Nobel Prize in Medicine 2021

by Abhigyan Ray - Wednesday, October 06, 2021

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The Nobel Assembly at the Karolinska Institute has decided to award the **2021 Nobel Prize in Physiology or Medicine** to **David Julius** and **Ardem Patapoutian** "***for their discoveries of receptors for temperature and touch***". David Julius is professor and chair of the department of physiology at the School of Medicine in the University of California, San Francisco and a trustee of the Howard Hughes Medical Institute (HHMI). Ardem Patapoutian is a HHMI investigator in the department of neuroscience at Scripps Research in California as well as an adjunct professor in the neuroscience program of the University of California, San Diego.

One of the most innate human qualities is the sense of touch. A warm embrace with a loved one or an enthusiastic high five after winning a game is an experience humanity shares across borders and cultures. Yet for something so intrinsic to being human, the molecular and physicochemical underpinnings of the sensation of touch eluded us before today's Nobel laureates set out to crack open the problem "*for the greatest benefit of humankind*" and win the very first prize in the field of sensory transduction. Their transformative discovery of receptors for temperature and pressure revolutionized the field of neuroscience by providing a molecular and neural basis for thermosensation and mechanosensation.

After training under a stellar lineage of Nobel winning academics, Julius started his own lab at UCSF in the early 90's trying to gain an understanding of how signals responsible for temperature sensation and other sensory phenomena are transmitted by the nervous system. In this quest, he exploited distinctive molecules from the natural world, like the capsaicin molecule and tarantula toxins, to elucidate the molecular mechanisms of pain sensation. Julius' group created a library of millions of DNA fragments corresponding to genes that are expressed in the sensory neurons which can react to pain, heat and touch. They then plugged genes from this collection into cells that do not normally react to capsaicin to find the single gene that caused the sensitivity. Using capsaicin (8-methyl-N-vanillyl-6-nonenamide), the compound in chili peppers that elicits the sensation of heat, they identified the gene encoding the first temperature sensor, the ion channel TRPV1 "heat" receptor. They went on to discover that TRPV1 is activated by high temperature, high concentrations of protons found in ischemic tissues and chemical compounds generated during inflammation, thus providing a molecular integrator for both thermosensation and inflammatory signals. Similar results were obtained with the detection of TRPM8 "cold" receptor in menthol, the cooling agent in mint leaves that evokes an icy cool sensation, and also with regards to the pungency of wasabi. The seminal discovery of TRPV1 initiated an intense investigation that has strongly established the critical role of a family of TRP channels for thermal sensation and conclusively showcase that several TRP channels gated at different temperature ranges act together to code for temperature and heat-induced pain in the somatosensory nervous system.

As Julius' seminal work was making waves in top journals like Nature, an Armenian immigrant fleeing the war in Lebanon who had come to the USA to become a doctor but quickly "*fell in love with research*", also began investigating the molecular bases of sensory perception. After briefly coinciding with Julius at UCSF during his postdoc, Ardem Patapoutian went on to found his own group at Scripps Research Institute that seeked to gain an understanding of the intricacies of physicochemical transmission of physical stimuli such as temperature and pressure. Patapoutian's lab used a functional screen of candidate genes expressed in a mechanosensitive cell line to identify a family of ion channels activated by mechanical stimuli and formed the basis of how we sense touch, pain, sound, and blood flow. Two mechanically-activated cation channels, named PIEZO1 and PIEZO2 (derived from the Greek word for pressure - piezos)), were identified and shown to represent an entirely novel class of ion channels functioning as mechanical sensors. Genetic studies established that Piezo2 is the principal mechanical transducer for touch, proprioception, and lung stretch, and that Piezo1 mediates blood-flow sensing, which impacts blood pressure regulation and vascular development. Additionally, the Patapoutian lab co-identified SWELL1 (LRRC8A), an ion channel critical for regulating cell volume in response to osmotic shock. They further demonstrated that Piezos forms pressure-sensing channels and that they are directly responsible not only for pressure sensing in the skin by Merkel cells, proprioceptors and touch sensory terminals but also to sense pressure by nerve terminals in blood vessels and in the lungs.

Thanks to the untiring efforts of these pioneering researchers and their seminal discoveries, that has been the subject of this year's Nobel Prize, we have been able to develop a finer understanding of mechanobiology in health and disease. Today we have a molecular and neural basis for thermosensation and mechanosensation which further enables us to apply it to multiple domains, right from devising ways to reduce chronic and acute pain associated with a range of diseases to better mechanisms to control blood pressure. We have gained insights into the mechanisms of proprioception that can help us treat neurodegenerative diseases that result in loss of balance and motor control, and are continuing to hunt for novel mechanosensors that affect red blood cell volume, vascular physiology, and underlie a broad range of human genetic disorders. Wielding an array of genetic, electrophysiological, and behavioral methods, researchers are now unravelling the contribution of the ion channels to detecting heat and cold as well as their activity modulation in response to tumor growth, infection, or other forms of injury that produce inflammation and pain hypersensitivity alongside the role of specific neurotransmitter receptors, such as those activated by serotonin or extracellular nucleotides, in physiological and behavioral processes, such as feeding, anxiety, pain, thrombosis, and cell growth and motility.

This year's Nobel Prize to a phenomenal set of neuroscientists, celebrates the great importance of curiosity driven fundamental research in the basic sciences. At a time when it is easy to get swayed by the hype over supposedly revolutionary technologies, it is important to remember that decades of basic research in the labs of folks like Julius and Patapoutian is what drives these innovations in the first place. Similarly, the vaccines for COVID19 might have been developed and got out into the market in well under a year's time but the underlying technology like mRNAs and lipid nanoparticles have been refined and studied for well over a couple of decades. The groundbreaking work in the labs of these two pioneers,

Julius and Patapoutian, was equally strenuous and spanned three decades of laborious efforts and relentless self belief by the researchers in their labs. Identification of the cellular target of capsaicin in the former's lab required painstakingly sifting through a cDNA library from sensory neurons in a functional screen to look for a gene that could confer capsaicin sensitivity to cells that were normally unresponsive. In the latter's lab too, the discovery of the gene encoding the receptors that enables nerve cells to sense pressure required a cell line in a petri dish that reacted to being poked by a micropipette with an electrical signal for which they went through 72 candidate genes before identifying the one that rendered the cells impervious to the pipette's touch.

Furthermore, the laureates overcame several economic and societal impediments to attain the pinnacle.David Julius's grandparents fled European anti-Semitism and moved to New York City and Ardem Patapoutian grew up in Lebanon, to an already displaced family that had escaped the Armenian genocide, and then immigrated to the US for educational opportunities as the situation spiralled out of control back at home. As the world turned more inward looking over the past decade due to the shameless demagoguery of elected authoritarians, it is prudent to remember the personal backgrounds of these laureates that serve to showcase that society progresses best when it offers a warm and welcoming place to everyone regardless of trivial distinguishing factors like colour, gender, creed, and ethnicity. Additionally, at a time when funding cuts are rampant for basic science research, with entire pure science departments shutting down on the whims of inept administrators, its important that as we celebrate the outstanding research of the newly minted Nobel Laureates on an innate human sensation, we should also raise a toast to the fundamental role curiosity driven basic research has played in advancing our society since time immemorial.
