



The NO pathway in Marfan disease: the way to go?



Patrick Sips, PhD



CENTER FOR MEDICAL GENETICS GHENT

Conflicts of interest

None



Aortic aneurysm progression





Increased NO production from NOS2 in MFS



Aorta of 16-week-old mice

Patient aortic media



Oller et al., Nat Med 23(2):200-212 (2017)

NOS2

NO

NOS2-derived NO is detrimental in MFS



16 weeks treatment of mice with 1400W in drinking water (100 mg/L), started at age of 12 weeks

1400W = specific NOS2 inhibitor approx. 1000x more specific for NOS2 than NOS1 or NOS3 NOS2

NO

1400W

sGC-PKG mediates NOS2-derived NO effects



de la Fuente-Alonso *et al.*, Nat Comm 12:2628 (2021)



NOS2 induction followed by production of large amounts of NO and overactivation of sGC-PRKG1 is detrimental in MFS

NO is required for protection by losartan

Fbn1^{C1039G/+}model





L-NAME treatment for 6 weeks (0.5 mg/mL in drinking water

+ bi-weekly i.p. injections first 2 weeks) started at 6 weeks of age

L-NAME = pan-NOS inhibitor

Sellers et al., Am J Pathol 188(3):574-585 (2018)

NOS3 signaling protects against MFS aortopathy

Fbn1^{C1039G/+}model



Ser1176 to Asp: phosphomimetic → increased NOS3 activity No effect on blood pressure

CavNOxin peptide treatment: 2.5 mg/kg, i.p. every 3 days for 12 weeks







Sellers et al., Am J Pathol 188(3):574-585 (2018)

CavNOxin NOS3

NO

cGMP-specific phosphodiesterase inhibition in MFS mouse model

Fbn1^{C1039G/+}model



18 weeks of sildenafil citrate treatment, started at 6 weeks of age (50 mg/kg/day in drinking water)

White et al., Am J Pathol 189(8):P1536-1546 (2019)

NOS2

NOS3

NOS1

cGMP-specific phosphodiesterase inhibition in MFS mouse model

Fbn1^{C1039G/+}model



18 weeks of sildenafil citrate treatment, started at 6 weeks of age (50 mg/kg/day in drinking water)

White *et al.*, Am J Pathol 189(8):P1536-1546 (2019)



NO produced by NOS3 has protective effects in MFS Role of cGMP is ambiguous



NO-dependent signaling: Detrimental vs protective?

Depending on source, amount, localization, timing, environment, downstream effectors, ...



NO-dependent signaling: Detrimental vs protective?

Depending on source, amount, localization, timing, environment, downstream effectors, ...



Julie De Backer Violette Deleeuw Laura Muiño Mosquera Karo De Rycke Marina Horvat Lisa Caboor Griet Desmet

Ghent University Special Research Fund

Acknowledgements





UP2 UZ GENT

Paul Coucke Anne De Paepe

Marjolijn Renard Liesbeth Van Wildero-Van Wouwe

f W O Opening new horizons

