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Brain Cellular Senescence as a Potential Mediator of Angiotensin II-Induced Hypertension

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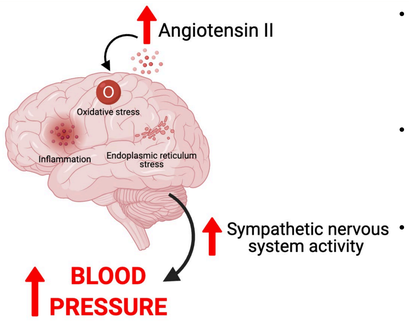
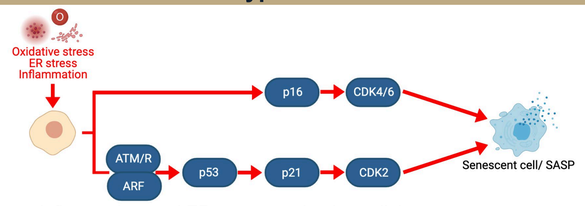
BACKGROUND

Elevated angiotensin II (Ang II) is a contributor to hypertension



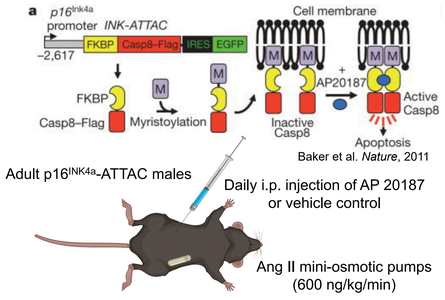
- The etiology of hypertension is unknown in 95% of cases. However, a subset of patients with hypertension display elevated levels of Ang II (Carretero & Oparil *Circulation*, 2000; Catt et al. *Br Med J*, 1969).
- The hormone Ang II is a driver of hypertension through sympathoexcitatory actions within the central nervous system (CNS) (Reid *Am J Physiol*, 1992; Fisher & Paton *J Hum Hypertens*, 2012).
- Ang II induces oxidative stress, inflammation, and endoplasmic reticulum (ER) stress in the CNS during hypertension (Zimmerman et al. *Circ Res*, 2004; Marvar et al. *Curr Opin Pharmacol*, 2011; Young et al. *J Clin Invest*, 2012).

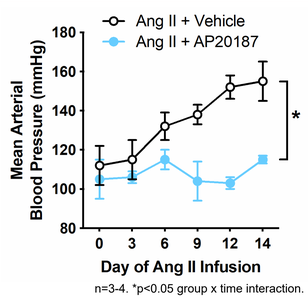
Cellular senescence may be an integrative mechanism for Ang II-induced hypertension



- Oxidative stress, inflammation, and ER stress can lead to cellular senescence (Childs et al. *Nat Med*, 2015).
- Cellular senescence is a cell state characterized by prolonged and irreversible cell cycle arrest. While commonly thought to occur in dividing cells, post-mitotic cells (e.g. neurons) can also undergo senescence.
- Senescence results in the senescence-associated secretory phenotype (SASP), altered cellular metabolism, and macromolecular damage.
- Cellular senescence contributes to conditions that are closely associated with hypertension, including aging and neurodegenerative diseases (Kritsilis et al. *Int J Mol Sci,* 2018; Sikora et al. *Curr Vasc Pharmacol*, 2014).

Removal of senescent cells prevents Ang II-induced hypertension





n=3-4. *p<0.05 group x time interaction.

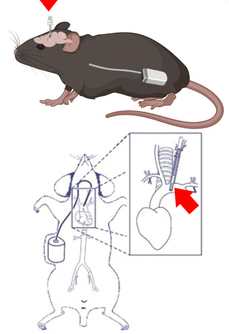
- The transgenic INK-ATTAC mouse model allows for selective elimination of senescent cells with the drug AP20187, which induces the dimerization of a caspase 8 fusion protein to drive apoptosis in senescent cells expressing *p16* (Baker et al. *Nature,* 2011).
- Adult p16^{INK4a}-ATTAC male mice were implanted with subcutaneous mini-osmotic pumps for continuous infusion of Ang II (600 ng/kg/min). Additionally, mice received daily injections of the activating drug AP20187 or vehicle control.
- Removal of senescent cells prevented hypertension development. However, it is unclear where senescent cells are accumulating.

HYPOTHESIS

CNS cellular senescence is a novel contributor to hypertension.

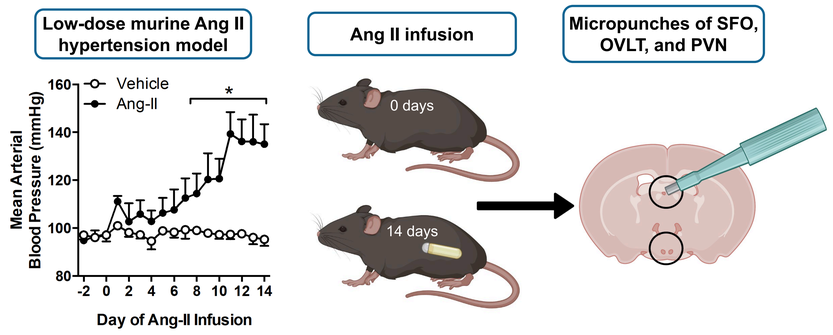
METHODS

Influence of CNS-specific cellular senescence on blood pressure regulation



- Adult C57Bl/6J male mice were implanted with radiotelemeters for continuous blood pressure recordings in conscious, freely moving mice.
- Mice were also instrumented with intracerebroventricular (ICV) cannulas.
- The senescence-inducing agent doxorubicin or vehicle control was administered ICV daily over 3 days.
- Following 3 days of ICV injections, ganglionic blockade was performed via administration of chlorisondamine (12 mg/kg).

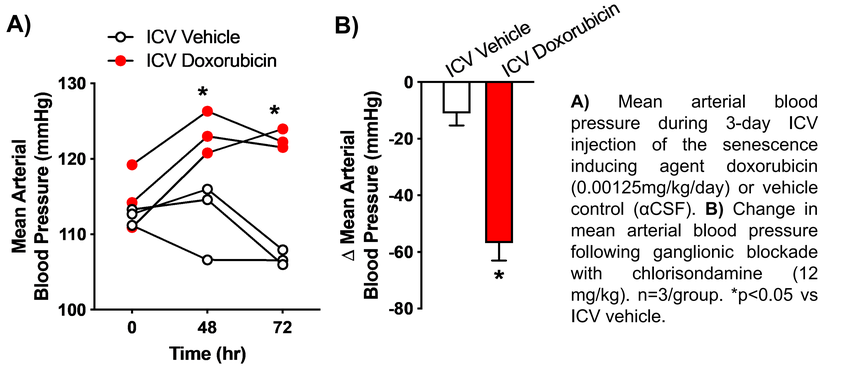
Profiling of cellular senescence/SASP in CNS cardioregulatory nuclei during Ang II hypertension development



- Adult C57Bl/6J male mice were implanted with subcutaneous mini-osmotic pumps for continuous infusion of Ang II (600 ng/kg/min). Brains were collected at baseline (day 0) and following 14-day Ang II infusion.
- Micropunches of cardiovascular/autonomic regulatory nuclei including the subfornical organ (SFO), organum vasculosum lamina terminalis (OVLT), and paraventricular nucleus of the hypothalamus (PVN) were collected for quantitative real-time PCR.

RESULTS

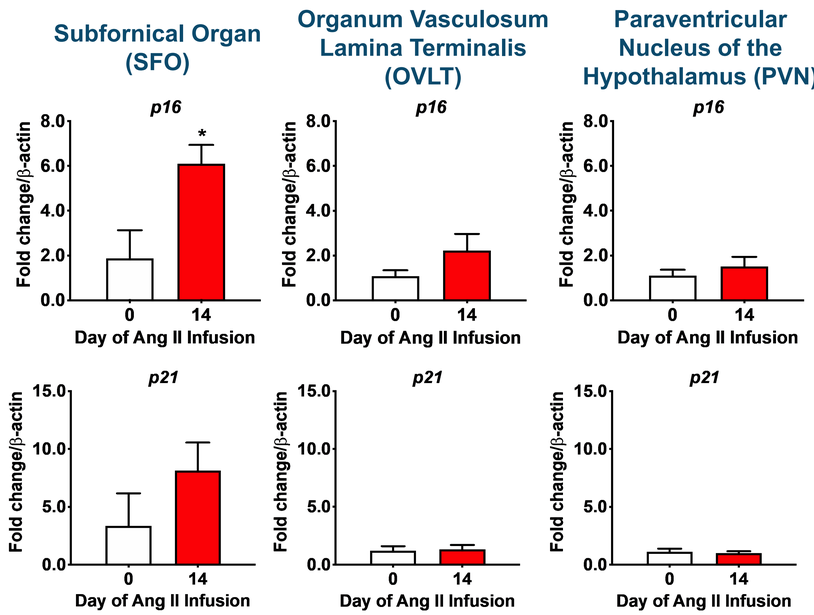
Induction of CNS senescence results in a hypertensive phenotype



A) Mean arterial blood pressure during 3-day ICV injection of the senescence inducing agent doxorubicin (0.00125mg/kg/day) or vehicle control (αCSF). **B)** Change in mean arterial blood pressure following ganglionic blockade with chlorisondamine (12 mg/kg). n=3/group. *p<0.05 vs ICV vehicle.

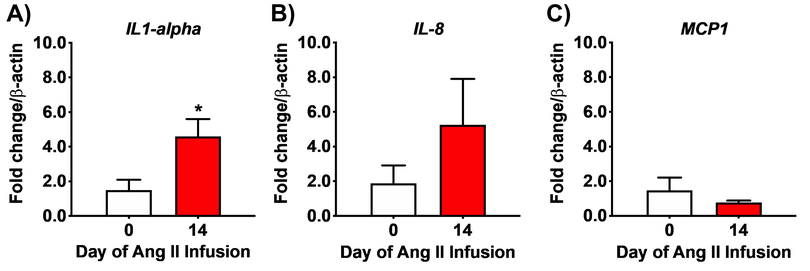
RESULTS

Ang II-induced hypertension is associated with changes in senescent gene expression in the SFO, but not the OVLT or PVN.



Real-time quantitative PCR analysis of the key senescent markers *p16* (top) and *p21* (bottom) in micropunches of the SFO (left), OVLT (middle), and PVN (right) at baseline (Day 0) and following 14 days of Ang II infusion. n=4-5/group. *p<0.05 vs Day 0.

Ang II-induced hypertension is paralleled by the upregulation of SASP markers in the SFO.



Real-time quantitative PCR analysis of the SASP markers **(A)** *IL1-alpha*, **(B)** *IL-8*, and **(C)** *MCP1* in micropunches of the SFO at baseline (Day 0) and following 14 days of Ang II infusion. n=4-5/group. *p<0.05 vs Day 0.

CONCLUSIONS

1) **Acute induction of cellular senescence selectively in the CNS results in elevations in arterial blood pressure.**
2) **Ang II elicits cellular senescence/SASP in the SFO, but not in other cardioregulatory nuclei including the PVN and OVLT.**

Collectively, these data may point to brain cellular senescence as a novel mediator of hypertension.

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