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Cellular signaling mediated by nitrated cyclic nucleotide and regulated by hydrogen sulfide

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Background

We have discovered earlier 8-nitroguanosine 3',5'-cyclic monophosphate (8-nitro-cGMP) formed as a second messenger for nitric oxide (NO) and reactive oxygen species (ROS), mediating a unique electrophilic cellular signaling. 8-Nitro-cGMP is formed via NO and causes protein S-guanylation. The regulation mechanism for intracellular 8-nitro-cGMP formation and its metabolic fate still remain unclear, however.

Results

Here we identified that hydrogen sulfide anion (SH-) rather than H2S gas per se is a potent negative regulator for endogenous 8-nitro-cGMP. SH- or free thiolate anion, effectively reacts with various 8-nitro-cGMP in cells to primarily generate each SH substituted, or sulfhydrated derivative via their direct chemical sulfhydration with SH-. This electrophile sulfhydration can therefore produce a new nucleophilic derivative, i.e., electrophile to nucleophile bioconversion to be caused by hydrogen sulfide. We also clarified that sulfhydration is functionally active in regulation of electrophilic cellular signaling, mediated by H-Ras oncogene. One of the major pharmacological effects of SH- was brought about by suppression of cellular senescence, caused by 8-nitro-cGMP-dependent Ras activation, involving downstream signaling molecules including Raf/Mek/Erk pathway finally activating p53 in cells.

Conclusion

This may thus indicate an entirely novel aspect of biological functions of hydrogen sulfide in that it eventually behaves as an anion form, rather than a gaseous molecule, and interacts 8-nitro-cGMP to modulate its signaling functions. Moreover, we now consider that 8-nitro-cGMP is a major second messenger regulating electrophilic cellular signaling occurring widely in different species of biota including plants. The discovery of 8-nitro-cGMP and its signal modulator (i.e. hydrogen sulfide) may thus not only open a new era of research on the nucleotide cell signaling but also promote better understanding of the NO-mediated signaling mechanism in both eukaryotic and prokaryotic cells in general.

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