Examining the acute problem of chronic disease

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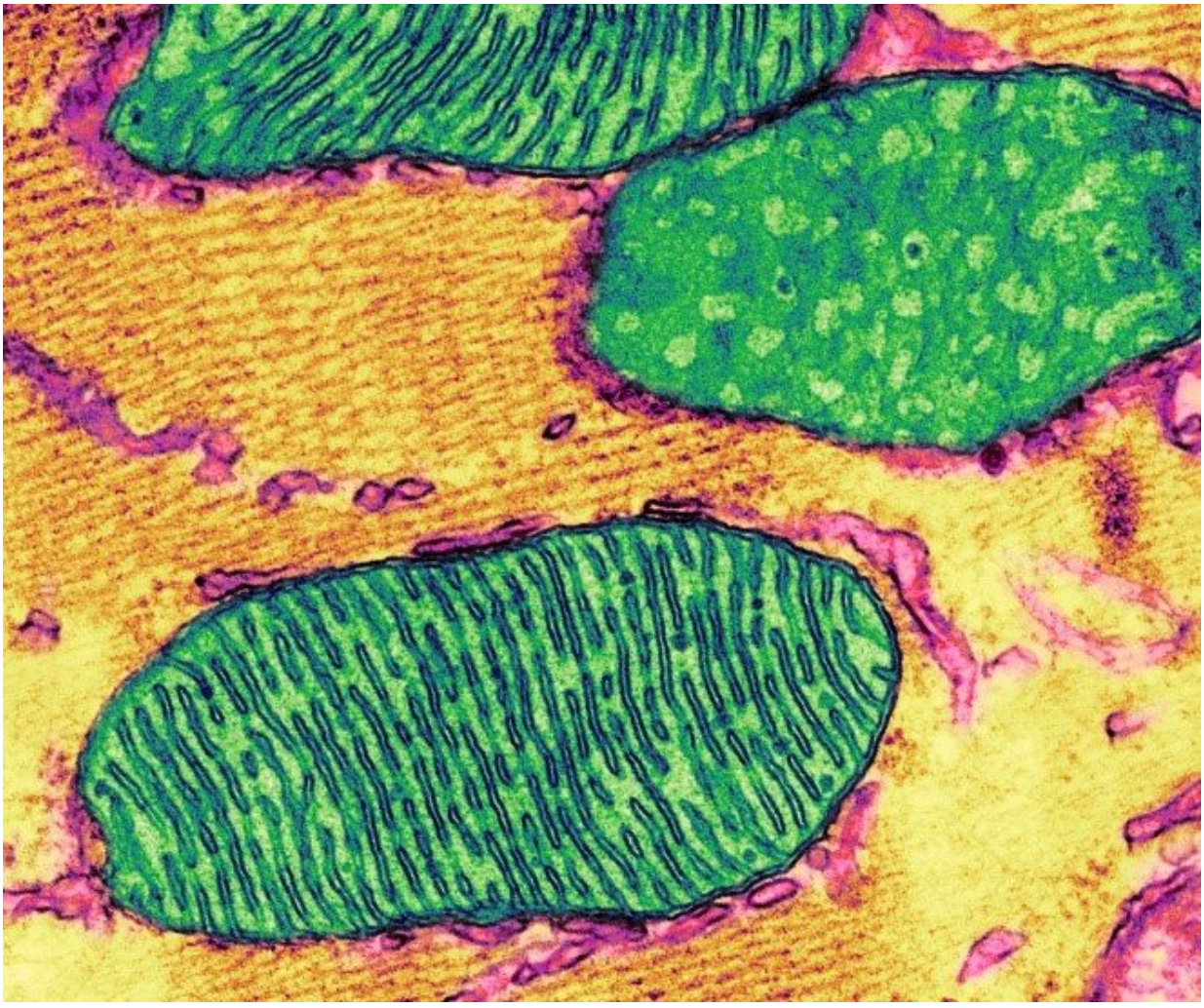

Mitochondria (green) within a cell are depicted in this colorized transmission electron micrograph. The folds are called cristae, and are where chemical reactions occur that produce energy for cellular and metabolic functions. Credit: Thomas Deerinck, National center for Microscopy and Imaging Research, UC

In medicine and science, the term "pathogenesis" describes the origin and development of disease. There is not, however, a broadly accepted term to describe the other half of the equation: the process of healing and recovery.

In a new and far-reaching paper, published in the journal *Mitochondrion*, Robert K. Naviaux, MD, Ph.D., professor of Medicine, Pediatrics and Pathology at UC San Diego School of Medicine, proposes both a term and, more importantly, outlines the array of processes and players, beginning with cellular mitochondria, that drive the healing process —and whose dysfunction underlies chronic illnesses from diabetes and autoimmune disorders to long COVID and autism spectrum disorder.

"Great strides in medicine since World War II have focused on and addressed the triggers and risk factors of disease," said Naviaux. "This pathogenesis-based approach has been very effective in developing treatments for acute illnesses, such as those caused by physical trauma, infection, vitamin deficiencies and poisoning."

The greater health threat now, he said, lies with chronic disease. Six in 10 adults in the United States have a chronic disease; 4 in 10 have two or more. These conditions, such as heart disease, cancer, diabetes, Alzheimer's and chronic kidney failure, account for 7 out of 10 deaths in the U.S. each year, according to the Centers for Disease Control and Prevention.

"In the last 70 years, not a single chronic illness is curable using current medical paradigms unless it has a cause that can be bypassed, killed, burned out or cut out," said Naviaux.

"When cures are achieved, they rely on recovery by spontaneous healing—an essential process that operates silently in the background and is still poorly understood. Antibiotics can cure a pneumococcal pneumonia and a stent can reopen an occluded (blocked) coronary artery, but active healing is required after the intervention to repair the damaged lung and heart."

"Without healing," said Naviaux, "multicellular life on Earth would not exist. Without healing, one injury predisposes to another, leading to disability, chronic disease, accelerated aging and death."

"In most cases, pathogenesis-based drugs like insulin for diabetes and statins for dyslipidemia (an imbalance of blood lipids, such as cholesterol, that leads to cardiovascular disease) must be taken for life because the root cause of the chronic symptoms is not changed by treatment."

In his new paper, Naviaux posits that the root cause of many chronic diseases lies with disruption in the normal sequence of mitochondrial transformations needed to initiate and complete the healing cycle. He has called this universal response to infection, stress, or injury, the cell danger response or CDR. The CDR is an evolutionarily conserved metabolic response that protects cells and hosts from harm. CDR is triggered by exposure to chemical, physical or biological threats. It is a normal part of the immune response that prompts cells to take protective measures.

But sometimes, as Naviaux has shown in past published work, including a preclinical study in 2014, and a Phase 1b/2a Clinical Trial involving young boys with autism published in 2017, CDR continues to sound the alarm even after the originating threat is gone. Inflammation and cell dysfunction persist, resulting in chronic symptoms.

"Abnormal persistence of any phase of the CDR inhibits the healing cycle, creates dysfunctional cellular mosaics, causes the symptoms of chronic disease and accelerates the process of aging," said Naviaux.

"New research reframes the rising tide of chronic disease around the world as a systems problem caused by the combined action of pathogenic triggers and anthropogenic factors (from human activity, such as pollution) that interfere with the mitochondrial functions needed for healing. Once chronic pain, disability or disease is established, salugenesis-based therapies will start where pathogenesis-based therapies end."

What is salugenesis?

Salugenesis derives from the Latin word for the Roman goddess of health, safety and prosperity, Salus. It is related to "salutogenesis," a word coined in 1976 by the medical sociologist Aaron Antonovsky to describe lifestyle choices and coping skills people use to produce, restore and preserve good health despite all manner of hardship.

Salutogenesis is a sort to big picture concept. Salugenesis is more narrowly focused on the sequential, hard-wired molecular, metabolic and cellular stages of the healing cycle. Both words involve redirecting energy to oppose and reverse the arrow of entropy or decay. They are the opposite of pathogenesis, which is about disorganization and disintegration driven by disease.

Naviaux's paper makes several key points, among them:

- Chronic diseases are currently and mistakenly studied in isolation. Diabetes, for example, looks a lot different from post-traumatic stress disorder. But both, and many other conditions, share an underlying failure of the body to fully heal. "Once the

pathogenic trigger has been treated or removed, chronic disease persists because healing is incomplete," said Naviaux.

- Disease is governed by biological logic, which is intrinsic and the result of millions of years of evolution to address internal problems. Modern medicine has advanced through engineering logic, which looks at external issues generally involving non-living systems.
- Health and healing are dynamic circles with a beginning, middle and end. The phases are the same whether the injury is a scrape or a stroke. They proceed sequentially by information exchanged between cells and with the environment, directing and informing what happens next. "Mitochondria generate most of the chemical energy needed to power a cell's biochemical reactions," said Naviaux. "But they are also cellular canaries in the coal mine, the early warning system that determines the nature and location of a problem or threat, and when to sound the alarm."
- Mitochondria naturally prioritize safety and respond to threats of all kinds—from microbial infections, to physical injury, to chemical pollutants in the air, water, and food chain—by stopping their normal anti-inflammatory functions, and shifting to pro-inflammatory functions needed to contain the damage, replace the cells lost, and finally, to restore normal metabolic communication between cells needed for optimum organ function.

CDR is both alarm and the proportional response to threat, he said. If mitochondria do not function properly—or CDR gets stuck in a phase—healing stops and disease prevails.

Curing chronic disease, according to Naviaux, must account for the fact that all such conditions are systems-wide failures, likely caused by multiple factors. "The same disease can be caused by different things in different people," said Naviaux. Most diseases involve factors such as

multiple genes, infection, environmental or microbial exposures, lifestyle choices and more.

With his work and latest publication, Naviaux argues for development of salugenesis-based research, which would explore the unified biological response to injury, harm and disease. Acute illness, he said, is a temporary state; chronic illness results from the long-term inability to heal completely after an acute injury has passed. They are two sides of the same coin.

Naviaux said he hopes that new research will lead to a "second book of medicine" that will collect new knowledge about the cause and treatment of complex chronic disease viewed through the lens of the healing cycle and salugenesis.

"If healing can be rebooted or unblocked after it has been derailed, cures of disorders once thought incurable may one day be possible," he said.

More information: Robert K. Naviaux, Mitochondrial and metabolic features of salugenesis and the healing cycle, *Mitochondrion* (2023). DOI: 10.1016/j.mito.2023.04.003

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