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The Biochemistry, Physiology, And Clinical Significance of Haptoglobin: A Review

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Abstract

Haptoglobin is a plasma glycoprotein and one of the major acute phase proteins, which is involved in physiological homeostasis, especially in inflammatory states and during haemolysis. Haptoglobin is highly polymorphic at the genetic level in biochemical terms, and for this reason it displays structural and functional variations, which impact on its antioxidant potential and haemoglobin (Hb)-binding capability. In the physiological perspective, haptoglobin prevents tissues from hemoglobin-induced oxidative injury by stably binding to free hemoglobin and aiding its clearance via macrophage scavenger receptors. Furthermore, it is involved in iron homeostasis, vessel integrity and modulation of innate and adaptive immune responses. Clinically, haptoglobin is commonly used as a marker for intravascular hemolysis and systemic inflammation, but there is increasing evidence that it also has significance in cardiovascular disease, metabolic syndrome, hepatic insufficiency and cancer. Changes in haptoglobin levels and glycosylation varieties have been correlated with disease severity and prognosis, indicating its potential value in diagnosis and prognostication. Although it is not disease specific, the interpretation of measurements of haptoglobin processing clinically have improved with modern molecular biology and proteomic techniques. This review

describes the biochemistry, physiology and pathophysiological relevance of haptoglobin in health and disease, highlighting its diverse roles: focusing on new areas that it has found applications, particularly in biomedical research and clinical care.

Keywords: Acute Phase Proteins, haptoglobin, hemoglobin, HP gene

Introduction

Haptoglobin (Hp) is an abundant plasma glycoprotein that is well conserved in mammals and which is produced mainly by hepatocytes but with some extrahepatic expression, depending on the tissue type rod of lung, kidney, fat cell and spleen especially under inflammatory conditions. Hp is a positive acute-phase protein and fulfils an important protective function through the scavenging free hemoglobin (Hb) liberated into the blood during intravascular hemolysis (Schaer et al., 2013). The resulting Hp–Hb complexes are cleared by macrophages through CD163 scavenger receptor, which prevents heme-mediated oxidative toxicity and supports iron recycling. By this means Hp promotes maintenance of cellular redox homeostasis during hemoglobin exposure, secures nitric oxide content and prevents endothelial damage, thereby defining its pivotal role in normal physiology as a redox buffer, vascular bed keeper and inflammation modulator (Andersen et al., 2012).

Human haptoglobin, structurally, have a distinct genetic polymorphism due to the duplication of the HP gene; Hp1-1, Hp2-1 and Hp2-2 are usually three common phenotypes. These phenotypes contrast according in their molecular mass, polymerization profile, antioxidant activity and hemoglobin-scavenging ability (Langlois & Delanghe, 1996). Hp1-1 binds weakly and in smaller complexes, but it is a superior antioxidant compared with Hp2-2, which forms large polymers that limit hemoglobin clearance. This structural diversity is clinically relevant as the Hp2-2 phenotype has been reported to be related to oxidative stress-related disease predisposition such as vascular dysfunction in diabetes mellitus and poor prognosis in acute inflammatory conditions including acute respiratory distress syndrome (ARDS) (Asleh et al., 2003).

In addition to scavenging hemoglobin, haptoglobin is functionally involved in innate immunity and regulation of inflammation. Its hepatic production can be up-regulated by pro-inflammatory cytokines, especially IL-6 along with a cooperation role of IL-1β and TNF-α. As a result, increased Hp levels are frequently detected in the context of systemic inflammatory reactions, infection, autoimmune diseases and malignancy and it has become an easily determined clinically useful albeit nonspecific inflammation marker (Bünger et al., 2023). Crucially, Hp is heavily post-translationally modified; proteolytic cleavage and N-linked glycosylation of the β-chain are known. Changes in Hp glycosylation patterns have also been proposed as a potential set of biomarkers for cancer, sepsis and various chronic inflammatory diseases, with certain glycoforms associated with disease progression (Váradi et al., 2013).

The hemodynamic effects of haptoglobin activity are most pronounced in the maintenance of vascular patency. This is due to the high nitric oxide (NO) scavenging property of free haemoglobin, an important mediator of vasodilation and endothelial function. Hp prevents vasoconstriction, platelet activation and endothelial dysfunction when it sequesters hemoglobin by nitric oxide signaling pathways (Schaer et al., 2013). Oxidative stress and vascular injury are exacerbated by Hp depletion in hemolytic diseases— sickle cell disease and mechanical hemolysis. In addition, through prevention of heme-iron driven lipid peroxidation and by promoting regulated iron recycling, Hp indirectly limits pathologic processes associated with atherosclerosis and metabolic disease (Andersen et al., 2012).

Clinically, haptoglobin is widely applicable in various medical fields. In haematology hematologist reduced serum haptoglobin is a classic indicator of intravascular haemolysis, and so it is commonly used as an in vivo marker when diagnosing hemolytic anaemia, transfusion reactions or hemoglobinopathies. Pathologic elevation of Hp levels in metabolic disorders indicate chronic low-grade inflammation and have been linked to cardiovascular risks especially in obesity and type 2 diabetes individuals. In addition, several studies have reported associations of Hp with HRP-2 and endothelial dysfunction (Váradi et al., 2013), providing evidence that supports the use of Hp for cardiometabolic risk stratification (Langlois & Delanghe, 1996). Increased Hp levels have also been associated with the severity of chronic inflammatory dermatoses, suggesting that it has a systemic significance.

New data have extended the clinical 2 importance of haptoglobin also to the context of critical care and infections. Similarly, in sepsis circulating levels of Hp and the dynamics of the Hp-Hb complex have been associated with survival likelihood in a manner that most likely reflects this protein's ability to mitigate hemolysis induced oxidative damage during life threatening systemic infection (Schaer et al., 2013). Differences in Hp phenotype could partly account for differential organ-failure susceptibility, such as lung injury and/or ARDS, in critically ill patients. These findings are consistent with the notion that Hp is

not only a passive biomarker but also an active player in host defense under inflammatory and hemolytic conditions.

In addition, haptoglobin is gaining attention as a therapeutic target. Preclinical experiments also demonstrate the potential benefit of exogenous Hp administration to mitigate hemoglobin-driven organ damage in sepsis and acute lung injury, by replenishing hemoglobin scavenging capacity and reducing oxidative distress. Despite limitations in clinical translation, these results support revitalization of Hp based therapeutic approaches and underscore the importance of understanding its biochemical, physiological, and clinical aspects (Kerchberger et al., 2019).

Biochemistry and Biosynthesis of Haptoglobin

As a hemoglobin-binding protein, haptoglobin (Hp) is a glycosylated plasma a2-sialoglycoprotein which belongs to acute phase proteins and structurally it is known as an alpha 2 macroglobulin protein. Hp is encoded in humans by the HP gene on chromosome 16q22. 1. Hepatocytes are the primary source of mature PT, but extrahepatic expression in other tissues like adipose tissue, lung epithelium and skin as well as immune cells has been reported especially under inflammatory conditions (Andersen et al., 2012). Knowledge of these biochemical origins is crucial to the interpretation of the growing clinical significance of Hp, not only as a biomarker but also as a potential drug-able target.

Molecular Structure and Genetic Polymorphism

Biochemically, it is distinctive by having a polymorphic structure derived from a partial duplication of the Hp gene. Two primary alleles, HP1 and HP2, produce three widely occurring phenotypes: Hp1-1, Hp2-1 or Hp2-2. The Hp1 and Hp2 alleles differ in that the former encodes a shorter α-chain (α1) than the latter (α2), which harbours an extra interior repeat domain. These structural variances have a dramatic effect on the polymerization, size, and functionality of the molecule (Jeon et al., 2022).

All Hp phenotypes are composed of two types of polypeptide chains (heavyl β-chain (40 kDa) plus a light α-chain (9 for α1 or ~16 kDa for α1) that are covalently joined together by disulfide bonds. Hp form dimers in solution, but the resulting complex is tetrameric for individuals of Hp1-1 genotype and polymeric (linear or cyclic) with a molecular weight proportional to the number of bound hp molecules for either Hp2-1 or Hp2-2 phenotypes. Indeed, these biochemical distinctions modulate hemoglobin binding affinity, antioxidant capacity and clearance kinetics (Andersen et al., 2012).

Post-Translational Processing and Glycosylation

Hp is first made as a single precursor polypeptide (pre-pro-haptoglobin), which then is proteolytically cleaved in the endoplasmic reticulum to produce the α chain and β chain. This cleavage is performed by the complement C1r-like protein (C1r-LP), and it is critical for functional maturation of Hp. Impairment of the cleavage would lead to abnormalities of Hp that are not able to establish stable complexes with hemoglobin (Wicher & Fries, 2004).

Glycosylation is a key biochemical characteristic of Hp and occurs only on the β-chain via various N-glycosylated sites. These glycan structures are highly diverse and dynamically modulated by inflammatory, cancerous and metabolic conditions. Changes in Hp glycosylation (fucosylation, branching) are also believed to affect immune signaling and macrophage receptor engagement, mostly by binding to CD163. Therefore, Hp glycosylation is not just a structural characteristic but also has biological and clinical significance (Váradi et al., 2013).

Biosynthesis and Regulation

Biosynthesis of Hp is greatly suppressed at the transcriptional level by inflammatory cytokines. Interleukin-6 (IL-6) is the major inducer of HP gene expression in acute phase response, and the signal through JAK/STAT3 pathway is induced by it. Additionally, other cytokines such as IL-1β and tumor necrosis factor α (TNF-α) have a synergistic effect through augmented IL-6-mediated transcription (Cray et al., 2009).

Physiologically Hp synthesis, at rest, maintains circulating levels which will be sufficient to bind lowered levels of free Hb. Hp levels can also increase 2–3 fold within 24–48 h in acutely inflamed state infectious or traumatic insult or cancer. On the other hand, under massive intravascular hemolysis conditions, due to consumption greater than hepatic production, Hp levels drop with remarkable speed rendering it a useful biochemical marker of hemolytic states (Langlois & Delanghe 1996).

Also, the extrahepatic biosynthesis of Hp in fact has been paid more and more attention. Adipocytes, pulmonary ECs and neutrophils are able to locally produce Hp particularly in chronic inflammatory scenarios. Such local production indicates a paracrine or autocrine function of Hp in control of tissue-specific redox-imbalance and immunoreactions (Andersen et al., 2012).

Hemoglobin Binding and Antioxidant Function

The key biochemical characteristic of Hp is its remarkable high-affinity interaction with free hemoglobin (Kd ~10^{-15} M). Hp binds hemoglobin dimers not tetramers, thereby stabilizing the dimer and reducing heme dissociation. This interaction is thought to block hemoglobin-promoted oxidative reactions such as lipid peroxidation and nitric oxide scavenging with the result that the endothelial function and vascular homeostasis are maintained (Schaer et al., 2013).

The Hp–Hb complex is bound by the macrophage receptor, CD163; an event which results in endocytosis and lysosomal breakdown. This is a major crossroads in redox biochemistry and immune regulation, since binding of CD163 stimulates an anti-inflammatory response coupled with heme oxygenase-1 (HO-1, regulated gene) that serves to ameliorate damage due to oxidative stress (Thomsen et al., 2013).

Biochemical Variability and Functional Implications

Most significantly, the biochemistry efficacy of Hp is also phenotype dependent. Hp1-1 has a better performance as an antioxidant and in hemoglobin clearance activities, compared to Hp2-2, HM binds larger polymers, that penetrate less into the tissue with decreased rate of clearance. Such biochemical heterogeneity has served to explain mechanistically some of the associations noted between Hp phenotypes and disease susceptibility, such as regarding cardiovascular and metabolic conditions (Váradi et al., 2013).

Physiology of Haptoglobin

Haptoglobin (Hp) acts as a key character in physiological homeostasis both under normal and diseased states. Traditionally considered as an acute-phase protein with anti-inflammatory properties, its Apo-H function goes far beyond the inflammatory response to cover hemoglobin scavenging, antioxidant defense, immune modulation and iron recycling and vascular protection. These functions position haptoglobin at the crossroad where redox biology, innate immunity and metabolism collide (MacKellar & Vigerust, 2016).

Hemoglobin Scavenging and Iron Homeostasis

Best known is the physiological function of haptoglobin to bind with high affinity free hemoglobin removed from circulation during intravascular hemolysis. Reactive free hemoglobin is very reactive and can catalyze the formation of ROS, induce lipid peroxidation, scavenge NO, causing endothelial dysfunction. Haptoglobin is thus able to protect by a sequestration of hemoglobin, forming a stable Hp–Hb complex and as a consequence the toxic effects of hemoglobin can be effectively neutralized as well as the development of oxidative tissue damage prevented (Schaer et al., 2013).

The Hp–Hb complex is rapidly removed from the circulation by binding to the CD163 scavenger receptor, expressed mainly on monocytes and macrophages including Kupffer cells in liver and splenic macrophages. This removal mechanism allows for the regulated degradation of hemoglobin and recycling of iron, thus avoiding loss of iron while limiting oxidative damage. Similarly, heme oxygenase-1 (HO-1) seems to be induced subsequent to CD163 mediated uptake by macrophages and participate in cytoprotection by producing anti-inflammatory as well as antioxidant products such as biliverdin and carbon monoxide (Andersen et al., 2012).

Antioxidant and Vascular Protective Functions

Biologically, haptoglobin is a significant antioxidant protein in the blood. Via scavenging hemoglobin, the Hp prevents heme-iron–imposed redox reactions that injure lipids, proteins and nucleic acids. This antioxidant function is especially critical in the vasculature, which experiences oxidative stress induced by free radicals that leads to endothelial dysfunction, thrombosis and atherosclerosis (Langlois & Delanghe, 1996). Hp also maintains NO bioavailability by restraining hemoglobin-mediated NO scavenging. Nitric oxide is important in vasodilatation, suppression of platelets and modulation of vascular tone. Accordingly, haptoglobin is indirectly involved in maintaining the flow of blood and preventing hypertension as well as vascular complications, particularly under inflammatory or hemolytic conditions (Schaer et al., 2013).

Role in inflammation and acute phase response

Haptoglobin is an acute-phase protein with a positive response, and its production increases significantly in reaction to inflammation, infection, injury and cancer. This increase, from a physiological perspective, is an adaptive reaction to reduce tissue injury provoked by oxidative stress and regulate immune

activation. Interleukin-6 (IL-6) is the major cytokine that induces Hp upregulation, with involvement of IL-1β and tumor necrosis factor-α (TNF-α) (Roh et al., 2025).

Hp is not only a passive inflammatory marker but involved in immune modulation. The Hp–Hb–CD163 pathway induces an anti-inflammatory macrophage phenotype (M2-like), with upregulation of IL-10 production and inhibition of proinflammatory cytokines. This process contributes to dampening inflammation and also drives tissue repair (Andersen et al., 2012).

Immunomodulatory Functions

Immunomodulation by haptoglobin does not require free hemoglobin uptake. It has been demonstrated to affect lymphocyte proliferation, dendritic cell (DC) maturation and neutrophil activity. Hp can attenuate T-cell activation, and dampen exaggerated immune responses, potentially protecting against tissue damage during inflammation. Further, Hp interacts with pattern recognition receptors and regulates complement activation providing major roles in innate immune defense while also participating in immune homeostasis. Such properties emphasize its role in physiological terms as a regulatory protein, rather than being merely an inflammatory byproduct (Langlois & Delanghe, 1996).

Metabolic and Extrahepatic Functions

Recent findings indicate a physiological role of haptoglobin in metabolic control. Hp is produced in adipose tissue and can give rise to local inflammatory reactions which are implicated in obesity and insulin resistance. Increased Hp protein concentrations in metabolic syndrome and type 2 diabetes are considered as a manifestation of chronic low-grade inflammation and enhanced oxidative stress (Wan et al., 2021s).

Local tissue protection is also supported by extrahepatic expression of Hp in the lung, skin, kidney, and immune cells. In the lung, Hp might protect the epithelial lining from oxidative damage, and in the kidney limit hemoglobin-induced nephrotoxicity associated with haemolytic disease (Andersen et al., 2012).

Physiological Impact of Haptoglobin Polymorphism

The biological activity of haptoglobin is genetically polymorphic. Hp1-1 has higher antioxidant and hemoglobin-binding function compared to Hp2-2, which polymerizes into larger polymers that are cleared more slowly. These variations have physiological implications such as exposure to oxidative stress, cardiovascular pathology and inflammationrelated disorders. This variability emphasizes the role of Hp phenotype in individual responses to hemolysis, inflammation and metabolic stress (Langlois & Delanghe, 1996).

Physiological Role in Disease Adaptation

At some physiological stress states, such as infection, trauma, or cancer, an increase of Hp levels is a beneficial adaptation. In contrast, reduced Hp levels such as those seen in severe hemolysis or end-stage liver disease undermine Hb clearance and increase susceptibility to oxidative damage. Hence, normal Hp production is necessary for physiological robustness (Cray et al., 2009).

Clinical Significance of Haptoglobin

Haptoglobin (Hp) is extremely clinically important in virtue of its pivotal role in Hb-scavenging, inflammation, controlling oxidative stress and modulating immunity. Clinically, considering that Hp is used as a biomarker in diagnostic medicine and its role is coming to the forefront increasingly as being able to predict prognosis in many different hematological, inflammatory, cardiovascular, metabolic and malignant diseases. The interpretation of this result is the knowledge of its physiological activity and genetic polymorphism (di Masi et al., 2020).

Haptoglobin as a hemolysis marker

Diagnosis of intravascular hemolysis Intravascular hemolysis is one of the oldest clinical Haptoglobin applications. Other hemoglobin, released into the plasma under hemolytic conditions, rapidly forms complexes Hp–Hb that are scavenged by macrophages through a CD163 receptor. Consequently, the levels of circulating Hp will fall acutely and can become undetectable in cases of severe hemolysis. This depletion renders Hp a sensitive laboratory marker for pathologies such as autoimmune hemolytic anemia, transfusion reactions, hemoglobinopathies and mechanical hemolysis related to prosthetic heart valves (Langlois & Delanghe, 1996).

Nevertheless, confounders need to be taken into account for interpreting Hp levels in clinical practice. Hp is an acute phase protein and inflammatory insults can lead to c overage of hemolysis through the, by Hp synthesis in liver. Thus, Hp levels are most relevant when considered in the context of additional laboratory values including lactate dehydrogenase, indirect bilirubin (IB), and reticulocyte count (Huntoon et al., 2008).

Role in Inflammation and Infection

In clinical terms, high Hp levels are indicative of a positive acute-phase response and are commonly found in infections, autoimmune disorders, trauma and cancer. Elevated levels of Hp are associated with systemic inflammation contains cytokine (interleukin-6 (IL-6)) stimulants. In infections, Hp plays a protective role in host defense by scavenging hemoglobin to limit iron availability for invading pathogens and exert an antimicrobial activity indirectly (Cray et al., 2009).

Hp levels have been also related to disease activity and severity in different chronic inflammatory states such as rheumatoid arthritis and inflammatory bowel disease. It is not specific for disease, but adds useful information to other markers of inflammation such as C-reactive protein and serum amyloid A (Chabuk et al., 2025).

Cardiovascular and Metabolic Diseases

Haptoglobin has becoming a novel emerging highlight in the field of cardiovascular medicine, especially its genetic polymorphism. Many studies have shown that individuals with the Hp2-2 type have lower antioxidant ability and higher vulnerability to oxidative stress compared with those carrying Hp1-1. This phenotype was associated with increased risk of coronary atherosclerosis, myocardial infarction and adverse cardiovascular events in patients, particularly diabetic patients (Langlois & Delanghe, 1996).

Increased Hp levels have frequently been observed in metabolic diseases such as obesity, insulin resistance and type 2 diabetes reflecting chronic subclinical inflammation. Adipose Hp expression indicates a metabolic inflammation-specific local function. From a clinical perspective, Hp has also been suggested as a biomarker for cardiometabolic risk stratification but routine phenotyping is not yet common practice (Váradi et al., 2013).

Oncological Significance

For oncological purposes, haptoglobin has become a promising marker of cancer diagnosis, prognosis, and monitoring. Increased serum Hp concentrations and abnormal Hp glycosylation have been documented in a variety of cancer types, such as lung, colorectal, gastric, ovarian and breast tumours. Such changes are believed to reflect a tumor-related inflammatory and cytokine enriched microenvironment, as well as cancer driven shifts in glycosylation processes (Váradi et al., 2013).

The relative abundance of Hp glycoforms has been reported to identify between cancer and non-cancer patients, as well as tumor staging and metastasis. While Hp is not cancer-specific, incorporation of this analyte into several marker panels might improve diagnoses and prognostication.

Liver Disease and Synthetic Function

Hp measurement is clinically important because it reflects the synthetic function of the liver. Secondary to impaired protein synthesis, a decreased Hp level is noted in advanced liver disease, cirrhosis and acute liver failure. In these circumstances, low Hp may indicate hepatic insufficiency rather than haemolysis. Therefore, Hp represents an indirect marker of liver injury if interpreted together with albumin, coagulation factors and other acute-phase proteins (Cray et al., 2009).

Clinical Relevance in Kidney and Transfusion Medicine

In the field of nephrology, Hp has a protective effect against hemoglobin-mediated renal damage. When Hb levels are low during hemolysis, the risk of Hb-mediated tubular injury leading to acute kidney injury is high. Hp depletion may also be therapeutically used to screen for a risk population on hemolysis induced renal post-injury. In transfusion medicine, Hp levels monitoring can be of use in early detection of hemolytic transfusion reactions. The rapid post-transfusion decrease in Hp is most compatible with a diagnosis of intravascular hemolysis and aids the clinical decision for appropriate intervention (Schaer et al., 2013).

Limitations and Future Perspectives

Although it is broadly clinically relevant, haptoglobin does not show disease specificity and cannot therefore be used as the sole diagnostic marker. When interpreting such assays, the impact of genetic polymorphism, inflammation and liver function poor analyte characterization will need to be taken into account.

However, the development of glycoproteomics and phenotype-specific assays might also contribute to the use of Hp in clinical practice with a more personalized medicine focus. More studies are focusing on possible purposes of Hp and the Hp–Hb–CD163 axis as new targets for treatment in hemolytic diseases, inflammation-related disorders, and cardiovascular diseases. These observations could extend the medical relevance of this pleiotropic protein even more.

Conclusion

Haptoglobin (Hp) is a multi-functional acute-phase glycoprotein with important functions in hemoglobin scavenging, antioxidant protection, immune modulation and systemic homeostasis. Its biochemical diversity and genetic variation play a major role in physiological reactions and resistance to diseases. In the clinic, haptoglobin plays a useful role as a biomarker of hemolysis, inflammation, metabolic disturbances and malignancies although its nonspecific nature requires critically thinking during its application. Molecular and glycoproteomic studies continue to uncover the diagnostic/prognostic value of this protein. Taken together, these findings highlight the role of haptoglobin as both a biological modulator and a clinically relevant protein.

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