INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student	:	Alok Kumar Pandey
Roll Number	:	176106024
Programme of Study	:	Ph.D.
Thesis Title:		Role of HSPA8 in pathological outcomes in the host during malaria.
Name of Thesis Supervisor(s)	:	Prof. Vishal Trivedi
Thesis Submitted to the Department/ Center	:	BSBE
Date of completion of Thesis Viva-Voce Exam	:	25-11-2024
Key words for description of Thesis Work	:	Hemin, HSPA8, Binding, hemoprotein, peroxidase, Heme polymerization, ATPase activity, competitive inhibitor, Functional modulation, Cytotoxicity, Cytoprotection.

SHORT ABSTRACT

Hemolytic diseases like malaria encompass a group of disorders characterized by hemolysis or accelerated destruction of red blood cells (RBCs). Hemolysis leads to the release of Hemoglobin and its derived products like methemoglobin, free heme, hematin, and hemin in the plasma. Although normal hemin levels are crucial for governing many physiological processes, hemin accumulation to abnormal levels is highly toxic to the corresponding cells, tissue, or organs and contributes to the various pathological outcomes of malaria.

The present study concludes that the chaperone HSPA8 has a cytoprotective role during conditions of high heme accumulation like malaria. HSPA8 binds to hemin through its N-terminal domain and behaves as a hemoprotein. This hemoprotein converts hemin into a less toxic heme polymer in the presence of H_2O_2. This polymerization is carried out via the peroxidase mechanism, similar to that exhibited by HRP, involving one-electron transfer and free radical formation. Further, we found that hemin competes with ATP for binding to HSPA8 thus competitively reducing its ATPase activity. The hemin-induced reduction in the activity leads to a reversible loss of the ATP-dependent protein folding function of the HSPA8.

We also found that hemin is highly toxic to HepG2 cells and hemin doses reduce the viability and cellular integrity of these cells. Hemin perturbs the proliferation of these cells by an arrest in the S-phase of the cell cycle. Hemin causes DNA fragmentation leading to apoptosis and necrosis of HepG2 cells. It triggers both the intrinsic and the extrinsic pathways of apoptosis by modulating the expression levels of a variety of apoptosis or necrosis-related proteins in HepG2 cells. HSPA8 being able to neutralize hemin protects HepG2 cells from hemin-induced toxicity.