The Alpha-7 Nicotinic Acetylcholine Receptor Mediates a Uniquely Human Response to Burn Injury

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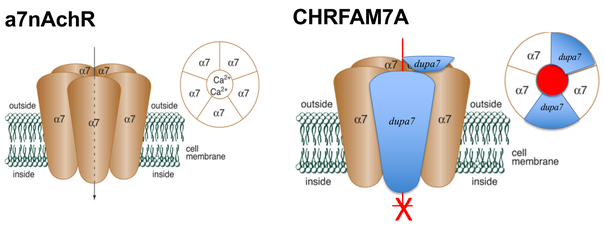
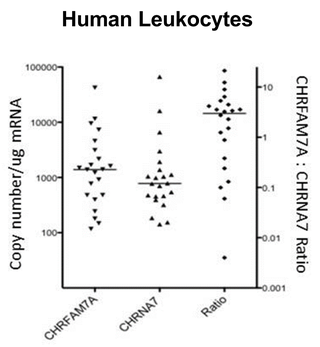
Background

- There is considerable human variability in the systemic inflammatory response (SIRS) to injury.
- The alpha-7 nicotinic acetylcholine receptor (α7nAChR), encoded by the CHRNA7 gene, is required for the anti-inflammatory response necessary to resolve tissue injury.
- The human genome encodes a uniquely human gene called CHRFAM7A that is a negative regulator of α7nAChR-mediated signaling.

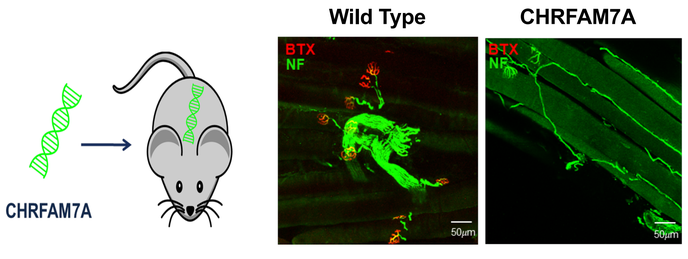
Human Leukocyte CHRNA7 and CHRFAM7A Expression is Highly Variable





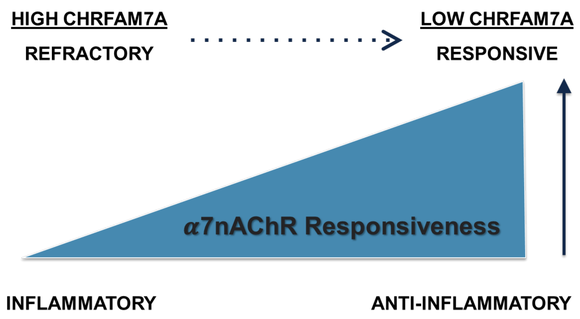
- Peripheral blood collected from healthy volunteers.
- The ratio of CHRFAM7A:CHRNA7 expression varies up to 10,000-fold between individuals
- The ratio of CHRFAM7A to CHRNA7 expression may predict α7nAchR-mediated anti-inflammatory responsiveness.

CHRFAM7A Expression Alters Binding to the a7nAchR



- Transgenic mice were engineered to express the human CHRFAM7A gene under control of the EF1α promoter in C57BL/6 mice.
- Muscle harvested and stained *ex vivo* with alpha-bungarotoxin (BTX, red) to visualize the α7nAchR and neurofilament (NF, green) to visualize the neuromuscular junction.
- Exposure matched confocal microscopy images demonstrate that CHRFAM7A decreases ligand binding to the α7nAchR in this transgenic mouse model.
- Defining the effects of a7nAchR loss on the injury response may give important insights into the effects of CHRFAM7A expression in humans

Binding to the a7nAchR Mediates the Anti-Inflammatory Response to Injury



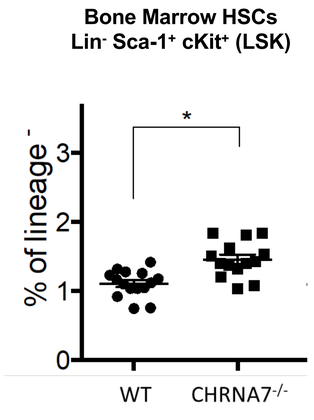
Hypothesis

- We hypothesized that loss of the a7nAchR would produce a phenotype similar to CHRFAM7A overexpression
- a7nAchR knockout mice would have an increased bone marrow reservoir of stem cells that would modulate myeloid cell mobilization after burn injury.

Methods

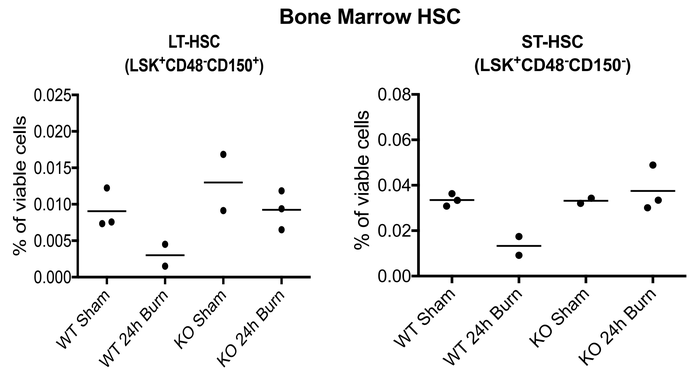
- Age and gender matched a7nAchR knockout mice (CHRNA7$^{-/-}$) compared to wild-type siblings
- 30% TBSA steam burn injury
- Animals resuscitated with saline
- Bone marrow and blood collected 24 hours after injury for flow cytometry

a7nAchR Knockout Increases the Bone Marrow Stem Cell Reservoir



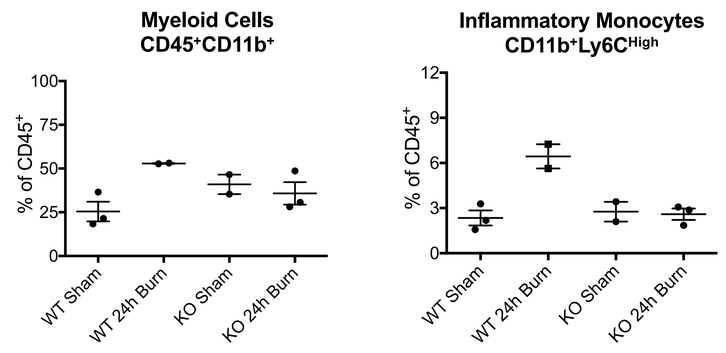
- Compared to WT mice, there was a significant increase in the bone marrow reservoir of Lin$^-$ Sca-1$^+$ c-Kit$^+$ (LSK) hematopoietic stem cells (HSC) in the bone marrow of a7nAchR knockout mice

Loss of the a7nAchR Attenuates Burn-induced HSC Exhaustion



- As expected, 30% TBSA burn injury decreased bone marrow Long-term (LT) and Short-term (ST) HSCs as they mobilize to sites of tissue injury.
- While LSK cells decrease after burn injury in a7nAchR KO mice, they maintain a reservoir of HSCs at levels similar to WT Sham mice.

a7nAchR Knockout Decreases Circulating Myeloid Cells after Burn Injury



Conclusion

- Loss of the a7nAchR increases myeloid cell mobilization into the circulation with increased trafficking to the lung after severe burn injury.
- Uniquely human genes like CHRFAM7A may contribute to individual variability in the SIRS response and alter the effects of vagal therapeutics that target the a7nAchR

References

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