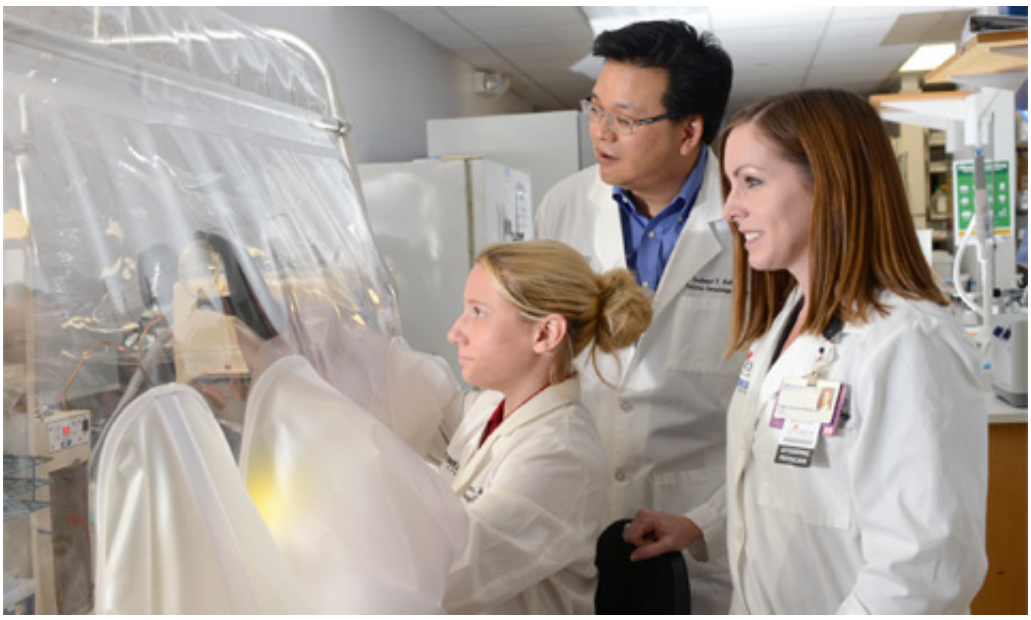
Boosting gut bacteria defense system may lead to better treatments for bloodstream infections

June 8 2015



Research assistant Laura Coughlin, seated, Dr. Andrew Koh, and Dr. Tiffany Simms-Waldrep use an anaerobic chamber as part of a study investigating how the gut's bacteria defense system fights off Candida albicans infection. Credit: UT Southwestern

An upset in the body's natural balance of gut bacteria that may lead to life-threatening bloodstream infections can be reversed by enhancing a specific immune defense response, UT Southwestern Medical Center researchers have found.

In the study, published online in *Nature Medicine*, scientists identified how a certain transcription factor - a protein that that turns genes on and off - works in partnership with a naturally occurring antibiotic to kill infection-causing fungi called *Candida albicans*.

These particular fungi, best known as a cause of yeast infections and oral thrush, can be lethal if they overgrow and invade the bloodstream from the gut. At high risk for this type of infection are stem cell transplant and leukemia patients whose immune systems are suppressed during treatment. Up to 25 percent of cancer patients develop bloodstream infections from bacteria or fungi.

"For a cancer patient with a *Candida* bloodstream infection, the fatality rate is about 30 percent. *Candida* is the No. 1 fungal pathogen," said senior author Dr. Andrew Koh, Assistant Professor of Pediatrics and Microbiology, and a member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern.

Certain antibiotics do fight invasive *Candida* infection, but they are not always effective and antibiotic resistance increasingly has become an issue. Dr. Koh's research team aimed to uncover how the body's natural immune defense system might be enhanced to fight a *Candida* infection.

About half of the population carries *Candida* in the gut, where the yeast is usually harmless. When the organism overgrows, it may leave the gut and cause infection. Commensal bacteria, the resident bacteria of the gut, normally defend against disease by inhibiting growth of potentially pathogenic organisms.

By studying how mice infected with *Candida* responded in different scenarios, the researchers discovered how to enhance the body's natural ability to eradicate infection, in this case *Candida*.

"The commensal bacteria stimulate gut tissue to make a transcription factor and a natural antibiotic, which then kills the *Candida* fungus," said Dr. Koh, Director of the Pediatric Hematopoietic Stem Cell Transplantation Program at UT Southwestern and Children's Medical Center Dallas. "When we gave the mice a pharmacologic agent called *L*-mimosine that stimulates the transcription factor, the agent knocked down *Candida* 100-fold, which translated into a 50 percent reduction in mortality from invasive *Candida* infection."

Specifically, the researchers found that enhancing the transcription factor HIF-1α with *L*-mimosine led to increased production of the natural antibiotic peptide LL-37, which in turn killed the fungi. *L*-mimosine is a natural product derived from seeds of the koa haole tree that is not approved as a drug but is known to boost HIF-1α activity. The study also suggested that certain gut bacteria - Cloistridial Firmicutes and Bacteroidetes - may be important in producing short-chain fatty acids that help fight infection.

More study is needed to pinpoint the optimal method of inducing the body's gut defense system, whether through use of an agent like *L*-mimosine or by administering short-chain fatty acids such as vinegar.

"Can we modulate the gut system to maintain balance so that it never gets to the point of pathogens invading the bloodstream?" asked Dr. Koh. "Boosting GI mucosal immune effectors to reduce fungal burden may be the key to tipping the balance back toward normal and preventing invasive fungal disease."

More information: Activation HIF-1α and LL-37 by commensal bacteria inhibits Candida albicans colonization, *Nature Medicine*, DOI: 10.1038/nm.3871

Provided by UT Southwestern Medical Center