Oxidative Stress and Poly(ADPribosyl)ation in Zebrafish Eyes After Exposure to Aluminium

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Article

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Anna Rita Bianchi [1], Valeria Guerretti [1], Alessandra La Pietra [1], Carmen Di Giovanni [2], Bruno Berman [1], Martina Falace [1], Teresa Capriello [1], Ida Ferrandino [1,*,†] and Anna De Maio [1,*,†]

[1] Department of Biology, University of Naples Federico II, Via Cinthia, 21, 80126, Naples, Italy

[2] Department of Pharmacy, Via Domenico Montesano, 49, 80131, Naples, Italy

* Correspondence: ida.ferrandino@unina.it (I.F.); andemaio@unina.it (A.D.M.)

† These authors contributed equally to this work and share senior authorship.

Abstract

Aluminium (Al) is a widespread environmental contaminant known to induce oxidative stress and genotoxic effects in aquatic organisms. While its neurotoxic properties are well-documented, the molecular impact of Al on the visual system remains poorly understood. In this study, adult zebrafish (*Danio rerio*) were exposed to 11 mg/L Al for 10, 15 and 20 days, to investigate the oxidative and genotoxic responses in ocular tissue. Activities of antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) were measured in eye supernatants to detect oxidative stress. Additionally, the activities of poly(ADP-ribose) polymerase (PARP) and poly(ADP-ribose) glycohydrolase (PARG) were assessed in tissue homogenates to evaluate oxidative DNA damage and repair processes. The results indicate that these enzymes respond to counteract the increased reactive oxygen species (ROS) induced by aluminium exposure. However, their activity may not sufficiently reduce ROS levels to fully prevent oxidative DNA damage, as evidenced by a significant rise in PARP activity during short exposure times. Over longer exposures, PARP activity returned to baseline, suggesting ocular cells may adapt to aluminium toxicity. We propose that this reduction in PARP activity is a cellular survival mechanism, as sustained activation can deplete energy reserves and trigger cell death. Finally, thin-layer chromatography confirmed that PARG facilitates the breakdown of poly(ADP-ribose) (PAR) into ADP-ribose, demonstrating the dynamic regulation of the PAR cycle, which is crucial to preventing parthanatos.

Keywords: aluminium toxicity; oxidative stress; PARP; PARG; zebrafish; DNA damage; antioxidant enzymes; eyes

1. Introduction

Wild fish populations are subject to various environmental stressors, including climate change, pollution, and emerging pathogens [1–5]. Recent research has extensively investigated the molecular, physiological, and organismal effects of temperature variations and chemical pollutants on fish [6–10]. Much of this work has focused on identifying the responses to abiotic stresses and understanding how these responses integrate across different biological levels. This is essential for unraveling why certain species adapt and thrive under stress, while others may face extinction [2,11,12]. Adaptation to environmental stressors and survival depend on several factors, such as energy availability, food acquisition, metabolic efficiency, and the ability to maintain aerobic capacity. These factors facilitate the mobilization of energy reserves required to offset the metabolic costs associated with defensive mechanisms [13,14]. The bioenergetic costs and stress responses- such as maintaining homeostasis, activating defense systems, and repairing cellular damage- are highly variable depending on the nature, duration, and intensity of the stressors [14]. Under short-term exposure to moderate stress, organisms can typically neutralize reactive oxygen species (ROS) through antioxidant defense

systems and repair mechanisms [15–18], allowing some species to activate compensatory metabolic strategies that minimize oxidative damage [13].

To counteract ROS-induced damage and maintain cellular homeostasis, organisms have evolved a complex antioxidant defense network, which includes both enzymatic and non-enzymatic components [19]. Among the most effective enzymatic defenses are superoxide dismutase (SOD) and catalase (CAT), which are responsible for breaking down superoxide radicals ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2), respectively [20]. Non-enzymatic defenses comprise low-molecular-weight antioxidants such as glutathione (GSH) and thioredoxin, as well as dietary antioxidants, including vitamins C and E, carotenoids, and flavonoids [20–22]. However, prolonged exposure to multiple stressors, resulting in excessive oxidative stress, can cause irreversible cellular damage, including DNA damage, which has long-term consequences for organ function and species survival [23–25]. This ultimately impacts population persistence [26–29]. One of the initial responses to DNA damage is poly(ADPribosyl)ation, a reversible post-translational modification in which ADP-ribose units are added to target proteins, particularly those containing glutamate, aspartate, or lysine residues [30]. The ADP-ribose polymer (PAR), formed from sequential addition of ADP-ribose moieties from NAD^+, can exceed 200 units and exhibit multiple branching points [30]. Poly(ADP-ribose) glycohydrolase (PARG) catalyzes the hydrolysis of PAR by cleaving ribose-ribose bonds, thereby releasing free poly(ADP-ribose) and ADP-ribose [31]. PARG has both endo- and exo-glycohydrolase activity, with a preference for the exo-glycosidic cleavage of the distal ADP-ribose units of the polymer [32,33]. The PARG gene in humans is located at a single chromosomal locus, and alternative splicing produces several isoforms localized in various subcellular compartments [34,35]. In zebrafish, two PARG isoforms (68 kDa and 87 kDa) are found in brain [36]. PARG plays a crucial role in preventing the accumulation of PAR, which can lead to parthanatos, a caspase-independent form of cell death [31,36]. Poly(ADPribosyl)ation is catalyzed by poly(ADP-ribose) polymerases (PARPs), a family of enzymes consisting of at least 18 members, which are encoded by different genes and share homology in their conserved catalytic domain [37–39]. PARPs are found across various eukaryotic species [40,41].

Among them, the nuclear PARP1 and PARP2 are the most well-characterized enzymes, known for their ability to auto-modify themselves through PAR addition in response to DNA strand breaks [42]. While PARP1 and PARP2 are primarily involved in DNA repair, they also participate in numerous other cellular processes, including cell proliferation, transcription, chromatin remodeling, and apoptosis [43–46]. PARP1 and PARP2 activation is key in determining whether cells survive or die after DNA damage. In cases of mild DNA damage, PARP activation facilitates DNA repair, promoting cell survival. However, in response to severe DNA damage, the hyperactivation of PARP leads to NAD^+ depletion and a subsequent loss of intracellular ATP reserves, driving cells towards necrosis or apoptosis [47]. Studies have also explored PARP modulation in response to abiotic stresses in plants [48–51] and marine organisms [52–55].

The activation of PARPs has been linked to a range of human diseases, including cardiomyopathies, inflammatory disorders, cardiovascular diseases, diabetic complications, and neurodegenerative diseases [56], positioning PARPs as promising targets for anti-cancer therapies [57]. A detailed poly(ADPribosyl)ation system has been characterized in the zebrafish brain following aluminium exposure over 10, 15, and 20 days [36]. Aluminium is neurotoxic to fish, and its effects on zebrafish brain tissue resemble the pathology observed in humans with Alzheimer's disease [58]. The highest PARP and PARG activities were recorded after 10 and 15 days of exposure, with a significant reduction in PARP activity after prolonged exposure. The initial increase in PARP activity was associated with DNA damage caused by aluminium, whereas the decrease in PARP activity at longer exposure times likely represents a cellular strategy to conserve energy and enable survival [36]. Pollutant toxicity has also been observed in the eyes of zebrafish, leading to visual dysfunction [59]. Fish eyes are particularly vulnerable to damage from pollutants because they are constantly exposed [60]. Visual impairments significantly increase the risks to individual survival and can threaten the viability of entire populations, as fish become unable to escape predators or locate food [61,62].

Previous studies revealed histological retinal damage during initial aluminium exposure, followed by partial recovery with prolonged exposure. This recovery was confirmed by increased expression of genes related to retinal regeneration, accompanied by elevated PARP enzyme expression [63].

Based on these findings and following the protocol previously applied, this study used the same aluminium exposure durations to assess potential oxidative DNA damage in zebrafish eyes.

In detail, the present research aimed to evaluate the activities of superoxide dismutase (SOD) and catalase (CAT) in the eyes of adult zebrafish, both unexposed and exposed to 11 mg/L Al for 10, 15 and 20 days. This was done to investigate whether changes in antioxidant enzyme activities were linked to the onset of oxidative stress during exposure. Additionally, oxidative damage to genetic material was assessed indirectly by measuring PARP activity. PARG activity was also determined to assess whether the balance between poly(ADP-ribose) synthesis and degradation, essential for maintaining genomic integrity, was disrupted by exposure. Thin-layer chromatography (TLC) was employed to identify PAR digestion products and confirm the role of PARG in PAR turnover. Lastly, a molecular mechanism linking DNA repair and the maintenance of genomic integrity to antioxidant enzyme activity was proposed.

2. Materials and Methods

2.1. Zebrafish Breeding

Adult zebrafish were breed in a glass tanks in the Department of Biology, University of Naples Federico II, at a constant temperature of 28 °C and a pH of 7.6, daily monitored, and with a photoperiod 12:12 h light/dark. Fish were fed with a commercial flakes (TetraMin Tropical Flake Fish®) commercial food supplemented with live *Artemia* sp. nauplii. The experimental protocols were conducted in accordance with the guidelines and policies dictated by European regulations on the wellness of animals employed for experimental purposes (Directive 2010/63/EU) and approved by the Italian Ministry of Health (licence 147/2019-PR).

2.2. Treatment and Sample Collection

The experimental conditions are the same as those already described in Capriello et al. [64]. Four groups of 11 fish each were set up in 25 L glass tanks. One group was exposed to to water only (1/3 distilled water, 2/3 tap water) and used as control group (Ctrl), while the others were treated with 11 mg/L of Al for 10 (T10), 15 (T15) and 20 (T20) days respectively. The water in the tanks was renewed daily, and food debris was removed. At the end of treatments, fish were sacrificed by an overdose of ethyl 3-aminobenzoate methane sulfonate (MS-222 solution, Sigma Aldrich, Germany, Cas No. 886–86–2) (300 mg/L) and eyes were collected.

2.3. Sample Preparation

Eyes from zebrafish unexposed (Ctrl) and exposed to Al were homogenized (Ultra Turrax T8, IKA-WERKE) in ice-cold homogenization buffer, containing 10 mM Tris-HCl (pH 7.5), 1 mM EDTA, 1 mM EGTA, 1 mM β-mercaptoethanol, 0.15 mM spermine, 0.75 mM spermidine, 1 mM PMSF, and 2 μg/mL protease inhibitor cocktail [63].

An aliquot of the homogenate was centrifuged at 10,000 xg for 10 minutes at 4 °C. The supernatant was further centrifuged at 8,000 xg for 15 minutes to obtain a clear supernatant which was used to measure superoxide dismutase (SOD) and catalase (CAT) activities [65]. The Bradford assay (BioRad, Hercules, CA, USA) was used to measure the protein concentration.

2.4. Enzymatic Antioxidant Measurements

2.4.1. SOD Activity

SOD catalyses the dismutation of the superoxide anion (O_2^-) into hydrogen peroxide and molecular oxygen. SOD activity was determined by colorimetric assay method, which utilizes a tetrazolium salt (WST-1) to detect superoxide radicals generated by the xanthine/xanthine oxidase system [66].

To perform the assay, 2 μg of the supernatant from the zebrafish eyes was added to a reaction mixture consisting of assay buffer (50 mM potassium phosphate, pH 7.4), xanthine oxidase (50 mM) and 1 mL WST-1 reagent, following the manufacturer's instructions for the SOD assay kit (SOD kit CS1000, Sigma- Aldrich). The mixture is incubated for 20 minutes at 37 °C. SOD activity was measured based on the degree of inhibition of WST-1 formazan formation at 450 nm, using a microplate reader (Multiskan Sky, Thermo Scientific). The SOD activity was expressed in U/mg of protein.

2.4.2. CAT Activity

CAT enzyme activity was measured in the supernatant of zebrafish according to the manufacturer's instructions of the commercial CAT colorimetric assay kit (CAT kit CAT100, Sigma-Aldrich). This method of analysis allows the measurement of hydrogen peroxide remaining after the action of catalase. Catalase converts hydrogen peroxide into water and oxygen. This enzymatic reaction is stopped with sodium azide and the reaction mixture is subjected to a colorimetric assay. The colorimetric assay uses the substrate (3,5-dichloro-2-hydroxybenzenesulfonic acid), which binds oxidatively to 4-amino antipyrine in the presence of hydrogen peroxide and horseradish peroxidase (HRP) to give N-(4-antipyryl)-3-chloro-5-sulphonate-*p*-benzoquinone-monoimine, a quinone imine red dye which absorbs at 520 nm. In detail, 1 μg of the zebrafish eye supernatant was added to the reaction mixture, consisting of assay buffer (50 mM potassium phosphate, pH 7.0), 20 μL of hydrogen peroxide (10 mM). Subsequently, the reaction mixture was incubated for 15 minutes at room temperature. The reaction was stopped by adding stop solution. CAT activity was calculated based on the decrease in absorbance at 520 nm, resulting from the decomposition of hydrogen peroxide, using a microplate reader (Multiskan Sky, Thermo Scientific). The CAT activity was expressed in U/mg of protein.

2.5. Poly(ADP-ribose) Polymerase (PARP) and Poly(ADP-ribose) Glycohydrolase (PARG) Activity Assays

PARP activity assay was performed as described by Bianchi et al. [36]. Two aliquots of homogenate (20 μg of protein each) were incubated in the presence of 0.4 mM [^{14}C]NAD$^+$ (10,000 cpm/nmole) in a reaction mixture consisting of 0.5 M Tris-HCl (pH 8.0), 50 mM MgCl$_2$ and 10 mM DTT. After 15-minute incubation at 25 °C, the reaction was stopped by the added of cold 20% trichloroacetic acid (TCA) (w/v). One of the aliquots was repeatedly washed with 7% TCA and then filtered on Millipore filters (HAWPP0001, 0.45 μm).

The second aliquot was centrifuged at 7,400 xg for 5 minutes at 4 °C. After washing in absolute ethanol, the resulting precipitate (consisting of both poly- and non-ADP-ribosylated proteins) was incubated for 15 minutes at 37 °C in PARG assay conditions, in a reaction mixture containing 100 mM Tris-HCl (pH 8.0), 10 mM DTT and 20 μg of homogenate [67]. The reaction was stopped on ice, and the precipitates obtained by adding 20% TCA were washed with 7% TCA and filtered on Millipore filters (HAWPP0001, 0.45 μm).

PARP and PARG activities were measured as the radioactivity of insoluble acid material using a liquid scintillation counter (LS 1701, Beckman, Milan, Italy) and were expressed as enzymatic milliunits per gram of tissue (mU/g).

2.6. Thin-Layer Chromatography (TLC) of Synthesised and Digested Poly(ADP-ribose)

Two aliquots of homogenate (200 μg of protein each) from zebrafish eyes were incubated in a reaction mixture containing 0.5 M Tris-HCl (pH 7.5), 50 mM MgCl$_2$, 10 mM DTT and 0.5 mM [^{14}C]NAD$^+$ (100,000 cpm/nmol), for 15 min at 25 °C under PARP assay conditions [64]. The reaction

was stopped on ice and the proteins were precipitated by the addition of 30% TCA (w/v). Following centrifugation at 1,200 xg at 4 °C for 20 minutes, the sample was washed three times with absolute ethanol. The resulting precipitate was then resuspended in a solution of 1 mM EDTA and 10 mM Tris-NaOH buffer at pH 12, and incubated for 3 hours at 60 °C. Pure protein-free [^{14}C]poly(ADP-ribose)was extracted three times with isoamyl alcohol/chloroform (1:24, v/v) [36].

An aliquot of extracted [^{14}C]poly(ADP-ribose) (2,000 cpm) was incubated in a reaction mixture containing 100 mM Tris-HCl (pH 8), 10 mM dithiothreitol and homogenate (200 µg) for 15 minutes at 37 °C in PARG assay conditions [67]. The reaction was then blocked at 4 °C and the precipitable TCA fraction was washed with absolute ethanol.

Finally, the poly(ADP-ribose) and its degradation products by PARG were analysed were analyzed by thin-layer chromatography (TLC) on PEI cellulose plates in 0.05 M ammonium bicarbonate [52]. Autoradiographic patterns of labeled poly(ADP-ribose) on TLC were acquired using a Phosphor-imager (model Fx, BioRad).

2.7. Statistical Analysis

Statistically significant differences were assessed by Brown-Forsythe and Welch one-way analysis of variance (ANOVA) tests followed by Benjamini and Yekutieli multiple comparisons test using the GraphPad Prism 8 Software. The results were reported in the graph as the mean ± standard deviation (SD) and the minimum level of acceptable significance was $p < 0.05$.

3. Results

3.1. SOD and CAT Activities

Superoxide dismutase (SOD) and catalase (CAT) are key antioxidant enzymes that play a crucial role in shielding the ocular region from oxidative damage. As the primary defense against reactive oxygen species (ROS) in the eye, these enzymes help maintain redox homeostasis, thereby reducing the risk of oxidative stress-related conditions such as cataracts and macular degeneration [68,69]. In this study, the activity levels of SOD and CAT were assessed in the supernatants of dissected zebrafish eyes following aluminium exposure for 10, 15, or 20 days. Both SOD (Figure 1a) and CAT (Figure 1b) activities were significantly elevated in all aluminium-exposed groups compared to control. However, no significant differences were observed among the different exposure durations.
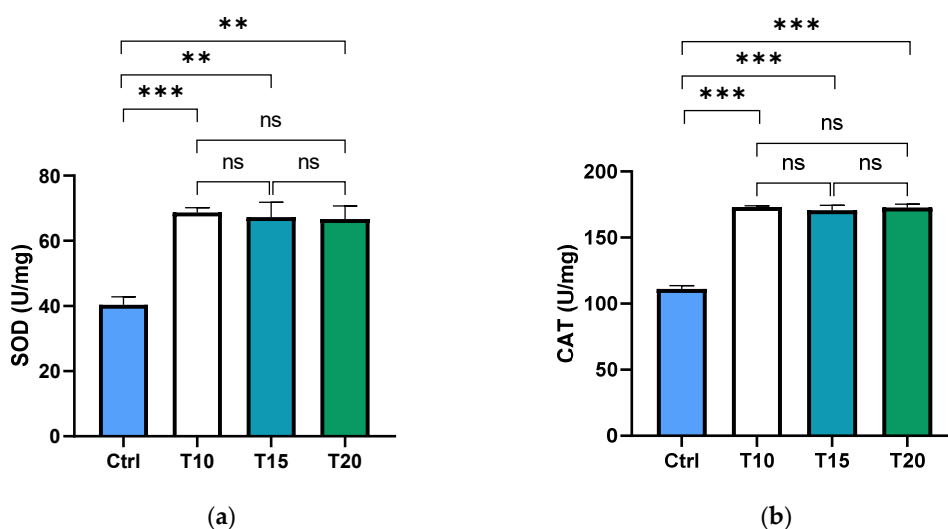

Figure 1. SOD (**a**) and CAT (**b**) activities were measured in the zebrafish eye supernatant of non-exposed (Ctrl) and aluminium-exposed for 10 (T10), 15 (T15) and 20 (T20) days fish. Data are presented as mean ± SD. Asterisks indicate statistically significant differences between the compared groups (**$p \leq 0.02$; ***$p < 0.001$); ns indicates not significant.

3.2. PARP and PARG Activities

PARP (Figure 2a) and PARG (Figure 2b) activities were assessed in eye homogenates from zebrafish either unexposed (Ctrl) or exposed to aluminium for 10, 15 and 20 days, in order to evaluate PAR synthesis and its degradation. Additionally, the percentage of PAR degradation was measured (Figure 2c). The highest PARP activity was observed at T10 (Figure 2a). Although enzyme activity decreased at T15 compared to T10, it remained significantly higher than the control level. By T20, PARP activity levels had returned to baseline and were comparable to those of the control group. PARG activity followed a similar pattern to PARP activity (Figure 2b). Across all eye homogenate samples, PAR degradation exceeded 95% (Figure 2c).
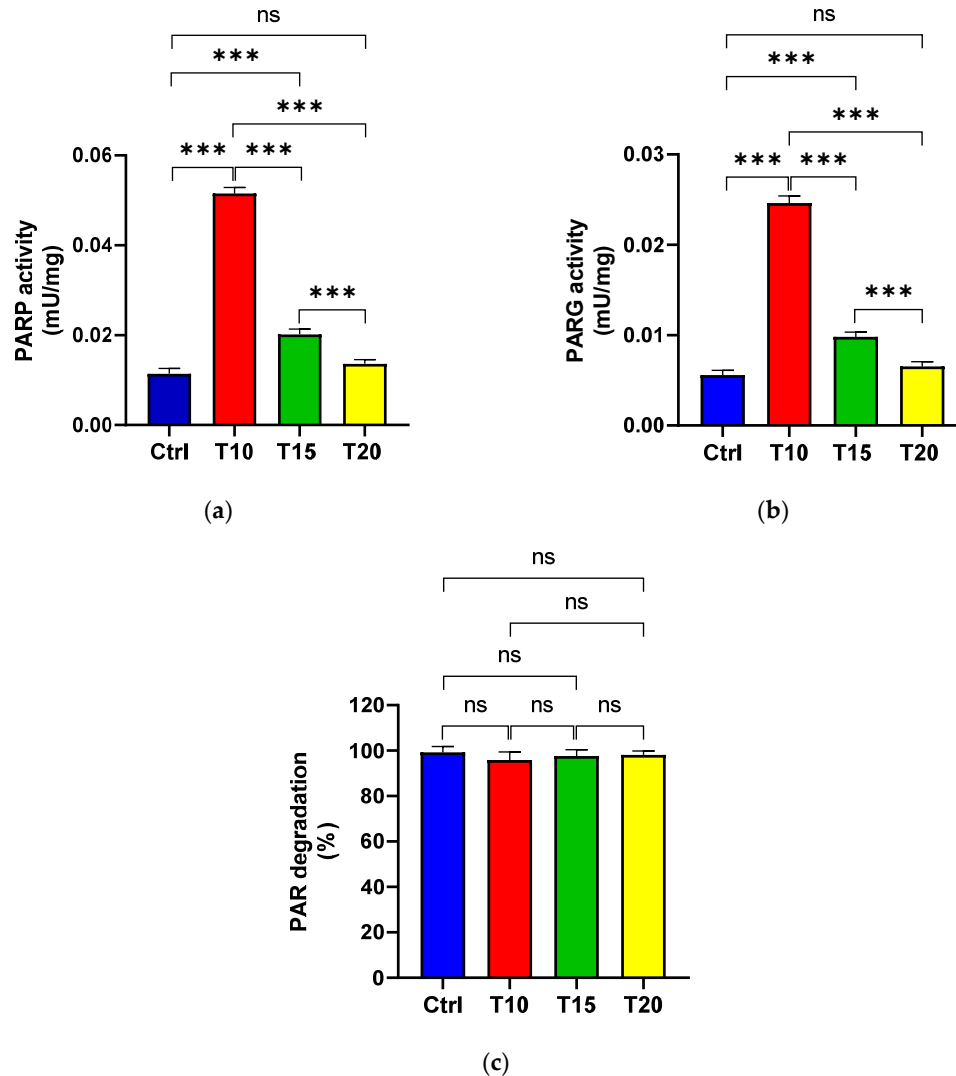

Figure 2. PARP (**a**) and PARG (**b**) activities, as well as the percentage of PAR degradation (**c**), were measured in zebrafish eyes from control (Ctrl) and aluminium-exposed groups at 10 (T10), 15 (T15), and 20 (T20) days. Data are presented as mean ± SD. Asterisks indicate statistically significant differences between the compared groups (**$p \leq$ 0.02; ***$p <$ 0.001); ns indicates not significant.

3.3. TLC of Poly(ADP-ribose) and Its Degradation Product

Purified [^{14}C]poly(ADP-ribose) (lines 2, 4 and 6) and its degradation product ([^{14}C]ADP-ribose) (lines 3, 5 and 7) by PARG were analysed via thin-layer chromatography. [^{14}C]NAD$^+$ (S1, line 1) and [^{14}C]ADP-ribose (S2, line 8) were used as nucleotide standards (Figure 3). The disappearance of the

radioactive signal at the TLC loading point and the simultaneous appearance of a signal co-migrating with the standard ADP-ribose were demonstrated in all analysed samples (Figure 3). These results indicated that the protein-free polymers were completely degraded to ADP-ribose.
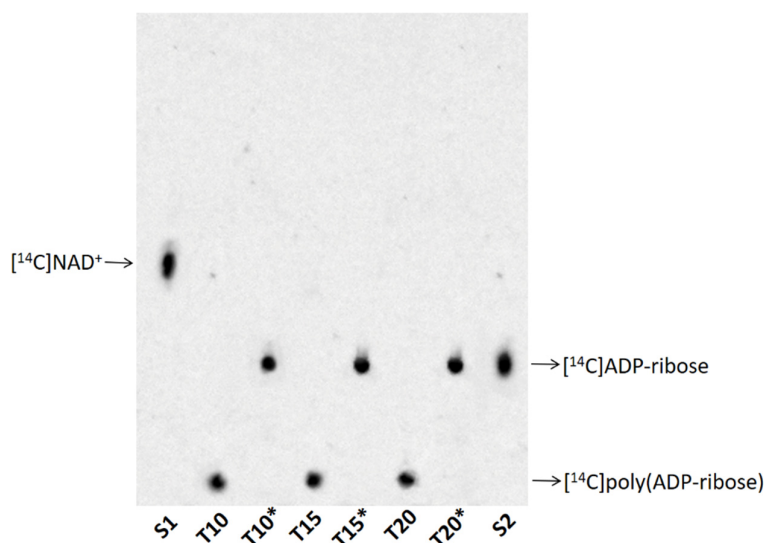

Figure 3. Protein-free [^{14}C]poly(ADP-ribose) (400 cpm) purified from eye homogenates exposed to Al for 10 (T10), 15 (T15) and 20 (T20) days and its degradation product (T10*, T15* and T20*) by PARG. Nucleotide standards were: [^{14}C]NAD$^+$ (400 cpm) (S1, line 1) and [^{14}C]ADP-ribose (400 cpm) (S2, line 8).

4. Discussion

Aluminium (Al) is one of the most abundant metals in nature and represents a significant environmental threat due to its ability to exert toxic effects on both terrestrial and aquatic organisms [70]. Numerous studies in fish have demonstrated that aluminium exposure can disrupt physiological functions [71], interfere with biochemical pathways [72], impair fertility [73], inhibit growth [74] and increase mortality [75].

In zebrafish embryos, aluminium exposure disrupts redox homeostasis and induces apoptosis [76]. In adult zebrafish, aluminium has been shown to cause histopathological alterations in muscle and gill tissues and to trigger neurodegenerative processes [77–79]. Our recent studies demonstrated that aluminium accumulation in the brain leads to oxidative DNA damage and modulates the poly(ADPribosyl)ation system [64]. A dynamic balance between poly(ADP-ribose) (PAR) synthesis and degradation was observed after 10 and 15 days of exposure. This regulation likely prevents excessive PAR accumulation, which acts as a trigger for parthanatos, a form of caspase-independent cell death associated with neuronal loss in several diseases [36,80]. Oxidative DNA damage has also been demonstrated in zebrafish eyes, where increased expression of PARP1 and PARP2 was observed after only 10 days of aluminium exposure. This suggests that genotoxic stress occurs before detectable histological damage, reinforcing the critical role of PARPs in maintaining genomic integrity [81]. Conversely, decreased PARP expression after 20 days of exposure indicated reinstated histological and molecular damage [63]. Given that oxidative stress, primarily through increased reactive oxygen species (ROS), is a major driver of DNA damage, the present study aimed to assess the activities of two key antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), in supernatants of zebrafish eyes following exposure to 11 mg/L Al for 10, 15, and 20 days. In parallel, PARP activity was measured in tissue homogenates to evaluate the DNA damage response. The marked increase in SOD, CAT, and PARP activities after 10 days of aluminium exposure supports the hypothesis that oxidative stress induces genotoxic DNA damage, triggering PARP activation. During this period, antioxidant enzymes attempt to mitigate ROS elevation but may be insufficient to fully prevent genotoxic stress, as reflected

by sustained PARP activation. This reinforces PARP's function as a DNA damage sensor involved in repair and genomic stability maintenance. At extended exposure durations (20 days), the observed reduction of PARP activity to control levels suggests cellular adaptation to aluminium toxicity, likely through energy conservation mechanisms that prevent depletion of NAD^+ and ATP pools [36]. Since PARP is a major intracellular energy consumer, downregulation of its activity supports the preservation of cellular energy homeostasis critical for survival [36,49].

In addition, PARG activity, responsible for hydrolysing PAR into ADP-ribose, was a measured too (Figure 3). The regulation of PARG across exposure times suggests its role in maintaining the equilibrium between PAR synthesis and degradation. This balance is crucial to avoid PAR overaccumulation, which would inhibit PARP activity and promote parthanatos [82].

5. Conclusions

For the first time, we report the presence of both poly(ADP-ribose) polymerase (PARP) activity, responsible for the synthesis of poly(ADP-ribose), and poly(ADP-ribose) glycohydrolase (PARG) activity, which mediates its degradation, in homogenates of zebrafish eyes following exposure to aluminium (11 mg/L) for 10, 15, or 20 days. The concurrent activation of the poly(ADPribosyl)ation pathway and elevated antioxidant enzyme activities observed at 10 days strongly suggests the occurrence of genomic damage resulting from oxidative stress. At later time points, we hypothesize that the resulting decrease in PARP activity is related to the maintenance of energy homeostasis, which allows cells to adapt to living exposure to aluminum.

Finally balance between PAR synthesis and degradation at every exposure time, would avoid PARP inhibition due to PAR accumulation and parthanatos induction.

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