Can We Teach an Old Drug New Tricks?

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Abstract
Malaria, caused by parasites of the Genus *Plasmodium*, is an infectious disease of global importance, claiming hundreds of thousands of lives annually. The dominant species contributing to mortality is *P. falciparum*. A major hurdle to *P. falciparum* eradication is the problem of drug resistance. The 4-aminopyrimidine, chloroquine (CQ), once a mainstay for malaria chemotherapy, has been rendered useless against most *P. falciparum* infections. This is due to the exquisite ability of the mutant parasite transporter, PfCRT, to efflux CQ out of its target organelle, the lysosome-like digestive vacuole (DV). Exploiting this resistance feature, we developed fluorescent CQ analogues that are able to differentiate CQ resistant from CQ sensitive isolates (Loh et al., 2014). These fluorescent CQ analogues were also adapted into a high-throughput screen for novel compounds that could block the PfCRT and hence resensitize the parasites to CQ (Ch'ng et al., 2013). In a concurrent study, we defined the parasite DV as a key mediator of *P. falciparum* CQ-induced cell death (Ch’ng et al., 2011), which is distinct from the classical anti-malarial mechanism of CQ. Using DV reporter molecules, we developed a high-content platform for identifying compounds that are potent DV-disruptors (Lee et al., 2014). Importantly, we show that CQ resistant parasites are susceptible to CQ-induced DV disruption and death. Our recent studies in mouse models show that higher, but non-toxic, concentrations of CQ mediate DV disruption of rodent malaria in rapid fashion (Ch’ng et al., 2014), leading us to suggest that a redosing of CQ for chemotherapy may facilitate its return as an attractive antimalarial option against *P. falciparum*. In summary, the ‘outdated’ CQ has shown promise in 2 areas: as a fluorescent tool for drug screening, allowing the discovery of potent CQ chemosensitizers and from the perspective of a new death mechanism, CQ can be exploited against drug resistant isolates through redosing or reformulation.

References


