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ZINC-BINDING DOMAIN EVOLUTION: NOVEL TARGETS IN APOPTOSIS

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Introduction. Zinc (Zn) is an essential trace element functioning as a crucial cofactor for a wide range of cellular proteins, including structural proteins and transcription factors. In malignant cells, Zn has a complex, cell-type-specific role in regulating apoptosis, acting either as a potent inducer or a protective agent depending on cellular homeostasis. This study explores the evolutionary trajectory of Zn-binding structural domains and their biochemical mechanisms in preventing abnormal cell survival through homeostatic regulation.

Materials and Methods. A systematic literature review was conducted to synthesize existing biochemical and bioinformatic data on Zn-induced apoptotic pathways. The study reviewed published computational models based on Zn-binding site prediction algorithms, such as the Geometric REstriction for Zn-binding (GRE4Zn). Additionally, existing comparative data regarding the distribution of 3-residue and 4-residue Zn-binding sites across evolutionary lineages (*Escherichia coli, Saccharomyces cerevisiae*, and *Homo sapiens*) were evaluated to trace their functional adaptation.

Results. The evaluated literature demonstrates that 3-residue and 4-residue Zn-binding sites maintain strict, phylogenetically conserved coordination geometries essential for protein stability. Evolutionary mapping shows a transition where these metal-binding motifs expanded from basic metabolic enzymes in prokaryotes to complex regulatory networks in eukaryotes. Biochemically, the precise spatial arrangement of coordinating residues, specifically cysteine and histidine, stabilizes the tertiary structure of core apoptotic regulators like the tumor suppressor protein p53 core domain. Under optimal Zn homeostasis, these conserved structural motifs preserve the conformational integrity required to trigger programmed cell death. Conversely, disruptions in Zn concentration or mutations within these geometric domains destabilize metal coordination, leading to protein misfolding and a subsequent failure to prevent pathological cell survival.

Conclusions. The evolutionary development of Zn-binding domains underscores their fundamental structural necessity in programmed cell death. Synthesizing data on these conserved geometric sites, while simultaneously accounting for cell-type-specific Zn homeostasis, highlights a highly specific biochemical strategy for preventing abnormal cellular proliferation.

Keywords: Zinc-binding domains, apoptotic regulation, computational biology, molecular evolution, Zn homeostasis.

[1] Kogan, S. & Carpizo, D.R. (2018). Zinc Metallochaperones as Mutant p53 Reactivators: A New Paradigm in Cancer Therapeutics. Cancers. 10(6). 166. 10.3390/cancers10060166. https://doi.org/10.3390/cancers10060166

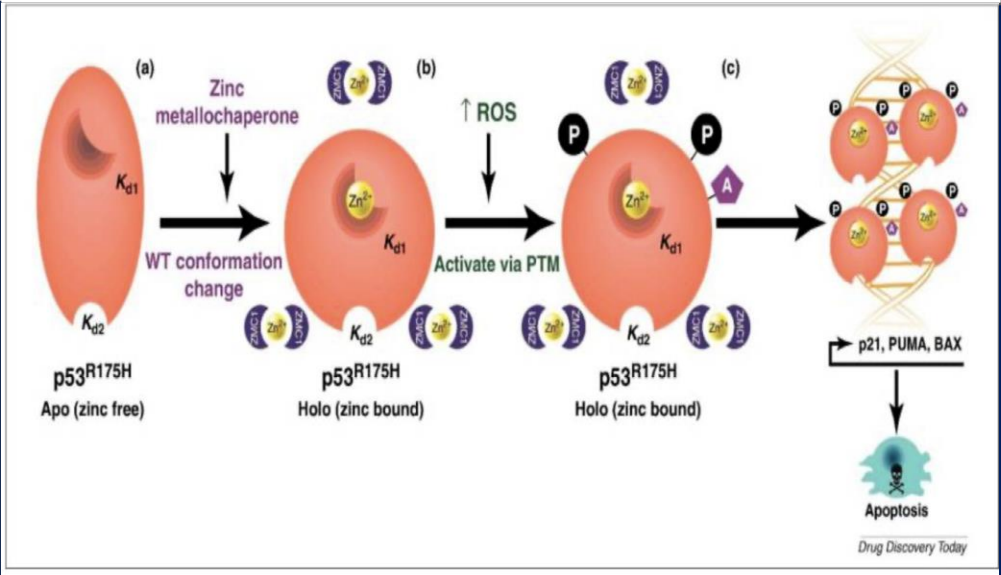

Fig.1. Loss of Zn^{2+} coordination leaves the p53 core domain misfolded and transcriptionally inactive; restoring zinc to the native ligation site recovers the wild-type conformation and the apoptotic programme.[1].

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