

A PATIENT-SPECIFIC HUMAN TRIGEMINAL NEURON MODEL FOR THE STUDY OF MIGRAINE MECHANISMS

R. Greco[1], M. Bordoni[2], J. Cazzola[3], F. De Luca[4], M. Francavilla[1], C. Demartini[1], S. Facchetti[1], O. Pansarasa[2], G. Vaghi[1], R. De Icco[1|5], G. Biella[3], C. Tassorelli[1|5]

[1]Headache Science and Neurorehabilitation Unit, IRCCS Mondino Foundation, Pavia, Italy; [2]Cellular Models and Neuroepigenetics Section, IRCCS Mondino Foundation, Pavia, Italy; [3]Laboratory of Biophysics and Physiology of Ion Channels, University of Pavia, Italy; [4]Laboratory of Cell Biology and Neurobiology, University of Pavia, Italy; [5]Behavioral Sciences, Department of Brain, University of Pavia, Italy

Background. Reliable animal models have been critical to the understanding of the mechanisms underlying migraine pain. However, species differences in trigeminovascular biology and CGRP signaling limit clinical translatability. Induced pluripotent stem cells (iPSCs) offer a promising avenue, as they allow the generation of patient-specific cells while preserving each individual's genetic background intact. This approach is amenable to study individual vulnerability as well as the factors underlying migraine occurrence and severity at the cellular and molecular levels.

Methods. Peripheral blood mononuclear cells (PBMCs) were obtained from two subjects with chronic migraine (CM) and one healthy control (HC) and reprogrammed into iPSCs. The iPSC lines were subsequently differentiated into trigeminal sensory neurons and subjected to gene expression profiling, immunocytochemistry, and electrophysiological characterization.

Results. All lines differentiated efficiently into mature neurons, as confirmed by expression of neuronal markers (TUBB3, MAP2, NEFH) and trigeminal markers (BRN3A, ISL1) by RT-qPCR. Distinct neuronal subtypes were also identified, including GABAergic ($GABA^+$) and glutamatergic ($vGLUT1^+$) populations. The analysis of nociceptive markers confirmed that the neurons expressed CGRP and TRPV1. Interestingly, CM-derived neurons showed reduced expression of both markers compared to the HC line, suggesting an altered nociceptive phenotype consistent with chronic receptor depletion and desensitization.

Conclusions. These very preliminary findings pave the way for the establishment of the first patient-specific in vitro model of human trigeminal neurons for CM. Additional iPSC lines derived from a large number of donors will be required to validate and strengthen the robustness of this platform. Future investigations will focus on characterizing intrinsic neuronal excitability, calcium dynamics, and the functional integrity of CGRP-mediated signaling pathways.