Insights into possible COVID-19 antivirals from a rare neurodegenerative disease

Drugs mimicking the effects of the rare neurodegenerative disease Niemann-Pick type C provide candidates for coronavirus treatment. These drugs block the actions of the NPC1 protein, whose proper functioning is predicted to be important for the coronavirus to enter cells and proliferate.

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Coronavirus family: A family of viruses that cause upper respiratory tract illnesses

COVID-19: The disease caused by the SARS-CoV-2, a strain of coronavirus first identified in December 2019 in Wuhan, China

NP-C disease: a rare (~500 cases worldwide) disease caused by the accumulation of cholesterol and lipids in the lysosomes of cells due to the improper functioning of the NPC1 protein

Cholesterol: an organic compound essential to the structure of cell membranes

Lysosome: an acidic membrane-bound compartment within cells that is the location for the redistribution of cargo such as cholesterol

As the **coronavirus** spreads quickly around the world, it is necessary to find therapeutic strategies that can be rapidly implemented. Although there is a lot of effort put into vaccine and antiviral design, it will take time for these interventions to be generally available. For current mitigation of **COVID-19**, it is advantageous to examine drug repurposing, as many therapeutic drugs used today could be applied to treatment of COVID-19, with a prime example being drugs that mimic the effects of Niemann-Pick type C disease (NP-C).

Niemann-Pick type C disease is caused by improper functioning of the Niemann-Pick type C-1 protein (NPC1) which controls the transport of **cholesterol**. NPC1 is located in the membrane of the **lysosome** and, when functioning properly, distributes cholesterol around the cell. This process halts when the protein is not working properly and cholesterol builds up in the lysosome and does not make it to the cell membrane, resulting in a fatal neurodegenerative disease (Figure 1). Research shows that this improper functioning of NPC1 can impair the ability of many viruses to enter host cells, making drugs that inhibit NPC1 function prime candidates for drug repurposing.

Figure 1: The effect of NPC1 inhibition on cholesterol distribution in a cell.

The NPC1 pathway is related to the coronavirus entry into cells because much of the coronavirus entry relies on proper

Coronavirus structure: The coronavirus is made up of genetic material (RNA) surrounded by a lipid membrane and various proteins

Engulf: The cell membrane invaginates and absorbs material from outside a cell, forming a compartment inside with the external molecules

Receptor: A protein in the cell that binds to a specific molecule which signals a cell to start a specific process, such as fusing with the coronavirus membrane

distribution of cholesterol in the membrane and lysosome. In order for the **coronavirus** to replicate itself, it needs to move its genetic code from inside its own membrane to inside the host cell. This process can happen in two ways: the virus can (1) directly release the genetic code into the cell (Figure 2a) or (2) be **engulfed** by the cell and release the genetic code from the lysosome (Figure 2b). In the first process, a protein on the viral membrane binds to a **receptor** of the host cell membrane, which allows the two membranes to fuse and the viral genetic code to pass through. This binding needs to occur in areas of the membrane that are **enriched** in cholesterol. In the second process, the host cell engulfs the virus and moves it to the lysosome, where the membrane of the virus is broken down and the genetic code is released into the cell. The level of cholesterol in the lysosome needs to be **normal** in order for this process to occur.

Figure 2: (a) The first method of coronavirus entry, where the virus directly releases the genetic material into the host cell after fusing with the cell membrane. If NPC1 is inhibited, this process cannot occur. (b) The alternative method of coronavirus entry, where the virus is engulfed and transported to the lysosome before releasing the genetic code. If NPC1 is inhibited, this process can't occur due to cholesterol buildup.

Imipramine: A tricyclic antidepressant used to treat depression, anxiety and panic disorders. It is sold under the name Tofranil.

Cepharanthine: An anti-inflammatory and anti-cancer drug isolated from a plant native to southern Asia.

Chloroquine: A medication commonly used to treat malaria. It also has antiviral effects, as it decreases the acidity of lysosomes.

Both entry mechanisms depend on proper cholesterol levels, which are altered with improper NPC1 protein function. If NPC1 is not functioning properly, there will not be enough cholesterol in the cell membrane to support viral entry (Figure 2a) and too much cholesterol in the lysosome to support viral entry (Figure 2b). If neither viral entry method is optimal, then the replication of the coronavirus can be slowed, therefore making NPC1 inhibiting drugs prime candidates for coronavirus treatment.

There are many readily available NPC1 inhibiting drugs with record of antiviral activity that can be repurposed to treat COVID-19, such as **Imipramine**, a drug used to treat depression and **Cepharanthine**, an anti-inflammatory and anti-cancer drug. **Chloroquine**, a drug used to treat malaria, may also be effective—though it likely does not directly inhibit NPC1, it does mimic the symptoms of NP-C disease. Such drugs that temporarily mimic the effects of NP-C disease could be tested as therapies to treat COVID-19, allowing more rapid treatment or mitigation of the proliferation of the disease. Most of these drugs are common and are already manufactured, which would make rapid scale-up and distribution relatively simple. The knowledge about this rare disease provides a window into possible treatments for coronavirus, which could mitigate the spread of the disease until other therapies, like vaccines, are developed.