



# RRM2 reduces cisplatin response in oral cancer by regulating cellular ROS production and mitochondrial DNA stability

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## Abstract:

### Introduction

Cisplatin has long been used as a standard and effective first-line chemotherapy for oral cancer treatment. However, it shows resistance in due course of treatment, leading to tumor relapse. Therefore, there is an urgent need to identify new therapeutic targets to enhance the response to cisplatin-based chemotherapy. From our previous study, we found that miR-203a mediated downregulation of Ribonucleotide reductase subunit M2 (RRM2) increases cisplatin-induced cell death in cisplatin-resistant oral cancer cells. This motivated us to verify how exactly RRM2 modulates the cisplatin response in this malignancy.

### Objective

To investigate how RRM2 modulation affects cisplatin-induced DNA damage repair, mitochondrial function, and apoptotic pathways in oral squamous cell carcinoma cells.

### Materials and Methods

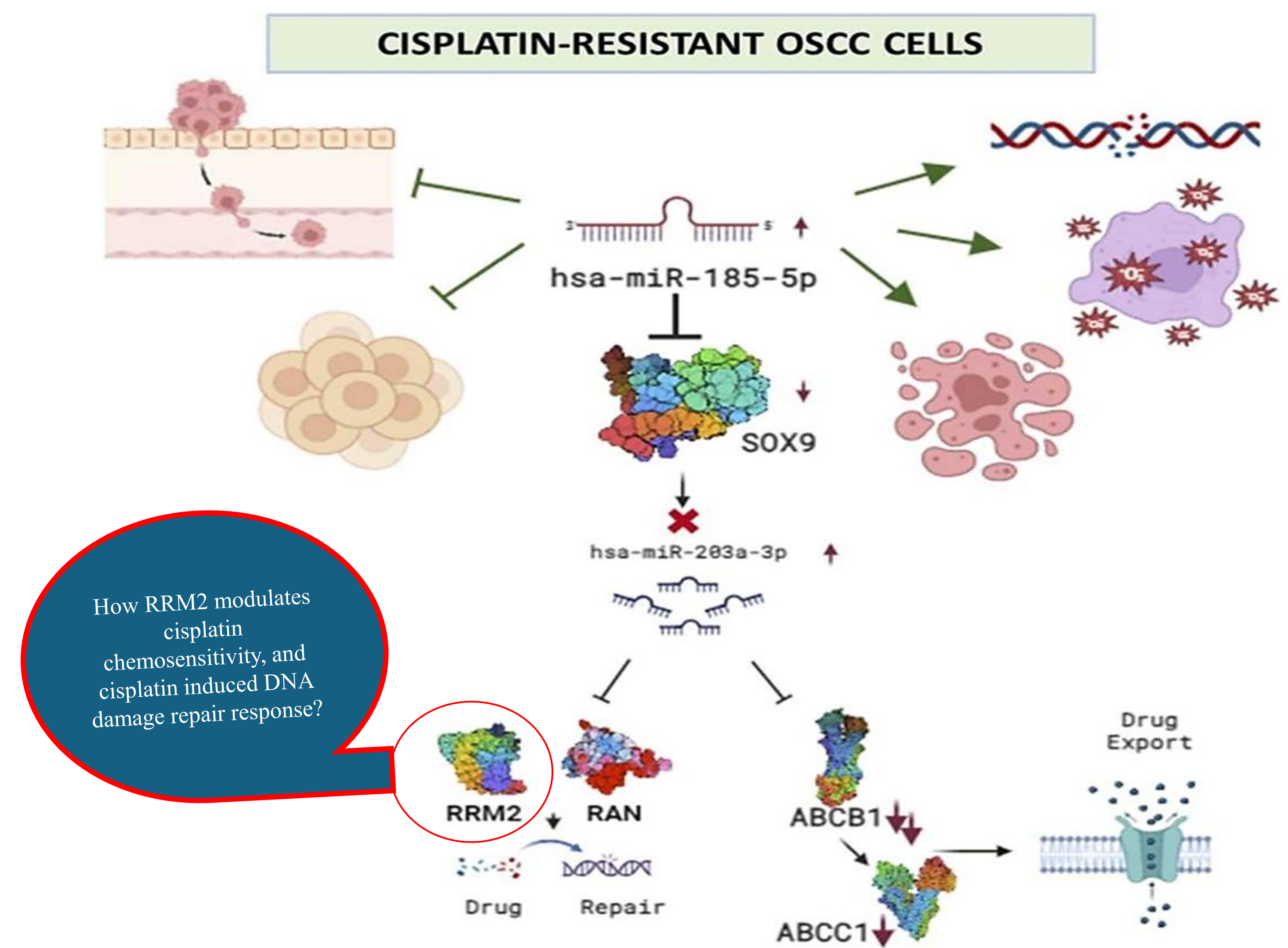
We assessed the impact of RRM2 on cisplatin response using molecular assays including qRT-PCR, Western blotting, MTDNA content analysis, fluorescence imaging (DCFHDA, Rhodamine 123, DHE, AO/EB staining), DAPI staining, and  $\gamma$ -H2AX accumulation assay.

### Results and Conclusions

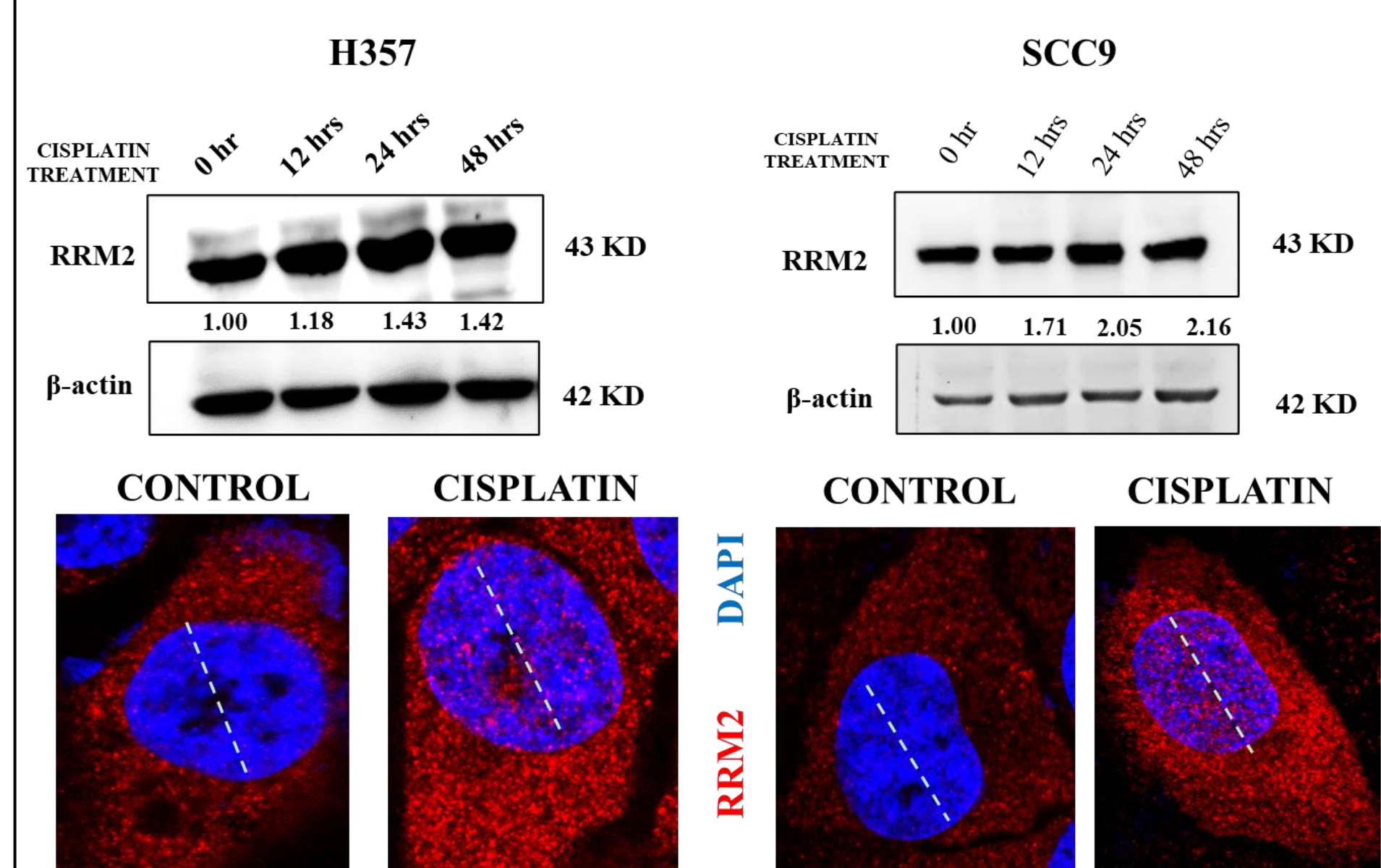
Upon cisplatin treatment, RRM2 expression is increased in SCC9 and H357 oral cancer cells, with RRM2 localizing to the nucleus, likely to support DNA repair. Intriguingly, we found that RRM2 significantly reduces cisplatin-induced apoptosis and DNA damage response. We also observed that RRM2 reduces cisplatin-induced ROS production, mitochondrial depolarization, and mitochondrial DNA content, indicating decreased mitochondrial DNA damage from cisplatin exposure. Taken together, our study revealed that RRM2 is a promising therapeutic candidate for the effective treatment of cisplatin-based chemotherapy.

## Background of the study:

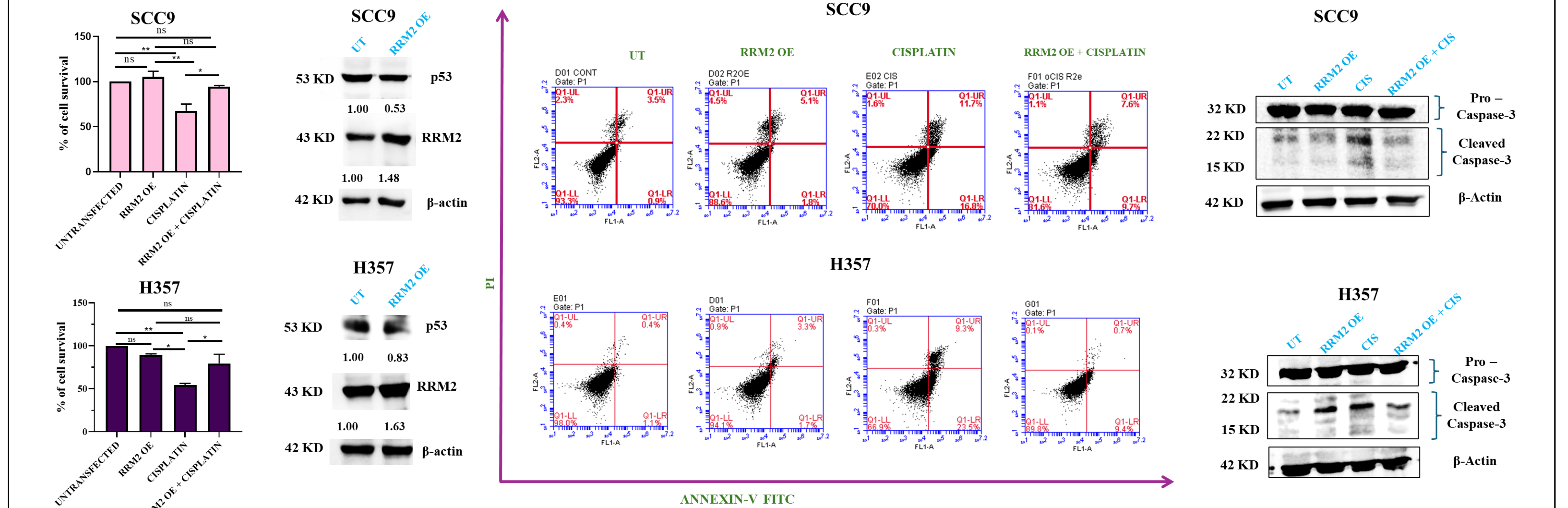
- Cisplatin induces DNA damage to kill cancer cells, but resistance arises through enhanced DNA repair, altered apoptosis, and reduced drug accumulation, leading to treatment failure.



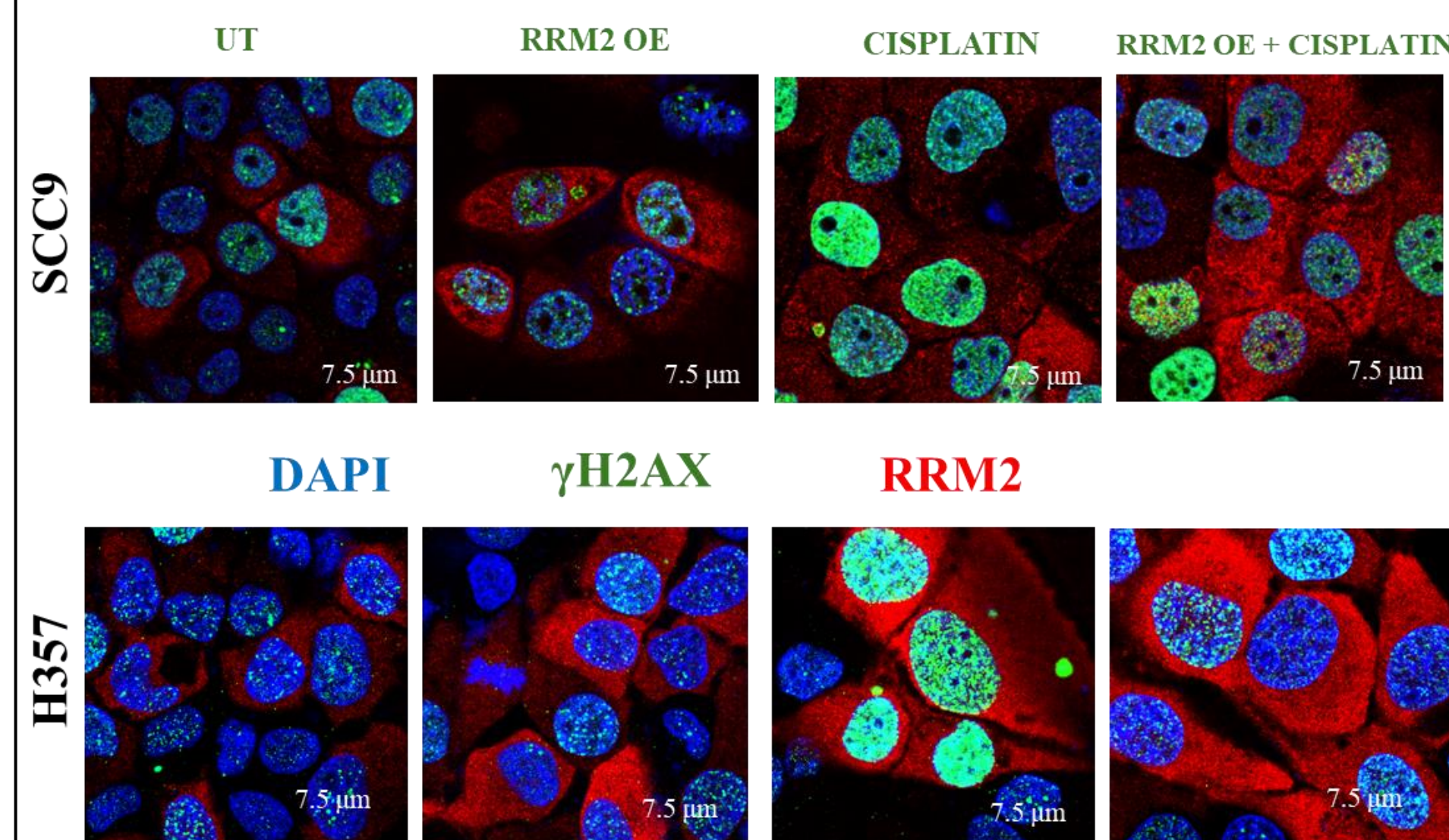
## Cisplatin treatment upregulates RRM2 in OSCC cells, enhancing its nuclear localization:



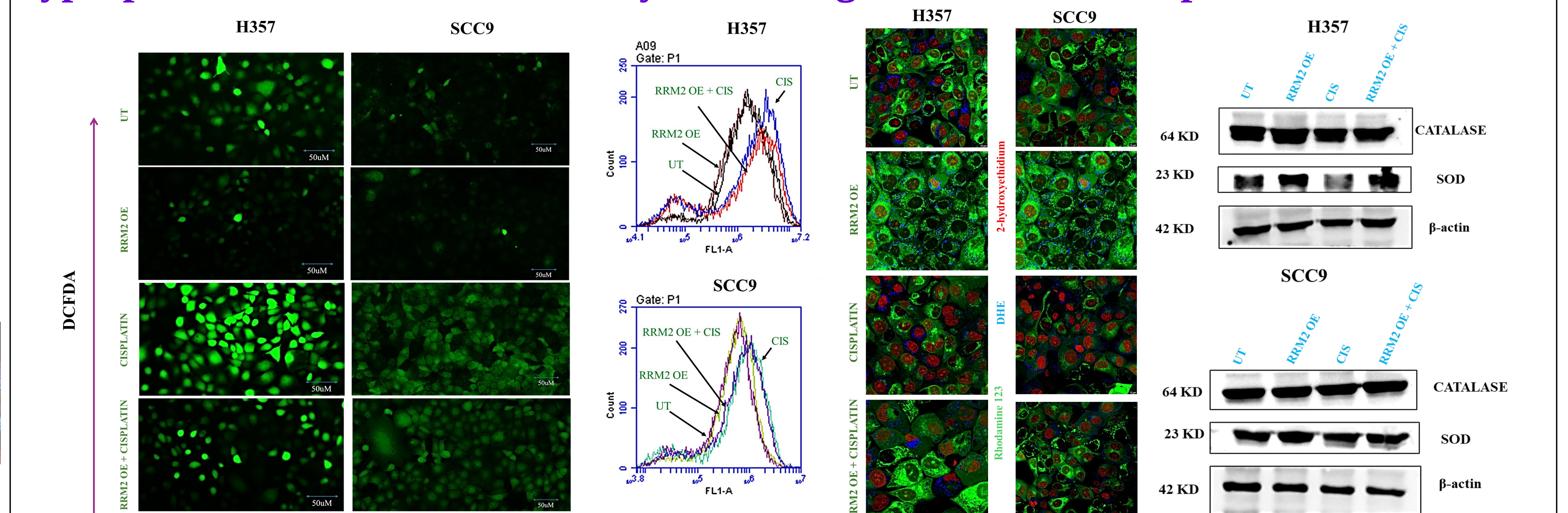
## RRM2 overexpression inhibits p53-driven caspase-3 activation, reducing cisplatin-induced cell death in OSCC cells:



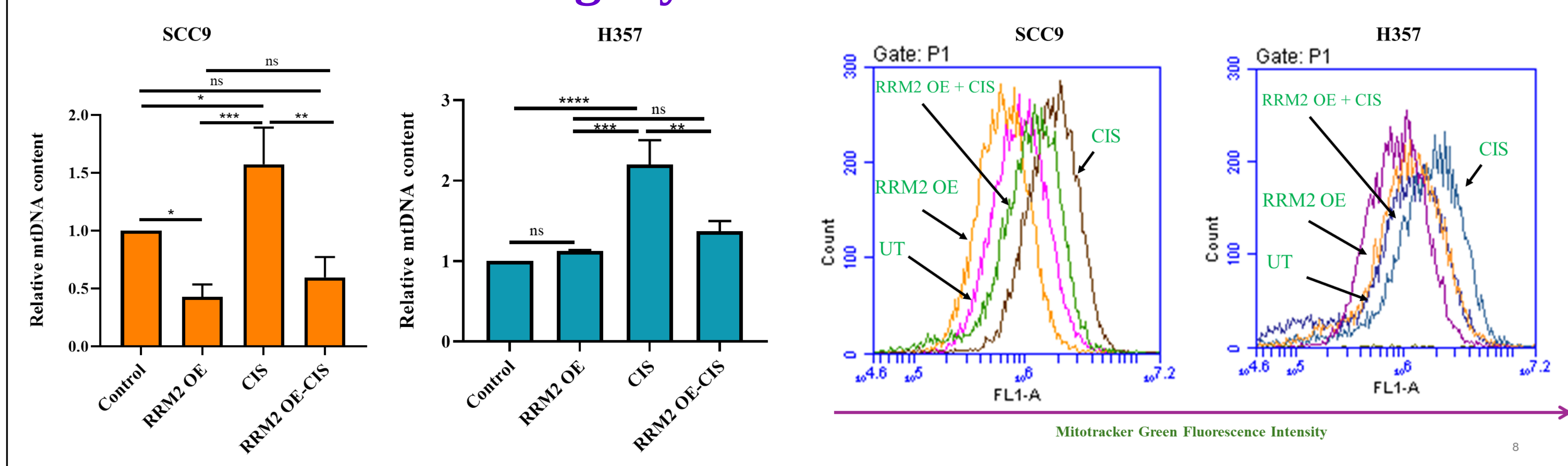
## RRM2 overexpression reduces cisplatin-induced DNA damage in OSCC cells:



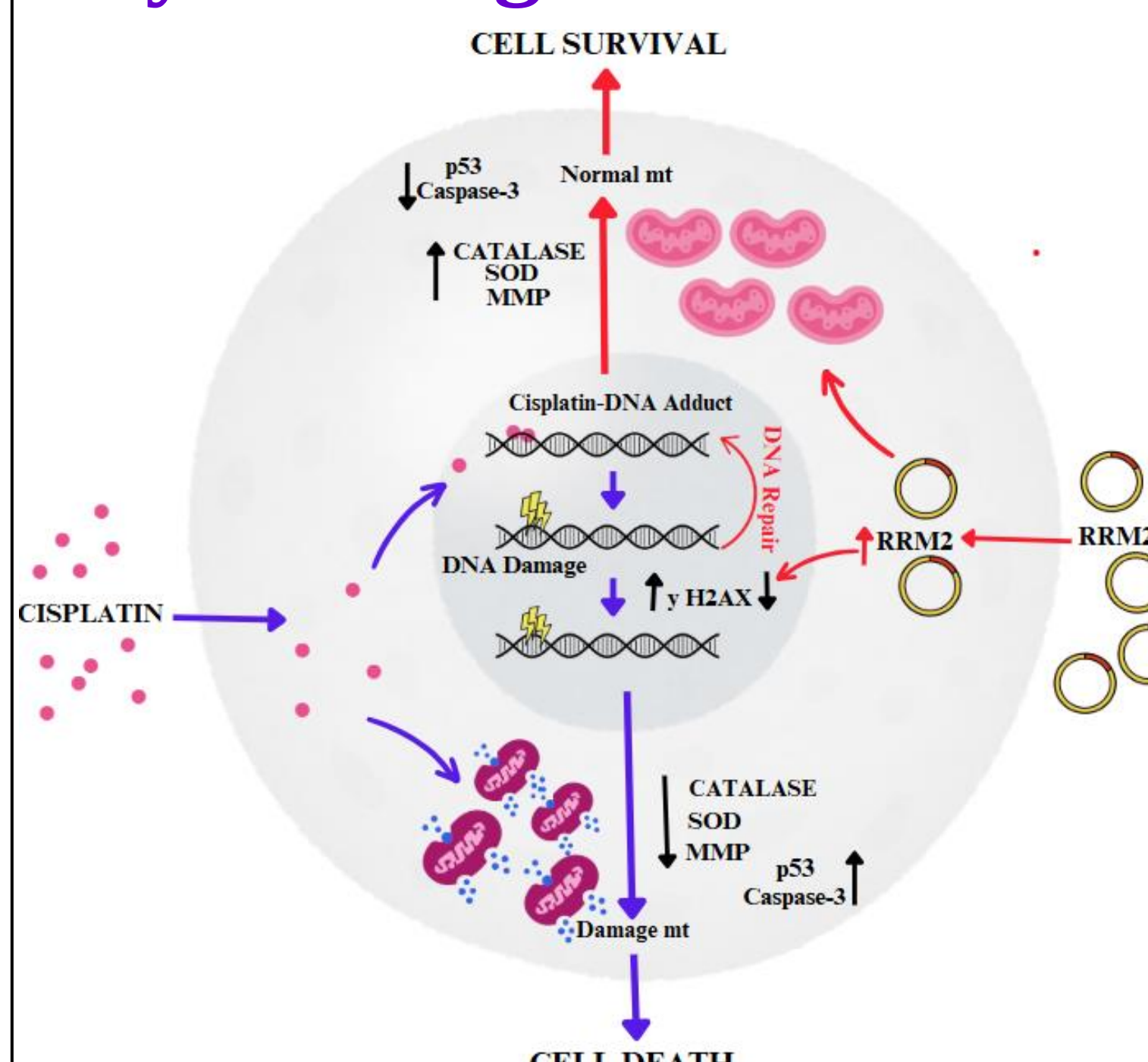
## RRM2 overexpression reduces cisplatin-induced ROS production and mitochondrial hyperpolarization in OSCC cells by increasing SOD and CAT expression:



## RRM2 overexpression maintains mitochondrial DNA copy number in cisplatin-treated OSCC cells by stabilizing mitochondrial DNA integrity:



## Key Findings:



## References:

- Biswal P, Mallick B. miR-185-5p rewires cisplatin resistance by restoring miR-203a-3p expression via downregulation of SOX9. DNA Repair (Amst). 2024 Oct;142:103750. doi: 10.1016/j.dnarep.2024.103750. Epub 2024 Aug 16. PMID: 39173500.
- Das B, Jain N, Mallick B. piR-39980 mediates doxorubicin resistance in fibrosarcoma by regulating drug accumulation and DNA repair. Commun Biol. 2021 Nov 19;4(1):1312. doi: 10.1038/s42003-021-02844-1. PMID: 34799689; PMCID: PMC8605029.

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