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Opinion

FAILURE OF LYSOSOMOTROPIC DRUGS TO BE REPURPOSED FOR COVID-19 PREVENTION OR TREATMENT

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INTRODUCTION

Several efforts have been made to repurpose medications that are already approved for use in other contexts as a result of the hope that an efficient COVID-19 drug therapy will be discovered quickly. Organic amines known as lysosomotropic drugs, such as chloroquine, hydroxychloroquine, and amiodarone, were found to disrupt the viral life cycle in vitro but failed in clinical trials. The critical role of lipophilicity, the central role of vacuolar (V)-ATPase for their concentration in acidic organelles, the altered function of these organelles, including impaired endocytosis and secretion, macroautophagic accumulation, and secondary phospholipidosis, are briefly reviewed in relation to the properties of lysosomotropic drugs and the vacuolar cytopathology they cause. Lysosomotropic drug repurposing for COVID-19 may have been unsuccessful due to the high concentrations required for a sustained disruption of vacuolar trafficking and the apparent preferential uptake of lysosomotropic drugs by phagocytic leukocytes (macrophages, neutrophils).

DISCUSSION

SARS-CoV-2's coronarivus disease (COVID-19), which results in significant morbidity and mortality, has had and continues to have a significant global impact on public health. Several efforts have been made to repurpose medications that have been approved for use in other conditions to treat viral pneumonia in the hope that an effective drug therapy will be discovered quickly. For instance, hydroxychloroquine, an antimalarial medication, has been the subject of clinical trials. In this vein, many drugs that have been shown to inhibit SARS-CoV-2 replication in vitro are false positives because they belong to a class of drugs that cause phospholipidosis in cultured cells. Most of the time, these drugs are secondary or tertiary amines and very lipophilic; they include antimalarials, antiarrhythmics, psychotropic agents (such as haloperidol), and others that transcend therapeutic categories. Tamoxifen (an estrogen receptor modulator), clemastine (an antihistamine), and numerous other classes exhibit antiviral activity in cultured cells. The antiviral activity is correlated with the concentration that triggers phospholipidosis in cultured cells at the threshold level. Chloroquine, hydroxycholoquine, and amiodarone are among the drugs on the list that have been tested in clinical trials for COVID-19 treatment or prevention without success [1-3].

Due to their sequestration in acidic cell organelles, cationic amphiphilic drugs cause phospholipidosis, which lasts for a long time. The definition of a cationic amphiphilic drug utilized

by Tummino et al. is synonymous with a lysosomotropic drug, which is a weak base that accumulates in the acidic cell compartment. In point of fact, there is evidence that these drugs are concentrated in endosomes and all acidic cell compartments expressing the proton pump vacuolar (V)-ATPase. As a result, it was hoped that these drugs might prevent the SARS-causing coronaviruses from multiplying and releasing themselves by disrupting the process known as endocytosis. The author, who studies the cellular effects of lysosomotropic drugs in basic science, provides a personal perspective that may help clarify the debate.

The model lysosomotropic drug quinacrine does not concentrate in mature red blood cells because these cells lack endocytic and lysosomal vacuoles. Despite the fact that phagocytic cells may concentrate such drugs with a higher apparent affinity than other types of nucleated cells, they still rely on a mechanism that is dependent on V-ATPase: Bafilomycin A1 prevented the drug from being absorbed in all of the aforementioned in vitro studies. Based on drug fluorescence, it was demonstrated that blood-derived human monocytic cells treated to functionally differentiate into macrophages concentrated a low concentration of amiodarone in vacuoles more intensely and at a lower concentration than smooth muscle cells did. On the basis of quinacrine uptake by murine cells, similar findings were made: Freshly isolated lung alveolar macrophages performed the vacuolar quinacrine uptake more strongly than cultured fibroblasts did in the micromolar concentration range. The use of fluorescence dissection microscopy to examine lung tissue served as the impetus for this comparison: Only intensely isolated fluorescent dots, which corresponded to alveolar macrophages, were observed in mice treated for 48 hours with a dose of quinacrine that was well tolerated. The alveolar epithelium was not significantly fluorescent [4-6].

CONCLUSION

The fact that antimalarial medications like chloroquine, hydroxychloroquine, and quinacrine are lysosomotropic may be of interest because it may indicate a particular parasite vulnerability. Amiodarone, an antiarrhythmic medication, has a lipophilicity that is very high in the Et3N series, and vacuolar sequestration can cause side effects in some chronically dosed patients: notably skin discoloration primarily caused by macrophages with autophagic LC3 immunoreactivity, and lung disease caused by macrophages that are "foamy." Although the physiopathology of COVID-19 is not particularly relevant to the tropism of lysosmotropic drugs for phagocytic leukocytes, the use of hydroxychloroquine as an immunomodulator agent may be relevant.

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