S ANANTHANARAYANAN

Quest for a vaccine

Four broad methods are being followed to develop a successful preventive for Covid-19

To control the spread of Covid-19, we need to block the path of the virus from infected to susceptible persons. One way is to physically separate all people. A more practical way is that a good number of people become immune, either by recovery from the disease, or, much better, because they are protected by a vaccine. The quest for a vaccine has thus become priority.

A vaccine is a substance that gives a person the ability to prevent the virus, if it should enter the body, from affecting cells and multiplying. The first use was in 1796 by Edward Jenner when he vaccinated a 13-year-old boy with the cowpox virus, which made the boy immune to infection by smallpox. Vaccines against a great many viral infections have been developed and many diseases are now controlled or eradicated.

Since the outbreak of Covid-19, the world is racing to develop a vaccine to block Sars-CoV2, the virus that is responsible for the disease. We now have sophisticated understanding of disease and biology and over a hundred candidate vaccines are under development. The journal, *Nature*, carries a news feature that explains the principal routes that scientists follow.

The virus, unlike bacteria or parasites, does nothing by itself – its action is to invade and induce host cells to generate copies of the invader. Engaging the host cell blocks the cells' own function in the body, while the virus multiplies. The virus uses two features to bring this about. The first is its outer shape or pattern, a "lock and-key-fit" with the exterior of the host cell – which gives the virus entry. The second is the contents of the virus envelope – a scrap of genetic material, which, once it enters, uses the cell's machinery to reproduce itself, and its outer shell.

The body has a mechanism of defense against viral attack. When virus enters, cells called *antigen presenting cells* (APC) engulf the invader and bring features of the virus to the attention of *T-helper cells*. T-helper cells activate *B cells* and *T cells*. B cells generate antibodies, or objects that attach to the virus and destroy its ability to enter a host cell. T cells go after cells that have been infected and destroy them, along with their viral contents.

Once these defender cells have been created, they remain in the body and if there is another infection, they act at once. A vaccine is an agent that mimics the virus to set up the B and T cells, but does not have the ability to overcome the immune system and cause disease. The present quest is to find a vaccine for Covid-19, and the *Nature* article describes the four main directions followed, based on viral features.

Weakened virus

One way is to use the virus itself, in a weakened or inactivated form. The virus will thus present the features that APC can use to bring about B and T cells, but the active features of the virus, to infect and multiply, are attenuated. Many existing vaccines are made in this way, vaccines for measles and polio, for instance. But this method can be dangerous and vaccines have to be carefully tested, to be sure that they are safe, before use. Sinovac Biotech in Beijing has started to test an inactivated version of Sars-CoV-2 in humans, the *Nature* article says.

Viral vector

The second method is to use another virus, called a "vector", which acts as a carrier of the features of CoV-2. The methods of genetic engineering, where portions of the genetic information in the virus are deleted or altered, are used to inactivate viruses, like the measles virus. The virus is then engineered so that the proteins that constitute its envelope resemble those of the target virus. This virus now becomes a "vector" that transfers the relevant features to the immune system, which develops antibodies against the target virus. A problem with this method, which some 25 teams are said to be using, is that the immune system may act to block the vector itself!

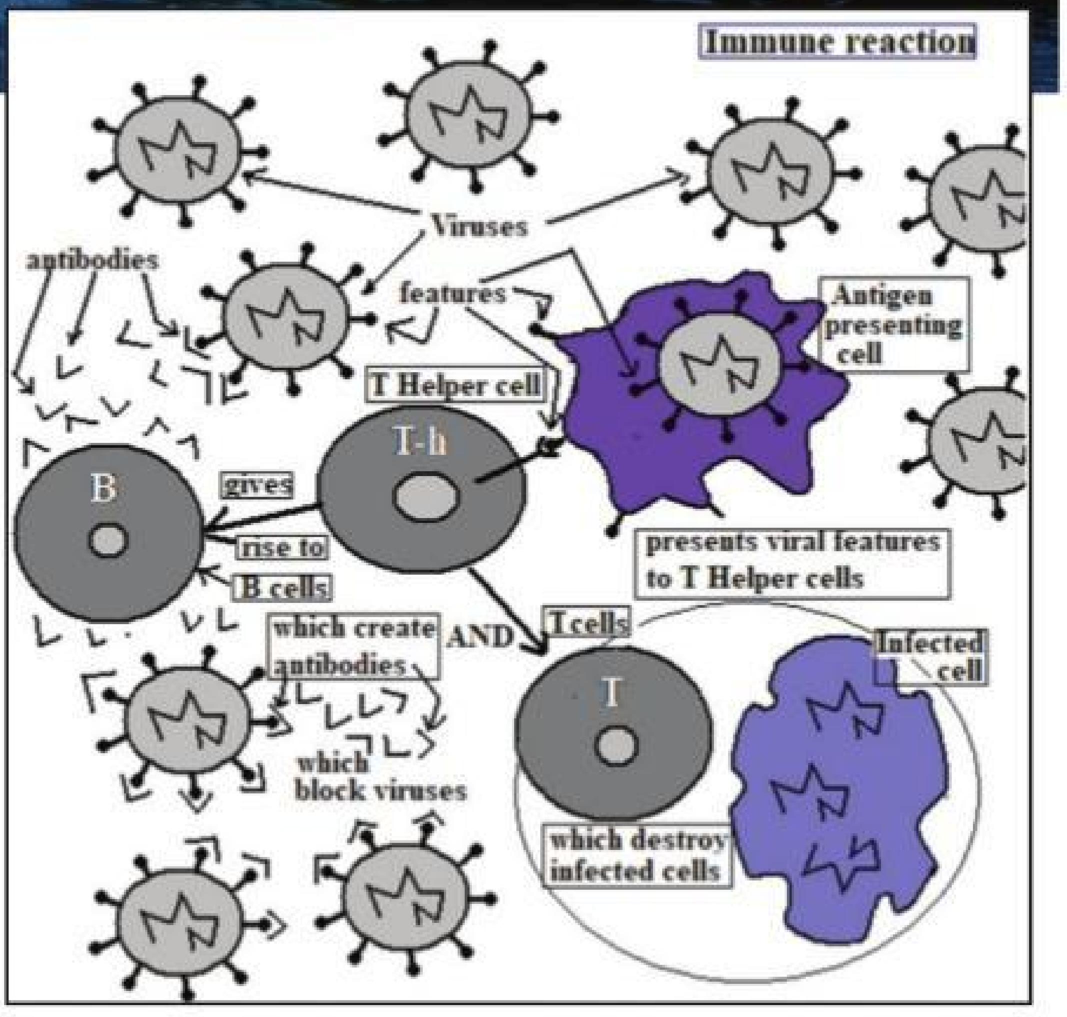
Nucleic acid vaccines

A third method is not to use viruses, but to put the genetic information of the target virus directly into body cells. The cells then create the proteins and surface features of virus, and the immune system creates the antibodies to combat the virus itself, should one be encountered. This is a safe method, but it involves generation of the genetic material and then ways to insert the material into host cells. The method is still unproven and no working vaccines have been developed so far by this method. Over 20 teams are said to be working in this way to find a vaccine for Covid-19.

Protein sub-units

Another step in the same direction is to insert not genetic material that would lead to proteins, but the proteins themselves. Twenty eight teams are said to be working on this method. The focus is on the coronavirus spike protein, or the domain that binds to the receptors of target cells. Vaccines developed in this way have worked with monkeys and the Sars virus, the *Nature* article says. These vaccines also need accompanying substances that stimulate the immune response and may need to be administered in multiple doses.

Another version of this approach is the virus-like particle, or bodies that have no genetic content, but are shells that present just the coronavirus structure. These particles, which are challenging to manufacture, evoke strong immune response but are not infectious, as they cannot replicate.



Encouraging prospect

With over a hundred groups at work on finding a vaccine, two of them have surged forward. US' Massachusetts-based Moderna has developed a synthetic scrap of genetic material, which induces cells to produce a protein that mimics the Sars-CoV2 envelope, and has proved effective in animal trials. Oxford University researchers, with the Edward Jenner Institute for Vaccine Research, in Berkshire, England, have announced a viral vector vaccine that has protected a test batch of six rhesus monkeys, exposed to large volumes of Sars-CoV2, for over 28 days. Both groups have moved to human trials and hope to have the vaccines approved and available by September. A Swiss enterprise has started production of the Moderna vaccine, and the Oxford group has tied up with seven manufacturers, including the Serum Institute of India at Pune, which has also started production in anticipation.

This rapid progress appears to be because the Moderna vaccine is not a virus, and the vector virus chosen by the Oxford group is proven safe, as it was successful with a related coronavirus. Hence, only the efficacy of the vaccines to prevent Covid-19 in humans needs to be established.

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PLUS POINTS

Turning sedentary

Parents and carers should ensure that physical activity is part of the routine for children and families during the Covid-19 lockdown, according to an international study.

The study, detailed in a comment article published in *The Lancet Child & Adolescent Health*, covers 15 nations. It found that time spent in places such as parks, beaches and community gardens reduced by nearly a third between the week ending 23 February – before the World Health Organization declared a Covid-19 pandemic – and the week ending 5 April. Travel by public transport was down by more than half – 59 per cent – over the same period.

While these and other restrictions are in keeping with the global effort to halt the spread of Covid-19, the researchers found that they were having the effect of reducing still further what were often already low levels of physical activity in children. They make a number of recommendations to families, health professionals, teachers and policy- makers on promoting healthy activity, including,

- taking the opportunity to go outdoors, while observing distancing regulations,
- incorporating physical activity into children's daily routines – supported by use of electronic media – and breaking up extended sedentary periods every 30 to 60 minutes; families should also be encouraged to join in while observing distancing regulations,
- keeping children's bedtime and rising time consistent, keeping screens out of the rooms where they sleep and avoiding screen use before bedtime,
- health professionals recommending current guidelines to parents, family members and caregivers,
- promotion by governments of healthy movement behaviours in children as part of response strategies and public messages,
- regular media messages promoting physical activity.

John Reilly from the University of Strathclyde's School of Psychological Sciences and Health, and a participant in the study, said, "It's important that people make whatever use of their environment they can and take the opportunities they can to keep physical activity going. The vast majority of children have access to outdoor spaces they can still use. We have found that they are much less active on the non-school days of weekends and holidays; our concern is that they are missing out not only in education but also in activity." The countries participating in the study were China, Australia, Chile, South Africa, Morocco, Brazil, Mexico, US, UK, Russia, Sweden, South Korea, Netherlands, India and Canada.

Hangover cure

Scientists from the Institute of Molecular Physiology at the Johannes Gutenberg-University, in Mainz, Germany, have revealed it is not a full English breakfast composed of various fried goods, which is best set to relieve hangover symptoms, but instead, a combination of extracts from "fruits, leaves and roots". The research, published in the British *Medical Journal*, also suggests current theories for the existence of hangovers – such as dehydration and loss of electrolytes – may be wrong.

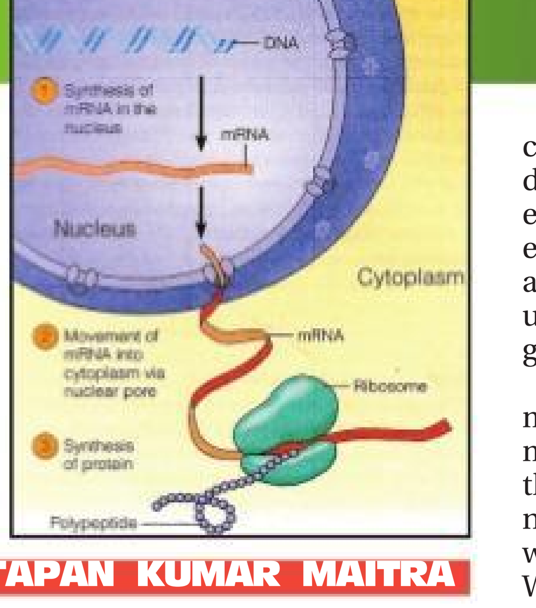
The team used some 214 healthy drinkers aged 18-65, split them into three groups, gave them alcoholic drinks, then fed one group "water soluble plant extracts" along with vitamins and minerals, the second group had the vitamins and minerals alone, and the third group was given a placebo. The results indicate consumption of the plant extracts resulted in a significant improvement in how drinkers felt after consuming alcohol. The plant extracts included Barbados cherry (Acerola), prickly pear, ginkgo biloba, willow and ginger root. The vitamins and minerals included magnesium, potassium, sodium bicarbonate, zinc, riboflavin, thiamin and folic acid.

Furthermore, the absence of any observed impact for vitamins and minerals on their own "suggests that alcohol might not affect electrolyte and mineral balance, as is commonly thought", the authors said. The analysis also showed levels of water content in the body weren't significantly associated with the amount of alcohol drunk. "Our results suggest that alcohol-induced increased fluid excretion does not necessarily lead to a significant dehydration process," they said.

The independent

Executing varied functions

Here's a look at the macromolecules of a cell



TAPAN KUMAR MAITRA

Each of the major kinds of biological macromolecules – proteins, nucleic acids, polysaccharides and lipids – consists of a relatively small number (from one to 20) of repeating monomeric units. These polymers are synthesised by condensation reactions in which activated monomers are linked together and water is removed. Once synthesised, the individual polymer molecules fold and coil spontaneously into stable, three-dimensional shapes. These folded molecules then associate with one another in a hierarchical manner to generate higher levels of structural complexity, usually without further input of energy or information.

Proteins are without a doubt the most important and ubiquitous macromolecules in the cell. In fact, their importance is implied by their name, which comes from the Greek word proteios, meaning "first place". Whether talking about carbon dioxide fixation in photosynthesis, oxygen transport in the blood, or the motility of a flagellated bacterium, all of them are dealing with processes that depend crucially on particular proteins with specific properties and functions.

Many proteins are enzymes, serving as catalysts that greatly increase the rates of the thousands of chemical reactions on which life depends. Structural proteins, on the other hand, provide support and shape to cells and organelles, giving cells their characteristic appearances. Motility proteins play key roles in the contraction and movement of cells and intracellular structures. Whereas regulatory proteins are responsible for control and coordination of cellular functions, ensuring that cellular activities are regulated to meet cellular needs.

Transport proteins are involved in the movement of other substances into, out of, and within the cell. Hormonal proteins mediate communication between cells in distant parts of an organism, and receptor proteins enable cells to respond to chemical stimuli from their environment. Finally, defensive proteins provide protection against disease, and storage proteins serve as reservoirs of amino acids. Most proteins are "monofunctional", which simply means that a specific protein has a single function – catalytic, structural, motile or regulatory. However, some proteins are "afunctional", which means that an individual protein plays two distinctly different roles.

Nucleic acids are of paramount importance to the cell because of their role in the storage, transmission and expression of genetic information. They are linear polymers of nucleotides, strung together in a genetically determined order that is critical to their role as informational macromolecules. The two major types of nucleic acids are DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). DNA and RNA differ in their chemistry and their role in the cell. As the names suggest, RNA contains the fivecarbon sugar ribose in each of its nucleotides, whereas DNA contains the closely related sugar deoxyribose.

Functionally, DNA serves primarily as the repository of genetic information, whereas RNA genetic mole-cules play several different roles in the expression of that information that is, in protein synthesis. Most of the cell's DNA is located in the nucleus, which is therefore the major site of RNA synthesis in the cell. A specific segment of a DNA molecule directs the synthesis of a particular messenger RNA (mRNA) in a process called *transcription*.

The mRNA is processed within the nucleus and then moves through nuclear pores (tiny channels in the nuclear membrane) into the cytoplasm, where the nucleotide sequence of the mRNA is used to direct the amino acid sequence of a specific protein in a process called *translation*. Translation takes place on ribosomes, which are complexes of ribosomal proteins and ribosomal RNA (rRNA) molecules. The rRNA is also synthesised in the nucleus, as are the transfer RNA (tRNA) molecules that bring the correct amino acids to the ribosome as the growing polypeptide chain is lengthened by the successive addition of amino acids.

The next macromolecules are the polysaccharides, which are long-chain polymers of sugars and sugar derivatives. Polysaccharides usually consist of a single kind of repeating unit, or sometimes an alternating pattern of two kinds, and are not informational molecules. However, shorter polymers called *oligosaccharides*, when attached to proteins on the cell surface, play very important roles in cellular recognition of extracellular signal molecules and of other cells. The major polysaccharides in higher organisms are the storage polysaccharides starch and glycogen, as well as the structural polysaccharide cellulose. Each of these polymers contains the six carbon sugar glucose as its single repeating unit, but they differ in both the nature of the bond between successive glucose units and the presence and extent of side branches on the chains.

Strictly speaking, lipids do not qualify for inclusion in the macromolecules because they are not formed by the kind of stepwise polymerisation that gives rise to proteins, nucleic acids, and polysaccharides. However, they are commonly regarded as such because of their molecular weights. Lipids are included because of their general importance as constituents of cells (especially membranes) and their frequent association with macromolecules, particularly proteins. Lipids differ substantially in chemical structure, but they all share the common property of solubility in organic solvents but not in water. The major classes of lipids include the triacylglycerols that make up fats and oils, the phospholipids and sphingolipids found in membranes, the glycolipids involved in recognition phenomena, and the steroids and terpenes, which perform a variety of functions in eukaryotic cells.

Because they are defined in terms of solubility characteristics rather than chemical structure, we should not be surprised to find that lipids as a group include molecules that are both functionally and chemically diverse. Functionally, lipids play at least three main roles in cells. Some serve as forms of energy storage, others are involved in membrane structure, and still others have specific biological functions such as the transmission of chemical signals into and within the cell.

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