The Magic of Being Alive : The Story of Our Cells

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There is enormous diversity of life all around us. Bacteria are having more than 35000 species with many more yet to be discovered. There are protozoa, and invertebrates which have more than 1 lakh species, while fishes and birds have around 30000 and 10000 species respectively. Mammals have more than 5000 species. Plants also have an enormous variety, more than 3,80,000 species, but a large number of species are now facing extinction. There is a common thread among all these—the principle of unity in diversity.

According to Swami Vivekananda, the great lesson to be learnt is that unity is behind all. The man and the cat and the dog and the plant and the tree; all come under the more general concept of *life*. Again all these, all beings and all materials come under the one concept of *unity*.

But how are we connected? We, in fact, all the living organisms are connected by a beautiful structure called 'CELL'. The cell has a central brain, called the nucleus. The nucleus contains the DNA which is not living. This DNA contains instructions to run our lives and the cell translates the information that is in the DNA. So, by using the macromolecular machinery of the cell, the information in the DNA is actually transferred. Each cell runs its own life. They are a sort of self-regulating semiautonomous units. Cells coalesce together to form an organ and organ is a part of the organism. Till about 17th century, cells were not known even though there were interpretations that we are consisting of smaller units; but nobody had any idea of the cell.

For each discovery/invention, we have almost been dependent on technology. Robert Hooke, a scientist, made a microscope through which cells were first seen by him. With his microscope, he looked at the section of a cork and could see some small chambers with walls around them. He drew this and, in 1665, published it in his seminal book named the *Micrographia*. So, he was the first human being to conceptualize a cell. He coined the name 'CELL' because he thought that it looked like rooms where monks stayed. This term is used till today.

Robert Hooke dealt with the dead cells. Almost 18 years after his death, a Dutch gentleman, Antonie Van Leeuwenhoek observed living cells with his tiny microscope which was more powerful than Hooke's microscope. He looked at the bacteria and made exquisite description of these; he then reported it to the Royal Society of London. He was not a scientist but a draper and was looking at the fibres of cloth with his microscope. He was later recognized as a fellow of the Royal Society which was a great honour to be given to a non-scientist. His drawings were exclusive where he clearly showed the movement of cells and the trajectory of the movement.

The concept of cell theory was evolving for the next 150 years or so. In 1838, cell theory was proposed by Matthias Jakob Schleiden and Theodor Schwann. According to them, the cell is the fundamental unit of structure and function of all living organisms. All known living things are made up of one or more cells, and all living cells arise from pre-existing cells by division, and the activity of an organism depends on the total activity of independent cells. The cell theory has changed now because of many inputs of modern biology.

We start our lives as a single cell and this cell divides into 2 cells, 4 cells, 16 cells and so on. Here the cells are to decide what cells they want to become; a heart cell, a lung cell, etc. It is all programmed.

During the growth of the cells, various events happen. In human body, there are about 30-50 trillion cells. These cells are replenished by cell division and an equal number of cells die. *Cell death is a process that is integral to our existence*; *both cell division and cell death have to be balanced for us to survive*. This is a continuous process; each moment, the cells are dying and are replenished. Nearly 330 billion cells are replenished daily which is equivalent to about 1% of our cells. In 80-100 days, 30 trillion cells are replenished which is almost our entire body weight. But this does not happen equally in all cells. For example, red blood cells live up to 120 days and the maximum turnover of cells is happening in the lining of our gut which live less than a week. Other organs of the body have also turnover.

The importance of cell death

This cell death is essential for keeping every person alive. Cell death actually shapes us for which cells at specific places have to die by a process called programmed cell death. The way a sculptor brings out a beautiful statue by sculpting a stone, similarly, cell death brings out our shape. Hence, this is a very important part of our lives.

What do we mean by programmed cell death? We have an inbuilt programme in our cells which is triggered due to stress or because it is programmed, it dies at a particular time.

The cells divide themselves into small balls and these do not burst which prevent the contents from being split. This is the beauty of the programmed cell death or apoptosis. If the balls break down, the soldiers of our immune system called the macrophages come in. They pick up the balls, digest them and release the regenerative material for reuse. Here, programmed cell death is the phenomenon and apoptosis is the process.

If apoptosis is deregulated, there may be excessive cell death or diminished cell death. In the former case (a) AIDS can happen, one particular type of immunity cell dies and so there can be all kinds of diseases, (b) infertility can occur and (c) neuro-degenerative diseases can also occur. In the latter case one may get tumours where the cells grow very rapidly, and autoimmunity and neuro-degenerative diseases may take place.

I'll give you one example of how cell death is essential. When we are in the mother's womb, we have webs between our fingers. Those cells have to die by programmed cell death for us to be able to wiggle our fingers. If these cells don't die, the fingers remain joined which are anomalies.

Now, we can summarize what has been discussed so far as follows. We have in our body 30-50 trillion cells that evolved from one single cell. Cell balance is maintained by cell division and cell death. Cell death process is built in our body and is called programmed cell death. It is a neat

form of death so that no inflammation is created. Finally, deregulation of cell death leads to various deformities and diseases.

For our research work, we use either primary cells, that is, the cells taken out of the organ, or we use cancerous cells. Microscopy has now advanced to such an extent that we can see even the minute details of the cells.

Now I am going to tell you a story about the value of our cells. One lady Henrietta Lacks died on 4 October, 1951 of cervical cancer in Baltimore's John Hopkins Hospital. Tumour cells removed from her were grown in the laboratory and even 73 years after her death, the cells, apparently immortal, keep growing in the laboratory. These are called HeLa cells after her name. More than 50 million tonnes of Henrietta's cells have grown since she died. 1,10,000 papers have been published and research with her cells continues to benefit many patients.

There are some important discoveries where HeLa cells played a crucial role. First, Dr Harald zur Hausen got the 2008 Nobel Prize for showing that viruses can cause certain cancers. He used the HeLa cell line to discover that a virus (HPV-18) is linked to cervical cancer. This discovery was the basis of designing a vaccine against cervical cancer. Secondly, Dr Elizabeth Blackburn won the 2009 Nobel Prize for her research with HeLa cells and this helped to develop cancer therapeutics. Thirdly, Jonas Salk didn't receive the Nobel Prize but made the first polio vaccine. HeLa cells were used for the propagation of the polio viruses. 99% eradication of polio has been achieved because of this discovery.

Henrietta Lacks was forgotten for many years, but was rediscovered in 2010 by one journalist. Sixty years after HeLa's death, her story made headlines about ethical issues as cells from Henrietta were used for research without any permission from her family.

Cell therapy

Since chemotherapy and radiotherapy may or may not work, thoughts about using cell therapy as a treatment has now originated. Cell therapy is the transfer of a specific cell type or types into a person to treat or prevent a disease. Cells can be one's own cells for treatment or from a matching person. Common disorders treated with cell therapies include cancers of the blood and bone marrow, cancers of the lymphatic system, plasma cell disorders, etc.

There are two kinds of cell therapy; stem cell based and non-stem cell based. The first category includes cancerous stem cells, neuro-protein stem cells and adult stem cells. The second type has two broad categories—the immune cells and the non-immune cells.

I shall cite two examples of immune cells to discuss how they have been used to treat our diseases. The first cell therapy done by E. Donnall Thomas is very important historically. This happened after the Hiroshima-Nagasaki bombing when there were lots of leukemia cases. Donnall Thomas, in 1957, pioneered the use of bone marrow transplants in leukemia patients from a healthy twin to the diseased one. Cell therapy is a procedure that transfers healthy blood-forming cells from a healthy donor to a patient who is not producing enough blood cells. Ten years after the first therapy, Donnall Thomas did a therapy for the matching person. He got the Nobel Prize in 1990 in physiology or medicine.

Let me now talk about the immune cells. During Covid-19, we heard a lot about immunity. It is something that keeps us free of diseases. We have many soldiers in our

immune system. There are large varieties of immune cells but I'll give the example of only one type, namely, the T cells which have been used to cure diseases by killing the invader cells. These are called cytotoxic T cells.

T cell roams around in our blood, goes into the tissues as well. It has receptors on its surface which latches on to a cancer cell or any cell infected by a virus or bacterium. It makes holes on them using enzyme and then puts a toxin inside the cell. This is the initiation of the programmed cell death and eventually the cell dies. This was used as a basis to design a therapy called CAR (Chimeric Antigen Receptors). This is engineered to produce the receptors on their surface. Then they propagate and when they flow in the blood, they recognize the cell with more efficiency. This is because now they have more receptors on their surface and they will kill the cancer cells.

In case of CAR-T cell therapy, the patient's T cells are actually collected. There is no rejection here because all cells are being used. So the T cells are collected, and then reprogrammed to produce the receptors and this is done by a lentivirus. These receptors are not expressed on the cells. We need more amount of cells to inject into a person. So, these are expanded in the test tube and then injected into the patient's blood stream where the cancer cells are killed by the CAR-T cells. This is just one example.

Emily Whitehead was just 6 years old when she had the recurrence of acute lymphoblastic leukemia. After about 16 months of chemotherapy, her parents were told that she would live no longer. She was then enrolled in a trial which was never tried on a child before. That was a CAR-T cell therapy. She went surprisingly into a remission and now she is back as a fresher in college. She has been free of cancer for a year now. So, the CAR-T cell therapy is now being used in children as well.

The good news is that Dr V.K. Gupta is the first Indian patient to be free of cancer by this method. The cost would have been 4 crores of rupees if done in U.S.A. but in India, it was done for rupees 42 lakhs. Dr Gupta is now cancer-free. This treatment which was a collaboration between Bombay I.I.T. and Tata Memorial Centre was launched by the president of India. The doctors are now trying to bring down the cost even more.

CAR-T cell therapy has been revolutionary and has produced effective and durable clinical responses. The efficacy is 68%-93% in case of acute lymphoblastic leukemia, 57%-71% for chronic lymphoblastic leukemia and 64%-86% for B cell leukemia. Future work needs to be done not only for reducing the cost but also to check some of the side effects that do happen with such treatments.

I'll give another example of immune cell which is the NK cell or the natural killer cells. NK cell is weaponized by the body to recognize infected cells and kill them. They do it much easier than T cells because T cells have certain restrictions which NK cells don't have. These cells latch on to the tumour cells and then they behave the same way as the T cells do by creating pores, injecting toxins and initiating cell death in that particular cell.

Stem cells

The magic of our living partly depends on our reservoirs which are the stem cells. These are special type of cells that are able to make more cells like themselves and can also become other cells. Our stem cells are valuable resources of our health. All organs have a population of stem cells that can come in use at the time of need. Most of the

stem cells are found in the blood. They develop into many different cell types in the body during early life and growth.

Pluripotent stem cells are derived from the cord blood (the cord which connects the embryo to the mother) which is a very rich source of stem cells. These are used with matching donors for making the cells and injecting into the bodies for repair.

Adult stem cells are found in a tissue or organ and can differentiate to yield the specialized cell types of that tissue or organ; for example, kidney cells into kidney tissues, heart cells into heart tissues, etc. Adult cells can also be reprogrammed. That has already been done by a Japanese researcher, Shinya Yamanaka, who got a Nobel Prize in physiology or medicine in 2012. He showed that mature cells can be reprogrammed to become pluripotent. This researcher has actually turned the clock back. This discovery being very young, clinical applications have not yet been done.

The stem cells from other sources have been used to treat several diseases like multiple sclerosis, heart attack, acute lymphoblastic leukemia, arthritis, Crohn's disease and many of these are in the stage of trial. Stem cells are also used in knee replacements. The body is efficient in healing itself. Broken bones, and cuts are easily repaired. For knee osteoarthritis, doctors are taking good cells from different places of the body, propagating them in test tubes and then injecting them back for growing our cartilage that is causing problems.

So the lessons are that there are trillions of cells in our body that divide and die to keep us alive. Deregulation of cell death causes deformities and diseases. Stem cells are the backup in time of requirement. Our cells are our wealth as they can provide treatment options. There are, of course, side effects of stem cell therapy and those are being worked out, the cost is also being worked out. But cell therapy is a boon that has come.

Now there is a technique called single-cell sequencing where one can actually study a single cell, something which was very difficult earlier. Machines have come with developed technologies to study the composition of proteins, enzymes, and the DNA in a single cell. Cell biology is at the centre of many things at present.

In the universe, there is a fixed rule that stars have to die and they die in about millions of years. Cells in our body die in a matter of hours, days and years. Our cells die and recycle in our lifetime. We know so much, yet we do not know enough. ■

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* This article is based on a lecture Chandrima Shaha, J. C. Bose Chair, Indian Institute of Chemical Biology, Kolkata, delivered at the Institute on 25 June, 2024. The lecture was organised by the Vivekananda Science Circle of the Institute.

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9 https://www.verywellmind.com/benefits-of-solitude-8722144

10 'Loneliness and Solitude', *Bulletin of RMIC*, December 2023, p. 19.

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