A Uniquely Human Mechanism Regulating the Inflammatory Response to Injury

Todd Costantini, MD, FACS
Division of Trauma, Surgical Critical Care, Burns and Acute Care Surgery
UC San Diego Health

* No Disclosures
Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin


Serum TNF-α

Development of Shock (Mean Arterial BP)

Vagal nerve stimulation protects against burn-induced intestinal injury through activation of enteric glia cells


Targeting α-7 Nicotinic Acetylcholine Receptor in the Enteric Nervous System

A Cholinergic Agonist Prevents Gut Barrier Failure after Severe Burn Injury


A pharmacologic approach to vagal nerve stimulation prevents mesenteric lymph toxicity after hemorrhagic shock

Koji Morishita, MD, Todd W. Costantini, MD, Akinori Ueno, PhD, Vishal Bansal, MD, Brian Eliceiri, PhD, and Raul Coimbra, MD, PhD, San Diego, California

Morishita et al. J Trauma Acute Care Surg. 2015;78:52-59
Alpha-7 nAChR Gene Knock Out Eliminates Vagal Responsiveness
Vagal Therapeutics Require the α7nAChR

Delivery of Ligands to Mimic the Natural Biology of α7nAchR

NATURE
(from vagus nerve)

Pharmaceutics
(nicotine, etc…)

α7nACh Receptor

ANTI-INFLAMMATION
Vagal Agonists Have Had Limited Effectiveness in Human Trials Thus Far…
Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis


*Amsterdam Rheumatology and Immunology Center, Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands; ©Laboratory of Biomedical Science, Feinstein Institute for Medical Research, Manhasset, NY 11030; 
©University Clinical Hospital, Mostar 88000, Bosnia and Herzegovina; ©Clinical Hospital Center Sestre Milosrdnice, Zagreb 10000, Croatia; §Sarajevo University Clinical Center, Sarajevo 71000, Bosnia and Herzegovina; ¶Department of Neurosurgery, Hofstra Northwell School of Medicine, Manhasset, NY 11030, and ¶SetPoint Medical Corporation, Valencia, CA91355
Does the Uniquely Human Gene CHRFAM7A Regulate a Human Response to Injury?
CHRFAM7A, a human-specific and partially duplicated $\alpha_7$-nicotinic acetylcholine receptor gene with the potential to specify a human-specific inflammatory response to injury

Todd W. Costantini, Xitong Dang, Raul Coimbra, Brian P. Eliceiri, and Andrew Baird
**EFFECTIVE**

- Mouse
- Humans with low CHRFAM7A

**NOT EFFECTIVE**

- Humans with high CHRFAM7A
- α7nAchR knock out mice
CHRFAM7A is a Uniquely Human Open Reading Frame that Produces Protein

A. anti-CHRFAM7A peptide Immunoblotting

3T3 | THP1
---|---
 Forced Expression (Mouse) | Over-Expressed (Human)

B. anti-CHRFAM7A peptide Immunostaining

Parental BALB-3T3 | CHRFAM7A BALB-3T3
CHRFAM7A Expression is Variable in Donor Leukocytes

200-fold Differences in CHRFAM7A Expression Between Normal Human Leukocyte Donors
CHRFAM7A to CHRNA7 Expression Ratio in Human Leukocytes

Up to 10,000-fold Differences in CHRFAM7A/CHRNA7 Ratio Between Normal Human Leukocyte Donors
Hypothesis:

CHRFAM7A contributes to human variability in the inflammatory response and modulates the response to vagal therapeutics
CHRFAM7A: Modulator of Human Vagal Responsiveness?
Does CHRFAM7A have Biologic Activity?
A Human-Specific α7-Nicotinic Acetylcholine Receptor Gene in Human Leukocytes: Identification, Regulation and the Consequences of CHRFAM7A Expression

Todd W Costantini,1* Xitong Dang,1,2* Maryana V Yurchyshyna,1 Raul Coimbra,1 Brian P Eliceiri,1 and Andrew Baird1

Vector THP1  THP1-CHRFAM7A

Pathways altered by CHRFAM7A gene expression

<table>
<thead>
<tr>
<th>Enriched Pathways</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-beta signaling pathway</td>
<td>2.76E-002</td>
</tr>
<tr>
<td>Insulin signaling pathway</td>
<td>2.23E-002</td>
</tr>
<tr>
<td>Leukocyte transendothelial migration</td>
<td>1.78E-002</td>
</tr>
<tr>
<td>RIG-I-like receptor signaling pathway</td>
<td>1.78E-002</td>
</tr>
<tr>
<td>Osteoclast differentiation</td>
<td>1.74E-002</td>
</tr>
<tr>
<td>Cytokine-cytokine receptor interaction</td>
<td>1.64E-002</td>
</tr>
</tbody>
</table>
CHRFAM7A Over-expression Decreases Leukocyte Migration

Migration Assay

Costantini et al, unpublished data
CHRFAM7A introduced into PC12 cells

PCR

CHRFAM7A      CHRNA7

Vector  CHRFAM7A  Vector  CHRFAM7A

Immunoblot

Vector  CHRFAM7A

42kDa

Costantini et al, unpublished data
CHRFAM7A decreases ligand binding to the a7nAchR
CHRFAM7A Gene Expression is Variable in Human Macrophages

Costantini et al, unpublished data
CHRFAM7A Transgenic Mice

CHRFAM7A PCR

Brain  Lung  Liver  Kidney  Adrenal  Spleen  Small Bowel  Colon
CHRFAM7A: Modulator of Human Vagal Responsiveness

- CHRFAM7A decreases binding to the α7nAchR
- CHRFAM7A expression levels vary widely between individuals
- CHRFAM7A is biologically active in macrophages
- CHRFAM7A alters macrophage gene expression in pathways related to inflammation and the immune response
- CHRFAM7A expression modulates the human anti-inflammatory reflex
CHRFAM7A: Modulator of Human Vagal Responsiveness?
UC San Diego Division of Trauma, Surgical Critical Care, Burns and Acute Care Surgery

Research Team:
- Andrew Baird, PhD
- Brian Eliceiri, PhD
- Raul Coimbra, MD, PhD
- Theresa Chan, MD
- Elliot Williams, MD
- Simone Langness, MD
- Emelie Amburn
- Olga Cohen
- Ann-Marie Hageny

Research Support:
- NIH 1R01GM121530: The Human-Specific Gene CHRFAM7A in Leukocytes

Prior Research Support:
- American Surgical Association Foundation Research Fellowship
- American College of Surgeons C. James Carrico Faculty Research Fellowship
- American Association for the Surgery of Trauma Faculty Scholarship Award