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Lead researchers interpret emerging findings at the cutting edge of immunological science, while also discussing their impact on the understanding and management of immunopathologies. Apologies are due to authors whose excellent work is not reviewed here due to space constraints.

Immune system–nervous system interactions influence a wide spectrum of physiological processes, as Godinho-Silva *et al.* (pp. 19–46) describe. Sympathetic nerves are found around niches of hematopoietic stem cell differentiation, and catecholamines have been shown to enhance export of hematopoietic cells. Stimulation of the vagus nerve inhibits TNF levels; conversely, members of the TNF family influence development of the nervous system. While IFN- γ can induce lethargy, IL-17 has been implicated in both autism and multiple sclerosis, and IL-4 is believed to contribute to processes that affect learning and memory. Much remains to be elucidated with respect to such interactions and their impact on human health.

As O’Leary *et al.* (pp. 47–72) discuss, T1Rs, T2Rs and T3Rs receptors on Tuft cells (mucosal epithelial cells) permit perception of sweet, bitter, and umami tastes. T2R bitter ligands induce Ca²⁺ depolarization, acetylcholine release, and the secretion of antimicrobial peptides. Tuft cell-derived IL-25, generated upon intestinal helminth infection, elicits the secretion of IL-13 from lamina propria ILC2 cells. The fact that Tuft cell numbers increase in murine gastric cancer and pancreatic cancer has generated considerable interest.

Infection by neurotropic RNA viruses can result in sustained pathology; Klein *et al.* (pp. 73–95) elaborate upon emerging information. Recognition of viral RNA up-modulates the expression of inflammatory cytokines, while also up-regulating the secretion of chemokines. TNF and IL-1 β activate MMP-9 and enhance Rho-associated protein kinase activity, actions compromise blood–brain barrier integrity; upon blood–brain barrier labilization, incoming CD8 T cells

play critical roles in viral control, while Tregs act to attenuate immunopathology. Migrant B cells, on the other hand, can contribute to the onset of autoimmunity.

Conventional fluorescence microscopy technologies are hampered by a 250 nm diffraction barrier. Super-resolution imaging, transmission electron microscopy, and proximity-ligand assays, working at nano-scale, are increasingly providing fresh insights into cellular structures, as Gold *et al.* (pp. 97–123) describe. Direct stochastic optical reconstitution microscopy (dSTORM) and photo-activated localization microscopy (PALM) generate images at 25–50 nm resolution, providing insight into B cell signalling events. A IgD/CD19 protein island probably pre-exists on B cells, and CD20 and CXCR4 may also be found in proximity. CXCR4-mediated signalling requires the presence of IgD as well as CD19, but not of IgM. Antigen-induced proximity of the CD45-containing IgM protein islands with the IgD/CD19 and Lyn-containing protein islands permits an exchange of components without apparent island fusion, an event required for signalling. Further appreciation of membrane organization at nanoscale will shed additional light on B cell function in health and disease.

Guedan *et al.* (pp. 145–171) describe advances in cancer therapeutics. Infusion of melanoma patients with autologous tumour-infiltrating lymphocytes results in some clinical benefit. Using T cells transduced with tumour-directed TCRs (against MART-1 and MAGE-A3, for example) often results in unacceptable side effects. Targeting specific tumour antigens (like NY-ESO-1) can result in anti-tumour efficacy without significant toxicity. Chimeric antigen receptor T (CAR-T) cells express chimeric molecules that combine the antigen recognition motifs of antibody molecules with the CD3 ζ chain and co-stimulatory domains. While CAR-T cells targeting CD19 exhibit high efficacy against several B cell malignancies, efficacy against solid tumours has been disappointing. ‘Off-the-shelf’ CAR-T cells in which endogenous TCR and MHC-I components have been deleted to prevent graft-versus-host disease and rejection are being increasingly considered. Neutralizing IL-6 can ameliorate the effects of ‘cytokine-release syndrome’, a frequent inflammatory outcome. Bystander effects can be reduced by requiring recognition

of two tumour-associated moieties for activation, incorporation of negative signalling upon recognition of ‘normal’ antigen, or by the inclusion of ‘suicide switches’. Increasing the extent of coverage also remains a significant challenge.

Schumacher *et al.* (pp. 173–200) describe current approaches to identify novel neoantigens on tumour cells, focusing on protein variants caused by single-nucleotide changes or structural modification, or variants resulting from frame-shifts arising due to insertions or deletions. From a therapeutic standpoint, such mutations should ideally reside in ‘driver’ (essential for tumour survival) genes as opposed to ‘passenger’ (non-essential) genes. Patient-specific strategies are often required which will represent an obstacle.

As Hammer *et al.* (pp. 201–224) describe, contact with an antigen-presenting cell results in formation of the mature immunological synapse (IS) on T cells, composed of three supramolecular activation clusters (SMAC). The myosin 2-rich actin network comprises the medial portion of the IS, in concentric arcs. The central supramolecular activation cluster comprises comparatively lower amounts of actin arranged in straight and branched filaments. Actin- and actomyosin-derived structures drive the assembly of TCR microclusters and contribute to the polarized secretion of cytokines and lytic granules. The caveats introduced by employing planar activating surfaces in current imaging studies need to be kept in mind, however.

Efforts at developing anti-malaria vaccines have been stymied by the complexity of the *Plasmodium* parasite, as Tan *et al.* (pp. 225–246) reveal. Sporozoites, introduced by mosquito bite, quickly infect the liver. The RTS,S vaccine contains a portion of the NANP repeat region of the circumsporozoite protein (CSP), along with a region that elicits T cell help; observations of transient protective efficacy upon immunization may be due to the inability of the elicited antibodies to bind invasion-specific regions on CSP. Data on merozoite antigens as possible vaccine candidates have also not always been encouraging; epitope sequestration and antigen polymorphism constitute considerable challenges. Whether human monoclonal antibodies targeting the parasite can provide sterile immunity would be interesting to determine.

DNA and RNA structures are evolutionarily conserved; break-down of mechanisms which permit preferential recognition of viral nucleic acids can result in monogenic type I interferonopathies. Ugenti *et al.* (pp. 247–267) highlight emerging findings in the area. The fifteen genes implicated in type I interferonopathies are involved in the sensing of nucleic acids. Defective negative regulation – arising due to mutations in ISG15 or USP18 – can also lead to enhanced type I interferon responses. Aberrant recognition of retro-viruses and retro-elements (for example, by mutant MDA5) can result in enhanced type I interferon signalling. The presence in the cytosol of mitochondria-derived dsRNA (caused by loss of either ribonuclease polynucleotide phosphorylase (PNPase) or the RNA helicase SUV3) can cause enhanced type I interferon synthesis. Treatment options include antibodies which target interferon or its receptor, as well as the use of JAK inhibitors.

Technological advance is permitting increasingly accurate assessment of cellular origin and fate, as Bassler *et al.* (pp. 269–293) discuss. Gene profiles indicative of precursors for monocytes, DCs, neutrophils, basophils, eosinophils, megakaryocytes and erythrocytes have been discerned in the adult bone marrow. Newer methods of analyses have also led to the identification of a common DC progenitor cell that differentiates into conventional DCs (cDC1s and cDC2s) and plasmacytoid DCs (pDCs). Increasingly, the traditional M1/M2 paradigm of macrophage differentiation is being challenged as newer phenotypic and functional differentiation states are defined.

Lin *et al.* (pp. 295–324) discuss how appreciation of the pleiotropic nature of cytokine function is leading to new therapeutics. While some polymorphisms in JAKs and STATs have been associated with autoimmune and inflammatory diseases as well as with malignancy, other polymorphisms offer protection. Th17 differentiation, while being IL-6-dependent (and so STAT3-dependent), is also influenced by IL-21 and IL-23; IL-2 (which activates STAT5) is an inhibitory influence on this process. The Th2 differentiation pathway requires the concerted action of both IL-2 and IL-4, with the latter activating STAT6. While IL-4 drives the primary differentiation process, IL-2 enhances IL-4 receptor ex-

pression. Similarly, the Th1 differentiation pathway requires IL-2 to enhance the expression of the IL-12 receptor, which then drives IL-12 responsiveness via STAT4. Tofacitinib (a JAK3 inhibitor) is being employed in the treatment of several inflammatory disorders, and Ruxolitinib (a JAK1/JAK2 inhibitor) is used in patients of myelofibrosis, polycythemia vera and myeloproliferative disease.

Iweala *et al.* (pp. 377–403) elaborate upon how food antigens and commensal bacteria are distinguished from noxious substances by the immune system. Luminal antigens, transferred across the gut epithelium, are taken up by DCs and by mononuclear phagocytes; these cells then migrate to the mesenteric lymph nodes where they induce Treg differentiation. Homing receptors allow Tregs either to traffic back to the lamina propria or to enter the bloodstream, where they contribute to systemic tolerance. The production of butyrate by commensal bacteria encourages the generation of Treg cells. A microenvironment high in IL-4, IL-5 and IL-13 can encourage the generation of antibodies of the IgE isotype, resulting in food allergy; commensal bacteria help mitigate such outcomes. The use of bacteria, microbial metabolites and insoluble dietary fibre are therapeutic modalities currently under investigation.

Three subsets of monocytes – ‘classical’, ‘intermediate’ and ‘non-classical’ – have now been described; Narasimhan *et al.* (pp. 439–456) provide a general overview. Classical monocytes are recruited to sites of infection where they secrete inflammatory cytokines. Non-classical monocytes patrol the vascular endothelium, helping to maintain homeostasis. Though some findings suggest contribution of non-classical monocytes to pathologies associated with autoimmune and inflammatory diseases, the weight of the evidence appears to favour a protective function. Deeper molecular understanding of non-classical monocyte function, in both sterile and microbe-induced inflammation, will pave the way for novel therapeutic intervention.

Exhausted CD8 T (Tex) constitute a distinct cell lineage, as McLane *et al.* (pp. 457–495) describe. While they do not produce IL-2, TNF and IFN- γ , they may still make chemokines and exhibit de-granulation. The inability of Tex cells to undergo IL-7- and IL-15-mediated

homeostatic renewal distinguishes them from memory T cells. The roles of individual transcription factors in the generation and sustenance of the exhausted state are being delineated. Significant epigenetic differences exist among Tex cells, T effector cells and T memory cells. An exhausted CD8 T cell phenotype is predictive of superior prognosis in patients of several autoimmune diseases, a fact driving the search for new therapeutics.

The location of tissue resident memory T (Trm) cells makes them ideally suited to respond to events that perturb immune homeostasis, as Masopust *et al.* (pp. 521–546) indicate. Trm cells hasten adaptive immune responses to re-infection. Not having access to survival factors and oxygen like circulating cells do, Trm cells have to adapt to the local environment. Aberrant activation of Trm cells is linked with inflammatory bowel disease, psoriasis and multiple sclerosis, making them attractive targets for therapeutic intervention.

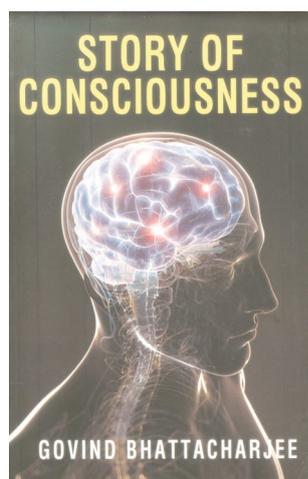
The last few years have seen great advances in genome engineering, as Simeonov *et al.* (pp. 571–597) describe. CRISPR has been used to knock out genes, and to add genetic sequences. The combined use of CRISPR libraries and single-cell RNA sequencing has permitted the correlation of genetic perturbation with transcriptome alterations. Engineered T cells specific for the tumour antigen NY-ESO-1, along with CRISPR-mediated deletions of the endogenous T cell receptor as well as of PD-1, are being assessed for clinical efficacy. More intricate reprogramming of immune cells by CRISPR technologies, possibly further fine-tuned to allay fears of potential side-effects, will no doubt give rise to newer therapeutic options.

Intestinal microbiota and the host immune system exert considerable influence on each other, as Brown *et al.* (pp. 599–624) discuss. In the intestine, Goblet cell-derived MUC2 helps form the first line of defence. Several Paneth cell-derived antimicrobial peptides also help maintain homeostasis. Secretory IgA impedes colonization, and IL-22 (mostly produced by innate lymphoid cells) as well as T cell-derived IL-17A are important for maintaining intestinal barrier function. Invasive microbes, colonizing microbes, non-invasive symbionts, and parasites are responsible for the polarization of CD4 T cells into Th1,

Th17, Tregs and Th2 cells respectively, in the gut. Several bacteria-sourced products can either drive pathogenesis or help to alleviate symptoms of Crohn's disease and ulcerative colitis. Faecal microbiota transplants from healthy individual to patients of ulcerative colitis, Crohn's disease, and multiple sclerosis have met with some success. Greater elucidation of the role of particular microbiota products play in disease onset or amelioration will give rise to more defined therapeutics for auto-inflammatory and autoimmune conditions.

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Story of Consciousness. Govind Bhattacharjee. Vigyan Prasar, Department of Science and Technology, A-50, Institutional Area, Sector-62, Noida 201 309, UP. 2019. xii + 372 pages. Price: Rs 450.

Bhattacharjee tried to narrate a story of something (called consciousness) which itself is a debated and little understood to the scientific community. He depicted the evolution of consciousness. In fact, the term consciousness has been mostly discussed and debated among the philosophers from the East as well as the West antiquity. The progress of modern science especially in neuroscience and

quantum theory raises new interest among the community. At first, we need to discuss 'what is consciousness'. The prerequisite for this discussion needs a comprehensive analysis of the methodology used in different knowledge systems, i.e. in science as well as in philosophy.

Various schools of Indian philosophy (including Buddhist one) discussed extensively this issue. Vedanta and Advaita Saivagam of Kashmir both made a comprehensive study on ultimate reality, nature of reality and consciousness.

The progress in neuroscience as well as in modern physics especially the birth of quantum theory raises interest about the nature of reality and its connection with consciousness. The motive of both philosophers and scientists is to understand the ultimate reality, though with different perspectives but arguably the same purpose to move closer in knowing the truth. Let us first discuss the methodology used in science. The approach called 'Empiricism' which over a period of time has become the standard and accepted method of science whereas the (ancient Indian) philosophers adopted a method called 'Introspection' thousand of years ago – sit and meditate after registering in memory all the information gathered by their senses and processed by their mind after consultation and discussion with their peers and absorbing the esoteric inputs from the scriptures. The methodologies are quite different – scientists constructed the theories mainly based on empirical data and adopted the approach known as reductionism. On the other hand, the ancient Indian philosophers used the data mainly based on introspection and also reasoning.

For example, scientists try to understand the macroscopic world (consisting of everyday objects) from microscopic world consisting of elementary entities like electron, proton, quarks, Higgs boson, etc. The birth of quantum theory in early twentieth century clearly shows that quantum theory is needed to explain the behaviour of microscopic entities which is different from Newtonian mechanics used in explaining the behaviour of the objects in the macroscopic world. Since the physical universe is ultimately composed of these elementary entities, it gives rise to the much-debated issue whether the universe itself is governed by quantum theory. This is related to nature of reality at various levels, i.e. at microscopic scale and macroscopic scale.

The scientists follow the deductive approach to understand the nature of reality.

Now to unravel the mystery of consciousness the scientists follow this reductionist approach. The pertinent issue to a scientist in understanding consciousness is: from where to start. In the laboratory, the scientists start with microscopic entities and their interactions to understand the various aspects of everyday world (macroscopic world). In the context of consciousness, the obvious approach is to start from billions of neurons or nerve cells in human brain (consists of 10^{12} neurons) because our thoughts, perception, etc. arise from neuronal firing due to the stimulus from the external world through our sensory organs. Looking at given stimuli results in neural sensations; a mental concept of the given stimuli results from comparisons of sensations; interpreting the thus formed mental concept (of the given stimuli) into consciousness (background) results in perception (of the stimuli).

However, there exists huge gap in understanding the correlation between thought and the neuronal firing. It is important to note that brain not only process information but also interpret it as emphasized by Karl Pribram. Scientists like Edelman, Tononi and others applied information theory in brain function and consciousness issue. We emphasize that one should look for a information measure with semantic aspect to understand the information processing in the brain as well as understanding consciousness. It is worth mentioning that so far the author knowledge goes no such information theory exists in science and technology where semantic aspect is included in the formulation. The discussions on this aspect of information might enrich the book (*Story of Consciousness*) though the works of Edelman, Tononi, etc. are discussed by the author in some other context.

The scientists are trying to understand consciousness as epiphenomena which emerge from the activities of billions of neurons in the brain. For this they are trying to identify the neuronal circuitry and neuronal dynamics based on the laws of physics. Neuroscientists are working on the functional states of neurons and consciousness. Rodolfo Llinás proposed that consciousness seems to result in some manner from an interaction between the thalamo-cortical scanning activity and the incoming stimuli from the