

POSTER PRESENTATION

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# Genetic silencing of sGC $\beta$ 1 in cancer: role of epigenetic regulation

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From 6th International Conference on cGMP: Generators, Effectors and Therapeutic Implications  
Erfurt, Germany. 28-30 June 2013

## Background

The nitric oxide (NO) receptor soluble guanylyl cyclase (sGC) is composed of two subunits of  $\alpha$ 1,2 and  $\beta$ 1,2, sGC $\alpha$ 1 $\beta$ 1 being the major heterodimer that catalyzes the formation of second messenger cGMP. NO-cGMP signaling plays a critical role in numerous processes, and retarded signaling function by either limited NO bioavailability, or decrease in expression or activity of sGC correlates with several disease states including hypertension, neurodegenerative disorders, inflammation, and cancer. Our analysis of human databases revealed a statistically significant reduction of sGC transcript levels in multiple human cancer specimens including glioma and breast cancers. We have recently demonstrated that restoration of sGC expression levels in glioma cell lines significantly reduced cell proliferation, colony formation, and growth of orthotopically implanted glioma cells in mice, suggesting a potent anti-tumor property for the sGC. However, the mechanism underlying the genetic silencing of sGC in cancer is unknown.

## Results and discussion

Here we report that sGC $\beta$ 1 is regulated epigenetically by histone acetylation in breast and lung cancers cell lines. Treatment with HDAC inhibitors LBH-589 (panobinostat), MS-275 (entinostat) and Trichostatin-A were able to increase expression levels of sGC $\beta$ 1 up to 25 fold above control in the triple negative breast cancer cell line MDA-MB-231. However, the treatment of cells with histone lysine demethylase inhibitor (BIX-0192); the histone lysine demethylase inhibitor (trans-2-PCPA), and DNA methylation inhibitors (5-aza-2'-deoxycytidine and chlorogenic acid) had no effect on sGC $\beta$ 1 expression. Thus, histone acetylation plays an influential role in regulating sGC $\beta$ 1

expression, while other epigenetic marks such as DNA methylation, and histone methylation do not. Over expression of histone deacetylase (HDAC) isoforms 1 and 3 significantly reduced sGC $\beta$ 1 expression, and pharmacological inhibition of histone acetyl transferase (HAT) p300/pCAF achieved a similar result. Further analysis of the molecular aspects of sGC $\beta$ 1 epigenetic regulation should offer opportunities to target diseases, such as cancer, that are marked by decreased sGC $\beta$ 1 expression.

Published: 29 August 2013

doi:10.1186/2050-6511-14-S1-P66

**Cite this article as:** Sotolongo et al.: Genetic silencing of sGC  $\beta$ 1 in cancer: role of epigenetic regulation. *BMC Pharmacology and Toxicology* 2013 14(Suppl 1):P66.

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