Inhibition of TNF-Alpha Signaling Can Prevent Degeneration of Parasympathetic Nerve by Upregulating ERK signaling

Hotaka Matsui\textsuperscript{1,2}, Nikolai A. Sopko\textsuperscript{1}, Max Kates\textsuperscript{1}, Xiaopu Liu\textsuperscript{1}, Emmanuel Weyne\textsuperscript{3}, Maarten Albersen\textsuperscript{3}, Trinity J. Bivalacqua\textsuperscript{1}

1. The James Buchan Brady Urological Institute, The Johns Hopkins School of Medicine, Baltimore, MD
2. Department of Urology, Doai Memorial Hospital and the University of Tokyo, Tokyo, Japan
3. Department of Experimental Urology, KU Leuven, Leuven, Belgium
Disclosure

I have no relevant financial relationships to disclose
• Erectile dysfunction (ED) is induced by cavernous nerve (CN) injury after radical prostatectomy (RP) [Walsh. J Urol 2007, Urology 2000].

• TNF-alpha (TNFA) was upregulated after bilateral cavernous nerve injury (BCNI) [Albersen. Sex Med. 2013].

• Upregulation of TNFA was shown to induce neuronal death following sciatic nerve injury [Shamash. J Neurosci. 2002].
TNF-Alpha Is Increased Following Cavernous Nerve injury

A. \( Tnfa \)

Relative Expression

Sham 6h 12h 24h 48h 7d 14d 21d

B. \( Tnfr1 \)

Relative Expression

Sham 6h 12h 24h 48h 7d 14d 30d 60d

C. \( Tnfr2 \)

Relative Expression

Sham 48h 7d 14d

\( \beta \)-actin

Matsui, et al. 2016 (under review)
Activation of ERK Signaling Is Crucial to Induce Peripheral Nerve Regeneration

- Activation of ERK signaling pathway induces Schwann cell dedifferentiation
  Harrisingh, et al. EMBO J. 2004

- Downregulation of ERK signaling resulted in delayed nerve regeneration
Objectives

To evaluate the effect of inhibition of TNFA signaling on

1. Penile smooth muscle function after BCNI
2. Activation of ERK signaling
Materials and Methods

Wild Type (WT)

TNFA-Receptor 1,2 Knock-Out (TNFRKO)

Sham (n=6)

BCNI (n=6)

Penises and MPG were harvested 48 h after surgery

Penises: Myographs
Contraction & Relaxation

MPGs: qPCR
Nos1, Chat, Th, Erk1/2
BCNI Enhanced Contraction of WT Penis

Penis EFS

* indicates p<0.05.

EFS: electrical field stimulation
BCNI impaired Relaxation of WT Penises

EFS Relaxation

-150
-100
-50
0
2 4 8 16 32
Frequency [Hz]
Relaxation [%max PE]

WT Sham
WT BCNI 48h
KO Sham
KO BCNI 48h

* indicates p<0.05.

EFS following precontraction by phenylephrine (PE) 10^{-4} M

* ns
Gene Expression of *Nos1* Was Upregulated in the MPGs of TNFRKO mice

*Nos1 codes for neuronal nitric oxide synthase*
BCNI Downregulated gene expression of *Chat* both in WT and TNFRKO MPGs

* indicates p<0.05.

*Chat* codes for choline acetyltransferase
Gene expression of *Th* was not affected by inhibiting TNFA signaling

*Th*

*Th* codes for tyrosine hydroxylase
mRNA Expression of ERK Was Upregulated by Inhibiting TNFA Singaling

* indicates p<0.05.

Erk codes for extracellular signal regulated kinases
Conclusions

- BCNI enhanced EFS contraction response in WT, which was not seen in TNFRKO
- BCNI impaired parasympathetic-mediated relaxation response of penile smooth muscle in WT
- However, BCNI did not affect relaxation response in TNFRKO
- TNFRKO mice showed enhanced gene expression of Nos1 (neuronal nitric oxidase) and ERK1/ERK2

**Inhibition of TNFA may prevent ED following RP may by activating ERK signalling and by protecting nitrergic nerve function**
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