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The Biochemical, Physiological, And Clinical Importance of Ceruloplasmin: A Review

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Abstract

Ceruloplasmin is a glycoprotein multicopper oxidase and the main copper transport protein in humans. It is responsible for metal homeostasis, redox equilibrium, and inflammatory response in human plasma. It is produced mainly in the liver and acts as a ferroxidase enzyme that catalyzes the oxidation of ferrous iron to ferric iron, enabling the transport of iron while reducing free radical formation from iron. In this way, ceruloplasmin participates in control of systemic iron homeostasis, antioxidant defense and tissue protection against oxidative damage. Furthermore, as a positive APPs itself, ceruloplasmin is considered the regulator of innate immune response and its circulating levels have been shown to raise during inflammation, infection and tissue injury. The clinical utility of ceruloplasmin testing is well established in the diagnosis and monitoring of disorders of copper metabolism, including Wilson's disease, with emerging applications in cardiovascular disease and metabolic syndrome, neurodegenerative diseases as well as chronic inflammatory diseases. Changes in the concentration, enzymatic activity and molecular structure of ceruloplasmin correlate with disease severity and prognosis. The aim of this review is to summarize the biochemistry, physiology and clinical implications of ceruloplasmin in view of recent

developments and new perspectives relevant to its function as a biomarker and mediator in health a disease.

Keywords: Acute Phase Proteins, Ceruloplasmin, Copper Metabolism, Hepatocytes

Introduction

Ceruloplasmin (CP) is a multicopper oxidase glycoprotein, mainly produced in the liver and released to blood stream, where it associates with most of circulatory copper (Cu). By its ferroxidase activity, CP oxidizes (Fe^{2+}) to ferric (Fe^{3+}) iron promoting the incorporation of iron in transferrin for systemic delivery and homeostasis of iron (Lopez et al., 2023). Although CP has been classically studied as a copper carrying protein in our understanding history, the increasing evidences indicate that its activity contributes to various physiological processes; including copper and iron homeostasis, the antioxidant defense system, acute-phase response, and cell redox-functioning. An understanding of these diverse roles is central to our comprehension of CP's biochemical and physiological relevance in health and disease (Wang et al., 2025).

Biochemically, the ferroxidase activity of CP is central to its function. The oxidation of iron by CP may be relevant for its ability to mediate efficient iron release from cells and connect with transferrin. When this oxidase activity is absent, iron accumulates in the cells causing oxidative damage and disruption of metabolic processes. Good old experimental systems have demonstrated that low activity ACh is a major player in the disruption of cellular to plasma iron flow depleting plasmatic body iron, despite normal net body iron stores. These results reflect how CP affects systemic iron homeostasis with regard to anemia, neurodegeneration and metabolic disease (Lopez et al., 2023).

CP is also an acute phase reactant with increased plasma levels in response to inflammation and injury, in addition to its role on metal metabolism. This feature has also made CP a potential biomarker in some pathological conditions like infection, cardiovascular disease and metabolic diseases. For instance, recent systematic researches have shown that the concentration of ceruloplasmin is significantly enhanced during infectious diseases such as malaria; this is in response to an acute-phase reaction and linked oxidative stress. These observations not only highlight the sensitivity of CP to systemic inflammation but also suggest a potential utility in monitoring disease progression and predicting prognosis (Liu et al., 2022).

The clinical significance of CP is illustrated by its relationship with chronic diseases. Elevated circulating levels of CP are associated with an increased likelihood of coronary heart disease expansion in observational studies, emphasizing the role of the protein in oxidative processes that contribute to atherosclerogenesis (Arenas de Larriva et al., 2020). In the same line, 2024 studies have demonstrated that CP levels are related to mortality in patients with advanced HF highlighting the prognostic role of CP in acute cardiac diseases . Together, these data further support the function of CP not only as a metal transporter but also as an integrator of oxidative, inflammatory and metabolic signals in chronic diseases (Smyła-Gruca et al., 2024).

Exploration of CP as a diagnostic tool has been prompted by progress in clinical research. In classical settings such as Wilson's disease (WD)—an autosomal recessive condition of copper metabolism—determination of serum ceruloplasmin concentrations is still regarded as a paradigm for diagnosis and monitoring (Jain et al., 2025). Differences in CP level are related to clinical severity of disease and response to chelation therapy, indicating that it is still a valid marker in the clinic. Studies in pediatric autoimmune hepatitis patients also imply that cerulopasmin, when utilized along side copper assays, will have noninvasive utility as a biomarker for advanced liver fibrosis/enlarging the application of its use (Nagi et al., 2025).

At the genetic level, mutations of the CP gene cause rare disorders such as aceruloplasminemia associated with disturbed iron homeostasis, brain degeneration and systemic iron overload. Functional characterization of this missense variants has more recently advanced our knowledge on how individual structural deficiencies in CP lead to disease phenotypes, and can provide genetic and structural input for future therapy. These new findings highlight the critical importance of CP in both health and rare monogenic disease (Ziliotto et al., 2025).

There is also a growing literature on CP and other diseases, including neurodegenerative and eye diseases. Early results in ceruloplasmin and ferritin level determinations on ocular fluid suggested putative contribution to early neuroinflammation changes around eye diseases, as well as to a broader process of neurodegeneration (Esposito et al., 2025). These types of exploratory investigations also widen CP's clinical profile to additional terrain as a repressor of tissue-specific oxidative and inflammatory pathways. And so, though we have made huge leaps forward, there are mechanistic roadblocks. Whether ceruloplasmin acts as a causative mediator, or merely reflecting marker of multifactorial disorders, such as cardiovascular and metabolic syndromes is debatable and warrants focused mechanistic, and interventional studies. Moreover, its biochemical role in copper and iron metabolism, its physiological

function on redox homeostasis and acute phase reaction as well as the clinical associations from a range of pathologies highlight the involvement of ceruloplasmin in human biology and medicine. Ongoing studies on the mechanism of and clinical application for CP will further define its use as a diagnostic, prognostic and potentially therapeutic modality for a variety of therapeutic scenarios.

Biosynthesis and Biochemistry of Ceruloplasmin

Ceruloplasmin (CP) is a multicopper oxidase glycoprotein that has a major function in the metabolism of copper and iron. Both its biosynthesis and some of the biochemical properties are marked by a highly regulated mechanism that comprises hepatic gene expression, intracellular trafficking, post-translational modifications and subsequent specific incorporation of copper necessary for its enzymatic ligand ability and physiological activity (Hellman et al., 2002).

Ceruloplasmin is produced from the CP gene and is expressed mainly in hepatocytes. Expression of this gene is regulated by inflammatory stimulus and iron availability, suggesting that it is an acute phase protein. After transcription, the CP mRNA is translated on ribosomes located to the rough portion of the endoplasmic reticulum (ER), and cotranslationally translocated through the ER membrane into its lumen. The main translation product is an apoceruloplasmin polypeptide which is composed of about 1,046 amino-acids (Lopez et al., 2023).

In the ER ceruloplasmin is first folded and N-glycosylated: that a post-translational modification which is important for protein stability, solubility and efficiency of secretion. A number of glycosylation sites have been defined, and though the glycans are not essential for enzymatic activity itself, they are important determinants that help to maintain a native conformation and to prevent degradation before secretion. ER quality control makes sure that the misfolded ceruloplasmin molecule is not secreted but is retained and degraded (Sato & Gitlin, 1991).

A key biochemical feature of ceruloplasmin is its content of copper. Mature holo-ceruloplasmin has six copper atoms/molecule that are essential both for the structural stability and the catalytic activity (Hellman et al., 2002). Copper is incorporated into ceruloplasmin however, not in the ER but in the trans-Golgi network, where dedicated copper-transport systems are present. The cytosolic copper is transported into the secretory compartment by metallochaperones, including ATOX1 that delivers copper to the P-type ATPase ATP7B. ATP7B mediates copper transport into the lumen of the Golgi, where apoceruloplasmin is transformed to holo protein.

The effectiveness of copper incorporation is crucial to ceruloplasmin stability. It has been shown that a defect in copper incorporation leads to secretion of apoceruloplasmin, which has a very short half-life in plasma and is rapidly cleared from it (Hellman et al., 2002). In contrast, Holo-ceruloplasmin is relatively stable in its structure and remains present in plasma for days. This difference is of clinical relevance, because deficiencies in ATP7B-mediated copper supply, as in Wilson's disease (WD), yield low circulating ceruloplasmin levels with normal hepatic synthesis (Lopez et al., 2023).

Among the three different copper centers of ceruloplasmin (Type I, Type II and Type III), which are classified from a chemical point of view by spectroelectrochemistry behaviors, it is known that it belongs to the multicopper oxidase family. The total three Cu sites are assembled to make a trinuclear copper cluster, which is responsible for effective mediation of electron transfer during catalysis. Type I copper sites receive electrons from substrates and the Type II and Type III centers act together to reduce molecular oxygen to water (Hellman et al., 2002). This catalytic scaffolding renders ceruloplasmin a ferroxidase activity that is responsible for the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), critical for loading this metal onto transferrin and its systemic circulation (Reilly & Aust, 1997).

Besides its ferroxidase activity, ceruloplasmin also has antioxidant qualities such as suppression of the generation of free radicals by iron. The ferric iron state of iron retained by ceruloplasmin lowers the quantity of Fe^{2+} that can enter Fenton reaction and thereby protects the cells from oxidative damage. These biochemical actions establish ceruloplasmin as the major regulator of redox state in plasma and tissues.

Upon maturation and metalation, hololipid ceruloplasmin is secreted into plasma to deliver >90% of circulating copper (Lopez et al., 2023). As well as its enzymatic function, ceruloplasmin is a copper pool for delivery of copper to remote tissues. Perturbations of ceruloplasmin biosynthesis and structure, as caused by a mutation in the CP gene, results in disease; for example aceruloplasminemia is characterized by iron deposition and oxidative stress occurring before neurodegeneration (Ziliotto et al., 2025).

Physiology of Haptoglobin

Ceruloplasmin (CP) exists as a copper binding glycoprotein and serves diverse physiological roles that go beyond its historical role simply as a plasma copper reservoir. The primary source of CP is hepatocytes, and it is released into the circulation where it performs essential functions in iron homeostasis, redox biology, inflammation and systemic metal balance. The knowledge of these physiological roles has general importance in human health, since deregulations of CP activity have been associated with metabolic, neurodegenerative and cardiovascular diseases (Lopez et al., 2023).

Iron Homeostasis and Ferroxidase Activity

The best characterized physiological role of ceruloplasmin is as a ferroxidase, that catalyzes the oxidation of ferrous (Fe^{2+}) to ferric iron (Fe^{3+}), a reaction required for binding to transferrin and eventual transport of iron in the circulation (Hellman & Gitlin, 2002). This function constitutes the central role of CP in iron homeostasis, as it promotes the mobilization of iron from storage cells (including macrophages and hepatocytes) to the plasma. If sufficient ferroxidase activity is not present, iron efflux can be reduced, resulting in intracellular iron accumulation and increased risk of oxidative injury due to free iron. In fact, copper deficient animals turned out indeed to be characterised by low levels of CP that was associ ated with hypoferremia and decreased transfer of iron from cell to plasma (Roeser et al., 1970), indicating the involvement of CP in iron homeostasis. Moreover, aceruloplasminemia subjects with a non-functional CP gene suffer tissue damage and neurological impairment due to iron accumulation in liver, pancreas and brain further corroborating the relevance of CP mediated systemic iron release (Hellman & Gitlin, 2002).

Antioxidant Defense and Redox Regulation

In addition to its ferroxidase activity, ceruloplasmin is a potent antioxidant. As well, the ferroxidase reaction itself also acts as an antioxidant: as the pool of Fe2+ is diminished to participate in Fenton chemistry that generates extremely reactive hydroxyl radicals. Due to the transition of Fe^{2+} to Fe^{3+}, ROS generation is indirectly reduced, and this protects them from oxidative damage of macromolecules in cell membranes (Liu et al., 2022). Its antioxidant role is particularly relevant in patients with chronic inflammatory and metabolic diseases, such as diabetes, obesity, and atherosclerosis, where systemic oxidative stress plays an important pathophysiological role. The plasma CP is generated under these conditions as one of APR and it may have a role in tissue protection against free radicals scavenging and protecting the organism from metal induced oxidative damage. In addition, ceruloplasmin might serve as a scavenger for radical and associate with lipid peroxide. Although detailed mechanisms remain to be elucidated, CP was found to modify oxidative status in the circulation and in tissues suggesting its involvement in roles other than those related with classical ferroxidase activity, placing it as one of the endogenous antioxidant systems implicated in the maintenance of redox balance under physiological and stress conditions (Liu et al., 2022).

Interaction with Nitric Oxide and Vascular Function

Recent studies suggest that ceruloplasmin also plays role in regulation of NO metabolism, therefore expanding its range of physiological activities. NO is an important mediator of vasodilation, blood flow and immune response. It has been demonstrated by studies that the metabolism of NO in plasma may be altered by CP, which will change the production of SNO tertiary nitrosothiols, a storage form for and biological vehicle of NO. While CP is not necessary for systemic NO plasma clearance, its effect on SNO product formation at physiological endogenous NO concentration levels implies a nuanced relation to vascular homeostasis and signaling especially in hypoxia and ischemia with profound implications on NO dynamics. This interaction places CP into context of mechanisms controlling vascular tone, and suggests that there may be a cross-relations between metal homeostasis and NO pathways (Vrancken et al., 2013).

Acute-Phase Response and Immune Modulation

Ceruloplasmin is a positive acute-phase protein and its plasma levels increase in the presence of inflammation, infection, trauma, or tissue damage. This upregulation is induced by pro-inflammatory cytokines including IL-6 and is consistent with CP's role in innate immunity. Increased concentrations of CP have been seen in metabolic diseases with the presence of chronic low-grade inflammation such as type 2 diabetes mellitus and coronary heart disease, indicating that CP has potential both as a biomarker and mediator in inflammatory causative signal. At the mechanistic level, induction of CP during inflammation may contribute to attenuate oxidative damage and facilitate iron metabolism in activated immune cells that are metabolically active during host defense (Liu et al., 2022).

Copper and Iron

Although ceruloplasmin is a minor player in copper transport compared with its functions in iron metabolism and antioxidant control, it does remain the most abundant (perhaps >95% of total) plasma copper-binding protein. While some of these carriers (e.g., albumin) promote transportation of copper from tissues to liver, CP is involved in buffering systemic copper and keeping it available for peripheral cells that need copper as a cofactor for enzymes. As such, ceruloplasmin stands at the crossroads of copper and iron metabolism through which it can regulate the distribution as well as redox chemistry of these important trace elements (Liu et al., 2022).

Clinical significance of ceruloplasmin

Ceruloplasmin (CP) has traditionally been considered the most important copper-binding protein in human plasma, but its clinical relevance is not limited to copper transport. Changes in the concentration, enzymatic activity or molecular integrity of ceruloplasmin are related to a numerousness of congenital and acquired diseases. Thus, CP is not only a diagnostic laboratory parameter but also a biomarker of alterations in metal metabolism, oxidative stress and inflammation or tissue damage.

Among the oldest clinical uses for ceruloplasmin determination is in the diagnosis and follow-up of patients with abnormalities of copper metabolism including Wilson's disease (Ramos et al., 2016). Wilson's disease results from defective biliary copper excretion caused by mutations in the ATP7B gene, which results in excess hepatic and brain and other tissue copper storage. Lowered serum ceruloplasmin concentration is commonly found in affected individuals and is a routine part of the diagnostic process. Although low ceruloplasmin is not 100% disease specific, when considered with serum copper and urinary copper excretion along with other clinical information, its measurement can greatly contribute in making the diagnosis as well as monitoring. Sequential evaluation of ceruloplasmin levels may also be useful to monitor response to treatment on chelation therapy (Jain et al., 2025).

In addition to inherited copper disorders, ceruloplasmin is gaining clinical importance in iron metabolism and associated pathobiology. As a ferroxidase, ceruloplasmin mediates the transition of ferrous iron into its ferric form to allow binding to transferrin and systemic dispersion. Absence or impairment of ceruloplasmin, as in aceruloplasminemia results in iron loading of liver, pancreas and to a lesser extent retina and central nervous system. This results in the clinical syndrome of diabetes mellitus, retinal degeneration, movement abnormalities and mental retardation. These data emphasise the important role of ceruloplasmin in preventing iron induced tissue toxicity, and its diagnostic relevance in idiopathic early onset iron overload (Hellman & Gitlin 2002).

Ceruloplasmin is a positive acute-phase reactant and its serum concentration increases following stimulation with pro-inflammatory cytokines like interleukin-6. High levels of ceruloplasmin have been described in the chronic inflammatory diseases, infections and autoimmune conditions and are an indication of upregulated innate immunity. Clinically, high levels of ceruloplasmin might be also employed as a nonspecific indicator to systemic inflammations in parallel with other acute phase proteins including CRP. Crucially, increased HAMP during inflammation might have functional relevance, namely by restricting the availability of iron to pathogens and mitigating oxidative tissue damage (Reștea et al., 2023).

Ceruloplasmin has been receiving considerable attention in cardiovascular diseases as both a biomarker and mediator of pathophysiology. Elevated serum ceruloplasmin concentration has been linked to risk for coronary artery disease, heart failure, and adverse cardiovascular events. Clinical evidence indicates that ceruloplasmin could mirror increased oxidation stress and inflammation in the vascular bed. In addition, ceruloplasmin may also affect nitric oxide availability and endothelial function leading to vascular dysfunction. In patient with severe HF, elevated ceruloplasmin levels have been an independent predictor of death, thus at least generating evidence for its value as a prognosis marker in the cardiovascular field (Smyła-Gruca et al., 2024).

The neurological disorders as well as neurodegenerative diseases are also reported with the higher clinical importance of ceruloplasmin. Normal ceruloplasmin activity is an important part of iron homeostasis and antioxidant protection against neuronal iron accumulation and damage. There are reports of decrease ceruloplasmin activity in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease as well as altered ceruloplasmin stability or function which are related to neuroinflammation and neuronal susceptibility. These results indicate that ceruloplasmin might be a biomarker of deranged metal metabolism in neurodegeneration and, likely, a therapeutic target (Squitti et al., 2010).

Ceruloplasmin changes are also significant in metabolic and hepatic disorders. Ceruloplasmin synthesis may be impaired due to liver disease which leads to decreased serum level by contrast, inflamed liver increases its output. In metabolic syndrome and

diabetes mellitus, the levels of ceruloplasmin have shown a correlation with oxidative stress and cardiovascular risk percentile, thus this protein reveals its role also as integrative marker of the metabolic and inflammatory status (Nagi et al., 2025).

Conclusion

Ceruloplasmin is an ancient multicopper oxidase with multiple capabilities that sits at the crossroads of copper metabolism, iron metabolism, redox control and inflammation. By its ability to function as a ferroxidase, ceruloplasmin has a critical function in the maintenance of systemic iron homeostasis and protection of tissues from iron-related oxidative stress. In addition to its classical role as a metabolic substrate, increasing evidence suggests that the metabolite also plays an important role in immune modulation, maintenance of vascular integrity and neuroprotection. On a clinical basis, modulations of ceruloplasmin levels and its activity being related to the extensive array of diseased states such as copper metabolism dysfunctions, cardiovascular problems, neuro-degenerative pathologies and chronic inflammatory conditions. Despite lack of disease specificity, improvements in the molecular, genetic and proteomic techniques have improved knowledge on the diagnostic and prognostic value of ceruloplasmin. Additional studies that investigate mechanistic pathways and utilize standard analytic methods will continue to refine its clinical value, leading to its adoption in the discipline of precision medicine/translational science.

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