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Enhancer extrachromosomal circular DNA ANKRD28 drives drug resistance via POU2F2-mediated transcriptional network in multiple myeloma

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INTRODUCTION

Multiple myeloma (MM) is still an incurable disease, mainly due to the emergence of drug resistance, and its underlying mechanisms are not yet clear.[1] Abnormal enhancer activity is crucial in transcriptional regulation programs, as it can promote drug resistance and tumor progression.[2] Extrachromosomal circular DNA (eccDNA) is commonly present in both coding and non-coding regions of tumor genomes, and its amplification of downstream oncogenes and/or resistance genes can drive tumor heterogeneity.[3] However, the role of the non-coding region of serum eccDNA serving as an enhancer in MM resistance is not clear. The purpose of this study is to explore the role of enhancer eccANKRD28 in drug resistance and MM progression.

RESULTS

1. We profiled the serum eccDNAs from NDMM patients and healthy donors, and there were no significant differences in the distribution and genomic landscape of nontargeted eccDNA among healthy donor and NDMM patients (Figure A).

2. The serum eccANKRD28 of MM patients mainly came from bone marrow CD138+ plasma cells and was also involved in the MM disease progression and VRd resistance.

3. High copy number of eccANKRD28 in serum had potential clinical predictive value for high-risk, poorly VRd responses, or poor prognosis MM patients;

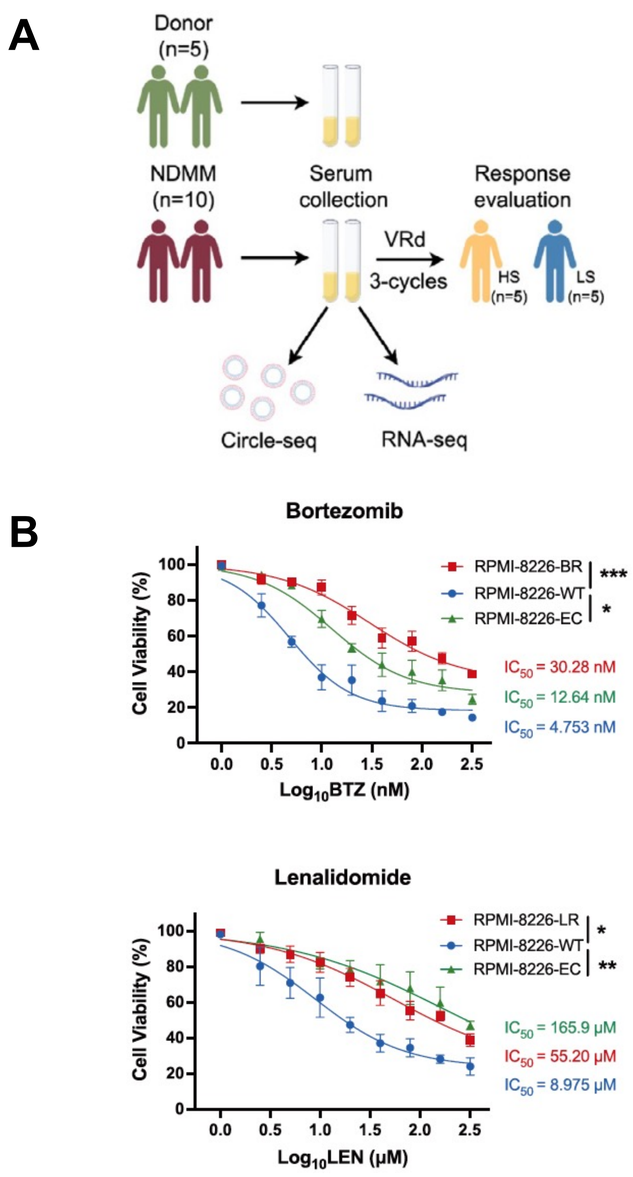
4. The copy number of eccANKRD28 in the constructed VRd-resistant cell lines (RPMI-8226, U266, and OPM-2) increased, and cells with high abundance of endogenous eccANKRD28 produced by CRISPR/Cas9 gene editing developed resistance to bortezomib and lenalidomide (Figure B);

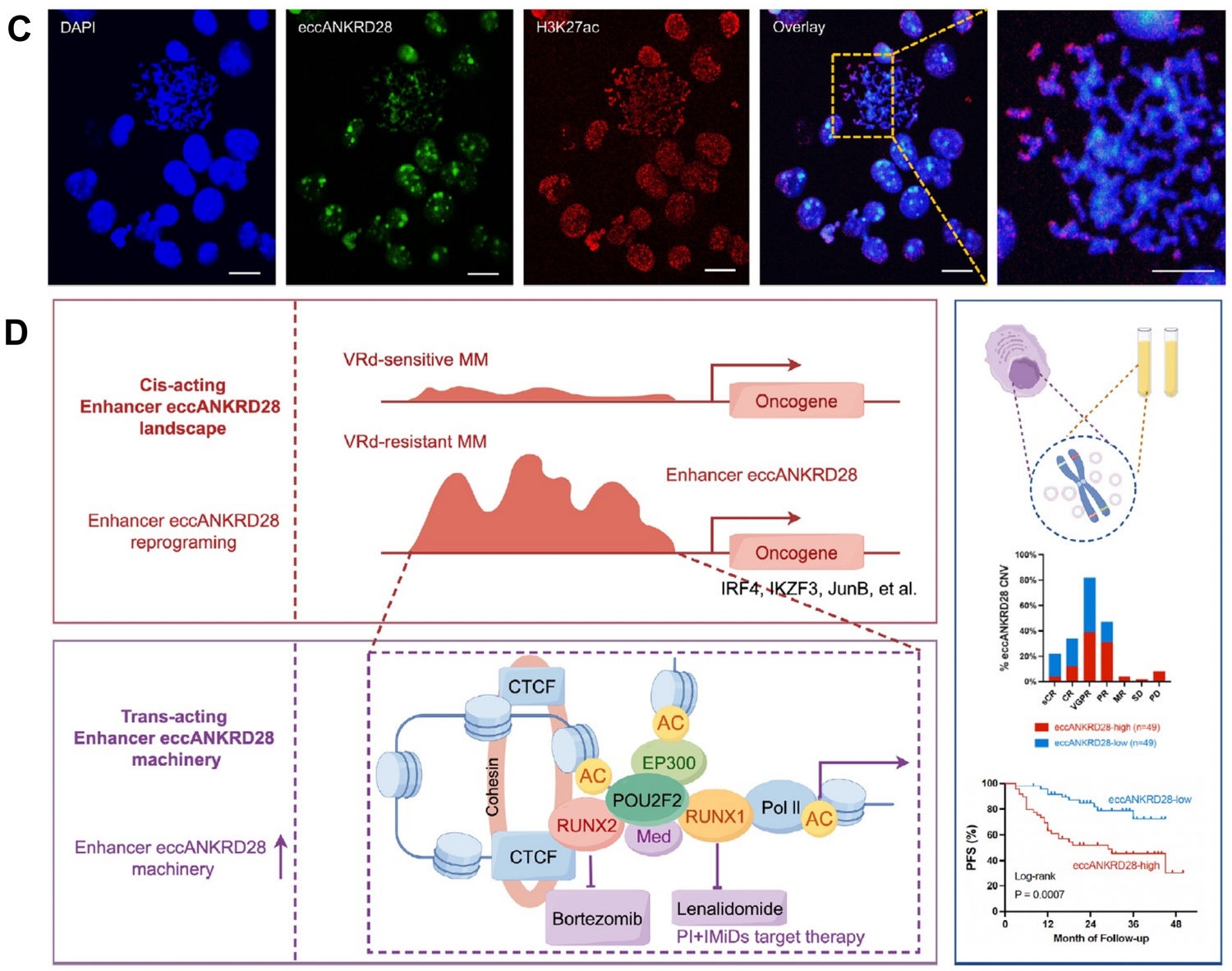
5. DNA damage caused endogenous copy number changes in eccANKRD28, leading to increased copy number and enhanced transcriptional regulation of oncogenes.

6. EccANKRD28 served as an enhancer in the process of MM drug resistance (Figure C), which is activated through its interaction with transcription factors POU and RUNX family.

7. The resistance-related transcription factor POU2F2 could bind to RUNX1 and RUNX2 to form the protein complex, at the same time, POU2F2 could also bind to the enhancer eccANKRD28 to activate transcription, directly regulating its downstream resistance-related oncogenes such as IRF4, JUNB, IKZF3, RUNX3, and BCL2, mediating VRd resistance and exerting a MM promoting effect (Figure D).

8. EccANKRD28 promoted tumor growth and induced resistance to bortezomib in tumor bearing mice.





CONCLUSION

This study demonstrated from multiple dimensions, including in vitro cellular level, clinical cohort, and in vivo animal experiment level, that the enhancer eccANKRD28 can bind to the transcription factor POU2F2. POU2F2 binds to RUNX1 and RUNX2 to form protein complexes, directly regulating downstream resistance-related oncogenes such as IRF4, JUNB, IKZF3, RUNX3, and BCL2, forming a cascade transcriptional regulatory network, promoting VRd resistance and MM disease progression.

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