Controlled Delivery of Reactive Sulfur Species for Stimulating Angiogenesis

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Reactive oxygen species (ROS)  
\[ \text{H}_2\text{O}_2, \cdot \text{O}_2^-, \cdot \text{OH} \ldots \]

Reactive nitrogen species (RNS)  
\[ \text{NO, ONOO}^-, \text{N}_2\text{O}_3 \ldots \]

Reactive sulfur species (RSS)  
\[ \text{H}_2\text{S, H}_2\text{S}_n, \text{RSS}_n\text{H, S}_2\text{O}_3^{2-} \ldots \]

ROS, RNS and RSS are small reactive molecules that are produced endogenously in cells and regulate cellular redox signaling.
H$_2$S is generated in cells through cysteine metabolism and oxidized to a series of sulfur species such as per/polysulfides via enzymatic and non-enzymatic processes.
RSS biology

Angiogenesis

Cytoprotection

Regulation of cancer cell proliferation

Proangiogenic activity of RSS

Neurotransmission

Brain: neuroprotective

Vasculature: protective, pro-dilatory, inhibits platelet aggregation

Lungs: relaxes airways

Heart: protective

Visceral pain: hyperalgesic

GALT: protective

Regulation of inflammation


Challenges in therapeutic applications of RSS

- Inherent instability, short half-lives in the body
- Time- and dose-dependent biological activities
- Complex sulfur biochemistry

Common Approach: Small donor molecules

RSS donor → RSS

Limitations

- Fast and uncontrolled rate of RSS release
- Side effects caused by the donor compounds and/or decomposition byproducts
- Poorly controlled pharmacokinetics
Our approach: Polymeric micelles for controlled release of RSS

- Sustained/controlled RSS release by optimizing micelle core design
- Inhibition of side effects caused by the donor molecules
- Improved solubility and stability of RSS donors
- Modulating interaction with cells and biological systems

Controlled H$_2$S release from the polymeric micelles

H$_2$S donor (ADT)
Hydrophobic

H$_2$S release in human umbilical vein endothelial cells (HUVECs)

1: n=74, m=21, x=21
2: n=100, m=21, x=18
3: n=100, m=21, x=12

Self-assembly

Micelle 1
Micelle 2
Micelle 3

Rigid core
Flexible core

Proangiogenic activity of the H$_2$S donor micelles

Figure. Blood vessel structure of the CAMs treated with growth factor reduced Matrigel containing (A) PBS (NT), (B) VEGF$_{121}$ (11 µg/mL), (C) ADT (0.58 mM) and (D) Micelle 3 (0.58 mM ADT moieties). The samples were placed on the CAM on embryonic day 9. On day 11, the CAMs were fixed, took out from eggs and observed using macro zoom microscope. Scale bar: 2 mm. (E) Semi-quantitative scoring. *** p<0.001 versus NT, n=8-10.

Can we further boost the proangiogenic activity of H$_2$S?

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Per/polysulfide delivery by catalytic polymeric micelle system

H$_2$S oxidation by MnPMCs

Proangiogenic activity of MnPMCs


* ADT: Small H$_2$S donor
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