



A Secret to Health and Long Life? Immune Resilience

People with greater immune resilience may be at lower risk for severe COVID-19, AIDS and recurrent skin cancer, NIAID grantees find.

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Do you know some people who almost never get sick and bounce back quickly when they do, while other people frequently suffer from one illness or another? NIAID-supported researchers have pinpointed an attribute of the immune system called immune resilience that helps explain why some people live longer and healthier lives than others.

Immune resilience involves the ability at any age to control inflammation and to preserve or rapidly restore immune activity that promotes resistance to disease, the investigators explain. They discovered that people with the highest level of immune resilience lived longer than others. People with greater immune resilience also were more likely to survive COVID-19 and sepsis as well as to have a lower risk of acquiring HIV infection and developing AIDS, symptomatic influenza, and recurrent skin cancer. In addition, women were more likely to have optimal immune resilience than men.

These findings suggest that knowing an individual's level of immune resilience could help healthcare providers assess the risk for a severe outcome in people with immunity-dependent diseases and identify mechanisms to extend lifespan, according to the investigators. The NIAID co-funded research was published [Juen 13] in the journal [Nature Communications](#).

The nine-year study was led by Sunil Ahuja, MD, the President's Council/Dielmann Chair for Excellence in Medical Research and professor of medicine at the University of Texas Health Science Center at San Antonio. Dr. Ahuja is also director of research enhancement programs at the university and director of the Veterans Administration Center for Personalized Medicine in the South Texas Veterans Health Care System in San Antonio.

Measuring Immune Resilience

Dr. Ahuja and colleagues developed two ways to measure immune resilience, or IR, one based on immune-cell levels in blood and the other on patterns of genes that are turned on, or expressed. The investigators evaluated these metrics in roughly 48,500 people ages 9 to 103 years who were exposed to pathogens and other immune-system stressors of varied types and severity levels,

including the natural aging process. The data on these people, who were Black, Hispanic, or White, came from more than 18 different studies conducted in Africa, Europe and North America.

One of the two IR metrics—the immune health grade, or IHG—is based on the relative quantities of two types of white blood cells, CD8+ T cells and CD4+ T cells, which coordinate the immune system's response to pathogens and kill other cells that have been infected. CD4+ T-cell counts in the blood have long been used to measure immune health, particularly in people with HIV. The IHG is innovative because it reflects the balance between CD8+ and CD4+ T-cell counts. The CD8+ to CD4+ T-cell balance in optimal IR is called IHG-I, while less optimal levels of IR are called IHG-II, IHG-III and IHG-IV.

The second IR metric is based on two patterns of gene expression: one that best predicted survival and another that best predicted death in two large groups of people after controlling for age and sex. The researchers labeled the survival-associated pattern SAS-1 and the mortality-associated pattern MAS-1. SAS-1 genes are largely related to immune competence—the ability to preserve or rapidly restore immune activity that promotes resistance to disease. MAS-1 genes are largely related to inflammation—the process by which the immune system recognizes and helps kill or remove pathogens and other harmful or foreign substances and begins the healing process. The scientists found that high levels of SAS-1 gene expression and low levels of MAS-1 gene expression indicated that a person had optimal IR and a lower risk of dying prematurely, while the opposite indicated poor IR and a higher risk of premature death. If SAS-1 and MAS-1 levels were both high or both low, IR and risk of premature death were moderate.

The investigators tested these two sets of metrics—IHGs and SAS-1/MAS-1—in the context of low-, moderate- and high-intensity stress to the immune system to determine how well the measures predicted health outcomes and lifespan after controlling for age and sex. The scientists identified groups of people experiencing these different intensities of immune challenges in the context of their daily lives. The group experiencing low-intensity immune stimulation comprised thousands of HIV-negative people ages 18 to 103 years participating in long-term studies of aging. The group experiencing moderate-intensity immune stimulation involved hundreds of HIV-negative people with SARS-CoV-2 infection, autoimmune disease, kidney transplant, or behavioral risk factors for acquiring HIV. Finally, the group experiencing high-intensity immune stimulation comprised thousands of people whose immune systems were responding to HIV replication in the blood soon after infection.

Variations in Immune Resilience

The researchers found that preserving optimal IR, as indicated by having either IHG-I or the combination of high SAS-1 and low MAS-1, was associated with the best health outcomes and longest lifespans. In addition, the risk or severity of negative immunity-dependent health outcomes increased as baseline IR level decreased. The scientists also demonstrated that the proportion of people with optimal IR (IHG-I or high SAS-1/low MAS-1) tended to be highest in the youngest people and lowest in the oldest people. Similarly, the proportion of people with the least optimal IR metrics (IHG-III or IHG-IV and low SAS-1/high MAS-1) tended to be lowest in the youngest age groups and highest in the oldest age groups. However, the investigators found that

each of the four immune health grades and related SAS-1/MAS-1 gene expression profiles appeared in people in every age group.

As people age, the researchers explained, increasingly more health conditions such as acute infections, chronic diseases and cancers challenge their immune systems to respond and—ideally—recover. Over time, these challenges degrade most people's immune health, accounting for the declining proportion of people with IHG-I and high SAS-1/low MAS-1 over the lifespan. However, some people who are 90 years old or more still have IHG-I and high SAS-1/low MAS-1—a reflection of their immune systems' exceptional capacity to control inflammation and preserve or rapidly restore immune activity associated with longevity despite the many immune health challenges they have faced.

By contrast, the researchers demonstrate that some young adults who are repeatedly exposed to immune threats may have the least optimal IR, as measured by IHG-III or IHG-IV and low SAS-1/high MAS-1. The investigators show how young female sex workers who had many clients and did not use condoms—and thus were repeatedly exposed to sexually transmitted pathogens—had drastically degraded immune health even if they did not acquire HIV. In addition, sex workers with nonoptimal IR, especially those with IHG-IV, had a higher risk of acquiring HIV infection regardless of their level of risk behavior. However, most of the sex workers who began reducing their exposure to sexually transmitted pathogens by using condoms and decreasing their number of sex partners improved to IHG-I over the next 10 years.

The scientists also observed this plasticity of IR in other contexts. For example, the researchers found that most people couldn't maintain optimal IR when they experienced inflammatory stress from a common symptomatic viral infection like a cold or the flu. In this situation, most people who the investigators studied developed low SAS-1/high MAS-1 within 48 hours of symptom onset, indicating poor IR and a high risk of dying prematurely. As people recovered from their infection, however, many gradually returned to the more favorable SAS-1/MAS-1 levels that they had before. Yet nearly 30% of those who had high SAS-1/low MAS-1 before getting sick did not fully regain that survival-associated profile by the end of the cold and flu season, even though they had recovered from their illness.

Interestingly, the investigators also found that the ability to maintain or develop optimal IR during a respiratory virus infection, as measured by high SAS-1/low MAS-1, correlated with an absence of symptoms.

Implications of Immune Resilience

The researchers suggest numerous implications of their findings for personalized medicine, biomedical research, and public health. First, some younger adults have low IR due to unsuspected immunosuppression, whereas some older adults have superior IR. These differences may account for why some younger people are predisposed to disease and shorter lifespans while some elderly people remain unusually healthy and live longer than their peers.

Second, reducing exposure to immune stressors may maintain optimal IR or give people with low

or moderate IR the opportunity to regain optimal IR, thereby decreasing risk of severe disease. Third, measuring people's IHG and SAS-1/MAS-1 profile in the early stages of illness could allow for detection of poor IR and initiation of more aggressive therapy. Fourth, it may make sense to balance the intervention and placebo arms of clinical trials by both IR status and common factors such as age and sex when testing interventions dependent on controlling inflammation and preserving or rapidly restoring immune activity associated with longevity.

Fifth, developing and implementing strategies to mitigate IR degradation may improve people's response to vaccination as well as their overall health and lifespan. Finally, strategies for boosting IR and reducing recurrent immune stressors may help address racial, ethnic, and geographic disparities in diseases such as cancer and viral infections like COVID-19.

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