Molecular mechanisms to control crystal nucleation

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Control of crystal nucleation is one of the holy grails of materials synthesis. Classical nucleation theory (CNT) highlights coarse handles to mostly enhance nucleation. Numerous industrial tasks require suppression of nucleation; elaborate structures in nature suggest precise nucleation control that consists of selective suppression or enhancement of local nucleation. We show that the nucleation of hematin crystals can be suppressed and fine-tuned via the properties of a population of nucleation precursors extant in the solution. Hematin crystals form in the digestive vacuoles of malaria parasite, where they sequester toxic hematin released as the parasite catabolizes hemoglobin from the host's erythrocytes. The addition of three antimalarial drugs, mefloquine (MQ), chloroquine (CQ), and pyronaridine (PY), and the heme adduct of another drug, artemisinin, H-ART, known to impact hematin crystallization, selectively invokes three outcomes: accelerated nucleation (H-ART), suppressed nucleation (PY), or no effect (CQ and MQ). The nucleation suppression by PY falls outside of the realm of CNT and suggests that hematin crystal nucleation may follow a nonclassical pathway. Transmission electron microscopy (TEM) reveals amorphous hematin particles with diameters ranging from 70 to 250 nm that host and assist the nucleation of hematin crystals. Oblique illumination microscopy reveals the presence in the solution of mesoscopic hematin-rich clusters with similar sizes. Remarkably, the responses of the cluster population to the four modifiers run parallel to the responses of crystal nucleation, coherently with the role of clusters as crystal nucleation sites. Collectively, the TEM observation of cluster-assisted nucleation and the parallel trends of additive activity on the cluster population and crystal nucleation support a mechanism of nucleation control employing additives that modulate the nucleation precursors. To elucidate the molecular mechanisms employed by the antimalarial drugs to boost or suppress the solute rich clusters we carried out all-atom molecular dynamics simulations. The simulations reveal that water nanodroplets assemble at the charged groups of both hematin and the tested drugs and stabilize the charges. Thus, the negatively-charged modifier H-ART repels the negatively charged hematin and act as a crowder to increase the chemical potential of the solute and enhance cluster formation. We used that the properties of the mesoscopic solute-rich clusters indicate a decisive role of transient solute dimers for the formation of the clusters. We modeled the formation of such hematin dimers in the presence of MQ, CQ and PY. We found that PY caused uninhibited loose aggregates of hematin, which lower its propensity to form clusters, whereas CQ and MQ are passivated by permanently binding to hematin. The found molecular mechanisms to enhance or suppress crystal nucleation illuminate intricate crystal architectures in nature and provide powerful tools for nucleation control for numerous tasks in industry and the laboratory.