The Antisense Transcript NUDT6 in Vascular Disease

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Disclosure

Speaker name:

.............Hanna Winter........................................................

I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

☐ I do not have any potential conflict of interest
Background

Atherosclerosis

AAA

Risk factors
hypertension, genetics, smoking

Abdominal aortic enlargement of >3cm
1. Local Inflammation
2. ECM Degradation
3. SMC Apoptosis

Stroke

Atherosclerotic lesions
Plaque Rupture
1. Local inflammation
2. Lipid formation + deposition
3. SMC Apoptosis

http://www.huntervascular.com/aaa/
**Non-coding RNAs**

- > 200nt
- Fully processed
- Transcribed from opposite strand of protein-coding transcript
  - Share complementary exons

**Natural Antisense Transcripts**

- miRNAs → Post-transcriptional gene regulation
- piRNAs → Germ line transposon silencing
- snoRNAs → RNA modification
- snRNAs → pre-mRNA splicing
- tRNAs → Translation
- H1 RNA → pre-tRNA processing
- RMRP → mtRNA processing, rRNA processing
- 7SL RNA → Direction of protein traffic
- TERC → Maintenance of telomere ends
- scaRNAs → RNA modification
- rRNAs → Translation
- Y RNAs → DNA replication, small RNA maturation

Boon et al. JACC 2015
Nudt6 – high levels in plaque and AAA

Transcriptomic profiling

Microdissected fibrous caps of human plaques

Stable

Ruptured

Human

Nudt6 mRNA (fold)

Control

AAA
Nudt6 – high levels in human plaque and AAA
Nudt6 – A Natural Antisense Transcript

“Survival factor”: Smooth Muscle Cell proliferation & apoptosis
Nudt6 modulation affects proliferation and apoptosis in human AoSMCs

control

Nudt6 overexpression

Proliferation

Apoptosis
NUDT6 inhibition using Antisense Oligonucleotide Gapmers

carotid artery ligation and cuff

Ligation + 4 d

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rupture (%)

- scr
  - n=11
- NUDT6 GapmeR
  - n=9

* p < 0.05

Scramble

GapmeR

Diameter [mm]

Time [days]
FGF2, Smooth Muscle Actin, Caspase 3, and Ki67 expression upon Nudt6 modulation
Summary and Perspectives

Non-diseased state: Nudt6 - Fgf2

Atherosclerosis:
- Proliferation
- Migration
- Matrix production
- Apoptosis

Nudt6 - Fgf2

Proliferation
Migration
Matrix production
Apoptosis

? ? ?
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Transfection of hAoSMCs

**FGF2 levels after NUDT6 silencing**

- scr+ANGII
- siR+ANGII

**Nudt6 level after Nudt6 silencing**

- scr+ANGII
- siR+ANGII
αSMA IHC

Scramble

GapmeR

NC

FC

T

NC

FC

NC
Nudt6 ISH and FGF2 IHC

NUDT6 levels

FGF2 IHC

Scramble

GapmeR

Scramble

GapmeR
αSMA IHC

Scramble

GapmeR