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HYDROXYCHLOROQUINE FOR VIRAL INFECTIONS UNDERLYING CELLULAR AND MOLECULAR EVENTS

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ABSTRACT

Anti-malarial agent hydroxychloroquine known to treat autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus. The long time believe of moSlecules which are interfering human cell membrane environment may block the viral entry into the cell. Further, Increment of intra cellular pH spoils organelles required acidic homeostasis. Augmented molecular evidences including glycosylation inhibition in viral proteins and hindering glycoprotein expression are the prominent for hydroxychloroquine ability as anti-viral. The ability of inhibiting UDP-N-acetylglucosamine 2-epimerasesenzyme which involved in sialic acid biosynthesis produces grater anti-viral properties with virus which use sialic acid moieties as receptors. Over a decade hydroxychloroquine have shown promising effect with Human Immuno Deficiency virus, type A and B influenza viruses,H5N9avian influenza virus,H5N1 type A avian influenza virus and recent pandemic of SARS Covid-2. The influence of hydroxychloroquine extended to Toll-like receptor 7 signalling pathways in plasmacytoid dendric cells and antigen-presenting cells plays vital role in immune activation, which is major contributor for viral load. However, effects like lysosomotropism and Autophagy are also having great consideration of molecular mechanism of Hydroxychloroquine for its anti-viral properties.

INTRODUCTION

Hydroxychloroquine (HCQ) differs from anti-malarial agent chloroquine by the presence of a hydroxyl group at the end of the side chain: the N -ethyl substituent is β-hydroxylated used in clinical practice more than half century.HCQ have similar pharmacokinetics profile with chloroquine (CQ) belongs to the same molecular family. However, HCQ possess rapid oral absorption and defers in dosage and toxicological profile with CQ. It is considered a disease-modifying anti-rheumatic drug, it can also can be employed for some symptoms of lupus and few strains of malaria. However, the effectiveness of HCQ in treating of autoimmune diseases is still less established, though few studies supports the ability of interferes with the communication of cells in the immune system.[1]The activity of HCQ is not only limited to malaria and interference in inflammatory process it also possess wide range of bacterial, fungal, and viral infections.Further, recent studies suggests HCQ inhibits autophagy which drive the malignant cells to apoptosis by indirect elevation of p62 autophagozome accumulation. However, in normal event sensitization of antiestrogens via increased LC3 levels which drives autophagy initiation.[2] Augmented evidences suggested that many virus particles adopts

autophagic machinery for both replication and survival advantage.[3] In other hand, HCQ believed to be employed with multiple viral infections by reduction in immune activation and a decrease in CD38+CD8+ T cells and Ki67 memory CD4+ T cells.[4&5] The pH increment into acidic cellular organelles including endosomes is major cause antiviral property of HCQ occurs in different mechanisms [4]. Majorly virus needs a sharp reduction in the pH to obtain conformational changes which enables fusion and penetration. [6] this will be crucially hindered by HCQ upon elevating pH which will also block the endosomal entry. [7] Further, viral post translation modification for viral envelop formation requires enzymes likeproteases and glycosyltransferases requires low pH for endoplasmic vesicles. [8] Therefore, the HCQ induced effect of elevated pH is directly impairing the viral maturation by blocking envelop formation. [9] Augmented *In vitro* studies suggested CQ from same molecular family possess anti-viral activity against RNA virus including HIV,[10] rabies virus,[11]poliovirus [12] etc. However, the clinical facts are different than *In vitro* promising. In other hand, HCQ shown potential adversity including cardiotoxicity signified with enlarged and vacuolated cells with abnormal lysosomes in electron microscopy.[13] Further, its neuromyotoxicity with muscle biopsy displayed curvilinear bodies and vacuolar changes. [14] The HCQ overdose also cause serious incidence including visual disturbance or ataxia and permanent neurotoxic vestibulopathy.[15] Long term establishment of HCQ treatment shown hemolytic anemia patients with glucose-6-phosphate dehydrogenase deficiency. However, this may be less common with African descent. [16] However, HCQ own proven advantage over rather side effects reported till date, mounting clinical importance of HCQ is unavoidable due to it wider therapeutic applicability. Even in case of virus the molecular similarity ATM and sugar moiety GM1 allows for its host mechanism where HCQ plays as competitive inhibitor role. [17]Multiple evidences strongly suggests HCQ can be a low cost substitute for anti-viral therapy for poor cost resource countries. Further, increased pandemic mortalities over past few decades drawn our greater attention to drive the molecular concepts. In this current review we attempt to drive molecular mechanical concepts of HCQ for various viral infections. However, HCQ possess wider therapeutic employment as antimalarial, rheumatoid arthritis and systemic lupus erythematosus will not be discussed in this review.

Zinc Ionophore

Zinc ionophores typically transport extracelluar Zn^{2+} ions across a cell membrane,Ionic zinc shown significant antiviral properties against a number of human viruses. [18-22] HCQ plays vital role as zinc ionosphere, elevated intracellular cytoplasmic Zn^{2+} ions were observed when Co-administration of zinc with HCQ. [23] Typically intracellular elevation of Zn^{2+} ions demonstrated various events in viral infections including inhibition of RNA-dependent RNA polymerase, [24]Interferencewith membrane fusion with histidine residue on E1 protein using acidic endosomal pH, [25]and modulating the secretion of interferons also modifying IFN-λ3 signaling; which results suppression of SOCS-1 and SOCS-3 cytokines and JAK protein signaling inhibition, finally this serial events leads preventing inflammatory stimuli. [26] The molecular similar CQ shown higher intracellular Zn^{2+} probed by TPEN metal binding detection compound along with elevation LC3B-II protein levels. [27] The Zn^{2+} inhibition of RNA-dependent RNA polymerase has greater advantage than RNA inhibitors which are does not cause intermediate chain termination.

Lysosomal pH modification- Autophagy

HCQ accumulation in the lysosome (lysosomotropism) is the major event occurs in $CD4^{+}$ T cells. [28] On other hand, HCQ targeting of palmitoyl-protein thioesterase 1 which is a key enzyme involved in lipid catabolism is also evidences its immunomodulatory potency. [29]Different viruses exploit endocytosis to enter into host cells to initiate infection. The pH dependent

activation of viral endosomal proteins majorly needs acidic. Prior to viral fusion the process of formation of fusion pores needs as prerequisite for release nucleocapsid, this event also partially depends on acidic pH.[30] During lysosomal autophagy, MiT super family transcription factors may bind with the coordinated lysosomal enhancement and regulation (CLEAR) network promotor regions. [31] The basic transcription factors includes Transcription Factor EC (TFEC), Transcription Factor EB (TFEB),(Microphthalmia-associated transcription factor (MITF) and Transcription Factor E3 (TFE3). Under HCQ induced lysosomal stress condition migration of TFEB and TFE3 to cytoplasm to nucleus happens in order to facilitate lysosomal biogenesis. [32] Further, mTORC1 facilitates the phosphorylation of TFEB/TFE3 and equipping lysosome-to-nucleus signalling mechanism. [33] Lysosomotropism is largely possible with HCQ due to its basicity. Further, the statement of Noble laureate Christian de Duve evidences the pH gradients of lumen and cytosol are normally about 4.5 and 7.4 eventually. Hence, the pH partition assists easy traverse lipid bilayers and HCQ being trapped in the acidic environment of the lysosome. This event results increase lysosomal pH. Typical increment of pH by CQ observed with ARPE19 cells evidenced under LTR staining. [34] The process of transportation and degradation of troublesome proteins by lysosomal pathway is known as Autophagy. Phagophores are transient sequestering structures its matured double membrane vesicles known as autophagosomes which are fuse with lysosomes and allows cargo degradation. [35&36]Autophagy-related proteins directs the generation of phagophore and autophagosomes sequentially.

TLR signaling

Toll-like receptors (TLRs) belongs to pattern recognition receptors (PRRs) family which are readily recognize and respond for repertoire molecules as pathogen-associated molecular patterns (PAMPs).[37] In case of viral infections, TLRs may transduce the signals to pledge innate and subsequent adoptive immunity.[38] Majority of nucleic acid ligands including dsRNA, ssRNA, and CpG-DNA from various virus and bacteria demonstrates good recognition with TLRs. [39] HCQ activates TLRs plays vital role in endosomal acidification process, particularly TLR7/8/9. [40]HCQ shows a serious significant levels when compared to newly developed small molecule inhibitors including quinacrine derivative of CpG-.[41] The inhibitory effect on B-cell activation by TLRs especially TLR9 may play viral role in HCQ clinical efficacy as antiviral. This event perhaps due to the occurrence of anti-dsDNA. [42] However, There is no significant differences in IFN-α/TNFα levels up on HCQ administered subjects up on TLR-7/9- stimulated. [43]

Biosynthesis of sialic acid

In many of viral attachment proteins have unique and complex with sialylated compound explored recently. Usually the monosaccharide sialic acid present in all eukaryotic cell surfaces. Further, the glycans terminating in sialic acid plays crucial viral receptor role for number of viruses including highly pathogenic Influenza A, B and C viruses etc. [44] Interestingly, many severe cases of viral pneumonitis indicates prominent role in lower respiratory tract infection. However, the severity of illness differs with viral binding properties. Many of virus has offers clues on specific amino acid changes in SAα2,3 and SAα2,6.[45] HCQ exhibits antiviral potential by hindering the receptor recognition process upon influencing sialic acid and ganglioside membrane fusion process. [46]The good fit of HCQ with sialic acid perhaps owing to cationic charges of HCQ interactions with viral 9-Oacetyl-N-acetylneuraminic acid. Further, HCQ potentially inhibits quinone reductase 2 which will play vital role in bio synthesis of sialic acid. Basically, the sialic acids are usually part of gangliosides and glycoproteins. HCQ establishes storng interface with ganglioside- rice microdomin with critical residues of Asp-111, Gln-134, Phe-135, Arg-158 and Ser-161.[47]

Regulation of pro-inflammation cytokines.

HCQ interferes with maturation and recognition in antigen presenting cells with process of endosomal pH modification. Normally viral entry happens in dendritic cells by either micropinocytosis or phagocytosis which activates T cells. Which is facilitated means of clathrin medicated endocytosis and clathrin-independent endocytosis. In both case pathogen internalization to T cells will allow to process the proteins which allows interactions with antigen presenting cells, which allows peptide mobilization of Major Histocompatibility complex (MHC). However, MHC class I which are loaded with antigens obtained by degradation of pathogenic proteins by endoplasmic reticulum. In other hand, endocytosed proteins will be processed via endosomal and lysosomal means. The acidic pH allows to activate protease for MHC class I antigen complex. [48 &49]HCQ significantly reduces phosphatidylinositol binding clathrin assembly protein (PICALM) and antigen processing as well which results reduction in T cell activation and differentiation finally the whole results in decrease of production of pro-inflammatory cytokins. [50] HCQ potentially blocks Ca2+ signaling and downstream events results reduced activation of T and B cell antigen complexes. [51] There are evidences of TLR 9 related activation of pro-inflammatory cytokines and chemokine such interleukin-6/12, interferons influences the inflammatory process. [51] Further, HCQ associated PLR 9 influences matrix metalloproteinase have direct influence in induced cytokine and chemokine in the inflammatory process. [52]Further, HCQ demonstrates phospholipase A2 inhibition and arachidonic acid cascades of prostaglandin and thromboxane formations which leads blockade of inflammatory process. [53] Majority of respiratory virus activates p38 MAPK pathways lead to release of cytokines such as TNF-α, IKK alpha and Beta, IL-1β and so on which is ultimately hindered by HCQ. [54]

Endosomal Ironrelease inhibition

Irons plays vital role in viral metabolic functions. Augmented evidences suggested that HCQ and CQ both possess significant inhibition on Tf/transferrin receptor 1(homodimeric type II membrane glycoprotein).[55&56] However Tf receptors are pH dependent for its metal binding.[57&58]depends on pH gradient in the cytosol TfR1 undergoes conformational changes which promote iron release and increases affinity to apo-Tf.As discussed HCQ is good candidate which greatly influence the cytosolic pH. The iron loaded Tf/TFR1 complex clathrin-mediated endocytosis and its cytosolic translocation is primary step to satisfy the cellular iron gaining. [59] Lower pH of endosomes diminish the strength of binding of Tf to Fe makes the release within the vesicles, the basic moity of HCQ elevates the pH of endocytic vesicles, limiting the iron removal form Tf at endosomes. [60] Hence, with in the cytosol the Fe^{3+} is reduced to Fe^{2+} by endothelial antigen the gradient driving transport of irons from endosome to cytosol is greatly influences by HCQ. These events may led the cytosol to starving for iron.

CONCLUSION

HCQ exhibits multiple cellular and molecular function including endothelial dysfunction, interface with viral coagulopathy and action on Neutrophil extracellular traps etc. However, multiple randomized control studies are warranted to explore therapeutic and safety profile of HCQ for various viral infections.

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