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-aminoquinoline, 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-tagged CQs 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 In summary, the ‘outdated’ CQ has shown promise in 2 areas: as a fluorescent tool for drug screening, allowing the discovery of potent CQ chemosensitizers and from the perspective of a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


