Insights from nanomedicine into chloroquine efficacy against COVID-19

Chloroquine — an approved malaria drug — is known in nanomedicine research for the investigation of nanoparticle uptake in cells, and may have potential for the treatment of COVID-19.

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Recent multicentre clinical trials[1] and cell culture studies[2] suggest that the 70-year-old malaria drug, chloroquine, may potentially display therapeutic efficacy against COVID-19 (corona virus disease 2019), a rapidly spreading viral infection that can cause pneumonia-induced death in approximately 2.5% of infected individuals[1,3]. Based on the preliminary clinical trial findings, chloroquine has been included in federal guidelines for treatment of COVID-19 in the People's Republic of China. However, caution should be exercised when making premature interpretations, as clinical trials are still ongoing and interim trial data have not yet been made available. Given the current lack of an approved and effective vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1], the virus causing COVID-19, it is important to evaluate potential prophylactic and/or therapeutic effects of drugs that are clinically approved for other indications. Chloroquine and its derivative, hydroxychloroquine, have a long history as safe and inexpensive drugs for use as prophylactic measures in malaria-endemic regions and as daily treatments for autoimmune diseases with the most common side effect being eye damage after long-term use[4]. Although previous studies have revealed that chloroquine has therapeutic activity against viruses[5], including human coronavirus OC43 in animal models[6] and SARS-CoV in cell culture studies[7], anti-viral mechanisms of chloroquine remain speculative. Chloroquine has been used in the field of nanomedicine for the investigation of nanoparticle uptake in cells, and, therefore, insights from synthetic nanoparticle interactions with cells in the presence of chloroquine may reveal mechanisms that are active at early stages prior to viral replication. Specifically, nanomedicine studies may provide clues on chloroquine-induced alterations of SARS-CoV-2 cellular uptake.

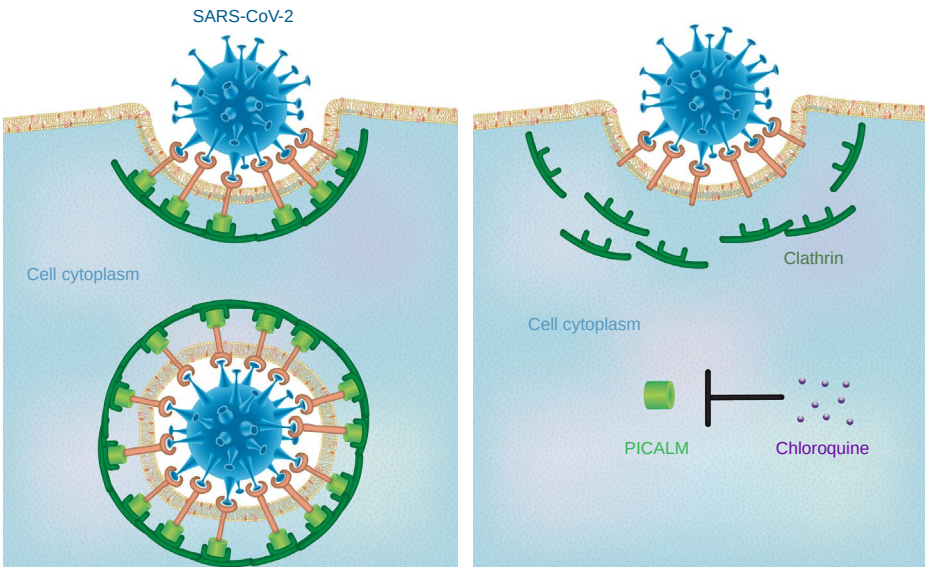

Fig. 1 | Potential mechanism by which chloroquine exerts therapeutic effects against COVID-19. The proposed mechanism involves chloroquine-induced suppression of PICALM, which prevents endocytosis-mediated uptake of SARS-CoV-2.

Chloroquine mechanisms of action

The precise mechanisms through which chloroquine may act to attenuate SARS-CoV-2 infections are of considerable interest, as this information could be valuable for identifying new prophylactic and therapeutic candidates. Chloroquine is a weak base that becomes entrapped in membrane-enclosed low pH organelles, interfering with their acidification[5]. In malaria-causing plasmodium parasites, chloroquine accumulates in the digestive vacuole where it is thought to prevent pH-dependent detoxification of heme, which is produced upon parasitic consumption of haemoglobin to obtain free amino acids[8]. This sequestering effect is also apparent in mammalian cells, in which chloroquine treatment leads to an increase in lysosomal pH. Speculation on chloroquine-induced antiviral effects include inhibition of pH-dependent viral fusion/replication and prevention of viral envelope glycoprotein as well as host receptor protein glycosylation[5]. Chloroquine may also inhibit virion assembly in endoplasmic reticulum-Golgi intermediate compartment (ERGIC)-like structures. Additionally, it is probable that chloroquine exhibits host effects, independent of direct viral action, by attenuating the expression of pro-inflammatory factors and receptors[5] that can induce acute respiratory distress syndrome, which is primarily responsible for coronavirus-associated mortality[3].

Chloroquine inhibits endocytosis of nanoparticles

It has been demonstrated that chloroquine is a broad-spectrum inhibitor of nanoparticle endocytosis by resident macrophages. Therefore, chloroquine decreases the accumulation of synthetic nanoparticles of various sizes (14–2,600 nm) and shapes (spherical and discoidal) in cell lines, as well as in the mononuclear phagocyte system of mice in response to clinically relevant doses of chloroquine[9,10]. Mechanistic studies have revealed that chloroquine reduces the

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Competing interests

The authors declare no competing interests.