Genes and viruses

**Why does COVID-19 affect people differently?**

- COVID-19 infection affects people very differently, even when factors such as age, sex and ethnicity are accounted for.
- Why are some people more likely to become very ill with COVID-19?
- Professor Richard Bucala at Yale University, USA, reveals that a particular gene’s expression may explain the tremendous variation in COVID-19 disease symptoms and risk for severe illness and hospitalisation – which has long been a mystery of the pandemic.
- Higher expression of the immune protein macrophage migration inhibitory factor (MIF) is associated with protection from COVID-19. However, once an individual is infected, it leads to worse outcomes.
- Higher MIF expression is due to naturally occurring genetic variation. Genetic profiling could identify individuals at the highest risk of disease, provide novel treatment options, and improve outcomes.

**Genetic susceptibility to COVID-19**

Vaccination status, age, underlying health conditions, and the variant of the virus can all contribute to different outcomes for patients infected with COVID-19. However, some people’s genetic code may make them more susceptible to developing a more severe form of COVID-19.

It’s already known that higher levels of inflammation are associated with worse outcomes for COVID-19 – and that using medicines that suppress the body’s overactive inflammatory response can be beneficial.

To explore this further, a research team led by Bucala investigated the links between COVID-19 and genes that are known to be involved with key inflammatory mechanisms within the body.

**MIF and its role in inflammation**

The team started by looking at levels of a signalling molecule called macrophage migration inhibitory factor (MIF) in patients with COVID-19 in the Yale New Haven Health System. MIF is closely involved with the immune system and can cause increased and prolonged levels of inflammation. MIF is already known to play a role in other illnesses, such as rheumatoid arthritis and sepsis, as well as being involved in the body’s first-line defence mechanisms against bacteria. A higher level of inflammation can actually be beneficial at times, as it’s essential to help the body fight off invaders during infection.

Bucala’s group also observed that patients with severe COVID-19 illness had higher levels of MIF in the blood than those with mild symptoms. Interestingly, this is in line with studies in mice which showed that higher levels of MIF led to more deaths in COVID-19-infected mice.

**Around 19% of individuals have the high-expression form of the MIF gene, which increases the risk of severe COVID-19 disease and hospitalisation.**

Estimates from the World Health Organization reveal that there have been 750 million confirmed cases of COVID-19 since the pandemic began in 2020, causing millions of deaths. However, there’s also been an enormous variety in the symptoms experienced by people infected with SARS-CoV-2 – the virus that causes COVID-19. Some people experience serious illness, while others are asymptomatic. Why is this? Professor Richard Bucala at Yale University, USA, is leading research efforts to uncover the reasons behind this. Could it be to do with a naturally occurring genetic susceptibility to COVID-19?

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A common gene variant – but potentially deadly

The scientists suspected that common genetic variation in MIF would influence the severity of COVID-19, so they analysed the structure of the MIF gene in patients diagnosed with COVID-19. They then compared this structure to data from a large control group, collected from before the virus appeared. The retrospective study included 1,171 patients recruited from three medical centres in the United States, Spain, and Hungary.

The frequencies of MIF genes with different structures, called gene variants, were compared between the two studied groups; this included high-expression (or high-inflammatory) gene variants and low-expression variants. The high-expression form of the gene causes the body to produce higher levels of MIF, increasing MIF levels during
inflammatory medications to genetically at-risk individuals. Such an risk stratification would also allow the earlier application of anti-or fatal diseases due to excessive inflammation. This type of clinical through early vaccination, as they are more likely to develop severe prioritised for protective measures in future pandemics, for instance which are most likely to carry a risk

The data show that around 19% of individuals have the high-inflammatory MIF gene, which increases the risk of severe COVID-19 disease and hospitalisation (regardless of age, sex, or other factors). While having a high-inflammatory variant of the MIF gene can help prevent infection, the same variant can be deadly for those who do become infected with the SARS-CoV-2 virus.

COVID-19 precision medicine

Proactively identifying patients with COVID-19 who also have the high-inflammatory MIF gene variant would mean that medical staff could monitor these individuals more closely, and therefore intervene sooner when severe symptoms begin to set in. They might also decide to treat the illness more aggressively and recommend hospital admission sooner to prevent the serious complications which are more likely to occur in these patients.

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The future of new infection treatments

Bucala’s work shows that genetic variation in the population influences susceptibility and severity of COVID-19. He explains that further studies are still needed to explore the links between COVID-19, MIF, and other genes, especially in the context of other risk factors for severe infection, such as age and metabolic and cardiovascular disorders. Research into COVID-19 is still in its infancy, therefore, longer-term studies are already being planned, such as those by Canada’s University Health Network in targeting MIF in Long COVID WiFi.


**Personal perspective**

What has been the biggest achievement of your career?

The focus of my research career has been to understand how protective immune responses can sometimes become harmful and cause disease. We provided new insight into this question by our discovery of MIF’s central role in coordinating the immune response and by showing that natural variation in the MIF gene influences a person’s susceptibility to different diseases. Our group also has been at the forefront of developing therapeutic agents, now in clinical development, that modulate MIF action, which can be applied based on a person’s particular MIF gene variant.

What are your plans for building upon this research?

We are assisting other groups in extending these fundamental genetic findings. For instance, an independent study recently showed that high expression MIF variants are more common in COVID-19 patients admitted to intensive care units, confirming the findings of our initial report. We are participating in a study of Long COVID to understand if MIF has a role in features of that disease. We also seek to accelerate the consideration of MIF-directed therapies for the treatment of the adult respiratory distress syndrome (ARDS), which is the proximate cause of death in COVID-19 but that also arises from other infections and inflammatory injuries to the lung.

What do you think will be the main focus of COVID-19 studies over the next 5-10 years?

An important lesson of the COVID-19 experience is that excellent science and medical care is insufficient to save lives in pandemic circumstances. Future studies will be focusing on the most effective means of surveilling emergent infectious diseases, optimising public health preparedness, and effectively implementing preventative and treatment strategies in different populations across the globe.