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Myoglobin-structure, function, and medical importance

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Abstract
This research provides a contemporary review of Myoglobin (Mb), the oxygen-binding protein in muscle. It focuses on its unique molecular structure, multifaceted functions (oxygen storage, nitric oxide regulation, intracellular oxygen transport), and its critical medical importance as a biomarker in the early diagnosis of myocardial infarction and rhabdomyolysis, while exploring its emerging role in cancer biology.

Keywords: Myoglobin, Protein structure, Heme, Cardiac biomarker, Myocardial infarction, Muscle injury, Rhabdomyolysis, Cancer

1. Introduction
Myoglobin (Mb) is a monomeric heme protein, present in high concentrations in skeletal and cardiac muscle (Ordway & Garry, 2004) [11]. It was the first protein to have its three-dimensional crystal structure determined, forming a cornerstone of structural biology. Traditionally known for its role in oxygen storage and transport, technological advancements have expanded our understanding to include vital regulatory functions and critical diagnostic medical applications particularly in acute cardiac diseases and muscle injuries with emerging evidence of its role in other pathologies such as cancer (Guo *et al*., 2021) [6].

2. Molecular Structure of Myoglobin
Myoglobin features a compact, evolutionarily conserved molecular structure

2.1 Primary & Secondary Structure: Composed of a single polypeptide chain (≈153 amino acids in humans) forming 8 α-helices (A-H) constituting ≈75% of the structure, interconnected by loops (Burmester & Hankeln, 2023) [1].

2.2 Tertiary Structure & Functional Pocket: The protein folds into a globular, compact structure. At its core lies the heme pocket, a hydrophobic environment containing: Heme group: A porphyrin ring centered by a ferrous iron atom (Fe^{2+}), the oxygen (O_2) binding site. Proximal Histidine (His F8): Coordinately bonds to the iron atom from below, stabilizing it. Distal Histidine (His E7): Positioned opposite the iron atom; stabilizes bound oxygen via hydrogen bonding and prevents high-affinity CO binding (Wittenberg & Wittenberg, 2024) [16].

2.3 Properties: Monomeric protein (17.8 kDa), lacks quaternary structure. Its red color (bright red for oxyMb, dark red for deoxyMb) stems from the heme group (Ordway & Garry, 2004) [11].

3. Physiological Function of Myoglobin
Myoglobin's functions extend beyond oxygen storage
3.1 Intracellular Oxygen Storage & Transport: Provides an immediate oxygen reserve at the onset of muscle contraction and facilitates oxygen diffusion from the cell membrane to mitochondria via facilitated diffusion (Wittenberg & Wittenberg, 2024) [16].

3.2 Nitric Oxide (NO) Regulation: Exhibits Nitric Oxide Dioxygenase (NOD) activity, converting NO to nitrate (NO_3^-) (Flögel *et al*., 2001; Hendgen-Cotta *et al*., 2023) [3, 8].

$Mb(Fe^{2+})\text{-}O_2 + NO \rightarrow Mb(Fe^{3+}) + NO_3^-$
*Protects mitochondria from NO-induced respiratory inhibition.
* Regulates local vascular tone and oxygen consumption.

3.3 Protection against oxidative stress: Can react with reactive oxygen species (ROS), potentially contributing to their generation or scavenging depending on cellular context (Gödecke *et al*., 2022) [5].

3.4 Emerging Roles
- **Oxygen Sensing (O_2 Sensing):** May participate in hypoxia response signaling pathways (HIF-1α) (Burmester & Hankeln, 2023) [1].
- **Fatty Acid Binding & Transport:** Studies suggest a potential link to lipid metabolism (Smith & Lynch, 2021) [14].
- **Modulation of Muscle Contraction:** Its interactions with NO influence contraction efficiency [3].

4. Medical Significance of Myoglobin
Its rapid release from damaged muscle underpins its diagnostic value.

4.1 Biomarker in Acute Myocardial Infarction (AMI)
- **Key Advantage:** Speed: Blood levels rise within 1-3 hours of symptom onset (the first cardiac marker to elevate), peak at 6-12 hours, and normalize by 18-24 hours (Thygesen *et al*., 2023; Kristiansen *et al*., 2021) [15, 10]. High Early Sensitivity: Surpasses high-sensitivity cardiac troponin (hs-cTn) sensitivity within the first 0-3 hours (Reichlin *et al*., 2021) [12].
- **Limitation:** Low Specificity: Elevates in any skeletal muscle injury (trauma, surgery, inflammation). Insufficient to confirm AMI alone (Thygesen *et al*., 2023) [15].

Current Diagnostic Role
- **Early Rule-Out:** Used within multi-marker algorithms. A negative result 2-3 hours post-symptoms, combined with normal hs-cTn and a non-diagnostic ECG, aids in confidently ruling out AMI, facilitating rapid discharge of low-risk patients (Risch *et al*., 2023) [13].
- **Complementary Role:** Useful very early (<3h) before hs-cTn shows significant elevation.

4.2 Primary Indicator of Rhabdomyolysis
- **Definition:** Rapid breakdown of skeletal muscle tissue and release of its contents (including massive amounts of Mb).
- **Causes:** Crush injury, extreme exertion, medications (statins), toxins, metabolic disorders, infection (Zimmerman & Shen, 2023) [17].

Role of Myoglobin
- **Diagnosis:** Large, early (hours) elevation in blood is the hallmark laboratory feature (Cervellin *et al*., 2021) [2].
- **Severity Assessment:** Its levels (along with CK) correlate with muscle injury extent and complication risk (KDIGO, 2024) [9].

4.2.1 Myoglobin-Induced Acute Kidney Injury (AKI):
Mechanism: When large amounts of myoglobin reach the kidneys:

Direct toxic effect on renal tubular cells
- Cast formation obstructing renal tubules, especially with dehydration and acidic urine.
- Renal vasoconstriction (KDIGO, 2024; Zimmerman & Shen, 2023) [9, 17].
- **Association:** Elevated blood and urine myoglobin levels strongly correlate with acute kidney injury (AKI) development (Guo *et al*., 2022) [7].
- **Treatment:** Aggressive hydration for forced diuresis is cornerstone. Urine alkalinization may be considered in specific cases (KDIGO, 2024) [9].

4.3 Indicator of Other Skeletal Muscle Injuries: Elevates in trauma, major surgery, intramuscular injection, myositis, acute hereditary myopathies, prolonged seizures (Smith & Lynch, 2021) [14].

4.4 Emerging Role in Oncology
Expression in Tumors: Myoglobin expression found in breast, colon, thyroid, lung, and prostate cancers (Flonta *et al*., 2023; Guo *et al*., 2021) [4, 6].

Proposed Mechanisms (Under Investigation)
- **Facilitating Survival in Hypoxia:** Oxygen transport or metabolic modulation to support tumor growth. Protection from Oxidative Stress: May shield cancer cells.
- **Effect on Proliferation and Metastasis:** May influence metastatic potential.
- **Prognostic and Therapeutic Marker:** Its expression may correlate with prognosis or treatment response in specific cancers (e.g., breast cancer-Flonta *et al*., 2023) [4].

5. Summary and Conclusions
Myoglobin remains a biomolecule of remarkable complexity despite its relative simplicity. Recent research confirms that:-
- Its unique structural features (protected heme pocket, proximal/distal histidine) underpin its multifunctional capacity.
- Its functions extend beyond oxygen storage to include critical roles in nitric oxide (NO) regulation, mitochondrial protection, and facilitated intracellular oxygen diffusion.
- Its paramount diagnostic medical importance lies in: Being the fastest-rising cardiac biomarker in myocardial infarction, making it indispensable in early rule-out strategies when combined with hs-cTn and ECG. Being the most sensitive laboratory indicator for diagnosing rhabdomyolysis and assessing the risk of its life-threatening renal complications.
- Its emerging role in cancer (promoting hypoxia survival, modulating metabolism) opens promising research avenues for understanding tumor biology and developing novel therapeutic strategies.
- Future challenges include refining diagnostic algorithm accuracy for cardiac diseases, elucidating its molecular mechanisms in cancer, and exploring its therapeutic potential (e.g., artificial oxygen carriers)

Conflict of Interest
Not available

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