Neuroscience

A cell atlas for migraine research

Philip R. Holland & Peter J. Goadsby

The trigeminal nerve has a key role in migraine. An atlas of cell types and gene-expression profiles for cells in this nerve in mice and humans promises to improve our understanding of head pain.

Migraine is a leading cause of years lost to disability in adults under 50 years of age[1]. Symptoms (including moderate to severe head pain, vomiting, cognitive dysfunction and more) often affect an individual's ability to participate in normal day-to-day activities. The trigeminal nerve is the main sensory nerve innervating the head, and has a key role in the pain of migraine and other headache disorders[2]. Writing in *Neuron*, Yang *et al.*[3] describe gene-expression profiles for the trigeminal ganglion neurons that make up this nerve in mice and humans. Their cell atlas highlights common and divergent cell types and gene-expression patterns between the species, and will support drug discovery for migraine – a buoyant field of research.

The trigeminal nerve arises from the trigeminal ganglion – a collection of neuronal cell bodies and associated cell types, including satellite glia and fibroblasts, that is hidden below the brain's cerebrum. The nerve has three main branches – the ophthalmic, maxillary and mandibular divisions – which transmit sensory information from the face to a sensory tract in the brainstem called the trigeminal nucleus. The ophthalmic branch also transmits sensory information from pain-producing layers of protective membranes called the meninges, which surround the brain (Fig. 1).

This anatomical distribution is highly evolutionarily conserved across species, enabling researchers to test therapeutic possibilities in animal models as well as humans. For instance, direct activation of sensory nerve terminals in the meninges of animals[4,5] has been used to explore potential therapies. In humans, experimental migraine-inducing agents[6] and direct measurements of messenger molecules called neuropeptides that are involved in migraine[7] have shed light on therapeutic possibilities. This research has led to impressive success in translating results to the clinic, enabling the development of three classes of drug. Two of these drug classes inhibit a neurotransmitter called calcitonin gene-related peptide (CGRP) or its receptor protein in neurons[8]. The third class activates a receptor for the neurotransmitter serotonin, the 5-HT_{1F} receptor[8].

Yang *et al.* now provide a translational road map to enhance future drug-development efforts. The authors isolated trigeminal ganglion neurons from the brains of mice and humans, and sequenced the neuronal RNA to generate gene-expression profiles for single cells from across the trigeminal nerve. They used these profiles to cluster cells into 15 cell types – 8 neuronal and 7 non-neuronal. They then compared the atlases for the two species to identify similarities and differences between them. The group also characterized the transcription factors and regulatory elements in DNA that govern gene expression in and across cell types.

Interestingly, the authors uncover clear species differences in the pathways targeted by CGRP-inhibiting and 5-HT_{1F}-receptor-activating drugs. They find that the gene *CALCA*, which encodes CGRP, is highly expressed in sensory neurons called pruriceptors in human samples but is lacking in pruriceptors in mice. The gene *HTR1F*, which encodes the 5-HT_{1F} receptor, is differentially expressed between species in both pruriceptors and another type of neuron – peptidergic nociceptors. These findings suggest that, although humans and mice share key receptors that regulate trigeminal sensation, the precise distribution of these receptors between neuronal subtypes differs (of note, because the drugs are not cell-type-selective, there is no reason to suspect that these differences would hamper their effectiveness in humans). In agreement with these differences between species, the authors show that human trigeminal ganglia contain a higher proportion of peptidergic nociceptors than those of mice. These differences can inform future drug-development programmes as they transition from bench to bedside.

Next, Yang *et al.* performed single-cell RNA sequencing in trigeminal ganglion neurons taken from two mouse models of head pain, and searched for gene-expression patterns indicative of cell activation in the sequenced cells. In one model, in which the meninges are experimentally inflamed, the authors saw clear activation patterns in non-peptidergic nociceptor neurons, and modest activation of peptidergic nociceptors. They also observed activation of satellite glia and fibroblasts – activation of satellite glia can influence neuronal excitability, and the fibroblasts are commonly involved in immune responses. Crosstalk between satellite glia, fibroblasts

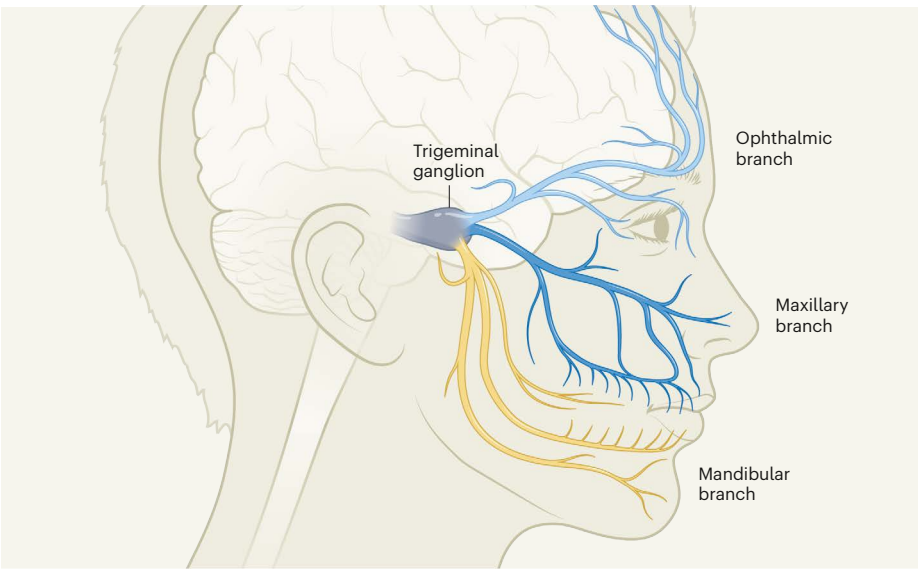

Figure 1 | The trigeminal nerve. This nerve has three branches, which transmit sensory information from the face to the spinal cord via a structure called the trigeminal ganglion. The nerve is involved in migraine and other headache disorders, and its anatomy is highly evolutionarily conserved – meaning that studies in animals can highlight potential therapeutic targets in humans. Yang *et al.*[3] mapped cell types and gene-expression profiles across the trigeminal nerve in mice and humans to gain insights into the cell types associated with head pain.

and neurons probably occurs through purinergic P2 receptor proteins, which are therapeutic targets of interest[9] that, when activated, result in the release of CGRP.

By contrast, in a mouse model of cortical spreading depression — the mechanism that underlies migraine aura — the authors found more-restricted activation of satellite glia and fibroblasts. The group also found differential upregulation of a range of other genes in the two models. Taken together, these data imply that multiple cell types are likely to have a role in the activation and sensitization of trigeminal sensory fibres. They also highlight the fact that both neuronal and non-neuronal cell types should be considered as targets for future drug discovery.

Yang and colleagues' work adds to our picture of the cell types, receptors and ligand molecules that play a crucial part in sensory processing of head pain. Their cell atlas also provides a publicly available translational toolbox for researchers to further explore molecules and targets of interest. Because the authors assessed all regions of the trigeminal nerve, the resource is useful not just for migraine, but for other forms of head pain, too. However, the wide scope of the study is also a disadvantage, precluding specific analysis of the ophthalmic branch, the anatomical distribution of which most accurately maps the human experience of migraine pain[10].

The atlas is complemented by existing mouse data sets, and will — in time — benefit from expansion to include more human samples and key migraine-relevant brain structures. One of the most obvious such structures will be the peripheral and central interface for head pain, which spans the trigeminal nucleus caudalis and the upper cervical spinal cord, the trigeminocervical complex[11].

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Finally, the authors have gone some way to answering one of the most commonly asked questions in preclinical migraine research: how can you tell that a mouse has migraine? The answer remains that you can't. However, thanks to Yang and colleagues, we can, with confidence, identify common pathways and cell-type-specific gene-expression profiles that underpin the sensation of head pain — one of the most salient and clinically disabling features of migraine.

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