

Heme Interactions

Subjects: [Immunology](#)

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Heme (Fe^{2+} -protoporphyrin IX) is a pigment of life, and as a prosthetic group in several hemoproteins, it contributes to diverse critical cellular processes. Direct interactions of extracellular heme with alternative pathway complement components (APCCs) may be implicated molecularly in diverse conditions at sites of abnormal cell damage and vascular injury.

heme

HeBPs

HBMs

complement

genetic

1. Pleiotropic Functions of Heme, Transport and Heme-Associated Pathologies

Heme (Fe^{2+} -protoporphyrin IX) is a pigment of life in all organisms ranging from bacteria to mammals [\[1\]\[2\]\[3\]\[4\]](#). In terms of structure, heme exhibits a protoporphyrin IX tetrapyrrole ring system that is coordinated by a central iron ion through the four nitrogen atoms of the assembled moiety [\[5\]](#). Heme also exhibits eight alkyl substituents (four methyl, two propionates and two vinyl groups) attached to its pyrrole rings. As a covalent prosthetic group in several vital hemoproteins, such as hemoglobins, myoglobins, cytochromes and enzymes, it serves as the essential gas carrier of oxygen (O_2), nitrogen oxide (NO) and carbon monoxide (CO) [\[6\]\[7\]\[8\]\[9\]](#).

In the hemoglobin chains, the iron ion is bound to a histidine residue and to oxygen which binds at the other coordinated position of iron. The iron ion in hemoglobin is in its ferrous state (Fe^{2+}) facilitating the reversible association with molecular oxygen. When the oxidation of hemoglobin occurs, iron transitions to its ferric state (Fe^{3+}), thus converting hemoglobin to methemoglobin, which has limited oxygen-carrying capacity. In the presence of chloride (Cl^-) ions, heme is converted to hemin, the oxidized form of iron protoporphyrin IX [\[5\]](#). Researchers current knowledge about the functions of heme has been derived from experimental work using hemin, the oxidized form of heme (Fe^{3+} -protoporphyrin IX) with a chloride ligand.

Heme is a major activator and regulator of erythropoiesis [\[5\]\[10\]\[11\]\[12\]](#), an essential constituent of the red blood cells (RBCs), and a central element in cellular metabolism and mitochondrial bioenergetics. In addition, heme contributes to globin biosynthesis [\[12\]\[13\]](#), induces cell signaling and sensing pathways [\[14\]\[15\]](#), and it also facilitates proteolysis via ubiquitination [\[14\]\[15\]\[16\]](#) among its several pleiotropic biological activities and properties summarized in **Table 1** as examples.

Heme is synthesized de novo in the mitochondria [\[3\]\[5\]\[17\]](#), while it is catabolized by heme oxygenases (HOs) into bilirubin and CO_2 [\[4\]\[5\]\[18\]\[19\]\[20\]](#). Unfortunately, despite being essential for erythropoiesis and pivotal for several

other molecular processes, heme as a free agent can be hazardous as a potent oxidant in the formation of volatile radical oxygen species (ROS) [14][21][22][23].

The diverse effects of heme suggest that under healthy conditions, its intracellular levels and trafficking are constantly monitored, and tightly regulated, by an extensively network of heme-binding proteins (HeBPs) [24][25][26][27][28][29][30]. These proteins are of diverse ontologies and contain often multiple heme-binding motifs (HBMs) that bind labile heme (biologically available and non-covalently bound) transiently with various affinities (K_d) [1][5][26][31][32][33][34]. These classes of motifs exhibit a primary architecture such as $X_4(C/H/Y)^0X_4$ and contain an amino acid, histidine (H), tyrosine (Y), or cysteine (C), coordinated to the iron ion of heme and surrounded by positively-charged amino acids or cysteine–proline motifs (CP motifs) or cysteine [35][36]. The transport of labile heme in and out of the cells is also achieved through its transient binding to several shuttle proteins, receptors and complexes [27][37][38][39]. Heme is extracellularly sequestered when damaged or ruptured cells release considerable amounts of hemoproteins and eventually labile heme into tissues, organs and into the circulation [22].

Table 1. Heme in diverse molecular processes and pathologies ¹.

Beneficial Effects (+)
• Serves as prosthetic group in hemoproteins such as hemoglobin, myoglobin, cytochromes and enzymes [1][2][3][4][5][10]
• Acts as a gas carrier for O₂, CO and NO [6][7][8][9]
• Enhances globin mRNA translation [12][13]
• Induces hemoglobin biosynthesis and erythropoiesis [5][11][13][40][41][42][43]
• Activates cell signaling and regulates sensing [14][15]
• Regulates mitochondrial respiratory bioenergetics [17][44][45]
• Binds to DNA G4 structural domains [46]
• Regulates the transcriptional dynamics of several genes [5][10]

- Activates chaperones such as the heat shock proteins HSP70 and HSP90 [\[47\]](#)

- Forms conjugation adducts with N-acetyl cysteine (NAC) and other thiols [\[21\]](#)

Harmful Effects (–)

- Stimulates toll-like receptors (TLRs) affecting the immune response [\[48\]](#)[\[49\]](#)

- Regulates complement and coagulation responses [\[50\]](#)[\[51\]](#)[\[52\]](#)[\[53\]](#)[\[54\]](#)[\[55\]](#)

- Promotes ubiquitination and proteolysis [\[14\]](#)[\[16\]](#)

- Acts as a major oxidant promoting ROS accumulation and cell stress [\[14\]](#)[\[22\]](#)[\[24\]](#)

- Stimulates stroke cell lysis and neuron ferroptosis [\[56\]](#)[\[57\]](#)[\[58\]](#)

- Inhibits neuronal functions such as the low conductance K⁺ channels [\[59\]](#)[\[60\]](#)

Heme-Associated Pathologies

- Severe hematological disorders such as acute intermittent porphyrias [\[61\]](#) and anemias [\[5\]](#) that include congenital sideroblastic anemia [\[62\]](#) and Diamond–Blackfan anemia [\[63\]](#)[\[64\]](#)

- Inflammation [\[48\]](#)[\[49\]](#)[\[65\]](#)

- Hemolytic syndromes [\[66\]](#)

- Severe sepsis [\[65\]](#)

- Stroke [\[38\]](#)[\[39\]](#)[\[56\]](#)[\[57\]](#)[\[58\]](#)

- **Neurodegeneration** [67][68]

- **Neurological disorders** [69][70]

- **Cardiovascular arrhythmias** [71][72]

Heme-Associated Complementopathies [73]

- **Hemostasis-driven thromboinflammation** [74]

- **Paroxysmal nocturnal hemoglobinuria (PNH)** [75][76]

- **Hemolytic diseases and cell lysis conditions such as hemolytic uremic syndromes, hemorrhage, sepsis and sickle cell disease** [53][77][78]

- **Age-related macular degeneration (AMD)** [75][79][80]

- **Ferroptosis in traumatic brain injury** [68]

- **Ischemic stroke with cerebral hemorrhage** [81]

- **Neurodegeneration** [82]

- **Huntington’s disease** [83]

[84] proteins [85],
[55] [54] [51] these direct
complement
associated
[55][86][87]. In
expression

of CD46/MCP and CD55/DAF, thus limiting the decay accelerative capacity of the compromised cells mainly to locally available CFH, and therefore promoting the formation of a hyperactive AP C3 convertase [54]. The interaction of heme with CFI blocks its proteolytic capacity against C3b, therefore also supporting the formation of a hyperactive AP C3 convertase [51].

The AP has recently attracted renewed interest due to its multidimensional involvement in important immune [88][89][90] and hemostatic processes [74]. Interestingly and in terms of the competing biochemical dynamics between the CP and AP, recent data have suggested that the contribution of the AP in complement activation on cell surfaces depends on the strength of CP initiation [91]. In that perspective, a heme-crippled C1q can enhance the AP activation dynamics, if there is lack of effective decay accelerating activity to control the formation of a C3bBb convertase.

Heme can downregulate CD46/MCP and CD55/DAF limiting the local decay accelerator factor potential to CFH, while it can also distort C3 [54] and block the proteolytic capacity of CFI [51]. The exposure of endothelia to heme can also promote the rapid exocytosis of Weibel–Palade bodies, the TLR4-dependent surface membrane expression of P-selectin known to bind C3b/C3(H₂O) and trigger the AP, and the release of the prothrombotic von Willebrand factor [54][77]. The occurrence of local noncanonical AP activation and its association with the induction of thrombosis hemostatic responses has been recently discussed for SARS-CoV-2 infection in COVID-19 [92][93][94][95][96]. In both of these quite different scenarios, the heme-induced stress and the viral infection, the disruption of the physiological heparan sulphate–CFH coating could be a common and pivotal attribute for the maintenance of a deregulated AP amplification loop [79]. Other parameters in the host background, such as natural genetic variation (e.g., indels, SNPs) and epigenetic modifications (e.g., phosphorylation) of complement AP components, may also synergistically favor the enhanced assembly of a deregulated AP amplification loop.

3. Heme Interactions with APCCs and Complement Deregulation

Therefore, the direct extracellular interactions of heme with complement components, and in particular with AP complement components (APCCs), are of particular interest towards understanding molecularly, diverse heme-associated pathologies mediated by complement deregulation. Such heme-associated complementopathies [73] (**Table 1**) are characterized by cell populations or sites of abnormal cellular damage and vascular injury. This potential involvement of the AP activation as a mediator of disease pathologies, triggered by heme-induced stress, formed the conceptual basis for investigating the heme binding interactions with APCCs. Given the recent progress in the advanced computational prediction of HBMs in HeBPs, the questions of whether the APCCs carry putative HBMs and whether these HBMs overlay with sites or residues that may genetically (encoded SNPs) and/or epigenetically (PTMs: post-translational modifications) vary among individuals were assessed. Such natural variability could be interesting in explaining, mechanistically, a tendency towards the deregulation of the AP, identifying potential personalized biomarkers of susceptibility for advanced diagnostics and revealing common targets for personalized pharmacological intervention in a diverse range of diseases induced by poorly controlled heme-driven cell stress.

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