

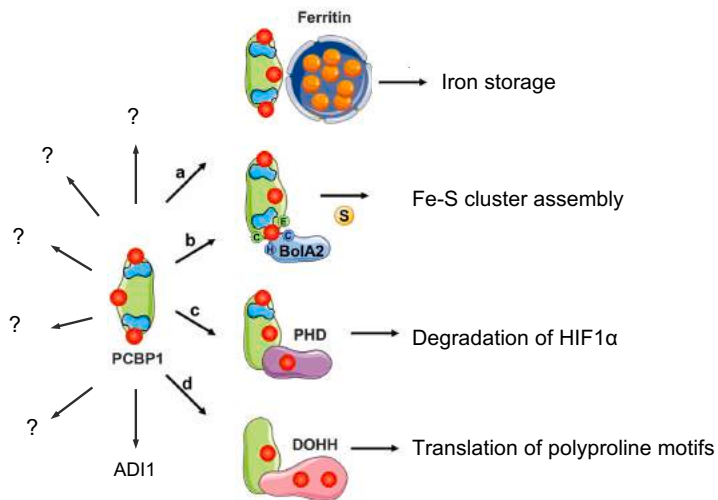
Analysis of the iron chaperone PCBP1 interactome: intersection of DNA repair and iron trafficking

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1. Iron is essential but toxic

Iron is used as an essential cofactor by several enzymes involved in DNA replication and repair. However, unchaperoned iron promotes redox stress that may affect DNA stability.

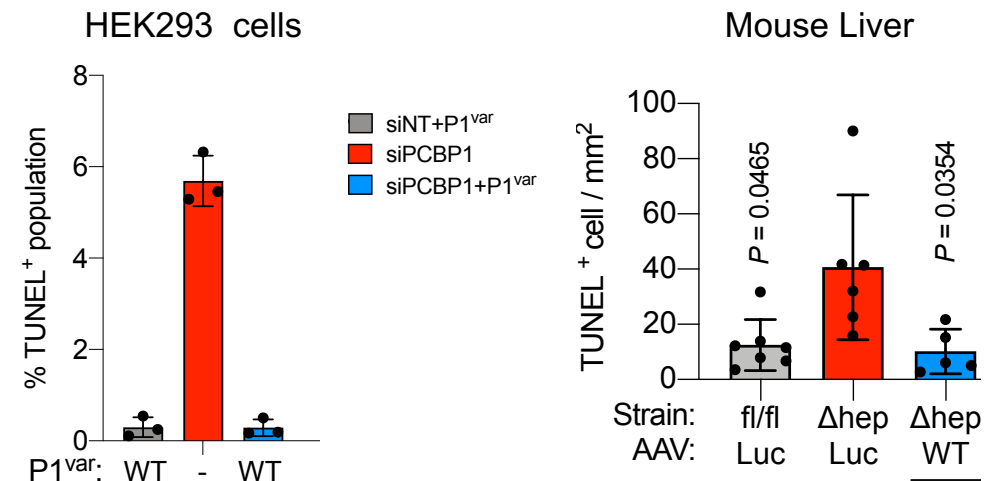


Mammals use the iron chaperone **PCBP1** to metalate several iron-dependent enzymes

Philpott, CC, et al. BBA - Molecular Cell Research (2020)

2. Increased DNA damage in cells lacking PCBP1

- Increased TUNEL⁺ in cells and tissue livers from mice lacking PCBP1.
- PCBP1 binds both, iron and single-stranded nucleic acids.
- The iron binding activity of PCBP1 controls suppression of DNA damage

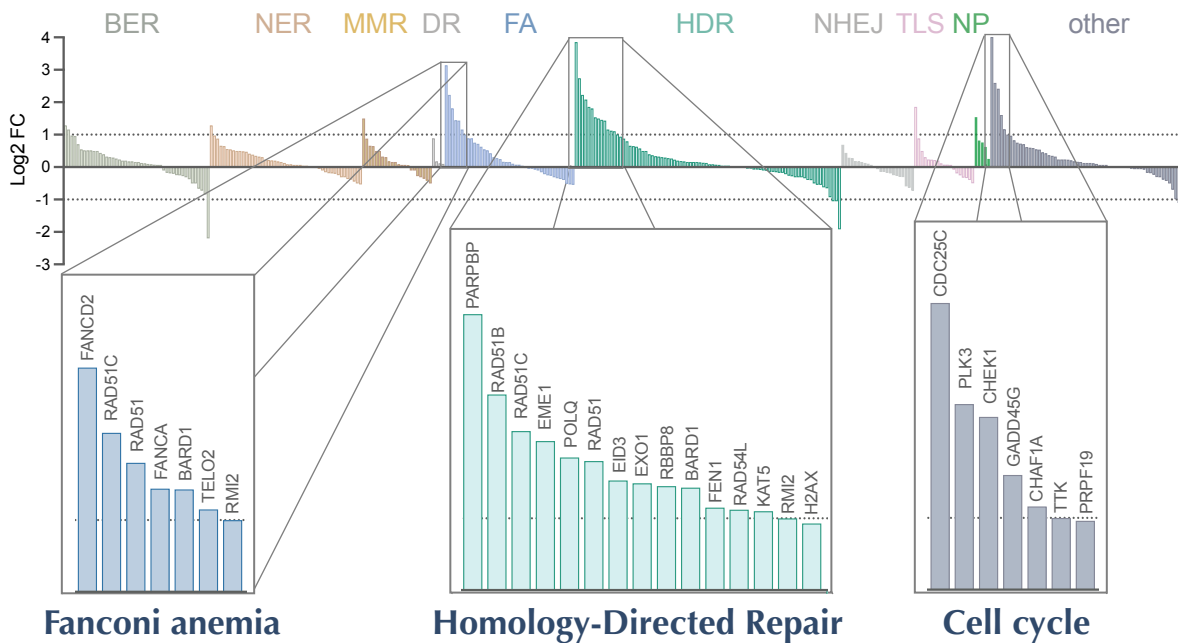


Sarju, P. et al. PNAS (2021)

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3. DNA repair pathways upregulated in PCBP1 mutant

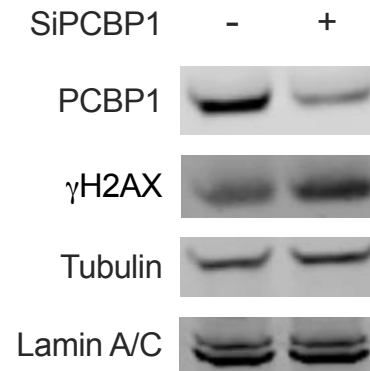
Transcriptomic analysis of PCBP1 depleted livers (RNA-Seq, KO vs WT) :



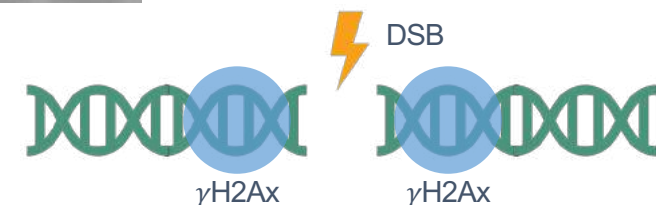
Genes from the Fanconi anemia, homology-directed DNA repair pathways, and cell cycle control were upregulated in PCBP1 depleted livers

4. Increased rate of DSBs on cells lacking PCBP1

- The CHK1 sensor (required for checkpoint-mediated activation of DNA damage response DDR), and the histone H2AX (early responder upon DNA double-strand break (DSB) occurrence) were upregulated.
- DSBs trigger phosphorylation of H2AX producing γ H2AX.
- Increased levels of γ H2AX suggest that DSBs occur in cells lacking PCBP1.

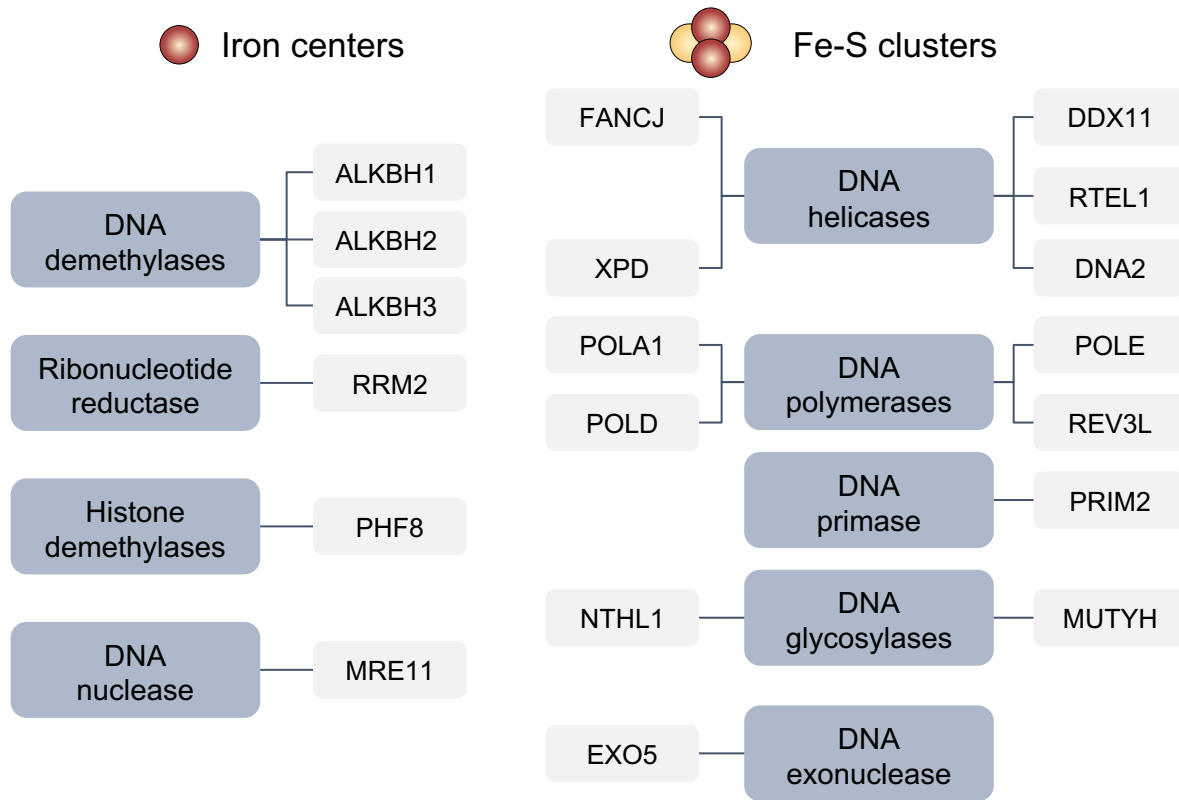


- DSBs are the most deleterious DNA lesions.
- Does PCBP1 play a role in the maintenance of enzymes involved in DDR that need iron for function?



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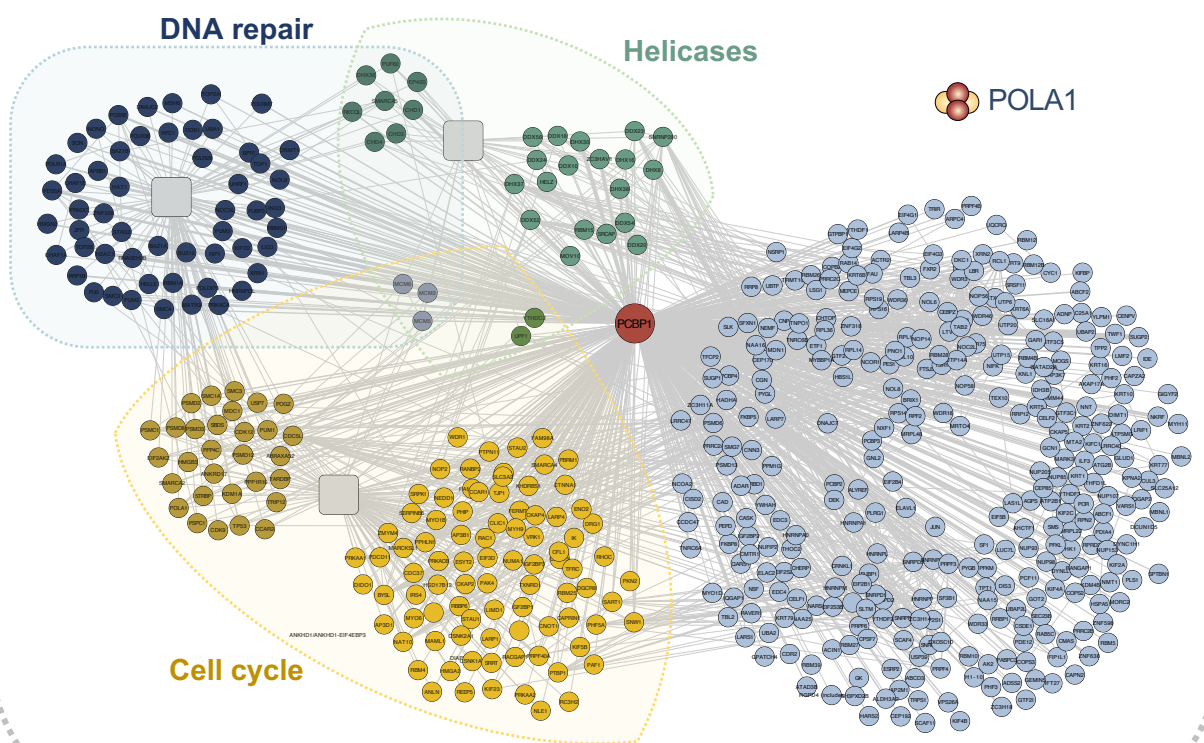
5. Several proteins involved in DDR use iron for function



The goal is to elucidate the relationship between DDR, iron metabolism, and PCBP1

6. Exploring PCBP1 interactome

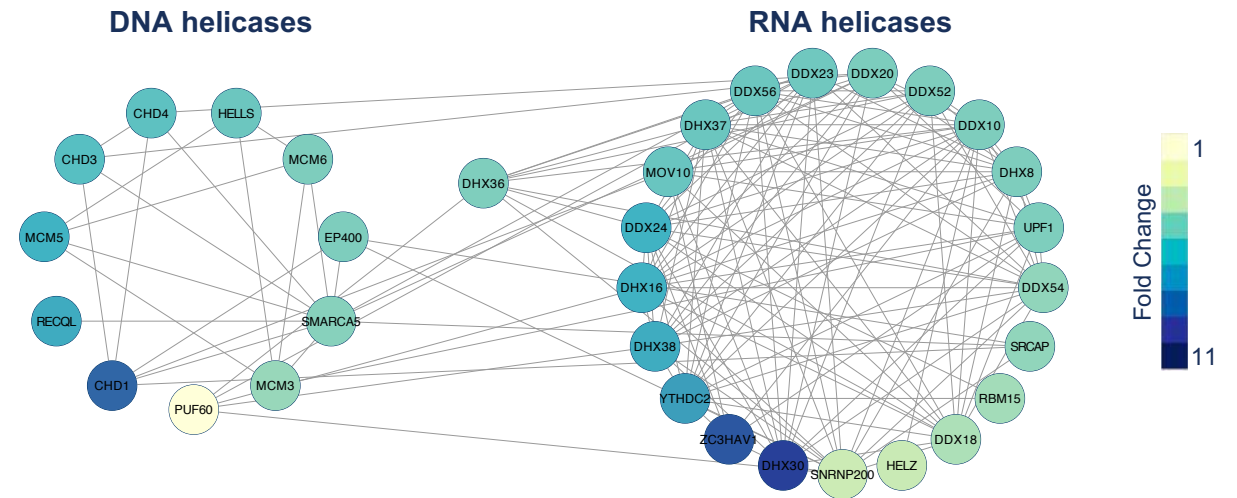
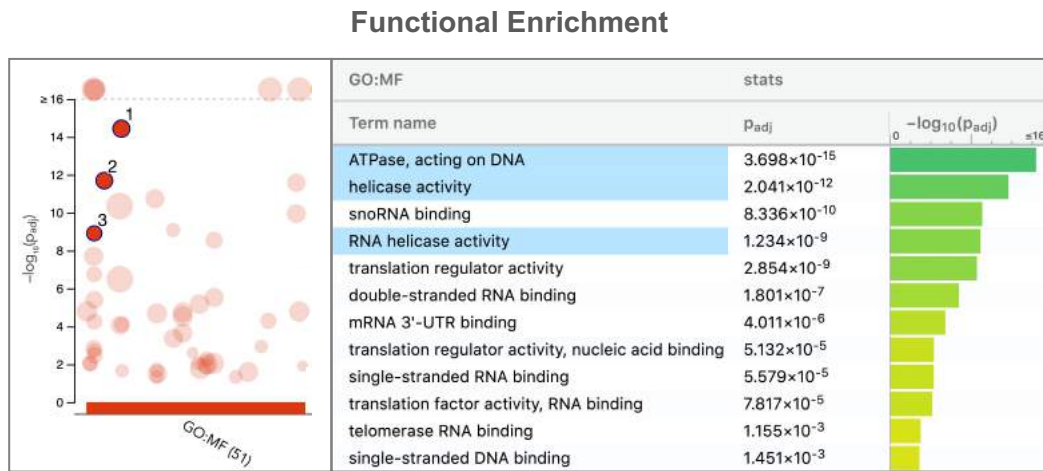
CoIP and proximity labeling approaches to identify PCBP1 interacting proteins



Several proteins involved in DDR appear as PCBP1 interactors

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7. The most prominent type of enzymes populating the PCBP1 interactome is the helicases



Although no Fe-containing helicases were found as part of the PCBP1 interactome, two alternatives are considered:

- Fe-binding motifs are not easily recognized on proteins. Then, some proteins from the PCBP1 interactome may in fact use iron as cofactor.
 - These proteins are part of large complexes where another protein is the one requiring iron for function.

What is the role of PCBP1 on DNA repair?