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Innovative cancer treatment found to be promising for the control of fungal infections

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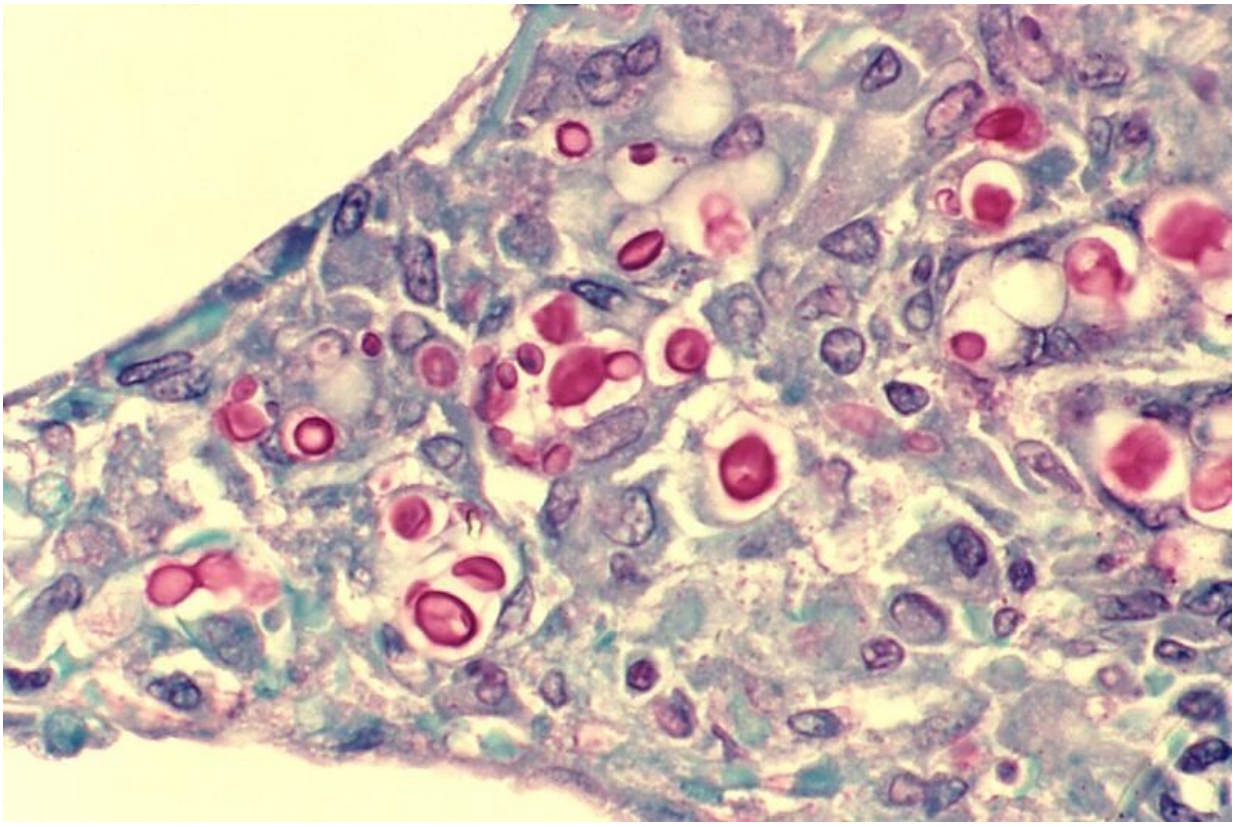

The use of CAR T-cells reprogrammed to “recognize” Cryptococcus spp. proved effective to combat the infection in vitro and in mice (pulmonary cryptococcosis; image: Wikimedia Commons)

An innovative cell-based treatment for cancer has been found promising for the control of infections caused by fungi. A study published in the

journal *Cytotherapy* reports that the use of chimeric antigen receptor (CAR) T-cells programmed to recognize Cryptococcus spp. fungi was effective in combating infection in vitro and in mice.

C. gattii and C. neoformans are present in soil with dead organic matter and places contaminated by the droppings of pigeons and other birds. They cause systemic mycoses in the human organism. They can infect the lungs and central nervous system, causing meningitis or meningoencephalitis. The symptoms vary according to the site of the infection, which can be fatal. Transmission occurs by inhalation of the fungi.

About 1 million cases of Cryptococcus infection are reported worldwide every year, according to the US Centers for Disease Control and Prevention (CDC). The mortality rate ranges from 20% to 70%, and 220,000 cases of cryptococcal meningitis occur annually, affecting mainly people living with HIV-AIDS.

To escape the host's immune response, Cryptococcus covers itself in a capsule made up primarily of glucuronoxylomannan (GXM), a polysaccharide considered its main virulence factor. It is difficult for the human immune system, especially T CD4+ and T CD8+ cells, to recognize and prevent the infection.

In the study, the group redirected T CD8+ cells to target the GXM in the capsule via expression of a GXM-specific CAR, in order to have the cells recognize the pathogen directly and contain its growth.

"The findings show that GXMR-CAR T-cells can be redirected to recognize C. neoformans. Future studies will focus on determining the therapeutic efficacy of such cells in an animal model of cryptococcosis," the authors conclude in the article.

The first author is Thiago Aparecido da Silva, a Brazilian researcher affiliated with the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP). In an interview given to Agência FAPESP, Silva explained that the infusion of GXMR-CAR T-cells not only contained the fungus's growth but also reduced the number of so-called titan cells that make the infection more virulent. These are abnormally large yeast cells with a diameter of more than 45 micrometers.

Silva is a researcher in FMRP-USP's Department of Cellular and Molecular Biology and Pathogenic Bioagents (Biocel) and is supported by FAPESP via a postdoctoral fellowship and a research internship abroad.

"This reduction in titan cells points to a good prognosis for new treatments for cryptococcosis," Silva said. "CAR T-cells can be used to treat other fungal infections and can be associated with conventional drugs to reduce their side-effects. CAR T-cells can establish immune memory and protect the patient against reinfection by invasive fungi."

Silva is now working on ways to optimize the protective response of CAR T-cells to fungal disease, including infections caused by Candida albicans and Histoplasma capsulatum, with support from FAPESP via a Young Investigator Grant.

Direct death of fungi

Researchers at MD Anderson Cancer Center in Texas (U.S.) who collaborate with Silva were the first to explore the direct death of fungi from redirected T CD8+ cells with a CAR targeting a carbohydrate found in the cell wall of Aspergillus fumigatus.

Interest in the use of CAR T-cells to treat cancer and other diseases has increased in several countries. In most studies involving the technique,

the researchers targeted the antigen CD19 to contain multiplication of abnormal B-cells causing lymphoma or other kinds of severe disease.

CAR T-cell therapy in various forms has been approved since 2017 by the US Food and Drug Administration (FDA), especially to treat leukemia and lymphoma.

In Brazil, a group of researchers at the Center for Cell-Based Therapy, hosted by FMRP-USP, tested this innovative cancer treatment with reprogrammed cells from the patient for the first time in 2019. CTC is a Research, Innovation and Dissemination Center, supported by FAPESP.

The technique was used to treat an advanced case of diffuse large B-cell lymphoma (DLBCL), a type of non-Hodgkin lymphoma. In February 2020, CDC published a book with practical information on the production of CAR T-cells.

Target recognition

Silva and the other authors of the latest study raise the hypothesis that redirecting GXMR-CAR T-cells induces cytotoxic activity against fungi that express GXM in the cell wall. The study shows that modified human T-cells expressing GXMR-CAR were capable of binding to GXM in vitro and interacting with the yeast form of C. neoformans.

"The most critical part of the construction of a CAR is the target recognition portion, in which we use monoclonal antibodies that interact with Cryptococcus," Silva said. "We use the DNA sequence that encodes the part of the antibody that recognizes the fungus and combine it with the DNA sequence that encodes the other portions of the CAR."

More information: Thiago Aparecido da Silva et al, Glucuronoxylomannan in the Cryptococcus species capsule as a target

for Chimeric Antigen Receptor T-cell therapy, *Cytotherapy* (2020). DOI: 10.1016/j.jcyt.2020.11.002

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