

## **Gas sensing in biology: fine tuning the chemistry**

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Nitric oxide (NO) is a signaling agent in many eukaryotes and also functions in the host-response to infection. NO is toxic so utilization in cell killing makes sense; however, signaling in aerobic organisms poses questions concerning selectivity and specificity. NO used in signaling is synthesized by the constitutive isoforms of enzyme nitric oxide synthase (NOS) that are tightly regulated by  $\text{Ca}^{2+}$  and calmodulin, leading to nM levels of NO. The inducible isoform of NOS synthesizes NO unregulated leading to  $\mu\text{M}$  concentrations in a localized site of infection. NOS catalyzes the conversion of arginine to citrulline and NO. This complicated reaction is carried out by an equally complicated protein. Using a low concentration of NO in signaling solves the toxicity problem but places a difficult chemical requirement on the NO receptor, the soluble isoform of guanylate cyclase (sGC). sGC contains a heme cofactor that acts to trap NO, thereby activating the enzyme. The heme in sGC is identical to the heme in the globins, yet sGC does not bind  $\text{O}_2$ . The heme domain of sGC was found to be part of the H-NOX (Heme-Nitric oxide OXYgen) family of proteins with homologues in aerobic and anaerobic prokaryotes. Structural and biochemical studies have provided a molecular explanation for the ligand discrimination against  $\text{O}_2$  in sGC, leading to the ability to predict ligand specificity and function in a wide range of organisms.