Team uncovers potential secret to viral resistance
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Scientists from Trinity College Dublin have unearthed a secret that may explain why some people are able to resist viral infections, having screened the immune systems of women exposed to hepatitis C (HCV) through contaminated anti-D transfusions given over 40 years ago in Ireland.

The extraordinary work, just published in the journal *Cell Reports Medicine*, has wide-ranging implications from improving our fundamental understanding of viral resistance to the potential design of therapies to treat infected people.

Between 1977 and 1979 in Ireland, several thousand women were exposed to the hepatitis C virus through contaminated anti-D transfusions given to Rhesus negative women who are pregnant with a Rhesus positive fetus. The medication prevents the development of antibodies that could be dangerous in subsequent pregnancies. Some of the anti-D used during the 1977–79 period was contaminated with hepatitis C.

From this outbreak, three groups of people were identifiable: those who were chronically infected; those who cleared the infection with an antibody response; and those who appeared protected against infection without making antibodies against hepatitis C.

Cliona O'Farrelly, professor of comparative immunology in Trinity's School of Biochemistry and Immunology, is the senior author of the research article. Cliona, who is based in the Trinity Biomedical Sciences Institute, said, "We hypothesized that women who seemed to resist HCV infection must have an enhanced innate immune response, which is the ancient part of the immune system that acts as a first line of defense.

"To test this we needed to make contact with women exposed to the virus over forty years ago and ask them to help us by allowing us to study their immune systems to hunt for scientific clues that would explain their differing responses.

"After a nationwide campaign over 100 women came forward and we have gained some unique and important insights. That so many women—many of whom have lived with medical complications for a long time—were willing to help is testament to how much people want to engage with science and help pursue research with the potential to make genuine, positive impacts on society. We are deeply grateful to them."

The scientists ultimately recruited almost 40 women from the resistant group, alongside 90 women who were previously infected.

In collaboration with the Institut Pasteur in Paris they then invited almost 20 women in each group to donate a blood sample that they stimulated with molecules that mimic viral infection and lead to activation of the innate immune system.

Jamie Sugrue, Ph.D. Candidate in Trinity's School of Biochemistry and Immunology, is first author of
the research article. He said, "By comparing the
response of the resistant women to those who
became infected, we found that resistant donors
had an enhanced type I interferon response after
stimulation. Type I interferons are a key family of
antiviral immune mediators that play an important
role in defense against viruses including hepatitis C
and SARS-CoV-2, or COVID-19.

"We think that the increased type I interferon
production by our resistant donors, seen now
almost 40 years after the original exposure to
hepatitis C, is what protected them against
infection.

"These findings are important as resistance to
infection is very much an overlooked outcome
following viral outbreak, primarily because
identifying resistant individuals is very difficult—since
they do not become sick after viral exposure, they
wouldn't necessarily know that they were exposed.
That's why cohorts like this, though tragic in nature,
are so valuable—they provide a unique opportunity
to study the response to viral infections in an
otherwise healthy population."

The lab's efforts are now focused on leveraging
these biological findings to unpick the genetics of
viral resistance in the HCV donors. Their work on
HCV resistance has already helped ignite
international interest in resistance to other viral
infections, including SARS-CoV-2, the virus that
causes COVID-19.

The O'Farrelly lab has expanded its search for virus-
resistant individuals by joining in the COVID human
genetic effort (www.COVIDhge.com) and by
recruiting members of the public who have been
heavily exposed to SARS-CoV-2 but never
developed an infection (www.viralresistanceproject.com).

More information: Cliona O'Farrelly, Enhanced
TLR3 responsiveness in hepatitis C virus resistant
women from the Irish anti-D cohort, Cell Reports
. www.cell.com/cell-reports-medi...