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**“Functional Dichotomy of a Newly Discovered Thioredoxin-
1/Soluble Guanylyl Cyclase Complex”**

by
Chuanlong Cui

Molecular Biology, Genetics, and Cancer Program

B.Sc., 2011, China Pharmaceutical University, Nanjing, China

M.Sc. 2013, New Jersey Institute of Technology, Newark, NJ

Thesis Advisors: Annie Beuve, Ph.D., Professor
Department of Pharmacology, Physiology and Neuroscience

Hong Li, Ph.D., Associate Professor
Department of Microbiology, Biochemistry and Molecular Genetics

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ABSTRACT

Soluble guanylyl cyclase (GC1) is an α/β heterodimer producing cGMP when stimulated by nitric oxide (NO). GC1 and the oxido-reductase Thioredoxin-1 (Trx1) form a complex that mediates NO signaling pathways as a function of the redox state of the cells. Under physiological conditions, reduced Trx1 (rTrx1) supports the canonical NO-GC1-cGMP pathway by protecting GC1 activity from thiol oxidation. Under oxidative stress, the NO-cGMP pathway is disrupted by S-nitrosation of specific Cysteines (Cys) on GC1, leading to GC1 desensitization to NO stimulation. We discovered that under oxidative conditions, GC1- α subunit increases cellular S-nitrosation via transfer of nitrosothiols to other proteins (transnitrosation) in cardiac and smooth muscle cells. One of the GC1 SNO-targets was the oxidized Trx1 (oTrx1), which is unidirectionally transnitrosated by GC1 with α C610 as a SNO donor. Because oTrx1 itself drives transnitrosation, we sought and identified SNO-proteins targeted by both GC1 and Trx1. We found that transnitrosation of the small GTPase RhoA by SNO-GC1 requires oTrx1 as a nitrosothiol relay, suggesting a SNO-GC1 \rightarrow oTrx1 \rightarrow RhoA cascade. The RhoA signaling pathway, which is antagonized by the canonical NO-cGMP pathway, was alternatively inhibited by GC1- α -dependent S-nitrosation under oxidative conditions. In addition, we designed an inhibitory peptide that blocks the interaction between GC1 and Trx1. This inhibition resulted in the loss of a) GC1 cGMP-forming activity *in vitro* and in cells, b) Trx1's ability to reduce the multimeric and oxidized GC1, and c) GC1's ability to fully reduce oTrx1, thus identifying GC1's novel reductase activity. Moreover, the inhibitory peptide blocked the transfer of nitrosothiols from SNO-GC1 to oTrx1. In Jurkat T cells, oTrx1 transnitrosates procaspase-3, thereby inhibiting caspase-3 activity. Using the inhibitory peptide, we demonstrated that S-nitrosation of caspase-3 is the result of a transnitrosation cascade initiated by SNO-GC1 and mediated by oTrx1. Consequently, the peptide significantly increased caspase-3 activity in Jurkat T cells. Taken together, we propose that SNO-GC1, via transnitrosation, mediates adaptive responses triggered by oxidation of the canonical NO-cGMP pathway and oTrx1 functions as a relay in GC1-dependent transnitrosation to regulate cellular functions. Our findings will provide insights into a better understanding of the mechanisms for NO signaling transduction, which plays an essential role in cardiovascular pathophysiology, and will provide a potential therapy for the treatment of cancers.