Cancer drugs show promise in preventing malaria

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Malaria researcher Associate Professor Justin Boddey.

A potential new approach for preventing malaria is on the horizon with the discovery that drugs currently used to kill cancer cells can also kill malaria-infected liver cells.

A team from the Walter and Eliza Hall Institute showed in preclinical models that anti-cancer drugs can kill Plasmodium-infected liver cells, while leaving other cells unharmed.

Liver infection is the first stage of malaria parasite infection in humans following a mosquito bite. The parasites' ability to hide and multiply in the liver before causing malaria in the bloodstream is a significant target

for effective malaria control.

The new approach outsmarts the malaria parasite by causing infected cells to die, while also boosting host immunity and decreasing the chance of parasites becoming drug resistant.

The research was led by infectious disease researchers Associate Professor Justin Boddey, Dr. Greg Ebert and Professor Marc Pellegrini at the Walter and Eliza Hall Institute, and was published in *Cell Reports*.

Targeting parasite-infected cells

Plasmodium parasites are estimated to infect more than 200 million people each year and cause 619,000 malaria-related deaths annually. Shortly after infecting the host, parasites set about exploiting their new environment in order to survive and spread. The first stop in this journey is the liver, where the parasites hide and multiply.

Associate Professor Boddey said the team revealed that Plasmodium parasites are able to survive and multiply in the liver by hijacking certain parts of the cell death machinery to stop their host cells from dying.

"A particular form of cell death called apoptosis, initiated by the extrinsic signaling pathway, has evolved to defend us against infection by parasites, bacteria and viruses, and is triggered as a way of fighting the infection," he said.

"We showed that malaria parasites hijack this pathway, increasing production of proteins called cIAPs (cellular inhibitors of apoptosis proteins). This tricks the body into keeping the infected cells alive and allows malaria parasites to happily hide away, multiplying in the liver."

Dr. Ebert said the team was excited to discover that cancer drugs called

IAP inhibitors, initially developed for cancer therapy, could be repurposed to override the parasite's cunning tactics and trigger the death of infected liver cells.

"Using IAP inhibitors, we were able to preferentially target parasite-infected liver cells and eliminate more than 95 percent of Plasmodium infection."

"The approach we took drew lessons from previous research, where we successfully harnessed the same strategy to eliminate all traces of liver-specific hepatitis B virus infection in preclinical models.

"But Plasmodium infection is different, you only need one parasite to complete the liver phase to infect the bloodstream and initiate malaria. So our challenge now is to stop the very small number of remaining parasites that are still entering the blood stream," Dr. Ebert said.

Boosting immunity, preventing resistance

Malaria's infamous ability to evade the immune system and evolve drug-resistance are among the major hurdles that make it such a difficult disease to eliminate.

Professor Pellegrini said the new study showed promise in both boosting host immunity and decreasing the potential for drug resistance.

"By targeting the host cell, the parasite isn't under selective pressure to develop resistance to the drug—this is a big plus."

"In addition, by causing infected cells to undergo programmed death, the parasite is no longer able to hide undetected in the liver. As a result, we observed that the immune system was reacting to the infection by mounting a T-cell response. This boosted host immunity and changed the

course of a subsequent infection for the better," Professor Pellegrini said.

Key to malaria elimination

Associate Professor Boddey said the research was an exciting proof of concept that host-based therapy could eliminate malaria parasites, and the next steps would be to try IAP inhibitors in combination with different other drugs in order to examine whether they could completely clear malaria infection of the liver in preclinical models.

He said targeting parasite-infected liver cells could be particularly useful in areas, such as the Asia-Pacific, where Plasmodium vivax (P. vivax) is a significant problem.

"P. vivax is especially insidious because it can lay dormant in the liver for months, causing patients to become sick again and again whilst also allowing further transmission in the community," he said.

"The only drugs available to kill dormant P. vivax infections can be very toxic to some people.

"New drugs that kill P. vivax at the liver stage of infection are very important for preventing relapse and giving us a real chance at eliminating malaria."

More information: Gregor Ebert et al. Targeting the Extrinsic Pathway of Hepatocyte Apoptosis Promotes Clearance of Plasmodium Liver Infection, *Cell Reports* (2020). DOI: 10.1016/j.celrep.2020.03.032

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