VCP/p97 system: a promising drug target for improved radiotherapy

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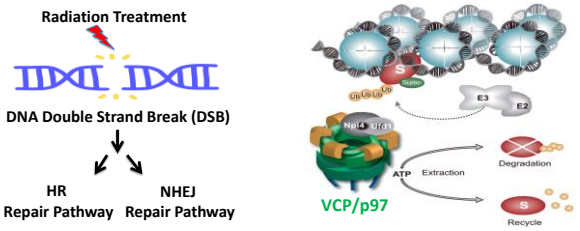
1: The bitter truth and horrifying predictions for cancer, highlighting the importance of radiotherapy

- Every 1 of 2 will be diagnosed with cancer in their lifetime.
- More than 50% cancer patients receive radiotherapy causing DNA double strand breaks (DSBs) and forcing cancer cells to die.
- Tumours often repair the damaged DNA and develop resistance, causing disease relapse and mortality.
- Urgent need to identify new drug targets and decode the resistance mechanisms.
- VCP/p97 is an ATPase, upregulated in many tumours, facilitating DSB repair, resistance to radiation therapy and cancer cell survival.

2: Aim- Investigate the role of VCP/p97 system in DSB repair to evaluate its potential as a novel drug target.



3: Methodology and Results

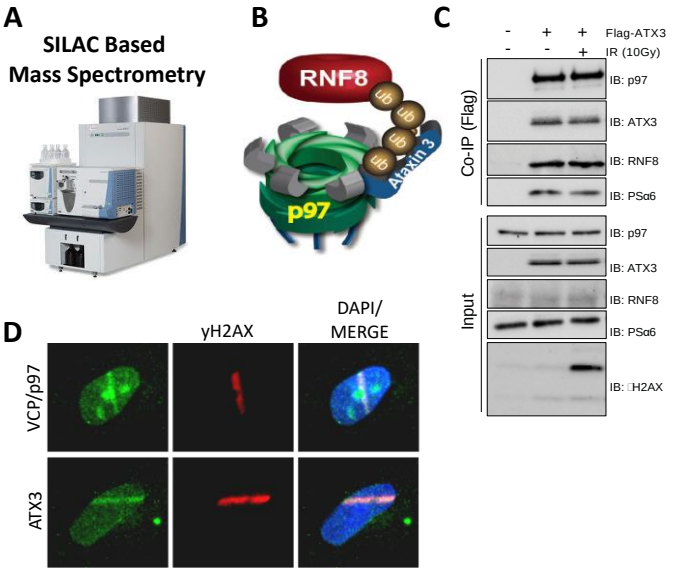


Figure 1 Schematic representation of **A)** Mass-Spectrometer used to identify VCP/p97 complexes in human cancer cells after ionising radiation (IR) treatment; **B)** one of the identified complex (p97-ATX3 complex). **C)** Confirmation of identified complex by Co-Immuno-Precipitation. **D)** Fluorescence microscopy showing the recruitment of identified complex components at the site of DNA damage.

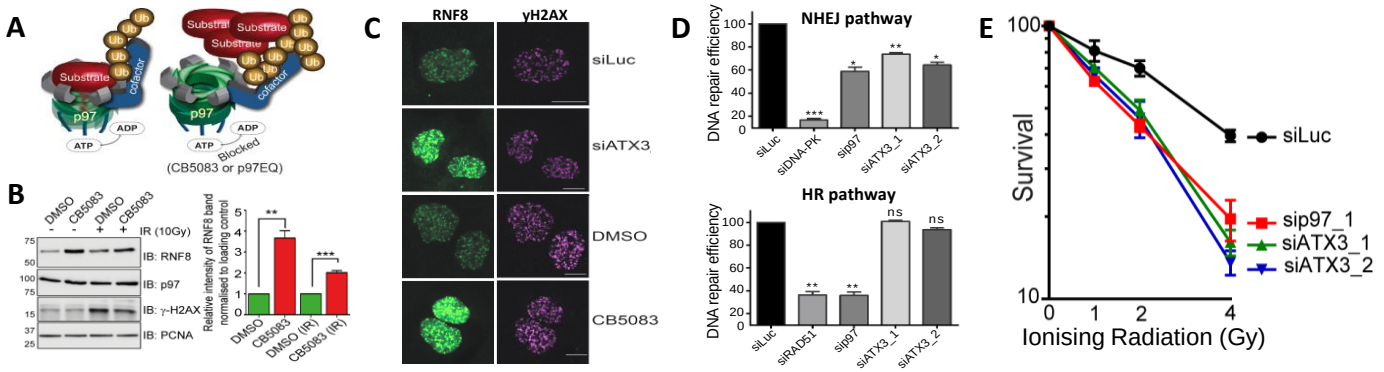


Figure 2 A) VCP/p97 mediated substrate processing by using ATPase activity. **B)** Immuno-blots showing substrate (RNF8) accumulation in HeLa cells after blocking ATPase activity of VCP/p97. **C)** Substrate (RNF8) accumulation at the site of DNA damage after blocking ATPase activity of VCP/p97 or depleting its cofactor ATX3 in human osteosarcoma (U2OS) cells. **D)** Efficiency of DSB repair under indicated conditions. **E)** Hyper sensitivity of human cancer cell line (HeLa) to IR treatment after VCP/p97 or its cofactor ATX3 depletion.

4: Conclusion: VCP/p97 system is a potential drug target for IR based cancer treatment.

- VCP/p97 and ATX3 both are DSB repair proteins, which come at the site of DNA lesion and cooperate for efficient DSB repair.
- E3 Ub-ligase RNF8 is a substrate of p97-ATX3 complex, which regulates RNF8 homeostasis and turnover at DSBs.
- VCP/p97 facilitates DSB repair through both (NHEJ and HR) repair pathways while ATX3 is specific for NHEJ repair pathway.
- Both VCP/p97 and ATX3 are potential drug targets and inactivation of either of these can hyper-sensitise human cancer cells to IR.

5: Impact: Targeting VCP/p97 system may significantly improve radiotherapy response and cancer treatment.

References:

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- Meerang et al., Nat Cell Biol, 2011.
- Boom et al., Molecular Cell, 2016.
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