Modulation of Chloroquine in nanoparticle uptake: a review
Modulação da Cloroquina na captação de nanopartículas: uma revisão
Modulación de la cloroquina en la captura de nanopartículas: una revision

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Abstract
The application of nanotechnology in several areas of medicine has been promising, however, there are still serious problems, such as in the area of oncology, for example. Although nanoparticles can accumulate 10 times more in tumors, less than 1% of the injected dose actually reaches the tumor, as they are retained mainly in the liver and spleen. Liver-specific macrophages, called Kupffer cells, are one of the main barriers to the use of nanoparticles for cancer treatment. These Kupffer Cells are part of the Mononuclear Phagocytic System (MPS) and exhibit endocytic activity against materials that pass through the blood and enter the liver. For this reason, Kupffer cells are central to the process of eliminating nanoparticles that cross the body's epithelial barriers. Still, chloroquine can act directly on the MPS, helping the nanoparticles reach their final target. This review addresses the main studies with chloroquine acting in the MPS, which could revolutionize cancer treatment or other biological applications.

Keywords: Chloroquine; Mononuclear Phagocyte System; Kupffer Cells; Nanoparticles; Liver.

Resumo
A aplicação da nanotecnologia em diversas áreas da medicina tem sido promissora, entretanto, ainda há sérios problemas como na área da oncologia, por exemplo. Apesar das nanopartículas poderem se acumular 10 vezes mais em tumores, menos de 1% da dose injetada atinge de fato o tumor, pois ficam retidas principalmente no fígado e baço. Os macrófagos específicos para o fígado, chamados de células de Kupffer, são uma das principais barreiras no uso de nanopartículas para o tratamento do câncer. Essas Células de Kupffer fazem parte do Sistema Fagocitário Mononuclear (SFM) e exibem atividade endocítica contra os materiais que passam pelo sangue e entram no fígado. Por esse motivo, as células de Kupffer são centrais no processo de eliminação de nanopartículas que atravessam as barreiras epiteliais do corpo. Todavia, a cloroquina pode atuar diretamente no SFM, auxiliando as nanopartículas a chegarem no seu alvo final. Essa revisão aborda os principais estudos com a cloroquina atuando no SFM, o que pode revolucionar o tratamento do câncer ou outras aplicações biológicas.

Palavras-chave: Cloroquina; Sistema fagocitário mononuclear; Macrófagos do fígado; Nanopartículas; Fígado.

Resumen
La aplicación de la nanotecnología en varias áreas de la medicina ha sido prometedora, sin embargo, aún existen problemas graves como la oncología, por ejemplo. Aunque las nanopartículas pueden acumularse 10 veces más en los
tumores, menos del 1% de la dosis inyectada llega realmente al tumor, ya que se retienen principalmente en el hígado y el bazo. Los macrófagos específicos del hígado, llamados células de Kupffer, son una de las principales barreras para el uso de nanopartículas para el tratamiento del cáncer. Estas células de Kupffer son parte del sistema fagocítico mononuclear (SFM) y exhiben actividad endocítica contra materiales que pasan a través de la sangre y entran al hígado. Por esta razón, las células de Kupffer son fundamentales para el proceso de eliminación de las nanopartículas que atraviesan las barreras epiteliales del cuerpo. Sin embargo, la cloroquina puede actuar directamente sobre el SFM, ayudando a las nanopartículas a alcanzar su objetivo final. Esta revisión aborda los principales estudios con cloroquina actuando en el SFM, lo que podría revolucionar el tratamiento del cáncer o otras aplicaciones biológicas.

**Palabras clave:** Cloroquina; Sistema mononuclear fagocítico; Macrófagos del hígado; Nanopartículas; Hígado.

1. Introduction

Chloroquine is a product created between wars, used initially to protect military personnel against malaria, but which civilians were also able to benefit from. Since the 1940s, the Food And Drug Administration (FDA) has approved chloroquine, but until today it is studied for various purposes, whether in the treatment of malaria, lupus, cancer, dengue and, more recently, against the new coronavirus - SARS - VOC-2 (de Souza & Pacheco, 2020; Hu et al., 2020).

One of the promising applications of chloroquine is modulation in the immune system to improve delivery of nanoparticles (Pelt et al., 2018). Nanotechnology provides some pharmacological advantages such as: reduction of treatment toxicity, dispersion of insoluble drugs in water, co-delivery and screening of two or more drugs for combined therapy (Ho et al., 2017; Pacheco, 2020). However, a 2016 study showed that less than 1% of administered nanoparticles were reaching the desired target, representing a major obstacle to better application of Nanobiotechnology (Wilhelm et al., 2016).

The low delivery of nanoparticle cells in the desired target is largely due to the Mononuclear Phagocytic System (MPS). MPS consists of phagocytic immune cells, such as macrophages, located in different parts of the body. It is these MPS cells that contribute to the greatest loss of injected dose of nanoparticles (dos Santos et al., 2017; Wilhelm et al., 2016). The clearance of nanoparticles occurs via opsonization and later lysosomal degradation (dos Santos et al., 2017).

The liver is the main site of metabolism and excretion of endogenous and exogenous agents. It receives blood either via the heart, via the hepatic arteries, or via the gastrointestinal tract, via the hepatic portal vein. Blood from these pathways arrives in the hepatic sinusoids, a region with a large amount of macrophages called Kupffer cells (H. Wang et al., 2015).

As Kupffer cells are important in the innate immune response, protecting the body against possible invaders or foreign molecules, however, this phagocytic clearance pathway is of little interest when the objective is to deliver nanoparticles carrying drugs for the treatment of some disease, as the drug carried can not reaching the desired target, affecting the treatment, in addition to possible unexpected side effects (Bertrand & Leroux, 2012; Wolfram & Ferrari, 2019).

Strategies can be used to prepare the immune system to reduce nanoparticle uptake, including: increasing the nanoparticle half-life; modify surfaces, nanoparticle shapes; biological camouflage and even functional saturation or macrophage depletion (Pacheco, 2020; Wolfram & Ferrari, 2019).

Some studies have shown that chloroquine can modulate MPS and be an excellent strategy to reduce the cost and with greater effectiveness in the treatment of several diseases. This review addresses the main mechanisms of chloroquine and when and how it is being used to modulate MPS.

2. Methodology

This is a narrative review using articles indexed in PubMed and Google Scholar to identify all relevant scientific studies based on our study objectives. There was no language restriction. The following keywords were used: “Chloroquine”, “Mononuclear Phagocytic System”, “Kupffer Cells”, “Nanoparticles” and “Endocytosis” were used between 2010 and 2021.
3. Results and Discussion

Chloroquine is a drug with tolerable safety and known for over 70 years. There are several applications of chloroquine, whether against malaria, lupus, cancer and it was even used against the 2019 Coronavirus Disease - COVID-19 (de Souza & Pacheco, 2020; Hu et al., 2020).

This drug is a weak base that becomes deprotonated in acidic environments, increasing the pH of acidic compartments, such as the lysosome involved in MPS endocytosis (J. Wolfram et al., 2017).

Due to the lysosome behavior chloroquine, is capable of altering lysosomal pH, interrupting an essential process of endocytosis, in which nanoparticles are degraded by MPS. (Hu et al., 2020; Pacheco, 2020; Pelt et al., 2018; Wolfram & Ferrari, 2019).

The liver is responsible for the clearance of endogenous and exogenous agents, an important defense mechanism. The liver's own morphology allows it to be the main barrier against nanoparticles. Both the hepatic portal vein and the coronary arteries flow into the liver sinusoids, a region largely constituted by macrophages, or Kupffer cells, components of the MPS, however, the pretreatment with chloroquine, via alteration of the lysosomal pH, can temporarily inhibit the endocytosis of liver macrophages, making nanoparticles more bioavailable (Figure 1) (Pacheco, 2020; Pelt et al., 2018).

The lysosome is usually the final compartment of the endocytosis process, which is the most common mechanism for internalization of nanoparticles into cells, however, it has been shown that chloroquine also acts in early stages of endocytosis, such as inhibiting the endocytosis assembly protein called Phosphatidylinositol-binding clathrin (PICALM) (Sahay et al., 2010; Joy Wolfram et al., 2017).

It's interesting to note that the lysosomal modification generated by chloroquine has the potential to act not only against the uptake of nanoparticles by the MPS, but also preventing the entry of viruses into cells by altering the endocytosis process. (Hu et al., 2020; Raftery et al., 2020; L.-F. Wang et al., 2015).

Furthermore, chloroquine itself may also have mechanisms against cancer, such as inhibition of autophagy, activation of apoptosis and normalization of tumor vasculature, so it is applied as an adjuvant therapy in some studies (Joshi et al., 2012; Kimura et al., 2013; Zhang et al., 2015).

Autophagy is a cellular process that involves the elimination and recycling of cytoplasmic components, which can increase cell survival by recycling nutrients and metabolites (Amaravadi et al., 2011; Cicchini et al., 2015; Kuma & Mizushima, 2010). Cancer cells that perform autophagy can be a problem for the treatment of cancer itself, however chloroquine, by increasing the pH of the lysosome in autophagy, is able to block cellular autophagy, making tumor cells more susceptible to apoptosis (Amaravadi et al., 2011; Pelt et al., 2018).

Other studies show the potential of chloroquine both in the reduction of metastasis and in the normalization of the tumor vasculature, which improves blood perfusion for better administration of nanocarrier drugs (Maes et al., 2014; Pelt et al., 2018).

Therefore, due to the lysosome behavior chloroquine, it is able to efficiently modulate MPS, reducing nanoparticle uptake by Kupffer cells, as well as helping with important underlying mechanisms such as autophagy inhibition and tumor vasculature normalization to improve nanoparticle delivery (Pacheco, 2020; Pelt et al., 2018).
Figure 1 - Mechanism of action of chloroquine in MPS. Chloroquine increases the pH of the MPS macrophage lysosome, affecting endocytosis and increasing the bioavailability of nanoparticles.

Source: Authors (2021).

4. Conclusion

Chloroquine is a drug with tolerable safety approved since the 40’s. Several studies show its potential against malaria, lupus, cancer and also in modulating the MPS barrier. Recent studies have shown that chloroquine may be important as a pre-treatment in cancer, since, due to its lysosomotropic behavior, it is able to modulate MPS endocytosis, especially in Kupffer cells, making the nanoparticles of interest more bioavailable to be delivered to the desired target. However, more safety and efficacy tests are still needed to validate all these benefits found with chloroquine for various off-label applications.

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