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CRISPR/Cas9 Library Screens Identified *Atp2a2* As an *In Vivo* Specific Tumor Suppressor in Myeloid Neoplasia

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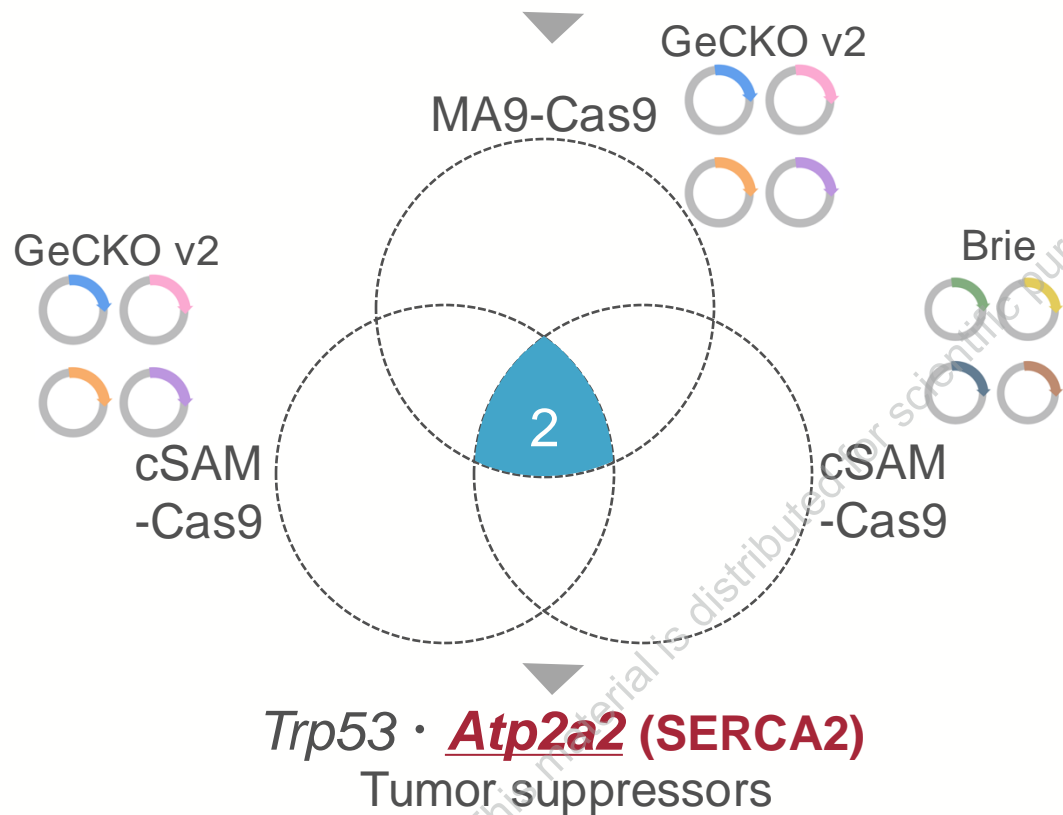
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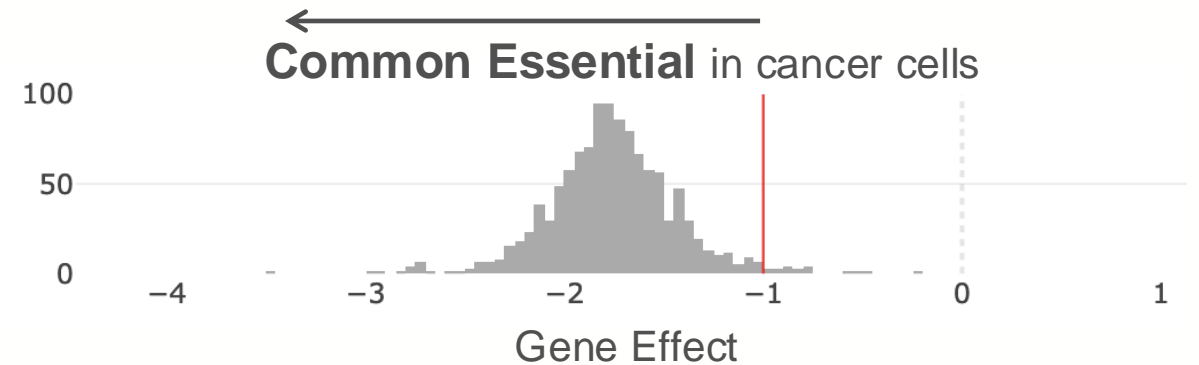
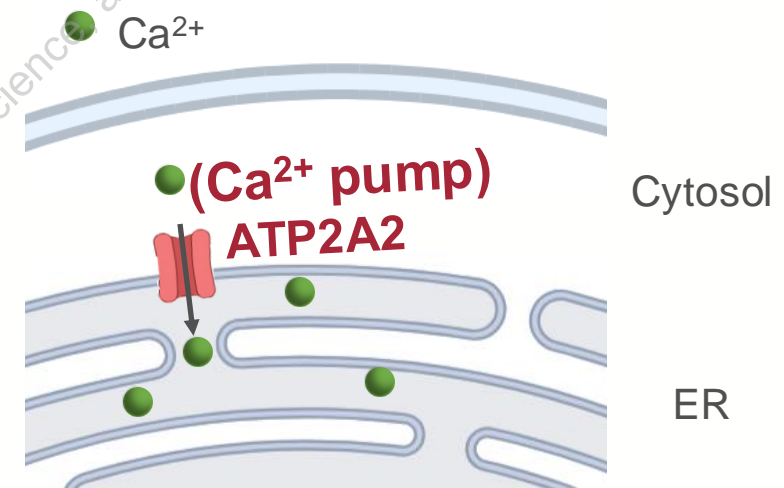
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We identify *Atp2a2* as an ***in vivo specific*** tumor suppressor by the CRISPR/Cas9 library screens.

- Mouse myeloid tumor models
- MLL-AF9 (MA9) cells
 - SETBP1/ASXL1 (cSAM) cells



Atp2a2 (SERCA2)

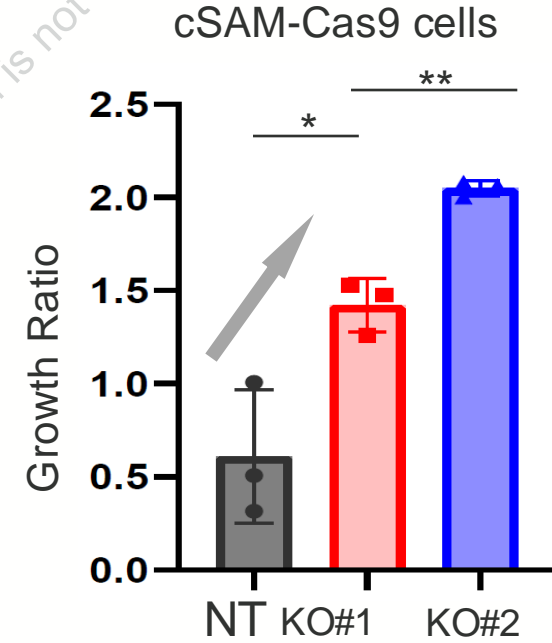
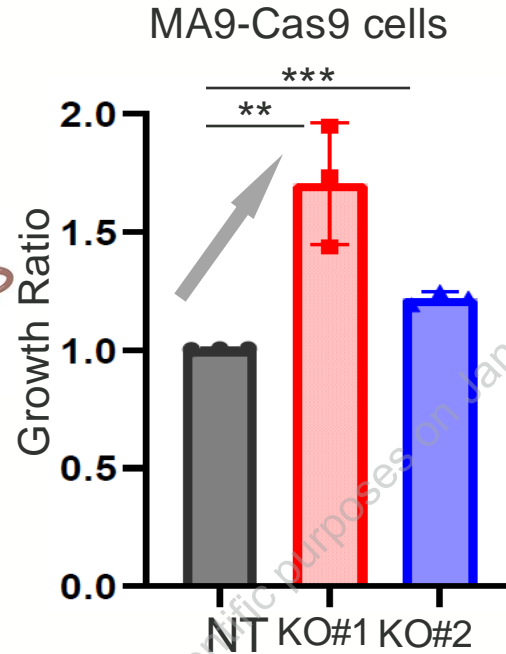


(DepMap data)

Cell, 170, 3, 564-576, 2017

Depletion of *Atp2a2* in myeloid tumors specifically accelerates tumorigenesis *in vivo*.

Atp2a2 depletion
promotes
tumorigenesis
in vivo



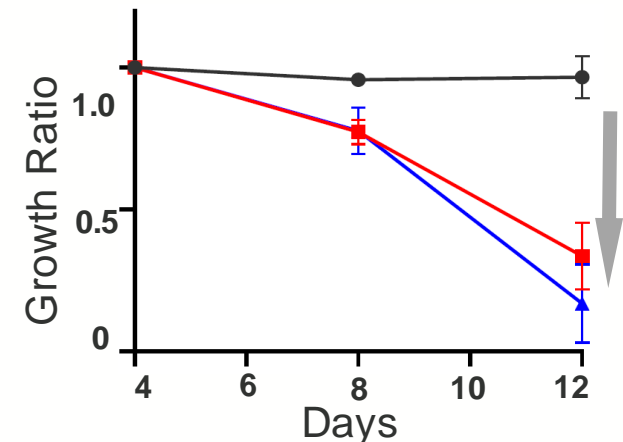
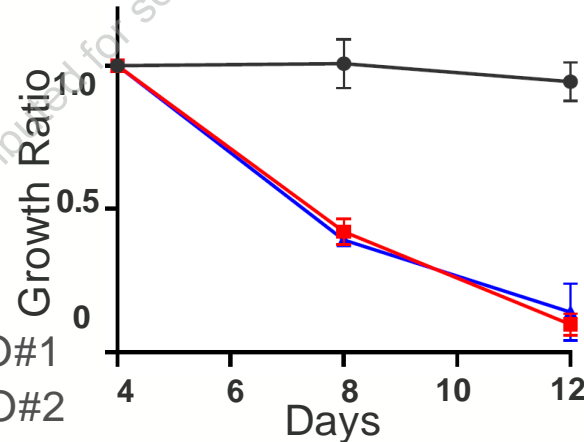
Contrasting results

Atp2a2 depletion
inhibits
tumorigenesis
in vitro

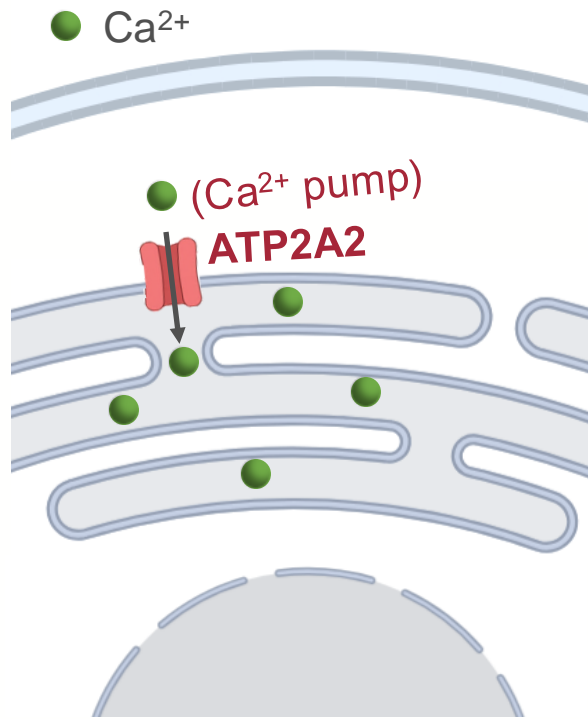


in vitro

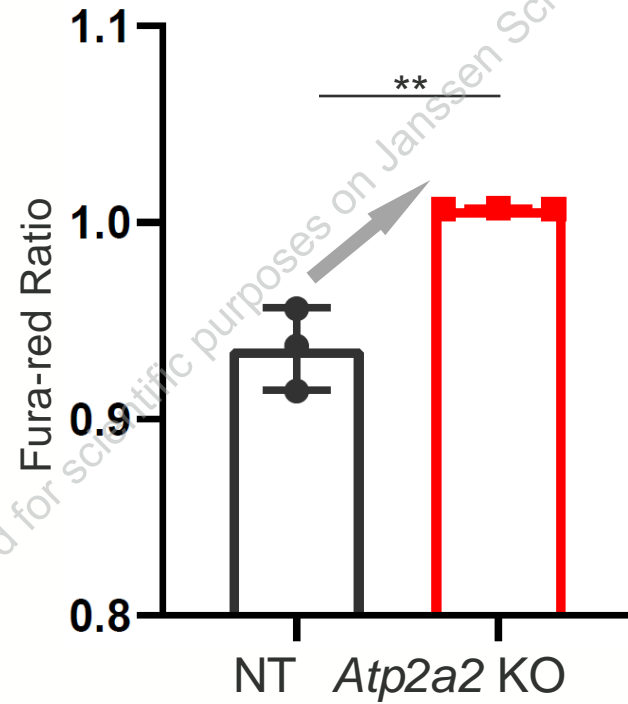
- NT
- *Atp2a2* KO#1
- ▲ *Atp2a2* KO#2



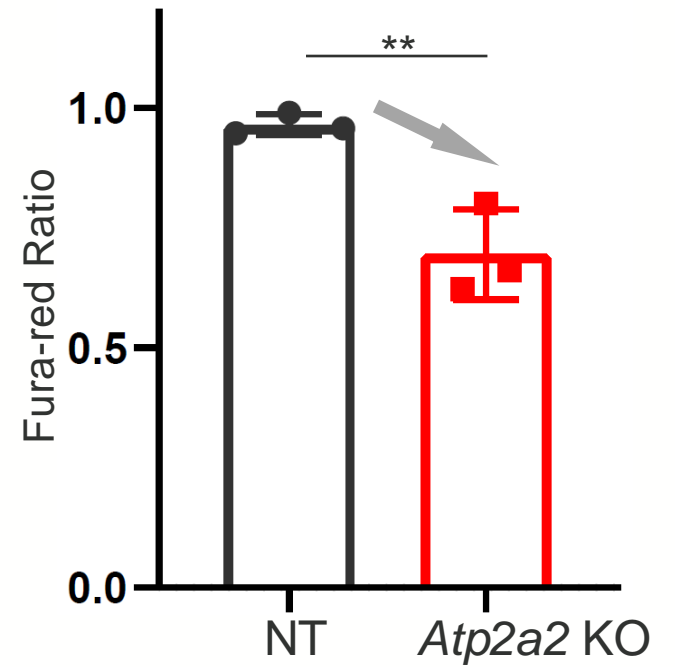
Deletion of *Atp2a2* alters Ca^{2+} homeostasis.



Cytoplasmic Ca^{2+} levels



ER Ca^{2+} levels

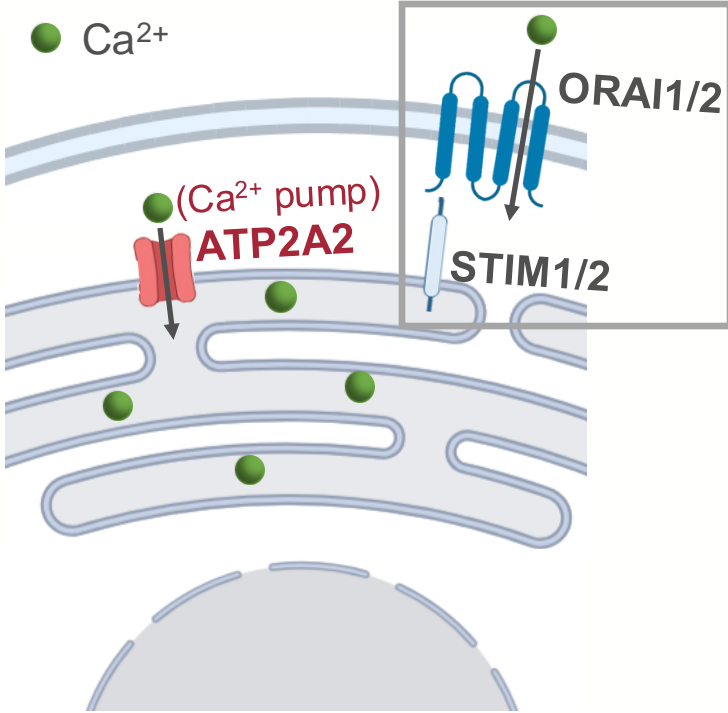


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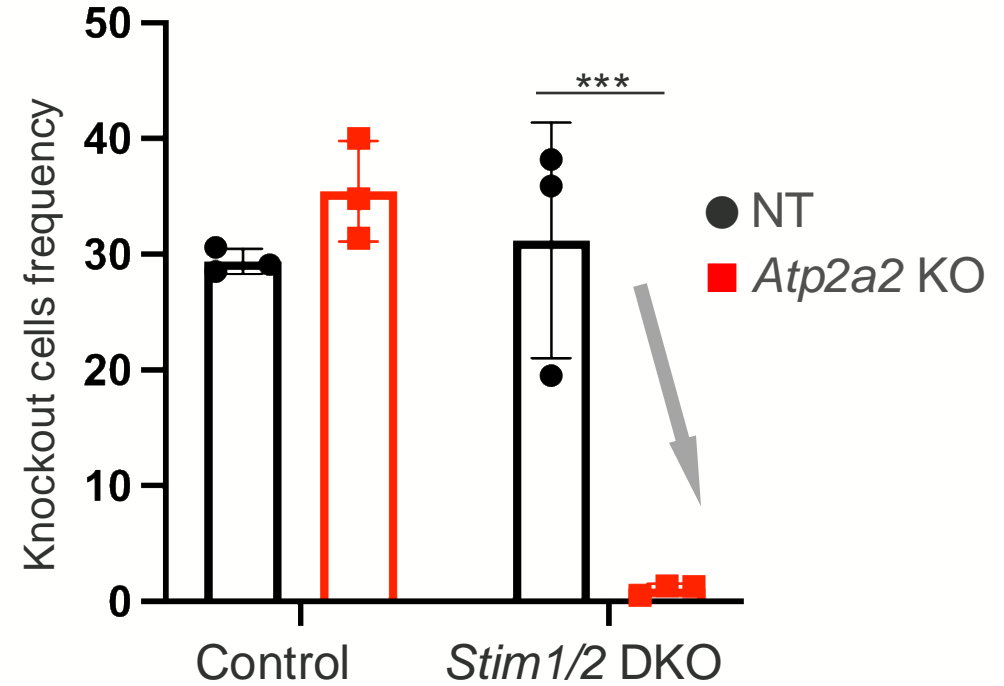
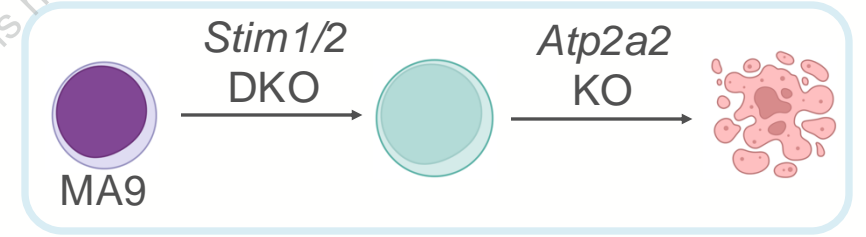
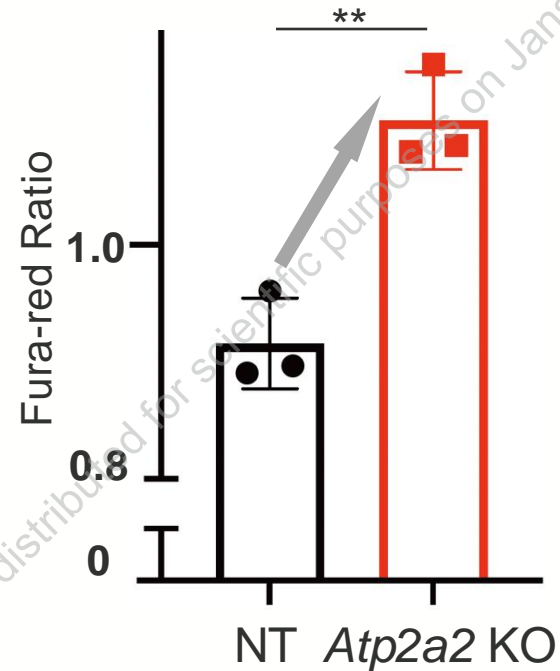
Atp2a2-depleted cells are dependent on SOCE and these would be synthetic lethal target.

(Store Operated Calcium Entry)

SOCE



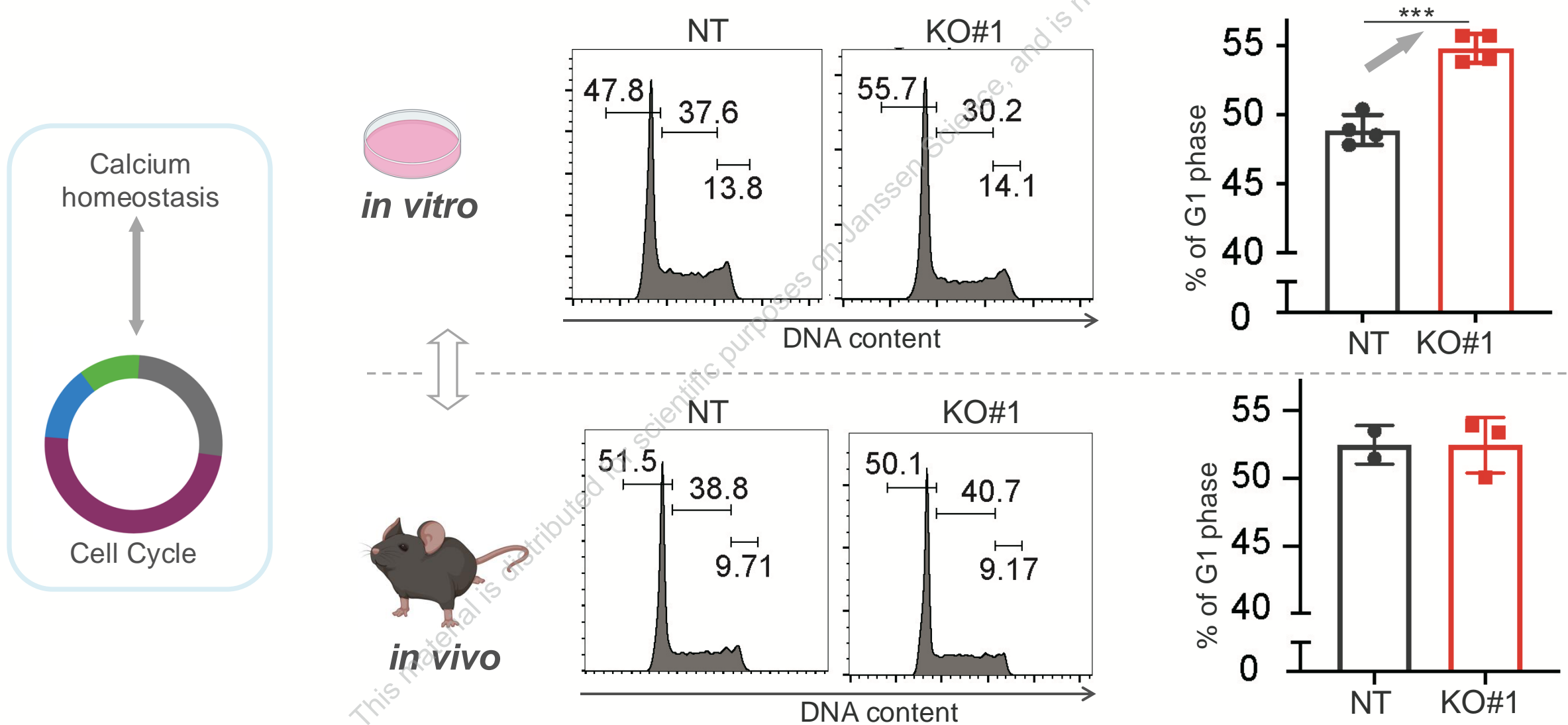
Importing Ca^{2+} levels



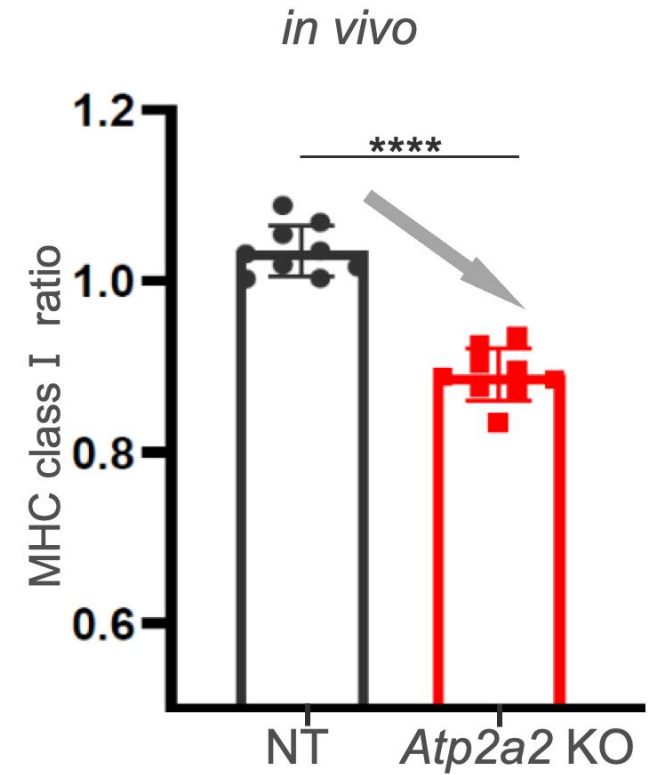
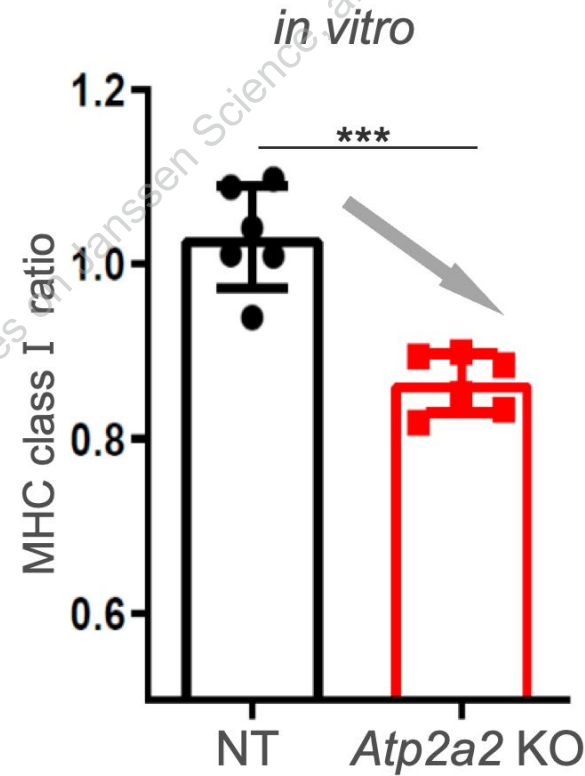
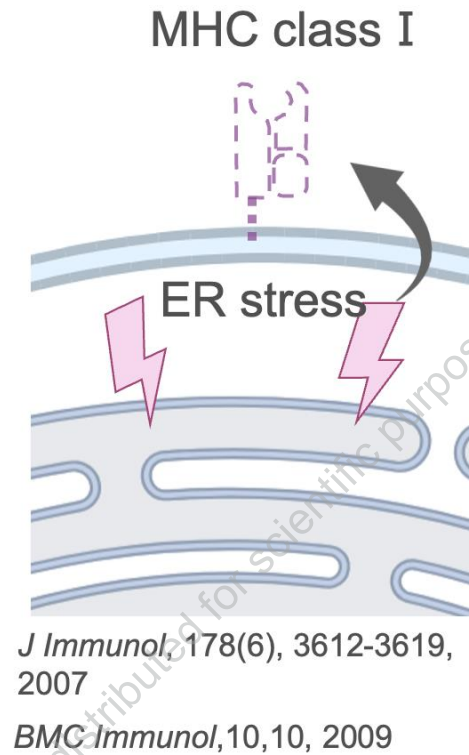
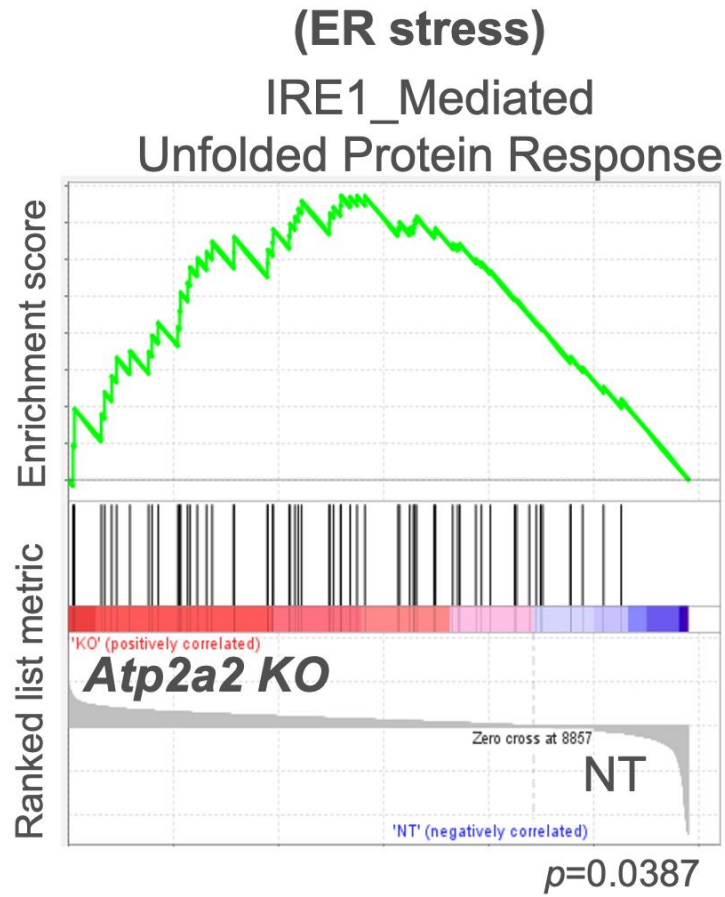
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Results

The context dependent role of *Atp2a2* in leukemogenesis is partially explained by its differential effect on cell cycle progression *in vitro* and *in vivo*.

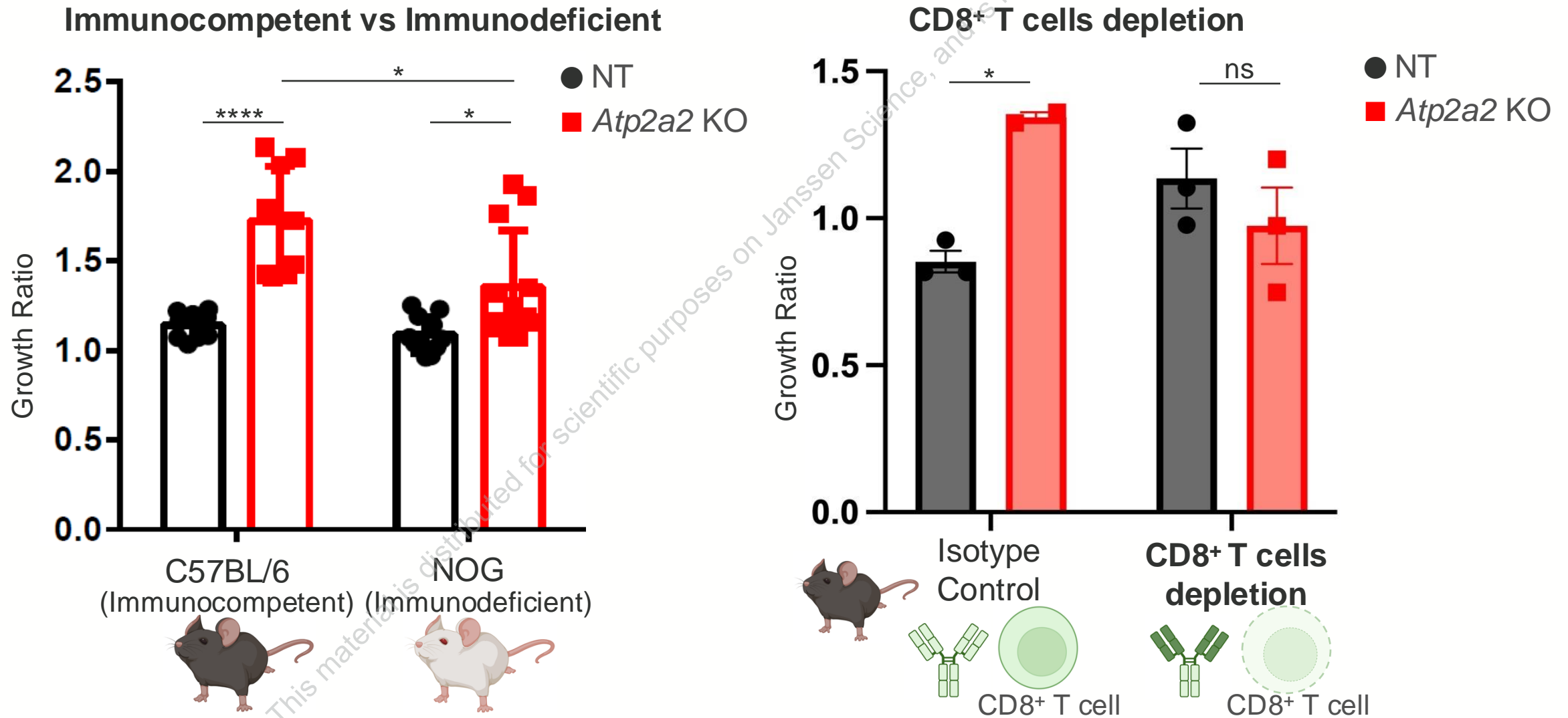


Deficiency of *Atp2a2* induces ER stress and downregulation of MHC class I expression.



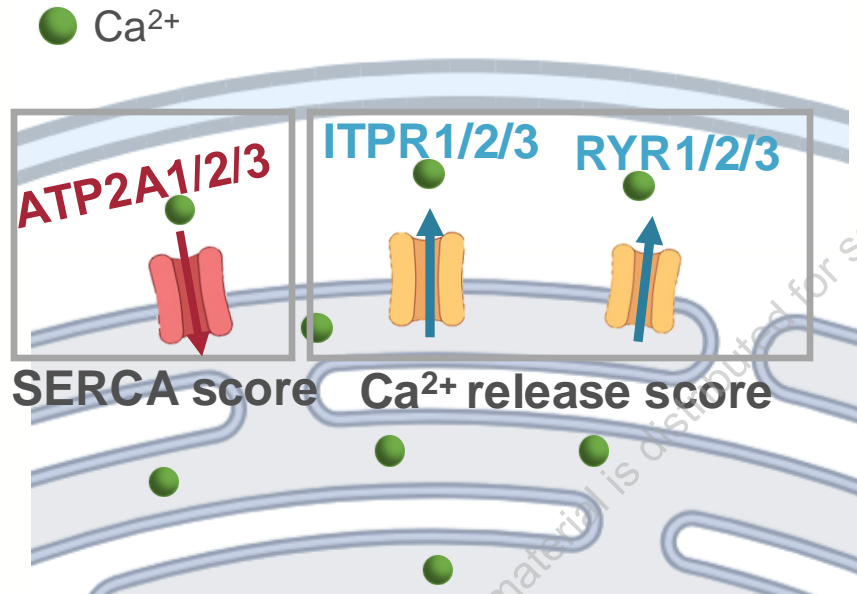
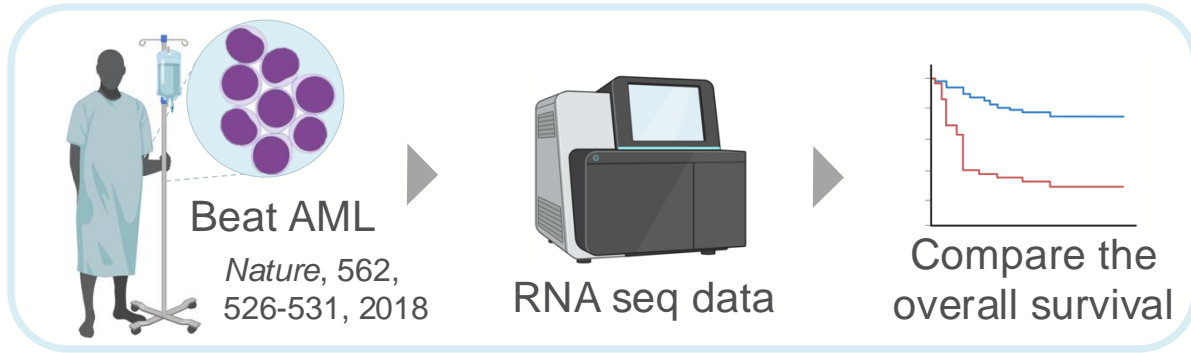
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Depletion of *Atp2a2* induces immune evasion and contributes to the proliferative advantage.

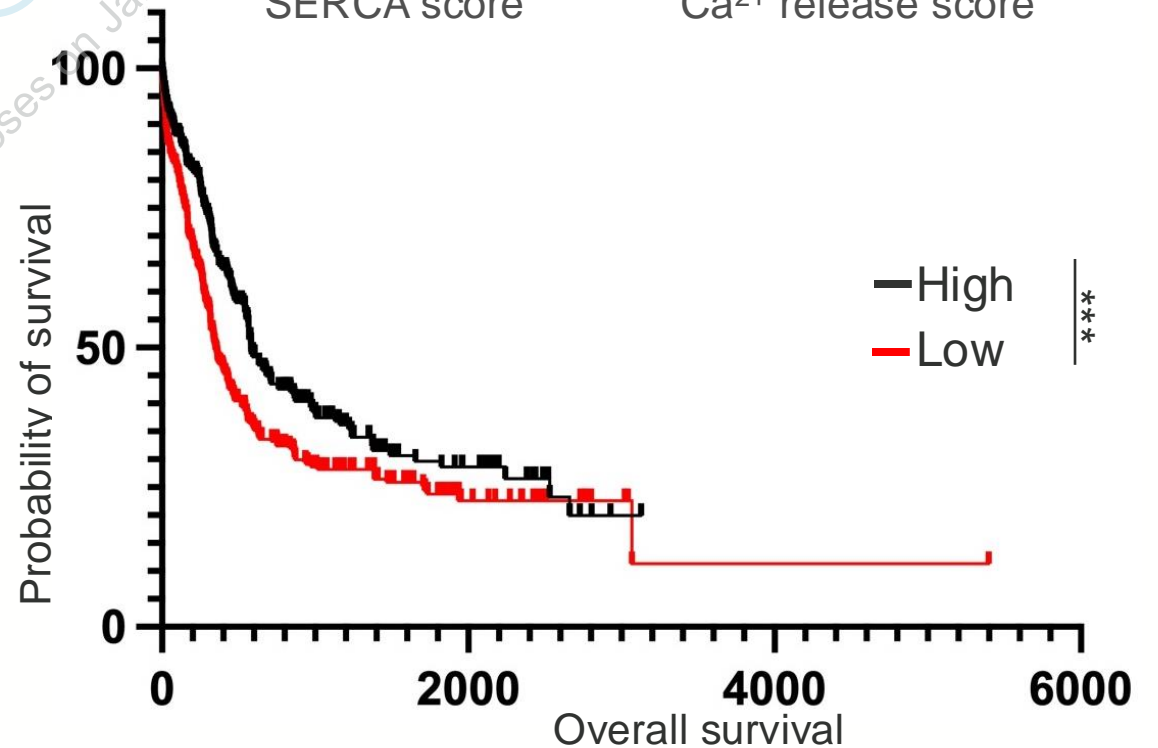


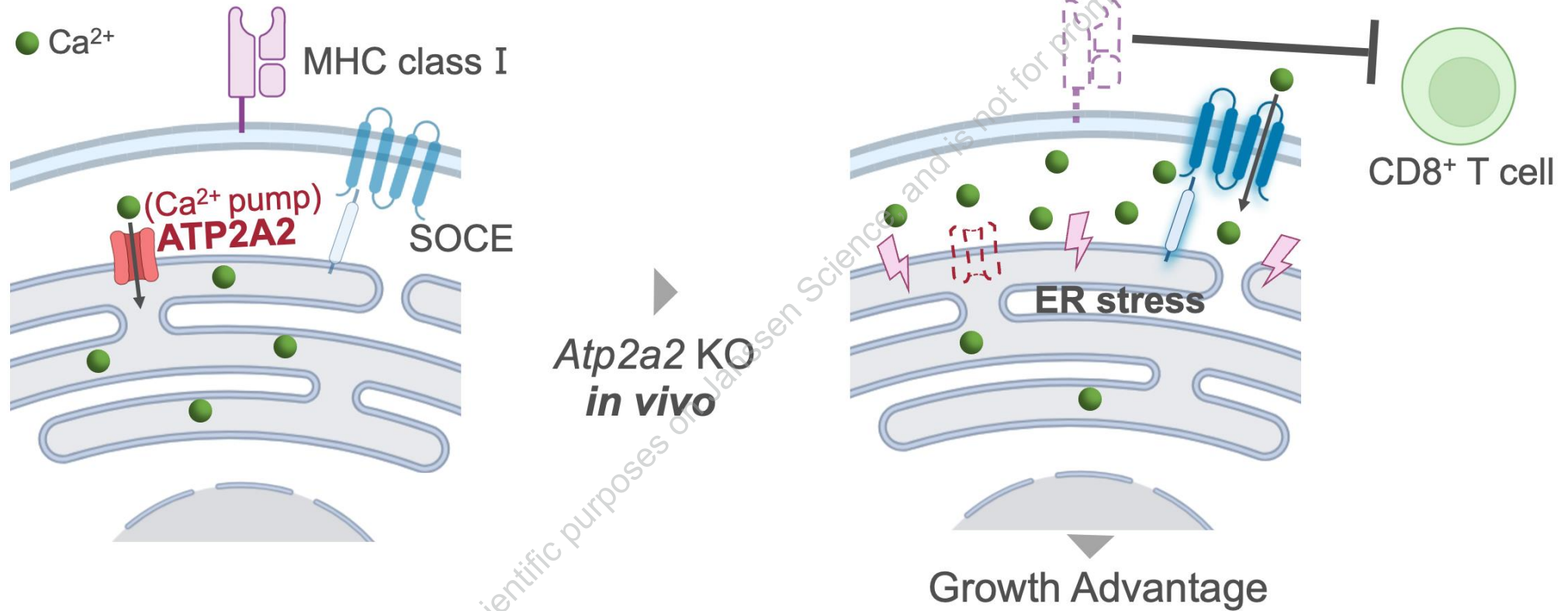
Results

The lower ER Ca²⁺ levels are associated with poor prognosis in human AML.



$$\text{Ca}^{2+} \text{ uptake score} = \frac{[ATP2A1/2/3]}{\text{SERCA score}} - \frac{([ITPR1/2/3] + [RYR1/2/3])}{\text{Ca}^{2+} \text{ release score}}$$





- *Atp2a2* depletion alters Ca²⁺ homeostasis and induces ER stress.
- *Atp2a2* deletion reduces immunogenicity and promotes immune evasion.

- ▷ *Atp2a2* as a novel *in vivo* specific tumor suppressor in myeloid tumors.
- ▷ Our data highlights the importance of *in vivo* CRISPR/Cas9 library screens to identify specific regulators *in vivo*.

Thank you for your attention.

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