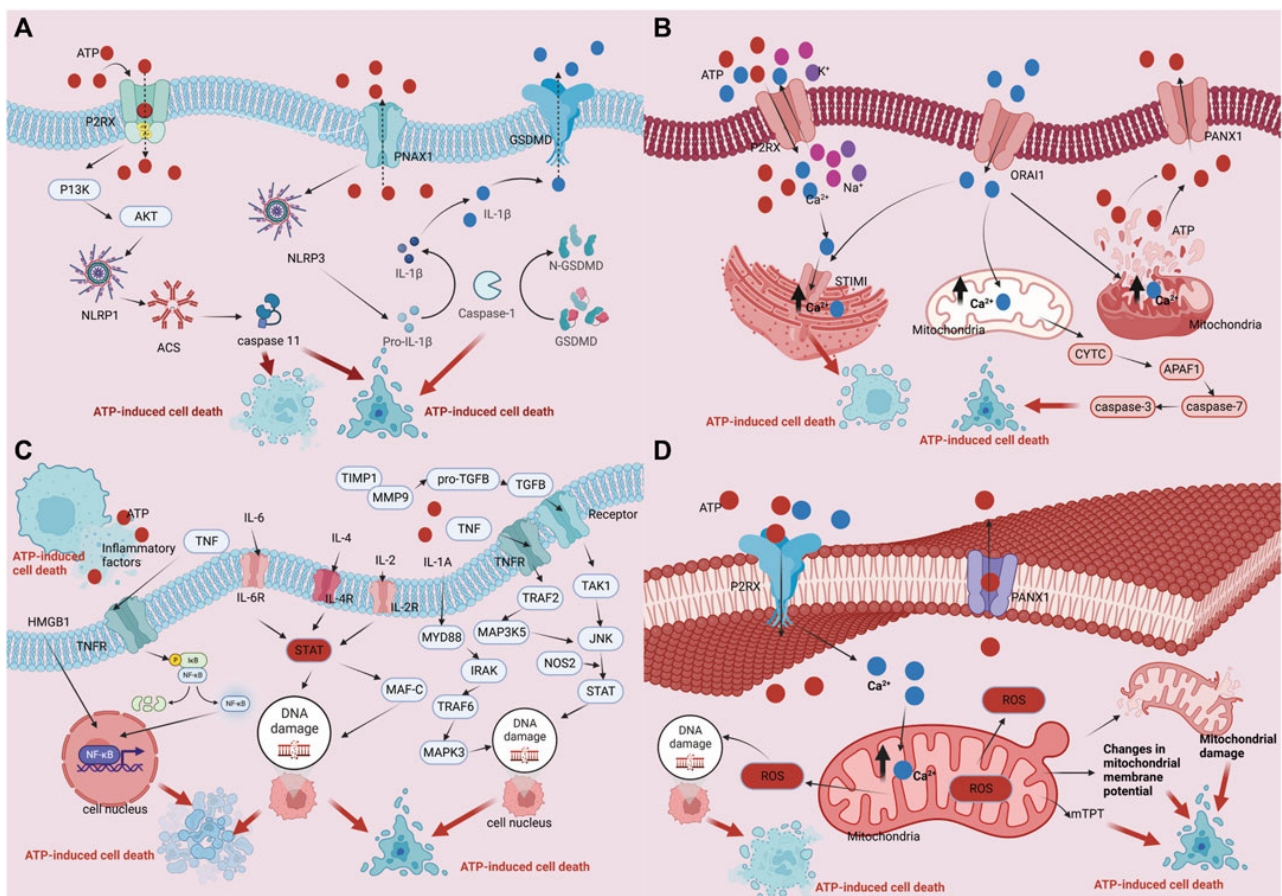


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Graphical Abstract



ATPexGen: ATP-induced cell death database

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Abstract: ATPexGen aims to establish a comprehensive database dedicated to ATP-induced cell death, addressing a critical gap in biomedical research. While ATP is the primary energy source for cells, its role in regulating cell death remains underexplored. Existing databases lack the systematic and detailed data required to support advanced research in this area. ATPexGen will integrate cutting-edge experimental data and literature, creating a multi-dimensional information platform to enhance understanding of ATP's role in cell death mechanisms. This platform will not only advance fundamental research but also facilitate drug development and therapeutic innovations. Given the global prevalence of cell death-related diseases, the development of ATPexGen is both urgent and impactful, offering robust support and valuable references for advancing research and clinical applications in this critical field.

Key words: ATPexGen; ATP-induced cell death; Database; Gene silencing; CTD; BioGRID.

Introduction

The ATPexGen project aims to build a comprehensive database dedicated to ATP-induced cell death, highlighting ATP's pivotal role in this process. The project encompasses key components such as data integration and standardization, mechanistic analysis, user platform development, and application promotion. By providing an efficient and comprehensive information platform, ATPexGen seeks to support researchers in exploring the mechanisms underlying ATP-induced cell death [1-4]. This integrated resource will facilitate significant advancements in both fundamental research and clinical applications, fostering progress in related scientific and medical fields [5-7].

To achieve its objectives, ATPexGen will actively collaborate with experts in biomedicine and drug development, fostering the application of data and the translation of research findings. The project aims to deepen understanding of ATP's role in cell death, providing novel insights for treating related diseases and driving advancements in the biomedical field. By bridging scientific research, drug development, and clinical application, ATPexGen seeks to accelerate progress in translational medicine, paving the way for innovative therapies and improved healthcare outcomes.

ATP-induced Cell Death Signaling

ATP-induced cell death manifests as either apoptosis or necrosis, each characterized by distinct morphological and biochemical features influenced by factors such as cell type, ATP concentration, and environmental conditions. Apoptosis is marked by cellular shrinkage, loss of cellular connectivity, mitochondrial membrane potential damage, cytochrome C (CYTC) release, nucleolar fragmentation, and DNA degradation into fragments of 180–200 base pairs. Apoptotic bodies are formed without inducing inflammation, as they are phagocytosed by surrounding cells. In contrast, necrosis is characterized by increased membrane permeability, cellular swelling, organelle deformation, rupture, and subsequent inflammatory responses. Following necrosis, tissue healing often results in fibrosis and scar formation. The mode of ATP-induced cell death is determined by a combination of cellular and environmental factors (Figure 1-4), primarily including: (A) activation of membrane-bound purinergic P2 receptors; (B) Ca²⁺ signaling pathways that induce cell death; (C) ATP-induced release of immune-inflammatory factors, which activate immune pathways; and (D) ATP-induced loss of mitochondrial membrane potential, disruption of mitochondrial integrity, production of reactive oxygen species (ROS), and alterations in mitochondrial membrane permeability, all of which contribute to cell death[1-7].

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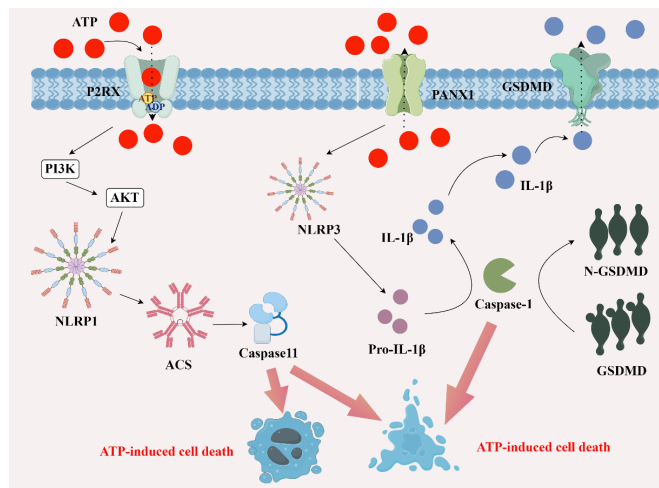


Figure 1. P2 receptor activation pathway

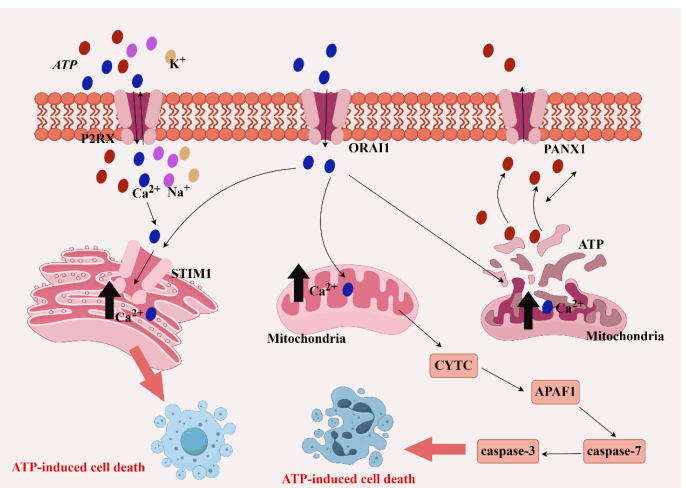


Figure 2. Ca²⁺ pathway induces cell death pathways

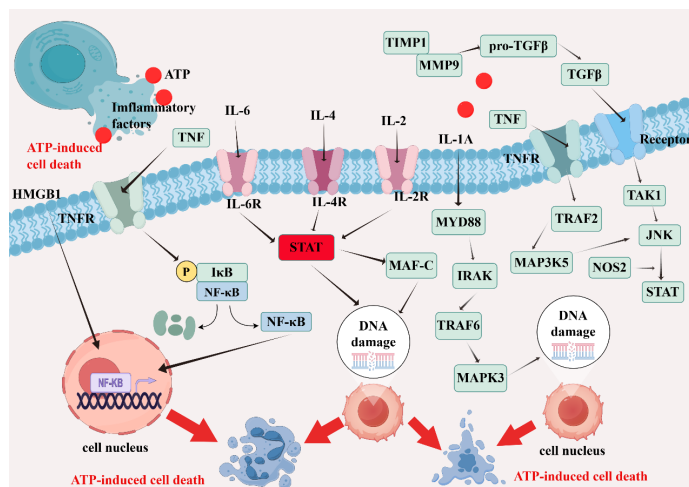


Figure 3. ATP triggers the release of immune-inflammatory factors from cells, activating immune pathways

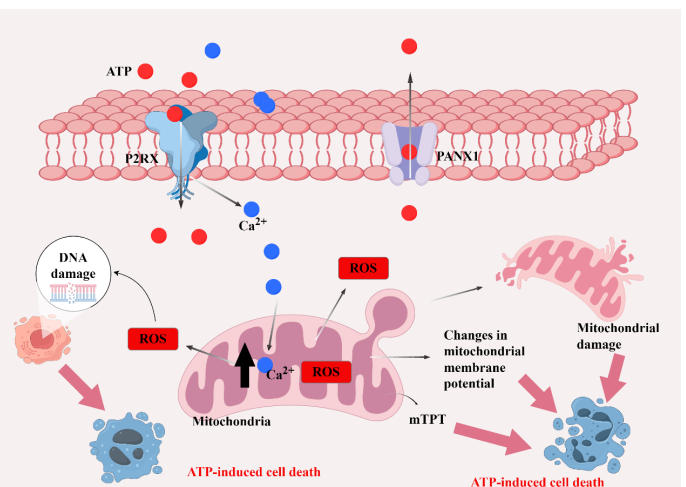


Figure 4. ATP causes the loss of mitochondrial membrane potential, the disruption of mitochondrial integrity, the production of ROS and alterations in mitochondrial membrane permeability, collectively leading to cell deaths

Main Functions of Database

ATPexGen is the world's first dedicated database focusing on ATP-induced cell death regulators and their associations with diseases. It categorizes ATP-induced cell death regulators into two main groups: (1) genes and (2) substances. Gene regulators include drivers, suppressors, markers, and unclassified regulators. Substance regulators encompass a diverse array of chemical entities, ranging from pure substances (e.g., ATP analogs, small molecule inhibitors) to mixtures (e.g., synthetic compounds, natural product extracts). These are further classified as inducers or inhibitors of ATP-induced cell death. Built on this framework, ATPexGen comprises seven independently curated datasets, offering a comprehensive resource for advancing research in this emerging field.

Gene Silencing

CRISPR-Cas9 technology is a powerful and efficient gene-

editing tool vital for functional genomics research. The GeCKO v2 library, developed by Feng Zhang's team and available via Addgene (IDs: #1000000048, #1000000049), comprises 123,411 gRNAs targeting approximately 19,050 human genes. This library enables high-throughput screens to identify key genes involved in biological processes and diseases by precisely disrupting target genes. Its accuracy and scalability make CRISPR particularly well-suited for studying complex genetic networks, especially in cancer research ([Supplementary material: Table 1](#)). Part of the show (see: <https://grswsci.top/ATPexGen/>).

RNA interference (RNAi) employs small RNA molecules to silence genes and is a widely used tool in biological research. Moffat et al. developed lentiviral shRNA libraries targeting transcription factor regulators, available through the GPP Web Portal. These shRNAs reduce mRNA expression, lowering protein levels and inhibiting target gene function. Unlike CRISPR, RNAi offers a reversible approach to gene regulation,

making it particularly suited for time-dependent or long-term studies. Part of the show (see: <https://grswsci.top/ATPexGen/>).

CTD

The Comparative Toxicogenomics Database (CTD) is a comprehensive, publicly accessible resource designed to enhance understanding of how environmental exposures impact human health. It offers manually curated data on chemical–gene/protein interactions, integrated with functional and pathway information. This integration supports hypothesis generation regarding the mechanisms driving environmentally influenced diseases ([Supplementary material:Table 2](#)). Part of the show (see: <https://grswsci.top/ATPexGen/>).

BioGRID

The Comparative Toxicogenomics Database (CTD) incorporates gene–gene and protein–protein interaction data from BioGRID([Supplementary material:Table 3](#)).Part of the show (see: <https://grswsci.top/ATPexGen/>).

Primer Design

ATPexGen contains primers for all genes, which can be referenced in later experiments ([Supplementary material: Table 4](#)).

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Author Contributions

Wei Wang was responsible for drafting the primary manuscript and conducting the data analyses;Yanfei Wang, Xuqiang Yang, Rui Zhao, DOBLIN SANDAI were involved in the data collection, and preparation of tables and charts, ZhiJing Song,HaoLing Zhang, Rui Zhao had pivotal roles in the research design, guiding the research group, and orchestrating the collaborative efforts of all authors; ZhiJing Song and HaoLing Zhang gave detailed guidance on the paper; All authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

The research did not involve any human participants or animals, and therefore did not require approval from an ethics committee. All data used in this study were obtained from publicly available sources and were analyzed in accordance with ethical guidelines and regulations.

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Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

All data needed to evaluate the conclusions in the paper are present in the paper or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

References

- [1] Wang, W., Zhang, H., Sandai, D., Zhao, R., Bai, J., Wang, Y., et al.(2023). ATP-induced cell death: a novel hypothesis for osteoporosis. *Frontiers in cell and developmental biology*, 11, 1324213.<https://doi.org/10.3389/fcell.2023.1324213>
- [2] HL Zhang, D Sandai, ZW Zhang, ZJ Song, D Babu, Y Tabana,, et al. (2023). Adenosine triphosphate induced cell death: Mechanisms and implications in cancer biology and therapy. *World journal of clinical oncology*, 14(12), 549. <https://doi.org/10.5306/wjco.v14.i12.549>
- [3] HL Zhang, S Doblin, ZW Zhang, ZJ Song, B Dinesh, Y Tabana,, et al. (2024). Elucidating the molecular basis of ATP-induced cell death in breast cancer: Construction of a robust prognostic model. *World Journal of Clinical Oncology*, 15(2), 208. <https://doi.org/10.5306/wjco.v15.i2.208>
- [4] Zhang H, Sandai D, Zhang Z,Song Z,Zhang H, Zhao R,et al.(2023). ATP-induced cell death mechanism. *Int J Biol Life Sci*, 4, 15-6.
- [5] W Wang, XM Wang, HL Zhang, R Zhao, Y Wang, HL Zhang, et al. (2024). Molecular and metabolic landscape of adenosine triphosphate-induced cell death in cardiovascular disease. *World Journal of Cardiology*, 16(12), 689. <https://doi.org/10.4330/wjc.v16.i12.689>
- [6] Z Zhang, H Zhang, Z Zhang, D Sandai, P Lu, H Zhang, et al. (2024). Identification and validation of mRNA profiles linked to ATP-induced cell death represent a novel prognostic model for breast cancer. *Frontiers in Immunology*, 15, 1483498. <https://doi.org/10.3389/fimmu.2024.1483498>
- [7] H Zhang, H Zhang, R Zhao, D Sandai, Z Song, Z Zhang, et al. (2024). ATP Cellotoxicity, ATP-Induced Cell Death and ATP Depletion[J]. *International Journal of Public Health and Medical Research*, 1(2): 35-38