Hidden ways of the vaccine

A current study looks into the mechanism of antibody production

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The team

The efficacy of vaccines against disease and how fast they create antibodies have become topics of interest. We have processes to create vaccines in the laboratory, but how the body uses the vaccine to create immunity and how the process is controlled are not understood in detail.

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The immune reaction of the body starts with the action of special cells that engulf foreign particles, and extract and display characteristic portions of the invader – to enable other immune-reaction cells to recognise and respond to them. Such special cells are called "antigen presenting cells", and the cells that receive their information are of two kinds, the B cells and T cells. While T cells either act to destroy body cells that are infected by the antigen, or to communicate with B cells, the B cells produce antibodies, which are special proteins that can neutralise the antigen itself.

The B cells and T cells originate from stem cells in the bone marrow. After development in the bone marrow, the cells migrate, through the blood, to the spleen or thymus, for maturation and activation. In mammals, B cells migrate to the spleen. B cells, historically, were first discovered in birds, and in birds, they migrate to an organ called the "bursa". That is the reason why they are called "B" cells. T cells get their name from the thymus, where they migrate for maturation.

The region of the organs, such as the spleen in the case of B cells, where the cells complete maturation, is called the germinal centre. These organs receive a constant stream of antigens, which bind to B cells, in the case of the spleen, by means of a surface structure known as the "B cell receptor" and the binding takes place with the help of cells called "T helper cells". The B cells then undergo rounds of cell division and produce antibody proteins, which, by a process of selection, are sculpted into the correct shape to fit the key surface features of antigens, such as viruses. It is thanks to such features that viruses can gain access to the cells that they infect. If the antibody molecule attaches to the virus and blocks this vital feature, the virus can no longer enter its target cell, which is to say, it cannot cause disease.

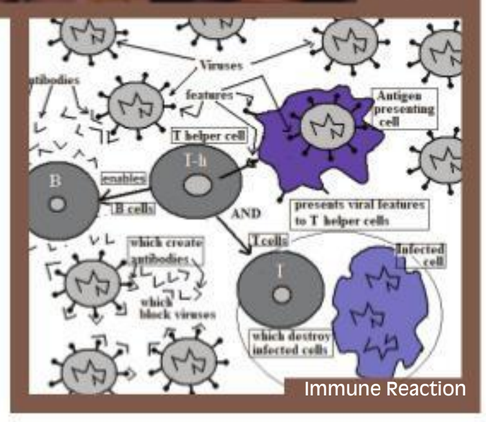
In addition to the T helper cells, which promote B cell processes that lead to antibodies, the germinal centre has "T regulator cells", whose role appears to be the restriction of T helper cells and the division of B cells. Their purpose would hence be to enable selective, greater production of the most suitable antibody variation. The fact of the matter is that even when not stimulated by antigens, many trillions of antibodies are possible and do exist. As one antibody can deal with more than just one pathogen, this collection of antibodies is an arsenal that could handle, and with some accuracy, a great many pathogens. When a pathogen does appear, however, and repeatedly, as in infection, B cells refine their antibodies for higher affinity, to deal with the antigen much more effectively, a process called "affinity maturation". And the process is orchestrated by changes of the balance in the activity of T helper cells and T regulator cells.

The paper in *Science Immunology* says that studying this balance of the two kinds of T cells has not been possible so far, because there is no way to simulate in the laboratory the process that takes place within living cells. That is apart from difficulties in accessing cells of organs like the spleen and associated systems. The authors of the paper employed a collection of techniques, which are most recent developments that have only now become available, of measuring gene expression in bulk and then making estimates of the genetic expression of individual cells.

Estimation of genetic expression is important because the process of generation of antibody proteins by B cells involves the shuffling of genes, or the portions of deoxyribonucleic acid, or DNA, of the cells, which code for proteins. And it is the effect of T helper and T regulator cells in this process that promote or retard the production of particular antibody proteins.

Genes lead to the formation of proteins through a process of copying themselves to molecules called ribonucleic acid, which then convey the genetic information to agencies that assemble proteins. The methods of identifying RNA are now in the news, as it is an RNA that the Covid-19 virus contains. The RNA, and hence the genes related to antibodies are also identified in the same way. There is a difference, however – in detecting Covid-19, only a known RNA needs to be detected. But for studying the growth of antibodies there are thousands of RNA concentrations arising from different cells and the task is to discover how the mix of T cells affects their growth and the promotion of desired antibodies.

The technique used, known as "single-cell transcriptomics", is truly state-of-the-art – a collection of methods to mark, label, sort and identify gene expression in thousands of cells, and do so simultaneously. The data collected is analysed using sophisticated computational techniques, and a seemingly impossible task of arriving at single-cell expression profiles is achieved. And, using those methods, the group was able to work out a scheme of how T helper and T regulator cells arise, and the mechanics of how antibody production is regulated.



Immune Reaction

The pace of antibody production resulting from different Covid-19 vaccines have been in the news now for several weeks. Some vaccines are found to be more effective than others and modifying the time-gap between the first and second dose of the vaccine has been found to affect the level of antibody production. The news does not suggest that there is anything more than statistical or anecdotal data to rely on. The current study would bring about a change and enable more directed paths of enquiry into how vaccines could be more effective. Understanding the internals of the immune reaction would also lead to methods to control excessive or unwanted generation of antibodies, as happens in autoimmune diseases.

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PLUS POINTS

Excess brain iron

Rare neurological disorders provide fascinating insights into the functioning of the brain and its diseases. Starting with examining brain specimens obtained from the infamous Nazi euthanasia programme (Aktion T4), it came to light that complex neurodegenerative disorders of the brain may result from excessive accumulation of iron in brain cells.

Such disorders manifest in childhood as global cognitive dysfunction and continue into adulthood as dementia and varied dysfunction of the motor system including Parkinsonism. One of the earliest disorders described was the Pantothenate kinase-associated neurodegeneration, formerly bearing the sinister eponym of Hallervorden-Spatz disease.

Utilising modern tools of genetics, mainly exome sequencing, an international group identified *de novo* mutations in the WDR45 gene located on the X chromosome in subjects with "static encephalopathy of childhood with neurodegeneration in adulthood". This gene encodes the beta-propeller scaffold protein WD40, which facilities protein-protein interactions.

Preliminary studies demonstrated the role of the protein in autophagy, a cellular process in which degenerated proteins are eaten up in a clean-up process. A key collaborator in this project, Dr Vasuki Himabindu Dandu (*in photo*), mentioned that brain magnetic resonance imaging scans have enormously helped to advance the understanding of the diseases.

Dr Dandu is currently director of the neuro-hospitalist programme at the North Little Rock Baptist Hospital in

Arkansas, United States. She explained the evidence of iron deposition in the brain region called the basal ganglia, which is responsible for fine tuning our gross body movements. Iron-sensitive brain MRI sequences helps serial monitoring of global cerebral atrophy, which is likely responsible for the manifestation of dementia with disease progression.

Beta-propeller protein-associated neurodegeneration, or BPAN, are singletons from diverse ethno-racial groups without consanguinity, suggesting autosomal recessive inheritance like other neurodegeneration with brain iron accumulations, or NBIA. These have been reported from India.

WD40 repeat proteins are not only defective in NBIA but in other neurological disorders like lissenpephaly-1. Defective WD40 proteins can also cause abnormality of the autonomic nervous system. For example, mutation in aladin, a WD40 repeat protein, causes AAA (Achalasia, Addisonianism and Alacrimia) syndrome. Deciphering a clear pattern of natural history, clinical course and imaging enable the identification of distinctive phenotypes of NBIA.

Identifying patients with BPAN will throw light on understanding the more common neurodegenerative disorders like Parkinson's disease, epileptic encephalopathies and Rett Syndrome (impairment in language and coordination and repetitive stereotypic movements like hand wringing), said Dr Dandu, an alumnus of the department of neurology at the University of Arkansas for Medical Sciences and currently an adjunct assistant professor at its graduate medical education programme.

With the ongoing Covid-19 pandemic, Dr Dandu has highlighted the multiple neuropsychiatric complications of the Sars-CoV-2 virus. Although the novel coronavirus is a respiratory pathogen in humans, it has a high affinity for the basal ganglia. A selective affinity of coronavirus MHV-A59 for the basal ganglia was described in mice by Fishman and his colleagues in 1985. The infected mice had Parkinson's-like features – a hunched posture, locomotion difficulties, neuronal loss and gliosis in the substantia nigra.

The aryl hydrocarbon receptor protein is one of the central players in coronavirus signalling. The virus induces upregulation of several AhR-dependent downstream effectors, which causes a "systemic AhR activation ayndrome".

Currently, the neuronal tropism of Sars-CoV-2 is relatively unknown, but it remains to be seen whether it has the potential to cause neurodegeneration, said Dr Dandu.

– SUBHENDU MAITI

CURING A 'CATARACT'

Artificial intelligence could help us with observing the Sun better

SOUVIK BOSE

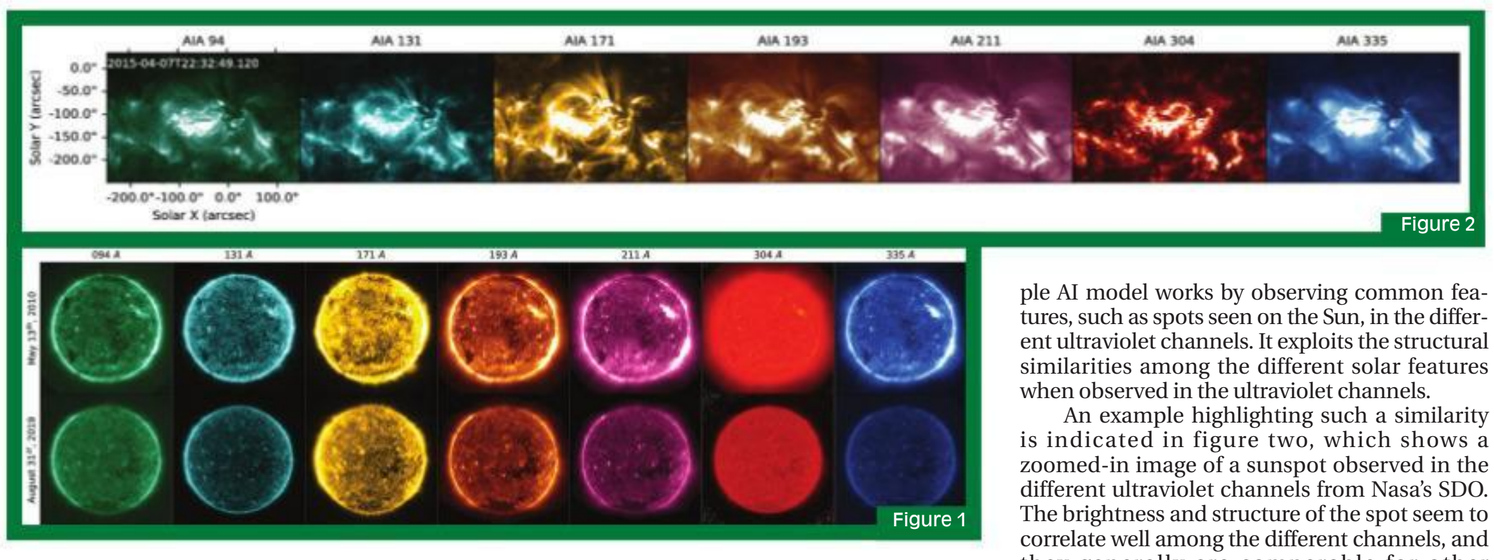

Figure 1

Satellites dedicated to the study of our closest star, the Sun, provide vital information that is necessary to understand the impact of its activity on the space weather around Earth. Space weather refers to the variation in the local space environment driven largely by the radiation and energetic particles that emanate from the Sun, during explosions such as solar flares or coronal mass ejections.

Constant monitoring of the space environment around Earth is important because it can have a significant impact on our daily lives. They include electronic failures in satellites, communication and navigation problems in airplanes, radiation hazards to our astronauts in space or on-board the International Space Station, and loss of satellites to atmospheric drag. Even electricity supply to homes and businesses can be interrupted by the so-called geomagnetic storms driven by blasts from the Sun.

The National Aeronautics and Space Administration currently manages the Heliophysics System Observatory that mainly consists of a group of satellites dedicated to the constant monitoring of the Sun, its extended atmosphere, and the space environment around Earth. One of the flagship missions of this fleet is the Solar Dynamics Observatory, which observes the Sun in the extreme ultraviolet, ultraviolet and visible light, and it has been instrumental in monitoring solar activity since its launch in 2010.

It is worth mentioning here that the Sun radiates light in all wavelengths starting from the ultraviolet to the infrared. Though not visible to the human eye, ultraviolet light from the Sun can cause sunburns on one's skin if a person does not use sunscreen lotion. Fortunately, most of the ultraviolet light is filtered by the atmosphere above Earth, so the chances of catching serious illnesses such as cancer are very unlikely.

For solar physicists like us, however, studying the Sun in ultraviolet light provides crucial information that could unlock the mysteries behind its activity. Therefore, we need instruments outside the influence of Earth's atmosphere (space missions) to record high-quality data round the clock. Unfortunately, instruments that are designed to record observations in that radiation spectrum suffer from degradation over time and that reduces their sensitivity. In simpler terms, the condition is similar to a cataract in the human eye where vision gets progressively dimmer.

To give an example, the top row of figure one shows ultraviolet images of the Sun in seven different wavelength channels (filters) acquired with Nasa's SDO satellite in 2010. The bottom row shows images corresponding to the same filters, from the same satellite but acquired more than nine years later. One can see that the latter images appear significantly dimmer than the ones in the top row.

To cure this "cataract" on the imaging instruments in space, Nasa currently relies on periodic sounding rocket missions that help to compensate or correct for this degradation. Such rocket experiments last only for a very short period, and they carry a near-replica of the instrument that is already in space. Thereafter, they compare the newer measurements with the existing older ones to achieve the desired correction.

Sounding rocket missions are no doubt extremely critical, but they can be complex to design, are quite expensive and rather infrequent. Furthermore, they are not an option if we are planning for a deep space mission, say the Mars mission, that is beyond the influence of Earth's gravitational field.

An alternative solution to this problem was proposed for the first time in 2019 when Nasa hosted the highly competitive Frontier Development Lab in the heart of Silicon Valley in California, United States. FDL applies Artificial Intelligence technologies to space science to push the frontiers of research and develop new tools to help solve some of the biggest challenges that humanity faces. Moreover, it brings the best researchers from around the globe working at the cutting-edge of AI and space sciences, and teams them up for a unique eight-week research sprint. The results far exceed what any individual could develop in the same period, or even in years of individual research.

As a part of this venture, we developed a novel AI-based model that aims to automatically compensate for the degradation suffered by satellites observing in the ultraviolet regime. This simple AI model works by observing common features, such as spots seen on the Sun, in the different ultraviolet channels. It exploits the structural similarities among the different solar features when observed in the ultraviolet channels.

Figure 2

An example highlighting such a similarity is indicated in figure two, which shows a zoomed-in image of a sunspot observed in the different ultraviolet channels from Nasa's SDO. The brightness and structure of the spot seem to correlate well among the different channels, and they generally are comparable for other sunspots too. We, therefore, asked ourselves a question – can we develop a method that examines the common properties of the different features observed in the Sun, and automatically corrects for the "cataract" by taking into account the similarities between the channels?

In a paper published recently in the journal, *Astronomy and Astrophysics*, we show that it is indeed true, and AI can be used to automatically calculate how much the instruments have degraded simply from the observations themselves. Moreover, when we compared the AI-based predictions with the actual data from sounding rocket missions since 2010, our results revealed that they are similar to each other with a resounding 20 per cent accuracy.

We believe that this is a novel and an important first step where AI has helped to solve a challenging problem. The result also instills confidence that AI may serve as an alternate option for missions which are in deep space, where it is impossible to send rockets. Many space-based missions, such as the European Space Agency's recently launched Solar Orbiter mission or the upcoming Aditya L1 mission from the Indian Space Research Organisation, which are designed to study the Sun from deep space environments, can benefit from such advanced techniques based on AI.

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