The Effect of BMAL1 on Pulmonary Hypertension

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Introduction

W.H.O. Group 3 pulmonary hypertension (PH) is a chronic disease without cure.[1] Circadian rhythm has been shown to contribute to immune function. Brain and muscle arnt-like 1 (BMAL1) is a circadian gene shown to repress or express disease with different manipulations.[2,3,4] BMAL1 overexpression and knockout mice in hypoxia will be used and analyzed for phenotypic changes.

Methods

1. Mice bred with Tet/Cre background inducible with doxycycline chow for 2 weeks.
2. Hypoxia chamber, FiO_2 at 10% for 4 weeks.
3. Pulmonary hemodynamic measurements (RVSP, RV:LV+S), T-cell suppression assay (TCSA), alpha- smooth muscle actin staining (α-SMA), and Western blot performed on:
   - BMAL1 OE
   - mBMAL1 KO
   - mBMAL1 OE (ongoing)

Results

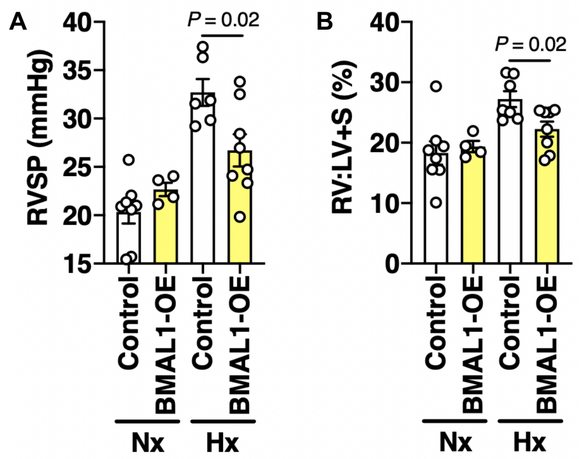

Figure 1. BMAL1 OE mice show reduced right ventricular systolic pressure (RVSP) values (mmHg) (1A) and lower right ventricle to left ventricle plus septal mass ratios (RV:LV+S) (1B) compared to control in hypoxic conditions.

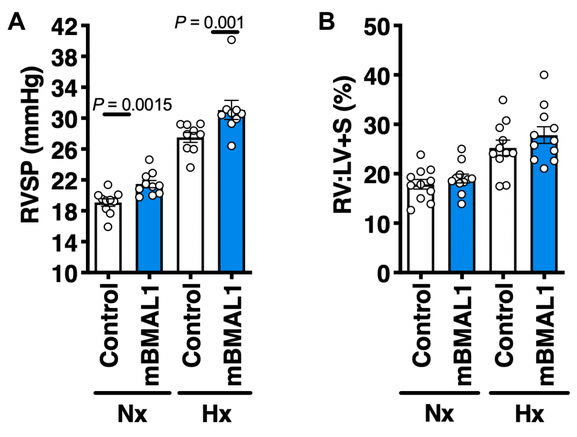

Figure 2. mBMA1 KO mice show higher RVSP values (mmHg) (2A) and higher RV:LV+S values (2B) compared to control in hypoxic conditions.

Image 1. Mouse model

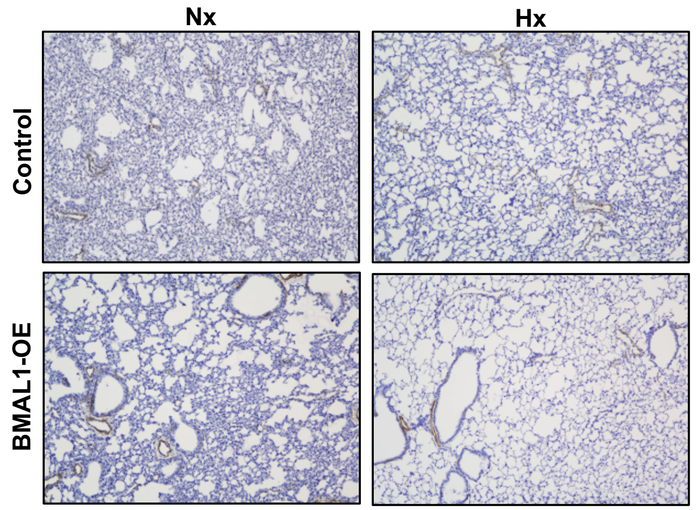

Figure 3. α-SMA staining of WT and BMAL1 OE mice in normoxia (Nx) and hypoxia (Hx). BMAL1 OE shows decreased muscle thickness compared to WT in hypoxia.

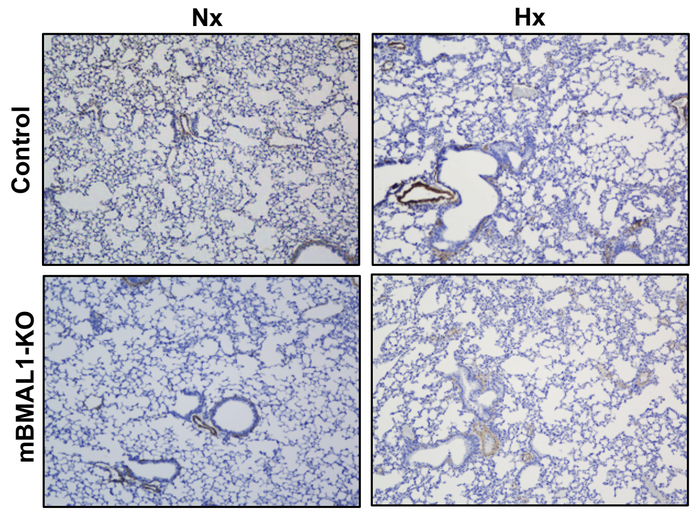

Figure 4. α-SMA staining of WT and mBMAL1 KO mice in Nx and Hx. mBMAL1 KO shows increased muscle thickness compared to WT in hypoxia.

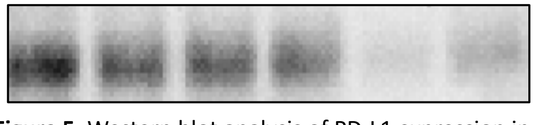

Figure 5. Western blot analysis of PD-L1 expression in wildtype (WT) n=3 and BMAL1 OE mice n=3, left to right. BMAL1 OE mice show decreased expression of PD-L1.

Conclusion

BMAL1 shows phenotypic changes correlated with PH. Global over expression of BMAL1 protected against PH and myeloid-specific BMAL1 knockout showed the opposite effect. The results show a correlation with circadian function and PH. BMAL1 OE showed decreased PD-L1 expression in a Western blot analysis. mBMAL1 OE are currently in trial. Future implications include further analysis of MDSC function in TCSA and investigating potential drug targets.

References

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