

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. The ***Early Access*** service lets users access peer-reviewed articles well before print / regular issue publication, significantly reducing the time it takes for critical findings to reach the research community.
These articles are searchable and citable by their DOI (Digital Object Identifier).

The **Monaldi Archives for Chest Disease** is, therefore, e-publishing PDF files of an early version of manuscripts that have undergone a regular peer review and have been accepted for publication, but have not been through the typesetting, pagination and proofreading processes, which may lead to differences between this version and the final one.
The final version of the manuscript will then appear in a regular issue of the journal.

E-publishing of this PDF file has been approved by the authors.

All legal disclaimers applicable to the journal apply to this production process as well.

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
Alpay M, Yildiz P, Acat M, Sungur MA. **Circulating poly(ADP-ribose) levels in lung cancer: an exploratory study**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.4348

Submitted: 24-09-2026
Accepted: 30-10-2026

©The Author(s), 2026
Licensee PAGEPress, Italy

Note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries should be directed to the corresponding author for the article.
All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Circulating poly(ADP-ribose) levels in lung cancer: an exploratory study

Merve Alpay,[1] Pinar Yildiz,[2] Murat Acat,[3] Mehmet Ali Sungur[4]

[1]Deparment of Medical Biochemistry, Faculty of Medicine, Duzce University; [2]Deparment of Chest Diseases, Faculty of Medicine, Duzce University; [3]Department of Chest Diseases, Memorial Hospital, Duzce; [4]Department of Biostatistics, Faculty of Medicine, Duzce University, Turkey

Correspondence: Merve Alpay, Deparment of Medical Biochemistry, Faculty of Medicine, Duzce University, Konuralp Duzce, 81060, Turkey.
Tel.: (0090)5057878799. E-mail: mervealpay@duzce.edu.tr

Contributions: Merve Alpay, Pinar Yildiz: experiments concept and design. Merve Alpay: experiments performing. Murat Acat, Mehmet Ali Sungur: analysis and interpretation of experiments results. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that no conflict of interest.

Ethics approval and consent to participate: the study protocol was approved by the Ethical Review Committee of the University of Duzce Health Science Assoc. (protocol no. 192 dated 2025/11/10).

Informed consent: before being included in the study, all participants were informed about the purpose and scope of the research, and their written informed consent was obtained.

Patient consent for publication: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: Duzce University Hospital Biochemistry Laboratory was used in the analysis of the samples. The authors would like to thank the employees who contributed to the stages.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: during the writing process, generative artificial intelligence and AI-powered technologies were used solely for the purpose of refining the text in terms of grammar, expression, and academic tone; they were not employed in the development of scientific content, data analysis, interpretation, or the formulation of research findings.

Abstract

Poly(ADP-ribose) (PAR) is a polymer generated during poly(ADP-ribosyl)ation, a post-translational modification involved in cellular stress responses and DNA repair. Although PAR-related pathways have been investigated in cancer biology, the clinical significance of circulating PAR levels in patients with lung cancer remains insufficiently characterized. With this study, we investigate the serum levels of PAR in patients with lung cancer and compare them with healthy individuals to assess its potential role as a prognostic biomarker. Serum samples from 23 patients with primary lung cancer who had not received prior cancer treatment and 21 healthy controls were analyzed using a commercial ELISA-based assay. Group differences were evaluated, including an analysis adjusted for age. Our findings demonstrated that the mean serum PAR levels in lung cancer patients were approximately twofold higher compared to the control group ($p<0.05$). The elevated PAR levels observed in lung cancer patients suggest an upregulation of poly ADP-ribosylation activity, possibly as a response to increased genomic instability and cellular stress associated with tumor progression. This finding supports the hypothesis that PAR metabolism is actively involved in lung carcinogenesis and may serve as a valuable biomarker in evaluating disease prognosis. Our results indicate that PAR levels are significantly elevated in the serum of lung cancer patients compared to healthy individuals. However, the results do not establish the diagnostic accuracy, prognostic value, treatment-predictive capacity, or clinical utility of circulating PAR. Larger, well-characterized prospective studies incorporating clinical and molecular data and serial measurements are needed to validate this observation.

Key words: ADP, upregulated ribosylation, circulating biomarker, lung cancer.

Introduction

As the population ages, the predominant cause of human mortality has passed from infectious diseases to chronic conditions, with cancer emerging as a significant threat to public health. Among them malignant tumors, lung cancer holds the second-highest incidence, claiming the top in mortality. Despite notable progress in treatment strategies, the collective 5-year survival rate for lung cancer still stays below 20%. Squamous cell carcinoma and small cell lung cancer tend to have a higher likelihood of being centrally located in the lungs and are closely linked to a history of smoking, especially among men. However, lung tumor development appears to duration several decades after the initial exposure to carcinogens, indicating that the long latency period contributes to the delayed onset of the disease. Additionally, biological aging likely plays a significant role, as telomeres progressively shorten with age, NAD+ metabolite levels decline and cells lose their ability to effectively repair DNA damage and monitor abnormal cellular activity [1,2].

ADP-ribosylation stands as a complex biochemical phenomenon fundamental for cellular operations, its correlation with lung cancer has recently become focal point in scientific inquiry. This post-translational modification is characterized by the transfer of ADP-ribose component from nicotinamide adenine dinucleotide(NAD+) to target proteins, facilitated by ADP-ribosyltransferases(ARTs). Its significance rebound across various cellular functions, contains DNA repair, gene expression, stress responses and programmed cell death [3,4].

This complicated process involve the addition of ADP-ribose units onto specific amino acid residues of target proteins, thereby inducing alterations in their structure and function. Within this domain, Poly(ADP-ribose) polymerases (PARPs) emerge as a well-recognized family of enzymes catalyzing ADP-ribosylation, thus promote substantial influence on genomic stability and cellular equilibrium. Despite it was first heard ADP-ribosylation description in the early 1960s, our understanding of the complicated cellular processes governed by this modification remains in newly formed stages [5].

Within the area of cancer biology, the misregulation of ADP-ribosylation emerges as a contributing factor to the onset and advancement of various cancers, prominently including lung cancer. Characterized by uncontrollable cell growth within lung tissues, lung cancer is susceptible to shifts in cellular signaling pathways. Disruptions in ADP-ribosylation processes, showing by irregularities in PARP activity or imbalances in ART enzymes, can create deep effects on principal cellular mechanisms. These disruptions, in turn, contribute significantly to the initiation and progression of cancer in the lungs [6,7].

PARP inhibitors, initially crafted for their effectiveness in cancers characterized by deficient DNA repair, such as BRCA-mutated breast and ovarian cancers, have now emerged as a promising treatment modality for lung cancer. The main principle here is use of synthetic lethality, with this approach cancer cells which have defective DNA repair mechanisms was unable to resist accelerated damage caused by PARP inhibition. It's a powerful strategy that targets weaknesses of these cells, offering hope in the fight against cancer. By exploiting these vulnerabilities, we can turn the tide, transforming despair into a potential breakthrough for patients [4].

Furthermore, ongoing research aim to brighten the therapeutic potential of directly or indirectly modulating ADP-ribosylation pathways to inhibit the progression of cancer within lung tissues. By strategically targeting the enzymes responsible for ADP-ribosylation or manipulating the multi-step processes reliant on this modification, innovative treatment strategies may emerge as potent tools against lung cancer [8].

Posttranslational modifications (PTMs) play a crucial role for managing the functions and interactions of proteins. Among these modifications, ADP-ribosylation stands out as a significant process where ADP-ribosyltransferases utilize nicotinamide adenine dinucleotide (NAD+) to modify target proteins by attaching ADP-ribose. This modification can manifest in either mono- or poly-ADP-ribosylation forms. Secondary, involves the creation of extensive ADP-ribose chains, each given with distinct properties shaped by the characteristics of the polymer [9,10].

The control of ADPr network is vital. Dysregulation of the enzymes responsible for orchestrating ADP-ribose signaling has been implicated in various inherited and acquired human diseases. These encompass a spectrum of conditions, including neurological disorders and cancer, underlining the actual role that whole regulation of ADP-ribosylation plays in cellular health and disease states [11].

Lung cancer is the leading cause of cancer-related mortality, accounting for around 1.8 million deaths globally in 2020. Additionally, it ranks as the second most frequently diagnosed cancer, with approximately 2.2 million new cases reported. This corresponds to about 11.4% of all cancer diagnoses and 18.0% of cancer-related deaths worldwide [12,13].

The treatment of lung cancer encompasses diverse strategies, including conventional surgical resection, chemoradiotherapy, as well as innovative approaches such as targeted therapies and immunotherapy [14].

Lung cancer has remained the primary cause of cancer-related mortality for many years, largely due to its late-stage detection, limited treatment success, and widespread occurrence. Consequently, it is crucial to discover novel therapeutic targets and prognostic markers to improve lung cancer management [15].

The progression of lung cancer is governed by receptor activity on the cell membrane and intracellular signaling pathways. These signals regulate processes such as angiogenesis, motility, adhesion, and apoptosis in the cell. The incomplete elucidation of specific molecular abnormalities in lung cancer cells poses challenges in identifying critical insights for improving long-term survival outcomes in cancer patients. In recent years, significant efforts have been made to identify molecular alterations in lung cancer that could serve as potential drug targets. However, the truth that we encounter that curative targets have only been identified in approximately 20% of lung cancer cases. On a positive note, the clinical benefits achieved through targeted therapies are substantially greater than those obtained with chemotherapy [16].

Consequently, there is a critical need for the discovery and advancement of novel, efficient therapeutic approaches for addressing the challenges in treating lung cancer. As the outcome of this goal, focus treatment options that target the molecular pathways used of lung cancer by controlling Poly (ADP-Ribose).

Materials and Methods

The study included patients who presented to the Pulmonology Clinic of our hospital with a preliminary diagnosis of lung cancer, underwent biopsy, and were subsequently diagnosed with lung cancer but had not received any prior treatment (radiotherapy, immunotherapy, or chemotherapy). A total of 23 patients who provided informed consent, excluding pregnant individuals and those under the age of 30, were enrolled in the study. Additionally, a control group consisting of 21 healthy individuals with a comparable mean age was included. Ethical approval (2025/192) for the research was obtained.

Blood samples (minimum volume of 5 mL) were collected via venipuncture and placed in biochemical test tubes containing gel. After collection, the tubes were left to rest for 15 minutes and then centrifuged at 1800×g for 10 minutes. The serum was separated, then samples were stored at -20°C. Due to collection of fresh samples at varying time points, all serum samples were later transferred from -20°C to -80°C for long-term storage until the time of analysis.

Serum poly(ADP-ribose) (PAR) levels were measured using a commercially available human-specific Enzymatic Assay Kit (Cat. No: MBS169573, MyBiosource CA-US) following the manufacturer's protocol. Absorbance was measured at 460 nm using a BioTek Epoch microplate reader. Concentrations were calculated from the assay calibration curve using CurveExpert software version 1.4 and expressed in the units specified by the assay protocol. The measured analyte was circulating PAR. The assay did not directly quantify PARP protein abundance, PARP-specific enzymatic activity, intracellular PARylation, or PARP activity within tumor tissue.

Statistical analysis

Statistical analyses were performed using IBM SPSS v.22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) software. The normality assumption for continuous variables was assessed by the Shapiro-Wilk test, and the Levene test was used for the homogeneity of the variances. Groups were compared with the Independent samples t-test. A one-way ANOVA was conducted to examine a statistically significant difference between patient and control groups on ADP controlling for age. Continuous variables were expressed as mean±standard deviation. A p-value of <0.05 was considered for statistical significance level.

Results

Our examinated pattern have shown that PAR levels were significantly elevated in lung cancer patients (approximately 2 fold) compared to healthy controls suggesting a potential link between cancer and PAR upregulation mentioned in Figure 1. This means cancer cells with the high proliferation rate and increased oxidative stress result in more frequent DNA damage, which in turn leads to heightened PAR activation as part of the cellular response. Excessive activation of PAR has been implicated in promoting tumor survival by assist in DNA repair mechanisms, thereby allowing cancer cells to skip apoptosis and support their growth. The elevated PAR levels observed in lung cancer patients may therefore reflect an adaptive response of tumor cells to genomic instability, highlighting the potential of PAR inhibitors as therapeutic agents in targeting DNA repair pathways in lung cancer (Figure 2).

The mean age and ADPr levels in groups were reported in Table 1. There was a significant difference between the groups in age and ADPr levels ($p<0.001$). When means of the groups

adjusted for age, there was also a significant effect of CA on ADPr after controlling for age (p=0.004).

Discussion

ADP-ribosylation, a fundamental mechanism driving cellular signaling, emerges as a significant possibility in unraveling the complexities of lung cancer. PAR is a polymer generated during poly(ADP-ribosyl)ation, a process involved in cellular responses to DNA damage and other forms of stress. PARP enzymes contribute to this process, and PARP-related pathways have been investigated as potential therapeutic targets in selected cancer settings. These established intracellular mechanisms provide a biological rationale for investigating PAR-related molecules in cancer research. Nevertheless, the present study measured PAR in serum and did not assess PARP protein expression, enzyme activity, intracellular PARylation, or PAR levels in tumor tissue. Therefore, the higher circulating PAR concentration observed here cannot be interpreted as direct evidence of increased PARP activity, enhanced tumor-cell auto-PARylation, or a specific DNA repair response in lung cancer [17,18].

The findings of this study should be interpreted in the context of its exploratory design. The study included 23 patients with lung cancer and 21 healthy controls. Although the sample size was relatively limited, it allowed us to perform an initial comparison of circulating poly(ADP-ribose) (PAR) levels between the two groups. Patient information was coded during the study to maintain confidentiality. The primary objective was to determine whether circulating PAR levels differed significantly between patients with lung cancer and healthy individuals, rather than to establish its diagnostic or prognostic value.

PAR levels were measured at a single pretreatment time point and compared between the groups. This approach provided an initial assessment of the potential association between circulating PAR levels and lung cancer status. However, the study was not designed to assess longitudinal changes in PAR levels, monitor treatment response, or investigate associations with disease progression or survival. Further studies incorporating serial measurements and clinical follow-up may help clarify the potential relevance of circulating PAR in these contexts.

In addition, more detailed clinical characterization, including histological subtype, tumor stage, and molecular profile, would allow a more comprehensive evaluation of the findings. Information on potential confounding factors, such as smoking status, comorbidities, and systemic inflammation, may also help refine the interpretation of between-group differences in future studies. Despite these considerations, the present findings provide preliminary data

that may support further investigation of circulating PAR levels in larger and more clinically characterized populations.

Therapeutic manipulation of ADPr has been shown to improve outcomes in various disease models in both humans and animals. It encompasses models ranging from cardiovascular and inflammatory disorders to autoimmune and neurological conditions. Considering the diverse potential of PARP inhibitors currently in clinical development, the degree of PARP inhibition necessary for optimal therapeutic efficacy and the extent to which off-target effects beyond PARP inhibition influence antitumor activity remain uncertain [19].

The clinical development of PARP inhibitors has predominantly centered on their use as chemosensitizers in combination with agents such as alkylating drugs, topoisomerase inhibitors, platinum compounds, and anthracyclines. When combined with chemotherapy, drugs like rucaparib, olaparib, and veliparib have been linked to heightened myelosuppression. This prompts the question of whether the inclusion of PARP inhibitors might enhance therapeutic outcomes even with reduced doses of chemotherapy. In a cohort of 48 assessable patients, the highest tumor response rates were observed in 37.5% of individuals with non-small cell lung cancer and 52.9% of those with breast cancer. Notably, unlike the increased myelosuppression seen with chemotherapy, no additional toxicity was reported, suggesting that this strategy warrants further exploration [20].

The ineffectiveness of current treatment strategies can largely be attributed to the evolution of drug resistance, which is linked to various factors including gene mutations, the presence of cancer stem cells, increased expression of oncogenes, and the deletion or inactivation of tumor suppressor genes. Current cancer treatment methods, including surgery and chemotherapy, fall short of being ideal approaches, particularly for tumors with high mortality rates, given the diversity of mutations exhibited by most tumors. In the context of tumor progression, where molecular mechanisms operate in a highly sophisticated and dynamic manner, RNA-based therapeutic strategies, due to their wide target range and drug-like characteristics, hold the potential to outperform conventional targeted therapies, including those aimed at protein drug targets. At the molecular scale, the complex interplay of cellular responses is directed by proteins and small molecules [21-23].

Conclusions

Normal cells possess mechanisms to protect themselves from the destructive effects of DNA damage, ensuring the maintenance of genomic stability. This stability is achieved through

various cellular processes, including DNA damage signaling regulation, recruitment of DNA repair effector proteins, chromatin remodeling, and the stabilization of transcription and replication bifurcates. However, in cancer cells, the stability is compromised. Based in lung cancer, genes frequently is mutated and contributing to tumor progression include ATM, BRCA2, ARID1, CHEK2, BRCA1, ATR, RAD50, and MSI. To address this genetic instability, PAR binds to damaged DNA sites, triggering its catalytic activity, which leads to chromatin relaxation. Auto-PARylation of PARP facilitates its release from DNA, allowing repair proteins to access the damaged site and complete the repair process. Similar to the PAR levels in different types of cancer, our study indicates that individuals with lung cancer exhibit increased ADPr levels compared to healthy controls, suggesting heightened auto-PARylation activity. This finding highlights the potential need for the development and enhancement of poly(ADP-ribosyl)ation-based therapeutic interventions. However it is not known whether this level stimulates the gene module in which DNA fragment to target proteins during tumor progression, causes genetic instability or mutates it. The further level of this study is to determine the gene damaged in DNA signaling mechanism in the same patient group and explain its relationship with PAR.

References

1. Thandra KC, Barsouk A, Saginala K, et al. Epidemiology of lung cancer. Contemp Oncol 2021;25:45-52.
2. Zhang Y, Wang DC, Shi L, et al. Genome analyses identify the genetic modification of lung cancer subtypes. Semin Cancer Biol 2017;42:20-30.
3. Liu Q, van der Marel GA, Filippov DV- Chemical ADP-ribosylation: mono-ADPr-peptides and oligo-ADP-ribose. Org Biomol Chem 2019;17:5460-74.
4. Aimi F, Moch H, Schraml P, Hottiger MO. Cytoplasmic ADP-ribosylation levels correlate with markers of patient outcome in distinct human cancers. Mod Pathol 2021;34:1468-77.
5. Albert JM, Cao C, Kim KW, et al. Inhibition of poly(ADP-ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models. Clin Cancer Res 2007;13:3033-42.
6. Guo MZ, Marrone KA, Spira A, Scott SC, et al. Poly(ADP-Ribose) polymerase inhibition in small cell lung cancer: a review. Cancer J 2021;27:476-81.
7. Barayan R, Ran X, Lok BH, et al. PARP inhibitors for small cell lung cancer and their potential for integration into current treatment approaches, J Thorac Dis 2020;12:6240-52.

8. Olivares-Hernández A, Roldán-Ruiz J, Miramontes-González JP, et al. Efficacy and safety of PARP inhibitor in non-small cell lung cancer: a systematic review with meta-analysis. Chin Clin Oncol 2023:12:62.

9. Poltronieri P, Miwa M, Mautani M. ADP-ribosylation as post-translational modification of proteins: use of inhibitors in cancer control. Int J Mol Sci 2021:22:10829.

10. Ummarino S, Hausman C, Di Ruscio A. The PARP way to epigenetic changes. Genes 2021;12:446.

11. Fernandes MP, Oliveira C, Sousa H, Oiveira J. New approaches in early-stage NSCL management: potential use of PARP inhibitors and immunotherapy combination. Int J Mol Sci 2023;24:4044.

12. Liu L, Chen G, Gong S, et al. Targeting tumor-associated macrophage: an adjuvant strategy for lung cancer therapy. Front Immunol 2023;14:1274547.

13. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.

14. Lahiri A, Maji A, Potdar PD, et al. Lung cancer immunotherapy: progress, pitfalls, and promises. Mol Cancer 2023;22:40.

15. Freeman B, Mamallapalli J, Bian T, et al. Opportunities and challenges of Kava in lung cancer prevention. Int J Mol Sci 2023;24:9539.

16. Politi K, Herbst RS. Lung cancer in the era of precision medicine. Clin Cancer Res 2015;21:2213-20.

17. Gupte R, Liu Z, Kraus WL. PARPs and ADP-ribosylation: recent advances linking molecular functions to biological outcomes. Genes Dev 2017;31:101-26.

18. Dulaney C, Marcrom S, Stanley J, Yang ES. Poly(ADP-ribose) polymerase activity and inhibition in cancer. Semin Cell Dev Biol 2017;63:144-53.

19. Do K, Chen AP. Molecular pathways: targeting PARP in cancer treatment. Clin Cancer Res 2013;19:977-84.

20. Yang G, Chen Y, Wu J, et al. Poly(ADP-ribosyl)ation mediates early phase histone eviction at DNA lesions. Nucleic Acids Res 2020;48:3001-13.

21. Gibson BA, Kraus WL. New insights into the molecular and cellular functions of poly(ADP-ribose) and PARPs. Nat Rev Mol Cell Biol 2012;13:411-24.

22. Kim DS, Challa S, Jones A, Kraus WL. PARPs and ADP-ribosylation in RNA biology: From RNA expression and processing to protein translation and proteostasis. Genes Dev

2020;34:302-20.

23. Martin-Hernandez K, Rodriguez-Vargas JM, Schreiber V, Dantzer F. Expanding functions of ADP-ribosylation in the maintenance of genome integrity. Semin Cell Dev Biol 2017;63:92-101.

Table 1. Age distribution and PAR levels: a comparative assessment.

	Patient (n=23)	Control (n=21)	p
Age	65.96±9.12	43.71±16.24	<0.001
PAR	0.3137±0.0633	0.2411±0.0357	<0.001

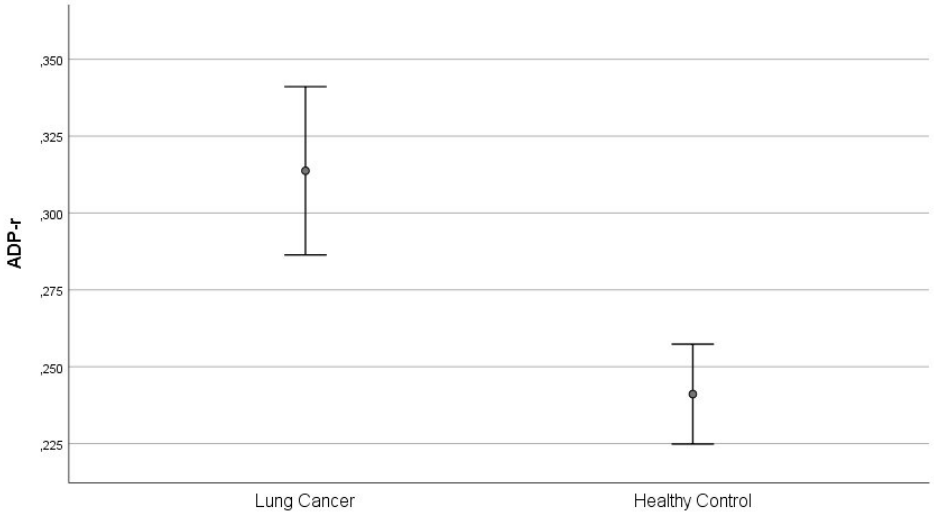


Figure 1. Circulating ADPr Levels in lung cancer patients: comparison with healthy controls.

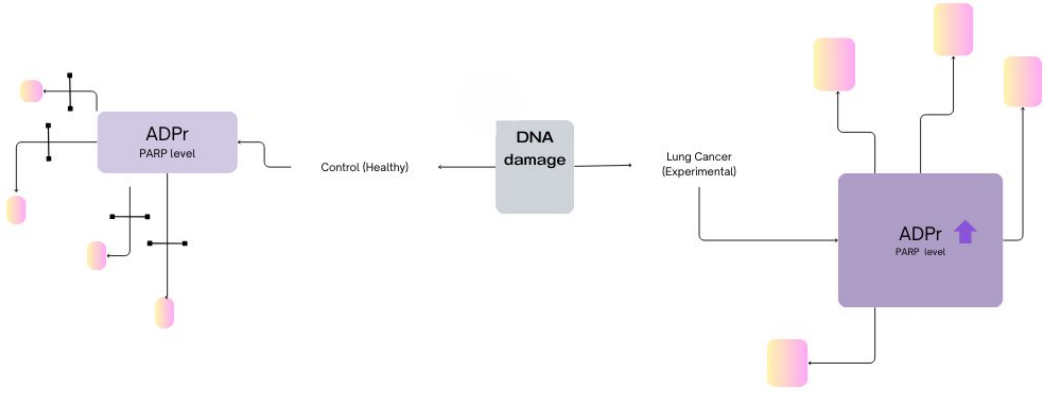


Figure 2. PAR signaling and their implications in cancer-related genomic instability.