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Structural Insights into the Inhibition of Human Ferroportin by Ciclopirox: A Putative Therapeutic Strategy for Iron Overload in β-Thalassemia

Abstract : Ferroportin (FPN), an iron exporter, emerged as a crucial therapeutic target for β-thalassemia due to the disease's characteristic ineffective red blood cell production and elevated systemic iron levels. By inhibiting FPN, the aim is to restrict iron availability, thereby mitigating both anemia and iron toxicity associated with β-thalassemia. Ciclopirox, an antifungal medication, was identified as a potential candidate for interacting with human iron transport proteins given its strong iron-binding properties. A study involving computational docking of Ciclopirox to the human FPN structure (PDB: 6w4s) yielded promising results. The docking analysis indicated a robust binding energy of –12.3 kcal/mol, suggesting the formation of a stable and effective complex. Further examination of the binding pose revealed that Ciclopirox effectively obstructed the central iron efflux channel of FPN. Specifically, the hydroxamic acid group of Ciclopirox established a critical hydrogen bond with Cys326, a residue known to be essential for regulation by the hormone hepcidin. These findings propose that Ciclopirox functions as a competitive inhibitor, effectively mimicking the natural action of hepcidin. This mechanism of action aligns with several novel inhibitors currently undergoing investigation for the treatment of β-thalassemia. Consequently, Ciclopirox is highlighted as a promising FPN inhibitor and a strong candidate for drug repurposing. Given its established oral bioavailability and favorable safety profile, Ciclopirox merits further experimental evaluation as a therapeutic option to manage iron overload in patients afflicted with β-thalassemia.

Authors: Mr M, Thejas (JAIN (Deemed-to-be University) school of sciences); Dr UMAKANTH NAIK, Vankadoth (JAIN (Deemed-to-be University))

Co-author: Ms P R, Akshaya (JAIN (Deemed-to-be University) school of sciences)

Presenter: Mr M, Thejas (JAIN (Deemed-to-be University) school of sciences)

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