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## **Nitrite Reductase Function of Deoxymyoglobin Oxygen Sensor and Regulator of Cardiac Energetics and Function**

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### **Abstract:**

Although the primary function of myoglobin (Mb) has been considered to be cellular oxygen storage and supply, recent studies have suggested to classify Mb as a multifunctional allosteric enzyme. In the heart, Mb acts as a potent scavenger of nitric oxide (NO) and contributes to the attenuation of oxidative damage. Here we report that a dynamic cycle exists in which a decrease in tissue oxygen tension drives the conversion of Mb from being an NO scavenger in normoxia to an NO producer in hypoxia. The NO generated by reaction of deoxygenated Mb with nitrite is functionally relevant and leads to a downregulation of cardiac energy status, which was not observed in mice lacking Mb. As a consequence, myocardial oxygen consumption is reduced and cardiac contractility is dampened in wild-type mice. We propose that this pathway represents a novel homeostatic mechanism by which a mismatch between oxygen supply and demand in muscle is translated into the fractional increase of deoxygenated Mb exhibiting enhanced nitrite reductase activity. Thus, Mb may act as an oxygen sensor which through NO can adjust muscle energetics to limited oxygen supply.

Key-words: Nitrite, hypoxia, myoglobin, cardiac function