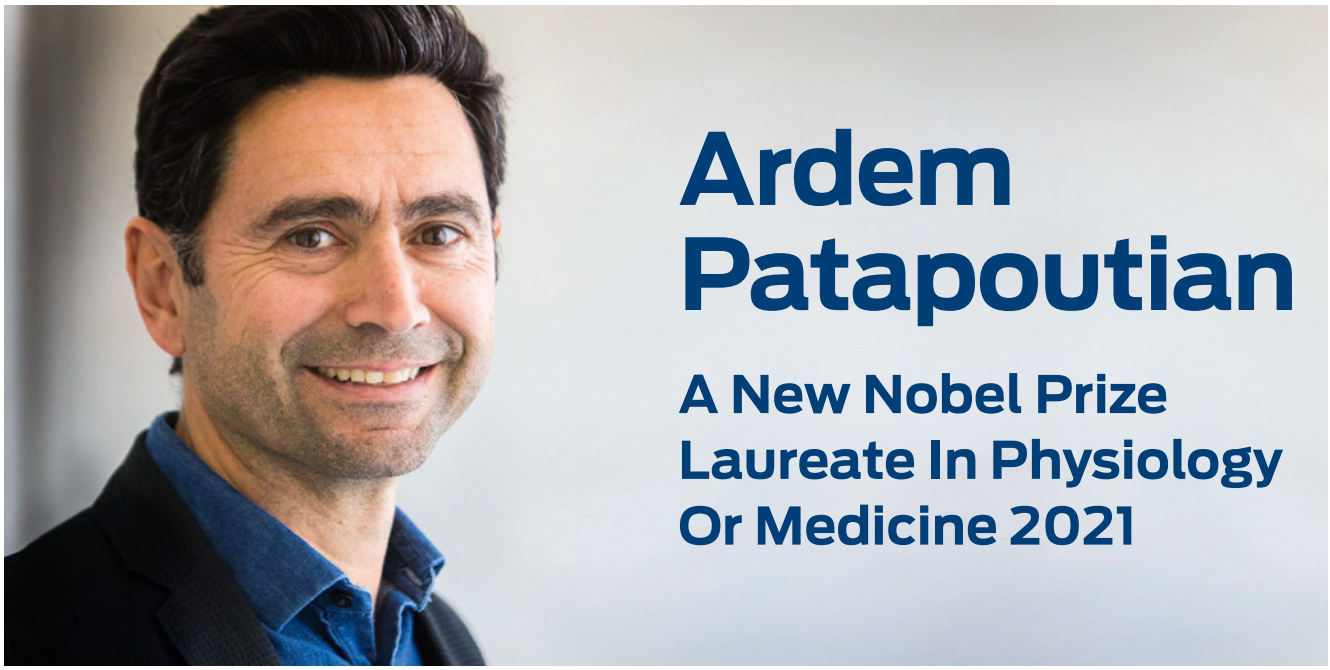

Ardem Patapoutian

A New Nobel Prize Laureate In Physiology Or Medicine 2021

It is almost impossible to imagine a form of life without the ability to feel – sensation. The sensory system in humans has been studied for centuries, starting from Aristotle's concept of the common sense, up to now when the discovery of new sensory receptors was made. A neuroscientist with Armenian origins Prof. Ardem Patapoutian and his colleague Prof. David Julius, were awarded the Nobel Prize in Physiology or Medicine in 2021 for an astonishing work: the discovery of receptors for temperature and touch.

Biography

Ardem Patapoutian was born in an Armenian family in Beirut, Lebanon in 1967. His family permanently moved to the United States when Ardem was 18. Four years later, in 1990, he received Bachelor's degree in Molecular, Cellular and Development Biology from the University of California, Los Angeles. Then, he received his PhD in Biology at the California Institute of Technology in 1996. The academic pathway was followed by a postdoctoral research program with Dr. Louis Reichhardt at the University of California, San Francisco. Mr. Patapoutian, an assistant professor since 2000, and an associate professor during 2005-2008, reached full professorship in 2008, has mastered in the Cell Biology during 2008-2012, and in the Molecular and Cellular Neuroscience during 2013-2017 at the Dorris Neuroscience Center, Scripps Research, San Diego, California. The latter is one of the most influential institutions worldwide, focused on the development of fundamental innovations in healthcare. Patapoutian's works were published in such well-established journals, as Nature, Science, Cell, etc. Since 2014 till now, Ardem Patapoutian is a professor, investigator at the Howard Hughes Medical Institute, Department of Neuroscience, Chevy Chase, Maryland. His work is well summarized on the special webpage https://patapoutianlab.org dedicated to his team's research activities. Here we try to present the most important aspects which have led to his career marking award.

The discovery of the molecular basis of heat (TRPV1) and touch (Piezo2) somatosensation

The sense of touch incorporates physical (thermal, mechanical) and chemical (pain, itch) components. The role of touch neurons is to distinguish between painful (noxious) and non-painful (innocuous) stimuli. Each time a noxious stimulus triggers touch neurons, a pain cascade is activated. This process is protective in the context of acute pain, i.e. due to acute injury of inflammation. However, chronic pain is a state beyond appropriate pain response. Chronic pain syndromes pose a real challenge for clinicians, so it is essential to identify the underlying mechanisms of pain, thus targeting new therapeutic sites.

The work of Prof. Patapoutian and colleagues was dedicated to the identification and characterization of ion channels activated by various changes in thermal energy ranging from noxious to innocuous affecting factors. These ion channels were defined as so-called molecular thermometers of the body. However, they

DOI:10.54235/27382737-2021.v1.2-8. Published online: 30 December 2021

also play essential role in pain and inflammation as they also act like polymodal chemosensors.

The interest around the sensory receptor research increased due to the studies performed in 1950s that discovered the first heat-sensitive receptor. Those studies showed that gustatory sweating occurred due to sensory influence of active component in chili peppers – capsaicin (8-methyl-N-vanillyl-6-nonenamide). Capsaicin was shown to be an activator of ion channels in sensory neurons.

Prof. Julius continued the research identifying the capsaicin receptor. Firstly, his team isolated a gene from the DNA, which was then revealed to be responsible for synthesis of a capsaicin-sensitive protein – a transient receptor potential (TRP) cation channel. The TRPV1 (vanilloid receptor 1) was ectopically expressed in cells. The results resembled electrophysiological properties of native sensory neurons, when evoked by capsaicin. Then, a heat-evoked response was observed for the TRPV1, with a thermal pain-like response when the activation threshold was crossed. This was an important finding, as it was later translated to the effect of increased sensitivity to heat during inflammation. The collaboration of Julius and Patapoutian resulted in the identification of TRPM8 receptors being activated by low temperature within temperature range, which causes sensation of innocuous cold. Besides these findings, recently a new molecule TRPA1 was identified in the Patapoutian's lab, currently in phase I clinical studies.

On the other hand, it is known that mechanical force plays an important role in somatosensory system, as well as others. It was identified that Piezo1 and Piezo2 receptors are ion channels involved in translating physical stimuli into chemical signals. The abovementioned receptors are mechanical transducers located in various cells: red blood cells, vascular endothelial cells, touch and proprioceptive neurons.

Prof. Patapoutian started the research in mechanoreceptors together with his postdoctoral fellow Berthrand Coste. They identified an intrinsically mechanosensitive cell line, called Neuro2A. A global gene expression analysis was performed for Neuro2A cells identifying 72 candidate genes, and the FAM38A gene with consecutively expressed PIEZO1 protein was identified as the one responsible for mechanical pressure sensation. PIEZO2 was discovered later, and it was also found to be expressed in the dorsal root ganglion sensory neurons, as well as to be responsible for light touch. It was shown by the Patapoutian group, that PIEZO2 is the principal transduction channel for proprioception in mice. The PIEZO family has not been identified in vertebrates before, thus representing a new protein family of mechanotransducers. PIEZOs were shown to play a role in mechanosensitivity in internal organs including studies on vagus and glossopharyngeal nerves: PIEZO1 and PIEZO2 are present in sensory neuron ganglia of those. PIEZO2 is involved in gastrointestinal system, i.e. enterochromaffin cells, thus being responsible for the formation of signaling response to enteric luminal mechanical stimulation. PIEZO1 is a sensor of mechanical forces in endothelial cells, red blood cells, being responsible for the regulation of vascular tone, cell volume homeostasis.

Why is this important?

The relevance of the identification of mechano- and thermo-receptors in cells should not be underestimated. Animal studies are the basis for clinical research and they are the key to possible solutions for various conditions. It was shown, that TRP channelopathies – genetic diseases in humans – cause alterations of temperature sensing, e.g. a TRPA1 channelopathy named Familial Episodic Pain Syndrome 1 manifesting as severe upper body pain triggered by cold, fasting and physical exertion, whereas PIEZO2 gene mutations were observed in mice as alteration in touch, vibration and proprioception sensations.

The genes discovered by the Patapoutian and his colleagues are an important step in neuroscience opening a new view on most pain-related conditions. The receptors may be a promising target for further research and implications in clinical science. More practically leading to solutions in pain medicine and improved quality of life among patients.

With great respect to our prominent compatriot and his work

Samson Khachatryan and Davit Abrahamyan
Co-Editors-in-Chief
Armenian Journal of Health & Medical Sciences

REFERENCES

- https://patapoutianlab.org.
- Syeda R, Qiu, Z, Dubin AE, Murthy SE, Florendo M, Mason DE, Mathur J, Cahalan SM, Peters EC, Montal M, Patapoutian A. LRRC8 proteins form volume-regulated anion channels that sense ionic strength. Cell. 2016;164:499-511.
- Ranade SS, Woo SH, Dubin AE, Moshourab RA, Wetzel C, Petrus M, Mathur J, Begay V, Coste B, Mainquist J, Wilson AJ, Francisco AG, Reddy K, Qiu Z, Wood JN, Lewin GR, Patapoutian A. Piezo2 is the major transducer of mechanical forces for touch sensation in mice. Nature. 2014;516:121-5.