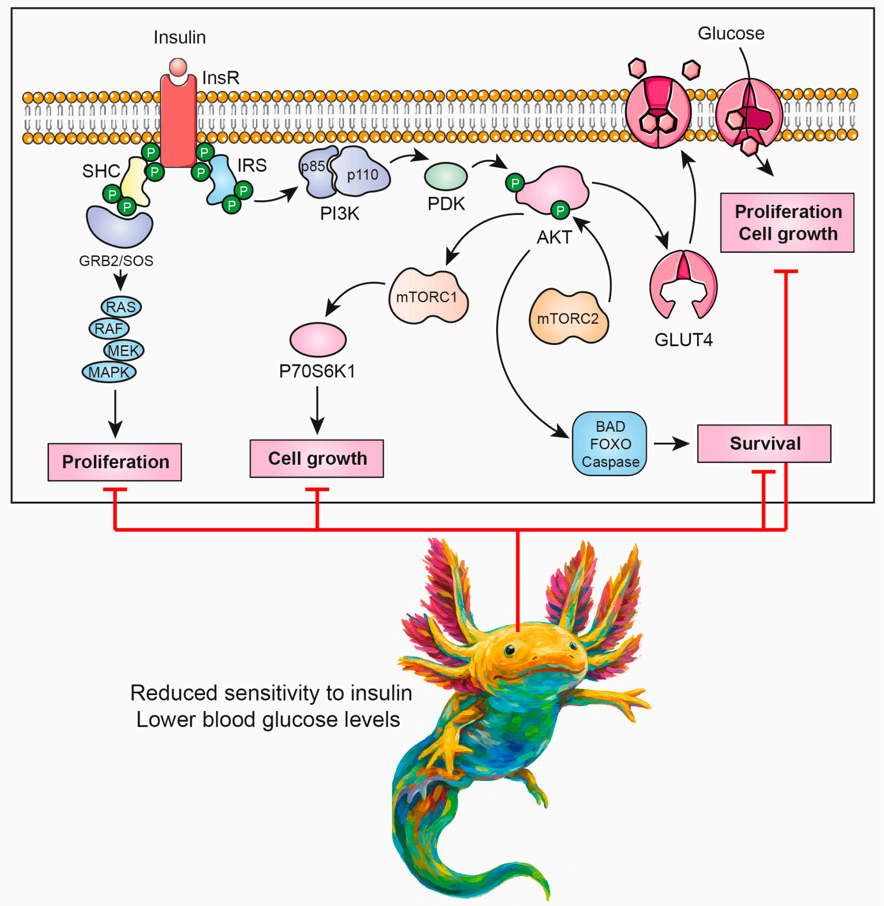

Figure 2. Axolotls show low insulin signaling. Axolotls exhibit lower blood glucose levels and reduced sensitivity to insulin, factors that may contribute to their lower incidence of cancer. Insulin binds to the extracellular α-subunit of the insulin receptor (INSR), leading to autophosphorylation and activation of its intracellular β-subunit. Once activated, the INSR phosphorylates several intracellular substrates, including members of the insulin receptor substrate family (IRS1–IRS4) and SHC. Phosphorylated tyrosine residues on IRS proteins provide docking sites for the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K). Activated PI3K initiates downstream signaling cascades, most prominently the activation of AKT (also known as protein kinase B), which promotes cell survival, metabolism, and growth. In parallel, phosphorylation of SHC by the INSR activates the mitogen-activated protein kinase (MAPK) pathway. SHC recruits growth factor receptor-binding protein 2 (GRB2), which, in turn, activates the guanine nucleotide exchange factor son of sevenless (SOS), leading to activation of the small GTP-binding protein RAS. Activated RAS triggers a kinase cascade involving RAF–MEK–MAPK, ultimately resulting in full activation of the MAPK pathway.

3.4. Intrinsic Natural Compounds with Antitumor Activity

Antimicrobial peptides isolated from axolotl skin mucus have demonstrated antitumor activity against breast cancer cells at concentrations as low as 1 μg/mL, primarily by upregulating tumor suppressor genes and downregulating oncogenes [50]. The antitumor activity of crude axolotl extract has also been observed in vitro at concentrations of 2 mg/mL, where it induced apoptosis and promoted differentiation toward the granulocytic lineage in a human acute myeloid leukemia cell line [51]. Breast cancer cells were reprogrammed using axolotl prophase oocyte extracts (5000 cells/μL extract). This reprogramming induced DNA demethylation and removed repressive histone marks at the promoters of tumor suppressor genes. As a result, cancer cell proliferation was reduced in vitro, along with decreased tumor growth in mouse xenograft models [52].

3.5. Genome and Epigenetic Characteristics

The axolotl genome is extraordinarily large, with approximately 32 billion base pairs (bp), about ten times larger than the human genome (Table 1) [19]. Although replication of such a large genome could increase the risk of mutations, axolotls appear to possess highly efficient and responsive DNA repair mechanisms that help maintain genomic stability [53–55]. In this regard, axolotl TP53 was phosphorylated and activated following exposure to UV irradiation (100 J/m^2) or treatment with an alkylating agent, indicating a conserved DNA damage response pathway [39].

In addition, despite this vast difference in genome size, the number of protein-coding genes in axolotls is comparable to that of other vertebrates with much smaller genomes. Axolotl genome expansion is largely attributed to a prolonged period of transposon activity, followed by a more recent and ongoing burst of repeat element proliferation. It is especially enriched in repetitive sequences, dominated by diverse classes of long terminal repeat (LTR) retroelements, some of which exceed 10,000 bp in length. This high repeat content has significantly impacted genome architecture, leading to a median intron length of 22,759 bp (approximately 13, 16, and 25 times longer than the median intron sizes in human [1750 bp], mouse [1469 bp], and frog [906 bp], respectively). Intergenic regions have also expanded substantially, ranging from 12 to 17 times larger than those in these other species [19]. This suggests that mutations in the axolotl genome are more likely to occur within LTR retroelements and other non-coding regions rather than in coding sequences. It remains unknown whether these genomic sequences contain unique features specific to the axolotl that might contribute to its ability to avoid cancer development, such as distinctive non-coding RNAs or genomic regions that act as “mutation buffers,” preventing potentially harmful mutations from affecting functionally or phenotypically important sites in cells. In this sense, it has been suggested that some redundancies in DNA, such as certain introns and repetitive sequences, may dampen sequence-dependent conformational effects, preventing these effects from interfering with the accurate reading of genetic information [56].

The exact number of tumor suppressor genes in the axolotl is not yet known or fully cataloged, but it is presumed to be comparable to that in humans. The most recent genome assembly report lists 39,753 transcripts based on homologous sequences and 1398 transcripts that have no matches in BLAST (basic local alignment search tool) but possess an open reading frame of at least 200 amino acids, suggesting that they could represent new protein-coding genes [19]. By examining the list of axolotl genes with sequences homologous to those of humans (using www.axolotl-omics.org [57]), approximately 150 well-characterized tumor suppressor genes were identified (e.g., TP53, RB1, PTEN, BRCA1, BRCA2, APC, and CDKN2A). However, further validation is required to confirm both their identity and functional activity. Additionally, some of the axolotl’s unique genes might include species-specific tumor suppressors that contribute to its enhanced protection, though this possibility remains to be explored.

Another noteworthy aspect is that axolotls exhibit minimal changes in global DNA methylation levels throughout their life span, suggesting a remarkably stable epigenome compared to other species [58]. This epigenetic stability may contribute to their resistance to age-related diseases, including cancer. DNA methylation plays a key role in tumorigenesis, as hypermethylation of promoter regions can silence tumor suppressor genes, while hypomethylation of regulatory sequences can activate proto-oncogenes and retrotransposons [59].

Taken together, these findings suggest that axolotls possess genomic and epigenetic features that help protect them against key cancer hallmarks, including sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality, activating invasion and metastasis, and reprogramming cellular metabolism (Table 2). Efficient DNA repair systems likely minimize genome instability and mutations. This stability may prevent proto-oncogene activation, maintain tumor suppressor gene expression, and ensure proper telomere regulation. The complementary action of tumor suppressor genes may further inhibit the evasion of growth suppression. Finally, robust epigenetic regulation appears to shield axolotls from cancer-associated epigenetic reprogramming.

3.6. Innate Immune System

Like higher vertebrates, the axolotl possesses both innate and adaptive branches of the immune system comprising the major classes of myeloid (neutrophils, eosinophils, and basophils) and lymphoid (T and B cells) lineages observed in mammals [60–62]. However, the overall diversity and functional specialization of these immune cell subtypes remain insufficiently characterized.

Axolotls possess a robust innate immune system [63], which may contribute to their apparent resistance to cancer, given that the ability to evade immune-mediated destruction is a fundamental hallmark of cancer (Table 2 and Figure 3) [64]. In this sense, non-specific cytotoxic cell receptor protein 1 (NCCRP1) expression has been detected in several axolotl tissues, including peripheral blood mononuclear cells, skin, lung, spleen, and limb blastema [64]. NCCRP1 is involved in antigen recognition and is a key receptor on nonspecific cytotoxic cells (NCCs), which mediate lysis of target cells (tumor cells and protozoan parasites) by binding to their natural ligand, the natural killer target antigen (NK Tag) [65]. NCCs are considered evolutionary precursors of mammalian natural killer (NK) cells [66] and may represent a component of the axolotl's antitumoral immune system. Furthermore, axolotl major histocompatibility complex (MHC) class I molecules exhibit strong conservation of nonpolymorphic peptide-binding regions on the α chain, along with a high degree of variability at other amino acid sites [62]. This structural arrangement suggests that axolotl class I MHC molecules are capable of presenting a wide range of antigenic epitopes, including potentially tumor-associated antigens.

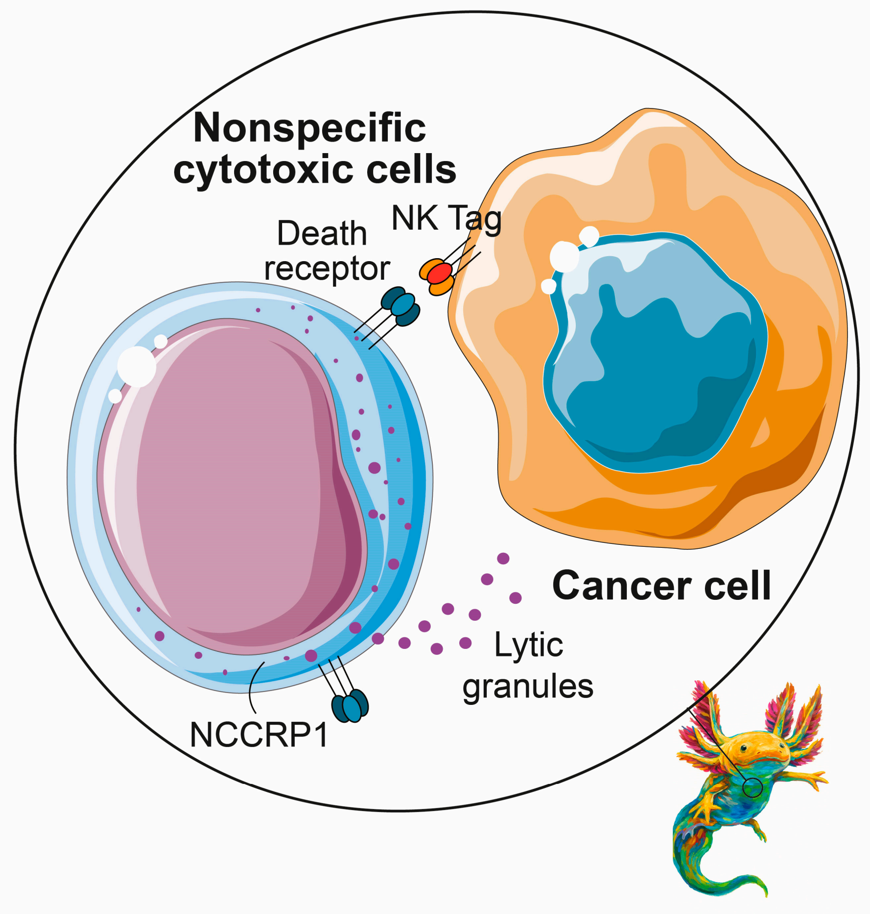

Figure 3. Innate immune system in axolotls. Non-specific cytotoxic cells (NCCs) may play a key role in the axolotl's innate immune defense. They can mediate the lysis of target cells, such as tumor cells, by binding to their natural ligand—the natural killer target antigen (NK Tag)—and releasing lytic granules. Expression of the nonspecific cytotoxic cell receptor protein 1 (NCCRP1), which is involved in antigen recognition, has been detected in multiple axolotl tissues, including peripheral blood mononuclear cells, skin, lung, spleen, and limb

blastema. NCCs are considered evolutionary precursors of mammalian natural killer (NK) cells and may contribute to the antitumoral immune response in axolotls.

Another remarkable feature of the axolotl is its ability to regenerate the thymus de novo after its complete removal [67]. The thymus is the main organ for T lymphocyte development and a key site for establishing self-tolerance and adaptive immune function [68]. This regenerative process of the axolotl completely restores thymus morphology, cellular diversity, and immune function, an exceptional ability among vertebrates [67]. In contrast, mammals undergo age-related thymic involution, leading to a progressive decline in T cell production and overall immune competence [69]. The absence of thymic involution in the axolotl may therefore allow it to maintain robust immune surveillance and effective antitumor activity for a longer period of its life.

On the other hand, axolotls exhibit a markedly attenuated adaptive immune response compared to other vertebrates [70]. Only two classes of immunoglobulins (IgM and IgY) have been identified in these animals, and both lack anamnestic (memory) responses [71]. As a consequence, axolotls generate antibodies more slowly and show minimal humoral or cytotoxic responses to viral infections [71,72]. This limited adaptive immunity is thought to be related to their neotenic state, as induction of metamorphosis has been shown to enhance humoral responses [73]. Despite this, the attenuated adaptive immune response of axolotls could offer some advantages in the context of cancer. For example, inflammatory responses, often associated with multiple stages of tumorigenesis [74,75], would be more tightly regulated and less likely to become chronic, thus counteracting, at least to some extent, another important hallmark of cancer: tumor-promoting inflammation (Table 2).

3.7. Regeneration Capacity

The axolotl's regenerative capacity is extraordinary, enabling it to restore complex structures such as limbs, the tail, parts of the eye and brain, and several internal organs [2]. In axolotls, the regenerative-permissive environment, comprising both cellular and acellular components, shares several tumor-like features. In fact, axolotl blastema cells can transiently express antigens similar to oncofetal antigens found in tumors, but their strict temporal regulation and immunological integration prevent malignant transformation and immune escape [76]. Notably, the initiation of proliferative signaling and blastema formation in axolotls involves a transient dedifferentiation process, during which mature cells revert to a progenitor-like state. These dedifferentiated cells display features commonly associated with cancer, including increased proliferation, proto-oncogene expression, and chromatin remodeling [16]. However, unlike the uncontrolled growth seen in tumors, axolotl regeneration is tightly regulated. The process is guided by precise control of cell cycle regulators to ensure balanced and orderly tissue restoration [77]. Similarly, Ty3 retrotransposon expression is suppressed during regeneration [78]. Additionally, these cells retain a memory of their original tissue identity and positional information, reducing the risk of malignant transformation [2]. Cancer cells often lose their normal identity and structure [79]. The remarkably stable epigenetic landscape of the axolotl probably also plays a crucial role in protecting against transformation [58].

Another key difference is that tumors are marked by extensive extracellular matrix (ECM) deposition, remodeling, and cross-linking, which contribute to fibrosis, stiffen the surrounding stroma, and promote malignant progression. This stiffened stroma supports tumor cell growth, survival, and migration, while also driving mesenchymal transition [80]. In contrast, axolotl wounds display only a temporary fibrotic response, ultimately leading to the regeneration of normal tissue architecture [81]. This regenerative response is marked by reduced levels of fibronectin and elevated levels of tenascin-C, creating a distinct tissue environment compared to mammalian wound repair [82]. Following limb amputation in axolotls, the number of macrophages and neutrophils increases at the wound site. Neutrophils play a key role in clearing cellular and molecular debris and promote collagen degradation by stimulating the production of matrix metalloproteinases. They also help activate anti-inflammatory macrophages by suppressing NF-κB signaling [83]. Macrophages, in turn, are essential for dampening the inflammatory response. Their presence is particularly critical during the early stages of heart regeneration, where they help regulate fibroblast activity and prevent excessive fibrosis [84]. On the other hand, ROS may also play a key role in extracellular matrix remodeling during blastema formation. In particular, hydrogen peroxide (H_2O_2) functions as an essential early signal that promotes both blastema initiation and progenitor cell reentry into the cell cycle during axolotl limb regeneration [85]. In addition, it has been proposed that ROS facilitate the recruitment of leukocytes to the site of injury to prevent fibrosis [86]. Specifically, inhibition of ROS activity has been shown to cause fibrotic tissue formation between the epithelium and the underlying remnant tissue, an effect similar to that observed with macrophage clearance [87]. Although transient ROS could cause a wide range of cellular damage, axolotl regeneration is supported by an antioxidant response that counteracts these harmful effects. At controlled or physiological levels—below the threshold of antioxidant capacity—ROS instead serve important roles in cell signaling, proliferation, and the maintenance of cellular homeostasis [88,89]. Notably, axolotl heart regeneration demonstrates remarkable resilience to the detrimental impact of hyperoxia [37].

Remarkably, axolotls retain their ability to heal without scarring even after undergoing metamorphosis, although the regeneration process becomes slower [82]. Likewise, the animals show a reduction in both the speed and fidelity of tissue regeneration, likely due to a slower cell cycle progression and decreased proliferative capacity [90].

4. Conclusions and Future Perspectives

Many questions remain unanswered regarding whether axolotls are truly resistant to cancer, as well as the underlying mechanisms that might contribute to a reduced risk of cancer development in this species (Table 3). Nevertheless, this manuscript reviews several well-established traits of the axolotl, such as neoteny, regenerative capacity, and high cellular plasticity, which may contribute to the development of cancer resistance. In addition, it brings attention to lesser-studied features, including their low metabolic rate, reduced thyroid hormone levels, decreased insulin sensitivity, presence of natural antitumor compounds, unique genomic and epigenetic profiles, and characteristics of axolotl innate immune system. These findings reinforce the potential of the axolotl as a valuable, yet underutilized, model in cancer research. Exploration of these traits would not only deepen our understanding of axolotl biology but also offers promising prospects for cancer prevention and treatment in humans.

Table 3. Outstanding questions and research opportunities in axolotl cancer research. Axolotl model could transform both basic biology and cancer research. Understanding whether axolotls are truly resistant to cancer and how their oncogenic pathways, immune system, and epigenetic regulation differ from mammals could reveal protective mechanisms that suppress tumor development. Likewise, dissecting the fine line between regeneration and tumorigenesis may provide insights into how proliferative programs can be directed toward healing rather than cancer. Comparative studies across urodeles and mammals could highlight evolutionary strategies of tumor suppression, opening new avenues for therapies.

UNANSWERED QUESTIONS

- **Tumor Susceptibility and Resistance**
    1. Is it true that axolotls are resistant to cancer?
    2. How does the incidence of cancer in axolotls change with aging?
    3. How do oncogene/tumor suppressor pathways (e.g., TP53, RAS, MYC) function differently in axolotls?
    4. Are there intrinsic anti-tumor mechanisms linked to regeneration?
- **Regeneration vs. Tumorigenesis**
    1. Why do axolotls regenerate their limbs instead of developing tumors after amputation?
    2. What distinguishes controlled regenerative proliferation from uncontrolled tumorigenic growth?
- **Immune System Involvement**
    1. How does the axolotl immune system recognize and eliminate abnormal or pre-malignant cells?

  2. Does immune tolerance during limb regeneration overlap with mechanisms that could affect cancer progression?

- **Epigenetics and Genome Stability**
  1. What is the mutation rate in axolotls?
  2. Are there mutation hotspots and mutation buffer zones?
  3. How do genome size, repetitive elements, and chromatin organization affect cancer susceptibility?
  4. Are epigenetic landscapes during regeneration protective against oncogenic transformation?
- **Microenvironment and Niche Factors**
  1. How do extracellular matrix remodeling and scar-free healing influence tumor initiation and metastasis?
  2. Does the pro-regenerative niche act as a “tumor-suppressive” environment?
- **Comparative Cancer Biology**
  1. Are there cancers unique to urodeles, and do they share features with human cancers?

RESEARCH DIRECTIONS

- **Multi-omics during regeneration and tumorigenesis**
  1. Compare the omics data between regenerated axolotl tissue, normal tissue, and induced tumors.
  2. Identify mechanisms related to cancer resistance
  3. Map signaling pathways that “tip the balance” from regeneration to oncogenesis.
- **Immune Profiling**
  1. Characterize axolotl immune surveillance mechanisms against tumors.
  2. Explore axolotl macrophages and T-cell-like populations in tumor suppression.
- **Drug Discovery and Screening**
  1. Explore natural tumor resistance mechanisms as potential therapeutic targets for human cancers.
  2. Comparative genomics and evolutionary oncology
  3. Cross-species analyses (axolotl vs. mammals) to identify evolutionary cancer-protective genes or mechanisms.
  4. Investigate conserved and unique tumor suppressor strategies in urodeles.

UNANSWERED QUESTIONS

- Tumor Susceptibility and Resistance

5. Is it true that axolotls are resistant to cancer?
6. How does the incidence of cancer in axolotls change with aging?
7. How do oncogene/tumor suppressor pathways (e.g., TP53, RAS, MYC) function differently in axolotls?
8. Are there intrinsic anti-tumor mechanisms linked to regeneration?

- Regeneration vs. Tumorigenesis

3. Why do axolotls regenerate their limbs instead of developing tumors after amputation?
4. What distinguishes controlled regenerative proliferation from uncontrolled tumorigenic growth?

- Immune System Involvement

3. How does the axolotl immune system recognize and eliminate abnormal or pre-malignant cells?
4. Does immune tolerance during limb regeneration overlap with mechanisms that could affect cancer progression?

- Epigenetics and Genome Stability

5. What is the mutation rate in axolotls?
6. Are there mutation hotspots and mutation buffer zones?
7. How do genome size, repetitive elements, and chromatin organization affect cancer susceptibility?
8. Are epigenetic landscapes during regeneration protective against oncogenic transformation?

- Microenvironment and Niche Factors

3. How do extracellular matrix remodeling and scar-free healing influence tumor initiation and metastasis?
4. Does the pro-regenerative niche act as a “tumor-suppressive” environment?

- Comparative Cancer Biology

2. Are there cancers unique to urodeles, and do they share features with human cancers?

RESEARCH DIRECTIONS

- Multi-omics during regeneration and tumorigenesis

4. Compare the omics data between regenerated axolotl tissue, normal tissue, and induced tumors.
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- Immune Profiling
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8. Investigate conserved and unique tumor suppressor strategies in urodeles.

This review highlights that axolotls possess certain protective mechanisms that may enable them to evade several distinctive features of cancer (Table 2). Their low insulin sensitivity helps limit sustained proliferative signaling, while efficient DNA repair systems minimize genome instability and mutation. A well-developed repertoire of tumor suppressor genes further supports growth inhibition, and low levels of thyroid hormones interfere with the metabolic and proliferative demands of tumor cells, restricting cancer-associated metabolic reprogramming. In addition, robust epigenetic regulation protects against tumor-related epigenetic alterations, and a strong innate immune system enhances the recognition and elimination of abnormal cells. Finally, favorable environmental and immune conditions help prevent the chronic inflammation and fibrosis that often promote tumor development.

An important avenue for research is the examination of cancer incidence in aging axolotls, especially given that most human cancers arise in older individuals. Studying older axolotls could provide valuable insights into their purported resistance to cancer and how it may change with age. Future research could also consider determining the mutation rate of the axolotl as a means of assessing the efficacy of its DNA replication and repair mechanisms. Although this is challenging due to the large size and highly repetitive nature of the axolotl genome, such investigations could provide valuable data. Identification of the genetic and metabolic mechanisms activated by the axolotl to maintain homeostasis and respond to various forms of cellular stress, such as replicative, oxidative, metabolic, and endoplasmic stress, could also provide valuable information.

The identification, characterization, and purification of compounds with antitumor activity in axolotl extracts would be highly valuable. Equally important is the molecular elucidation of the mechanisms underlying their effects. These compounds could hold significant potential for the pharmaceutical industry, either as direct-acting anticancer agents or as adjuvants to enhance existing cancer therapies.

Investigating the unique tumor suppressor mechanisms present in the axolotl has the potential to significantly advance our understanding of cancer biology and could have a profound impact on the scientific community. Equally crucial is uncovering the evolutionary origins of these mechanisms—understanding how and why axolotls developed such effective cancer resistance could reveal fundamental principles applicable to other species, including humans.

Future research should also extend beyond traditional studies of DNA methylation to explore other epigenetic modifications that may contribute to tumor suppression. Additionally, a comprehensive characterization of all immune cell subtypes in the axolotl is needed. Particular attention should be paid to elucidating the specific antitumor roles played by components of the innate immune system, as well as investigating the potential involvement of adaptive immunity in cancer resistance. Such insights could open new avenues for the development of innovative cancer therapies inspired by the axolotl’s biology.

This review has several limitations, primarily due to the limited availability of data, which at times meant that certain observations were based on a single original source. In general, the article aims to present interpretations based on the available evidence; however, in some cases, reasoned speculation is offered when data are limited or suggestive. Further research in this field is necessary to draw definitive conclusions, and this manuscript aims to encourage and inspire continued investigation.

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Abbreviations

NCDs	Noncommunicable diseases
ROS	Reactive oxygen species
TP53	Tumor protein p53
HPT	Hypothalamo-pituitary-thyroid (axis)
NCCRP1	Non-specific cytotoxic cell receptor protein 1
NCCs	Nonspecific cytotoxic cells
NK	Natural killer (Cells)
NK Tag	Natural killer target antigen
MHC	Major histocompatibility complex
ECM	Extracellular matrix
H_2O_2	Hydrogen peroxide
SASP	Senescence-associated secretory phenotype
IGF-1	Insulin-like growth factor
BLAST	basic local alignment search tool

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