



HEALTH

Enzyme blocks body's immune response

Researchers point to new drug target for treating COVID

Researchers from Cleveland Clinic's Florida Research and Innovation Center (FRIC) have identified a potential new target for anti-COVID-19 therapies.

Led by FRIC scientific director Michaela Gack, Ph.D., the team discovered that a coronavirus enzyme called PLpro (papain-like protease) blocks the body's immune response to the infection. More research is necessary, but the findings suggest that therapeutics that inhibit the enzyme may help treat COVID-19.

"SARS-CoV-2 — the virus that causes COVID-19 — has evolved quickly against many of the body's well-known defense mechanisms," Gack said. "Our findings, however, offer insights into a never-before characterized mechanism of immune activation and how PLpro disrupts this response, enabling SARS-CoV-2 to freely replicate and wreak havoc throughout the host. We discovered that inhibiting PLpro may help rescue the early immune response that is key to limiting viral replication and spread."

One of the body's frontline immune defenses is a class of receptor proteins, including one called MDA5, that identify invaders by foreign patterns in their genetic material. When the receptors recognize a foreign pattern, they become activated and kick-start the immune system into antiviral mode. This is done in part by increasing the downstream expression of proteins encoded by interferon-stimulated genes (ISGs).

In this study, published in *Nature Microbiology*, Gack and her team identified a novel mechanism that leads to MDA5 activation during virus infection.

They found that ISG15 must physically bind to specific regions in the MDA5 receptor — a process termed ISGylation — in order for MDA5 to effectively activate and unleash antiviral actors against invaders. They showed that ISGylation helps to promote the formation of larger MDA5 protein complexes, which ultimately results in a more robust immune response against a range of viruses.

"While discovery of a novel mechanism of immune activation is exciting on its own," Gack said, "we also discovered a bit of bad news, which is that SARS-CoV-2 also understands how the mechanism works, considering it has already developed a strategy to block it."

The research team shows that the coronavirus enzyme PLpro physically interacts with the receptor MDA5 and inhibits the ISGylation process.

"We're already looking forward to the next phase of study to investigate whether blocking PLpro's enzymatic function, or its interaction with MDA5, will help strengthen the human immune response against the virus," Gack said. "If so, PLpro would certainly be an attractive target for future anti-COVID-19 therapeutics."

Postdoctoral fellow GuanQun "Leo" Liu, Ph.D., a member of Gack's laboratory at the FRIC, is the lead author on the study, which was supported by the National Institutes of Health. The FRIC — which complements and expands research underway at Cleveland Clinic's Lerner Research Institute and Cleveland Clinic Florida's five regional hospitals — is located in Port St. Lucie, Florida, and is closely integrated with the Global Center for Pathogen

Research & Human Health.

About Cleveland Clinic

Cleveland Clinic — now in its centennial year — is a nonprofit multispecialty academic medical center that integrates clinical and hospital care with research and education. Located in Cleveland, Ohio, it was founded in 1921 by four renowned physicians with a vision of providing outstanding patient care based upon the principles of cooperation, compassion and innovation. Cleveland Clinic has pioneered many medical breakthroughs, including coronary artery bypass surgery and the first face transplant in the United States. U.S. News & World Report consistently names Cleveland Clinic as one of the nation's best hospitals in its annual "America's Best Hospitals" survey. Among Cleveland Clinic's 70,800 employees worldwide are more than 4,660 salaried physicians and researchers, and 18,500 registered nurses and advanced practice providers, representing 140 medical specialties and subspecialties. Cleveland Clinic is a 6,500-bed health system that includes a 173-acre main campus near downtown Cleveland, 19 hospitals, more than 220 outpatient facilities, and locations in southeast Florida; Las Vegas, Nevada; Toronto, Canada; Abu Dhabi, UAE; and London, England. In 2020, there were 8.7 million total outpatient visits, 273,000 hospital admissions and observations, and 217,000 surgical cases throughout Cleveland Clinic's health system. Patients came for treatment from every state and 185 countries. Visit us at clevelandclinic.org. Follow us at twitter.com/ClevelandClinic. News and resources available at newsroom.clevelandclinic.org.



A date with Ramadan. Inset: Dr Hussain Saadi

Health issues can be avoided with better preparation

Simple steps prevent problems in Ramadan

Experts at Cleveland Clinic Abu Dhabi, an integral part of Mubadala Health, are providing practical health advice ahead of the Holy Month of Ramadan, to enable people to avoid common health issues.

Typical problems reported by patients include dry eye, allergic rhinitis, gastrointestinal problems, headaches and hypertension. A 2018 study conducted by Cleveland Clinic Abu Dhabi found that 49 percent of people who were fasting in the UAE had concerns about managing their diet, physical activity, medications and chronic illnesses before the Holy Month began.

"In patients who do not suffer from chronic conditions, most health issues are caused by a sudden change in routine, unhealthy eating habits and sleep patterns. For patients with chronic diseases, symptoms can intensify if they do not seek advice from their doctor on how to manage their conditions while fasting," says Dr. Hussain Saadi, the Chair of the Medical Subspecialties Institute at Cleveland Clinic Abu Dhabi.

"We always tell patients to ease into the month of fasting by making simple changes to their daily routine before Ramadan so that their body is not shocked into adjusting."

Dr. Saadi says that the three main areas people must focus on are their diet, sleep and managing any preexisting diseases.

"Start by detoxifying your body with a generous, well-balanced breakfast and plenty of water early in the day and end with a light meal to prep the body for the coming month. Additionally, cut out caffeine in the lead up to the month to prevent withdrawal symptoms during the first few days of Ramadan."

Adequate good-quality sleep is also essential to avoid fatigue and hormonal imbalances, and to remain alert. "Disruption in sleep patterns is common during Ramadan but this can be addressed by staying away from heavy foods during Iftar, going to bed earlier and taking naps to make up for lost sleep at night."

For patients who suffer from chronic diseases and are on medications, it is important that they consult their doctor before Ramadan for a complete health management plan.

"If patients choose to fast, their doctor will be able to recommend changes or adjustments to their drug regimen to allow for safe fasting."

To help patients over the Holy Month, Cleveland Clinic Abu Dhabi is providing evening clinics from 9:00PM to 1:00AM for the most in-demand services including Primary Care, Endocrinology, Cardiology, Pulmonology, Allergy, Neurology, Gastroenterology, Ophthalmology, Urology, ENT, Podiatry and Pain Management.

Top health concerns during Ramadan

Gastrointestinal Problems

Fasting can improve health, but a diet full of oily and sugary foods can lead to bloating, belching, acid reflux and indigestion even in people who do not suffer from gastric problems. The frequency of peptic ulcers — open sores that develop on the inside lining of your stomach — which cause stomach aches are also higher during Ramadan. Overeating and opting for fried and spicy foods can stress the digestive system and trigger reflux. Experts suggest hydrating properly between fasts, eating slowly and having well-balanced meals with plenty of fiber. Aid digestion by including exercise and walks into your daily routine.

Allergic Rhinitis

Also called hay fever, this is a type of inflammation in the nose caused by an overreaction of the immune system to allergens in the air. It causes a runny or stuffy nose, sneezing, and itchy and watery eyes. A regular complaint during the summer months, the issue can be more pronounced in Ramadan when patients who fast change their routines. Experts suggest creating a dust-free environment at home by controlling temperature and humidity, keeping the air-conditioning vents clean and using air purifiers to prevent attacks.

Dry Eye

Dry Eye is a condition that occurs when tears aren't able to provide adequate lubrication for the eyes. A change in diet and reduced intake of nutrient-rich foods can impact the functioning of the eye muscles and tear glands. Patients with a preexisting dry eye condition can exacerbate the situation during Ramadan if a healthy diet and sleep pattern is not maintained. Experts

recommend consulting a physician as soon as symptoms occur.

Hypertension

A change in eating and sleeping patterns can cause fluctuations in blood pressure. People with mild to moderate hypertension can fast safely by maintaining a healthy lifestyle, exercise and medication protocol on the advice of their physician.

Headaches

Dehydration, caffeine withdrawal, low blood sugar and lack of sleep can contribute to headaches. Experts say adopting a steady routine during Ramadan, eating complex carbohydrates to maintain the blood sugar level, drinking at least eight glasses of water, and getting seven hours of sleep everyday can help reduce the occurrence of headaches.

About Cleveland Clinic Abu Dhabi

Cleveland Clinic Abu Dhabi, an integral part of Mubadala Health, is a multispecialty hospital on Al Maryah Island in Abu Dhabi, UAE. Cleveland Clinic Abu Dhabi is a unique and unparalleled extension of US-based Cleveland Clinic's model of care, specifically designed to address a range of complex and critical care requirements unique to the Abu Dhabi population.

Cleveland Clinic Abu Dhabi has the following Institutes: Heart & Vascular, Neurological, Digestive Disease, Eye, Respiratory, Critical Care, Surgical Subspecialties, Medical Subspecialties, Emergency Medicine, Anesthesiology, Pathology & Laboratory Medicine, Imaging, Quality & Patient Safety, and Clinical & Nursing. In all, more than 40 medical and surgical specialties are represented at Cleveland Clinic Abu Dhabi.

The facilities at Cleveland Clinic Abu Dhabi combine state-of-the-art amenities and world-class service standards. The hospital is a 394 (expandable to 490) bed facility, with five clinical floors, three diagnostic and treatment levels, and 13 floors of critical and acute inpatient units. It is a physician-led medical facility served by North American/European Board Certified (or equivalent) physicians. Cleveland Clinic Abu Dhabi provides patients in the region direct access to the world's best healthcare providers and Cleveland Clinic's unique model of care, reducing their need to travel abroad for treatment.

editor's choice

