REVIEW ARTICLE

HAPTOGLOBIN: MULTIFACETED FUNCTIONS IN HUMAN PHYSIOLOGY AND DISEASE

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Abstract: *Haptoglobin is a conserved plasma protein mainly produced in the liver, it is well recognized for its high-affinity binding to free haemoglobin, protecting tissues from oxidative damage during haemolysis and inflammation. It exists in three major phenotypes—Hp 1-1, Hp 2-1, and Hp 2-2—derived from polymorphic Hp1 and Hp2 alleles, each with distinct structural and functional profiles. Beyond Hb clearance, Hp influences antioxidant defence, nitric oxide regulation, prostaglandin synthesis, immune modulationand exerts bacteriostatic and angiogenic effects. Disease association studies across diverse populations indicate that the Hp1 allele is frequently linked to increased susceptibility to cancers such as breast, cervical, and lung, while the Hp2 alleleparticularly the Hp 2-2 phenotypeis more often implicated in chronic and inflammatory diseases including diabetes, cardiovascular disorders, and chronic kidney disease.The variable distribution and impact of Hppolymorphisms underscore its emerging role as a biomarker in disease prognosis, risk stratification, and potential therapeutic targeting.*

Keywords: Haptoglobin, plasma protein, prostaglandin synthesis, Haemoglobin.

INTRODUCTION

Haptoglobin (Hp) is a conserved plasma α2β2-sialoglycoprotein produced mostly by the liver and also expressed through the kidney. First described in 1938, it is best known for its high-affinity binding to free haemoglobin (Hb).This binding (1:1 ratio) prevents oxidative tissue damage, making Hp a key antioxidant and Hb scavenger. Synthesized predominantly during inflammation and haemolysis, Hp also exhibits pro-inflammatory and immunomodulatory properties. Its levels rise significantly in response to acute-phase reactions, and it is increasingly recognised as a potential biomarker in various diseases, including cancers and inflammatory conditions. Haptoglobin has three polymorphic variants,Hp 1-1, Hp 2-1, and Hp 2-2determined by the inheritance of the Hp1 and Hp2 alleles(1). The population distribution of haptoglobin types is approximately 15% Hp 1-1, 50% Hp 1-2, and 35% Hp 2-2(2).The Hp1allele is predominantly found among Nigerians, Easter Islanders, and Chilean Indigenous, African and European populations(3–6). The Hp 2 allele is most commonly observed in Jordanian Arabs, North Queensland Australians, Indians, and Han Chinese(7–9).

Haptoglobin Structure

The haptoglobin (Hp) gene is mapped to chromosome 16q22 and has three allelic variants: Hp1S,Hp1F, and Hp2. These variants result in sixdistinct phenotypes: 1S-1S, 1F-1F, 1F-1S, 2-1S, 2-1F, and 2-2. Hp1F and Hp1S are often considered as a single Hp1 allele due to the difference that relies solely on point mutations that have no impact on functional differences(10,11). Hp phenotypes are classified into three primary types:Hp1-1, Hp2-1, and Hp2-2, based on the inheritance of Hp1 and Hp2 alleles(12). The Hp2 allele evolved from Hp1 through a 1.7-kb intragenic duplication, resulting in an extended α-chain coding region(13). Hp is initially synthesised as a single polypeptide precursor that includes both α- and β-chain sequences, which are subsequently processed in the endoplasmic reticulum (ER). During endoplasmic reticulum transit, the signal peptide is cleaved, and site-specific proteolytic cleavage occurs at Arg84 in pre-Hp1(α1β) and Arg143 in pre-Hp2(α2β), resulting in the separation of the α1, α2, and β chains(14–16). A few times, Pre-Hp2 is not cleaved and retains its full-length form. The intact form is termed as zonulin(17). Haptoglobin is a tetrameric protein made up of two light α-chains (α1 or α2) and two heavy β-chains.Disulfide bonds connect these chains, resulting in the formation of αβ-dimers, which subsequently assemble into larger structures based on the phenotype(18,19). Haptoglobin (Hp) phenotypes exhibit variations in structure, molecular weight, and morphology. The Hp1-1 phenotype is characterised by a tetrameric structure represented as $(\alpha1\beta)_2$, with an estimated molecular weight of 86 kDa. TheHp2-1 phenotype is more complex, made up of both $(\alpha1\beta)_2$ and a varying number of (α2β) units (between 1 and 3), which creates a linear structure with a molecular weight that ranges from about 86 to 300 kDa. The Hp2-2 phenotype consists solely of (α2β)n units, with n varying from 3 to 10 or more, resulting in a ring-shaped polymer with a molecular weight ranging from approximately 170 to 900 kDa(20,21).

Haptoglobin functions in human body

1. Haemoglobin Binding

Haptoglobin is essential for the binding of free haemoglobin (Hb) that is released during intravascular haemolysis, which is the process of destroying senescent red blood cells (RBCs)at high rates(22). Hb is a key protein in the blood that transports oxygen and helps detoxify reactive oxygen and nitrogen species. However, when Hb is freely being released into the bloodstream, its iron content causes oxidative stress and inflammation. People with comorbid diseases such as diabetes, infections, trauma, and cancer are at a higher risk from the oxidative stress and inflammation caused by free Hb in the bloodstream(23). Hp forms a stable, non-covalent Hp-Hb complex by binding free Hb with a very high affinity. Lys13 and Lys21 in the Hp heavy chain are involved in Hb binding(24).This binding prevents iron loss and lowers Hb-mediated oxidative damage, thereby protecting tissues, especially the kidneys, from damage. If free Hb is unbound, it can be filtered out by the

glomeruli and cause damage to the kidneys(25,26). In the kidneys, oxidative reactions at the heme moiety of haemoglobin lead to globin deposition, lipid peroxidation, and renal tubular damage(27,28). Hepatocytes, tissue macrophages, and Kupffer cells all expressed through CD163, which facilitates receptor-mediated endocytosis, which quickly removes the Hp-Hb complex from circulation(29–31).CD163 expression is modulated by cytokines, with upregulation occurring in response to IL-6 and IL-1, while TNF-α, IL-4, and IFN-γ lead to downregulation(32,33). Upon internalisation, the complex undergoes degradation, and heme is metabolised by heme oxygenase-1 for iron recycling. The clearance time for free Hp is 3 to 5 days, whereas the Hp-Hb complex is cleared in approximately 20 minutes(34). The β chain of Hb has two significant Hp binding sites (residues β11-25 and β131-146), according to molecularstudies, while the αchain has one (residues α121–127)(35,36).The Hp αβ subunits and Hb αβ dimers bind stoichiometrically.Although there are polymorphic forms of Hp, the most researched are Hp 1-1 and Hp 2-2. When compared to Hp 1-1, the Hp 2-2 complex is less effective at preventing oxidative stress because it is physically bigger and less permeable in extravascular fluids(37).As a consequence, those with the Hp 2-2 phenotype are more susceptible to oxidative damage from free Hb(19,38).

2. **Antioxidant Activity**

Haptoglobin (Hp) acts as a crucial antioxidant, protecting the body from damage caused by free radicals. The release of iron by free haemoglobin makes it highly harmful because it facilitates the Fenton and Haber-Weiss reactions, which in turn produce reactive oxygen species (ROS)(39,40). These ROS, especially hydroxyl and superoxide radicals, can harm endothelial cells, oxidise low-density lipoproteins (LDL), and aggravate diseases like diabetes, atherosclerosis, and inflammatory tissue damage. Hp prevents the release of iron and mitigates the downstream oxidative damage by sequesteringfree Hb.Genetic variation has a significant impact on the antioxidant efficacy of Hp, especially its phenotypic variants, Hp1-1, Hp2-1, and Hp2-2. Despite having comparable Hb-binding affinities, the three phenotypes differ greatly in their capacity to counteract oxidative stress because of variations in molecular size and clearance efficiency. The smallest phenotype, Hp1-1, provides the most antioxidant defence by quickly removing the Hb-Hp complex and inhibiting the production of ROS caused by iron, the Hp 2-2 complex is less effective at preventing oxidative stress because it is structurally larger and less permeable in extravascular fluids(41). This results in extended exposure to iron and free haemoglobin, which raises oxidative stress, particularly in diabetes. The protective capacity of the Hp2-1 phenotype is moderate.However, it has been discovered that Hp has a greater antioxidant capacity at extravascular locations than vitamin C (42). This indicates how essential Hp is for maintaining redox balance and avoiding oxidative damage, particularly in stressful situations like infection, ischaemia, or chronic metabolic disorders.

3. Inhibition of Nitric Oxide (NO)

Nitric oxide (NO), also known as endothelium-derived relaxing factor (EDRF), is an important signalling molecule that regulates vasodilation, neurotransmission, platelet aggregation, and immunological defence. NO is produced by various cells, such as cytokine-activated macrophages and vascular endothelial cells. At low concentrations, it maintains vascular tone, and at greater concentrations, it aids in cytotoxic immune defence(43,44). However, endothelium-dependent vasodilation becomes impaired by NO's high reactivity and quick inactivation by free haemoglobin (Hb). Although haptoglobin (Hp) by itself has no direct effect on NO, it does indirectly contribute to NO depletion by its interaction with free Hb to create the Hp-Hb complex. This complex still has the ability to scavenge NO, limiting its availability and vasodilatory action. Increased amounts of free Hb or Hp-Hb complexes worsen NO loss, encourage endothelial dysfunction, and raise the risk of cardiovascular disease, particularly during haemolysis or vascular stress(45). Crucially, Hp-Hb complex clearance is phenotype-dependent. While people with the Hp2-1 or Hp2-2 phenotypes have slower clearance, longer NO scavenging times, and decreased vasodilation, those with the Hp1-1 phenotypehave more effective clearance, maintaining NO function and vascular health(46). This phenotype-dependent effect is supported by clinical data that shows the Hp1-1 phenotype provides vascular protection by increasing the availability of nitric oxide (NO), whereas Hp2 variants are linked to reduced NO bioavailability and worse outcomes in conditions such as preeclampsia(47). Therefore, haptoglobin indirectly controls vascular function and NO bioactivity, and phenotype is a major factor in influencing this relationship.

4. Inhibition of Prostaglandin Synthesis

Haptoglobin (Hp) acts as a potent endogenous inhibitor of prostaglandin (PG) synthesis by sequestering heme, an essential cofactor for prostaglandin-producing enzymes such as cyclooxygenase (COX) and 12-lipoxygenase(LOX). This mechanism has substantial anti-inflammatory effects by decreasing the synthesis of critical pro-inflammatory mediators, such as Prostaglandin E2 ,Prostaglandin F2 alpha, thromboxane A2, and leukotrienes(37,48). Crucially, the Hp1-1 phenotypehad the highest inhibitory impact, while Hp2-2 was significantly less effective, indicating that inflammation is modulated in a phenotype-dependent manner(49). These results were corroborated by functional in vivo tests, which demonstrated decreased tissue responses to bradykinin and arachidonic acid in the presence of Hp(50). Additionally, the Hp-Hb complex activates anti-inflammatory signalling via macrophage CD163 receptors, and Hp is a positive acute-phase reactant that is quickly elevated during inflammation(51). Everything considered, Hp functions as a natural anti-inflammatory agent by removing free Hb and by directly inhibiting the synthesis of

prostaglandins and leukotrienes by heme sequestration; this effect is influenced by Hpphenotypeand is supported by enzymatic, cellular, and in vivo models.

5. Bacteriostatic Effect

In innate immunological defence, haptoglobin (Hp) is required because it has a strong bacteriostatic impact by sequestering free haemoglobin (Hb), which restricts the availability of iron, a resource that is essential for bacterial development. Creating stable Hp–Hb complexes, Hp creates an iron-restrictive environment that stops bacteria from multiplying(52). This was shown in studies where rats were treated with Escherichia coli and Hb and were fully protected from death by Hp co-administration(53). Beyond its role in iron deprivation, Hp boosts immunological responses by adhering to surface molecules on bacteria, such as lipoteichoic acid on Staphylococcus aureus, which promotes phagocytosis and clearance(54,55). Furthermore, the growth of Gram-negative bacteria like Proteus mirabilis and Pseudomonas aeruginosa is locally suppressed by HP released by mucosal progenitor cells. The continuous evolutionary arms race between host defence and pathogen survival is highlighted by the fact that certain bacteria, such as Neisseria meningitidis, Campylobacter jejuni, Bacteroides fragilis, and Vibrio vulnificus, have developed complex heme acquisition systems that enable them to extract iron even from the Hp–Hb complex(56–58).

6. Angiogenesis and Lymph angiogenesis

Hp stimulates vascular signalling pathways to promote angiogenesis, especially in its precursor form,prohaptoglobin (proHp). Vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR-2) are important mediators of endothelial cell proliferation, sprouting, and new capillary formation, and proHp upregulates their expression(59). This upregulation promotes the formation of vascular networks and the branching of endothelial cells. Additionally,(60) found that serum Hp levels positively correlated with angiogenesis in vitro, indicating that Hp functions as a compensatory mechanism to promote collateral vessel formation in ischaemic conditions. It seems that the angiogenic potential of Hp is depending on phenotype. It has been discovered that one of the prevalent genetic variations, the Hp 2-2 phenotype, is more angiogenic than Hp 1-1 and Hp 2-1(60,61). This characteristic has ramifications for pathological neovascularisation even though it helps to promote tissue healing following ischaemic injury or inflammation. Excessive angiogenesis within atherosclerotic plaques, for example, can cause hypoxia, macrophage infiltration, plaque instability, and ultimately raise the risk of plaque rupture in diabetes and atherosclerosis(62,63). Increased angiogenesis associated with Hp activity may worsen the course of age-related macular degeneration and tumour growth. Consequently, Hp has two opposing roles: on the one hand, it promotes tissue healing, while on the other, it aids in pathological angiogenesis(64).

7. Immune System Interactions or Immunoregulatory Activity

Haptoglobin (Hp), categorised as an acute-phase protein, has been identified as a significant immunomodulatory molecule. Post-immunisation, individuals with the Hp2-2 phenotype exhibit increased antibody production and other indicators of immunological response(65). Hp influences both innate and adaptive immunity through the modulation of cytokine release, immune cell signalling, and lymphocyte activity. The liver produces it in greater quantities while stimulated by cytokines such as IL-6, IL-1β, and TNF-α. Downregulating Th2-associated cytokines while promoting IL-2 and IFN-γ production shifts the immune profile towards a Th1-dominant response, which is crucial for combating intracellular infections. Hp-Hb complexes, particularly those associated with the Hp1-1 phenotype, markedly enhance the production of IL-6 and IL-10 via the CD163 receptor and casein kinase II signalling pathways. This indicates that Hp1-1 individuals exhibit a more pronounced anti-inflammatory and vasoprotective effect. Moreover, Hp engages directly with various immune cells. Hp modulates cellular adhesion, migration, and activation through receptors such as CD22 on B cells and CD11b/CD18 on neutrophils and monocytes. (66,67). This process mitigates oxidative tissue damage during inflammation, particularly in ischemia-reperfusion scenarios, by attenuating the neutrophil respiratory burst. It also influences the development of dendritic cells, thereby impacting the strength and quality of adaptive immune responses(68,69).

Haptoglobin and Disease associations

This compiles findings from multiple international studies examining the association of Hp phenotypes and alleles (Hp1 and Hp2) with various diseases.

The Hp1 allele appears to be associated with increased cancer susceptibility in multiple regions. For instance, studies from India, Greece, and Jordan have reported a higher frequency of the HP1 allele in breast cancer patients (70–72). Similarly, lung cancer studies from Sweden and Taiwan have documented a greater prevalence of the Hp1 allele, particularly in female adenocarcinoma cases(73,74). Additionally, in cervical cancer cases reported in Portugal and Canada, individuals carrying the Hp1 allele or exhibiting the Hp1-1 phenotype were at higher risk or had a greater occurrence of the disease (75,76). The Hp1-1 phenotype has also been linked to increased susceptibility and severity of falciparum malaria in Sudanese patients (77).

Hp1-1 phenotype was significantly more prevalent in individuals with leukaemia and liver cancer compared to the control group in Sudanese population(78). Furthermore, serum haptoglobin has been identified as a novel marker of adiposity, likely influenced by adipose tissue metabolism (79).

The Hp 2-2 phenotype has been significantly associated with several other diseases. The Hp 2-2 phenotype has been frequently over-represented in atherosclerotic plaques, as observed in a New York-based study (80). The Hp 2-2 phenotype independently predicts postoperative AKI and poorer survival after cardiac surgery in diabetic patients(81). It shows a strong association with diabetes in populations from the USA and India (82,83), gastric cancer in India (84),and pancreatic cancer in China (85), Interestingly, in ovarian cancer cases from Italy, the HP 2-2 phenotype has been linked to a better prognosis, possibly due to its immune-enhancing properties (86). Hp 2 allele and Hp 2-2 associated with more severe cases like Sickle cell anaemia in eastern India (87).

The Hp 1-1/Hb complex triggers a weaker immune response than the Hp 2-2 variant, resulting in lower production of inflammatory cytokines and subsequently reducing oxidative stress and inflammation(88,89).

The Hp 2-2 has been strongly associated with an increased risk and progression of chronic kidney disease (CKD) across various populations. In Taiwan, it was found significantly more often in CKD patients compared to controls(90). Similar associations have been reported in Israeli, Irish, and Egyptian populations, particularly linking Hp 2-2 to diabetic nephropathy(91–93). Additionally, diabetic individuals with the Hp 2-2 phenotype face a higher risk of postoperative acute kidney injury(94). In Jordan, Hp 2-2 was more prevalent among chronic renal failure patients, especially those with underlying conditions like polycystic kidney disease, hypertension, and diabetes(95).

Further studies in India, including South Indian and Visakhapatnam populations, have confirmed the association of Hp 2-2 with increased CKD risk, faster disease progression, and higher mortality(96). The phenotype also contributes to iron-induced oxidative stress in CKD patients(97). A long-term study in Israel showed that Hp 2-2 was linked to reduced glomerular filtration rate (GFR) and elevated ESRD risk in type 1 diabetes patients(98). While Hp 2-2 is widely implicated in severe kidney outcomes, the Hp 2-1 phenotype has shown significant association with CKD of unknown etiology(CKDu), in the Uddanam region(99). Moreover, the Hp2 allele or the Hp 2-1 phenotype has been associated with higher risks of oesophageal cancer in India and head and neck cancers (84,100).

Overall, these studies suggest that different Hp phenotypes and alleles contribute to disease susceptibility, prognosis, and progression, with significant variation across diseases and geographic regions.

Conclusion

Haptoglobin serves as a critical mediator of haemoglobin clearance, oxidative stress regulation, inflammation modulation, and immune system function. This review summarizes current knowledge on the role of haptoglobin in the human body and its association with disease susceptibility.The phenotypic diversity resulting from Hppolymorphisms significantly influences the

extent and efficiency of these biological functions. While the Hp 1-1 phenotype exhibits superior antioxidant and anti-inflammatory activity, the Hp 2-2 variant is more prone to promoting oxidative damage, impaired nitric oxide bioavailability, and pro-angiogenic responses, often correlating with more severe outcomes in diseases such as diabetes, CKD, and cardiovascular complications. Conversely, certain cancer types may be more prevalent in individuals carrying the Hp1 allele. These phenotype-specific associations suggest that Hpplasma analysis could be of clinical value in predicting disease risk and developing therapeutic interventions. Further research on the molecular basis of Hp function and polymorphism-specific effects could provide novel insights into precision medicine and disease management techniques.

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