CellPress

Review

New Mendelian Disorders of Painlessness

Michael S. Nahorski,[1,*,2] Ya-Chun Chen,[1,*,2] and C. Geoffrey Woods[1,*,2]

Erroneous activation of the pain-sensing system, as in chronic or neuropathic pain, represents a major health burden with insufficient treatment options. However, the study of genetic disorders rendering individuals completely unable to feel pain offers hope. All causes of congenital painlessness affect nociceptors, evolutionarily conserved specialist neurons able to sense all type of tissue damage. The discovery of new genes essential for sensing pain (*SCN11A*, *PRDM12*, and *CLTCL1*) has provided unexpected insights into the biological mechanisms that drive distinct stages of nociception. Drugs targeting two previously discovered painlessness genes, *NGF* and *SCN9A*, are currently in late-stage clinical trials; thus, characterization of these new painlessness genes has significant potential for the generation of new classes of analgesics.

Trends

Chronic pain and neuropathic pain are common, and their treatment expensive, complex, and often incomplete. Better analgesic treatments are needed, but pain mechanisms are still incompletely understood.

Rare people are born unable to feel pain. These people have Mendelian genetic disorders caused by mutations in genes essential for pain-sensing in humans. In the past year three new human pain genes have been reported.

Studies of human pain genes has revealed hitherto unknown mechanisms of nociceptor (pain-sensing neuron) function. Of more general importance, they have also generated new classes of analgesic which are in clinical trials at present.

Introduction to Hereditary Painlessness

Pain-sensing in humans represents a delicate balance; pain is not only a sense essential for the warning of impending and actual tissue damage, but is also a debilitating and unwanted burden in those people for whom the pain-sensing system has become over- or erroneously activated. Noxious stimuli, which are perceived as painful, are detected by specialized peripheral sensory neurons, the **nociceptors** (see Glossary), which are considered to be necessary for both chronic and acute pain-sensing [1]. Nociceptors have a single axon which is either an unmyelinated C fiber or thinly myelinated Aδ fiber of small diameter, the peripheral terminals of which innervate target organs such as the skin. The cell bodies of nociceptors lie in the dorsal root or trigeminal ganglion, from where they provide connectivity to the dorsal horn of the spinal cord, with secondary neurons able to project to various higher regions of the brain [2].

While there are many effective options to treat acute pain, the treatment of chronic or recurrent pain remains challenging [3]. **Chronic pain** is a significant health burden. In Europe as many as one in five people is affected by some form of chronic pain state [4,5], and **analgesics** represent the most commonly prescribed class of medicines [6]. Unfortunately, many currently available pain therapies display limited efficacy, and the National Pain Audit reports that a third of people do not receive adequate pain relief despite significant medical intervention [7,8]. Furthermore, many pharmaceutical companies have now closed their pain research programs. However, hope for the generation of new analgesics has arrived from an unlikely source – a small number of individuals who, from birth, are unable to feel pain anywhere in their body. The majority of these have **Mendelian** disorders of painlessness, where disruptive mutations in a single gene are solely responsible for their inability to sense pain. All known Mendelian pain genes identified to date affect nociceptors.

Genetic disorders of painlessness can be categorized as (i) degenerative disorders of nociceptive pathways where nociceptor function is progressively lost, (ii) non-functional nociceptors such as in **congenital insensitivity to pain** (CIP) due to mutations in voltage-gated sodium

[1]Cambridge Institute for Medical Research, University of Cambridge, Cambridge CB2 0XY, UK
[2]These authors contributed equally to this work.

*Correspondence: msn27@cam.ac.uk (M.S. Nahorski), ycc33@cam.ac.uk (Y.-C. Chen), cw347@cam.ac.uk (C.G. Woods).

 http://dx.doi.org/10.1016/j.tins.2015.08.010

channels resulting in nociceptors being unable to detect tissue damage, and (iii) disorders of failed nociceptor neurodevelopment where pain-sensing neurons do not develop (Figure 1). A handful of genes have been described which, when mutated, are responsible for these disorders (Table 1). Subsequently, two of the culpable proteins have been acknowledged as potential targets for analgesic development, and several drugs are in late-stage clinical trials (Concluding Remarks). Research into the genetic causes of hereditary painlessness has historically provided novel and often unexpected discoveries about the molecular make-up of the human pain-sensing system.

In this review we focus on the most recently identified causes of hereditary painlessness, mutations in *PRDM12* (PRDI-BF1 and RIZ homology domain-containing protein 12) [9], *CLTCL1* (clathrin, heavy chain-like 1) [10], and *SCN11A* (sodium channel, voltage gated, type 11 ∝ subunit) [11], as well as on the increased understanding of the first 'congenital anesthesia' gene identified, *SCN9A*.

Painlessness Caused by Aberrant Function of Voltage-Gated Sodium Channels

Voltage-gated sodium channels (Nav) are integral membrane proteins that function to conduct sodium ions Na^+ through the neuronal plasma membrane. Sensory neurons rely on such channels for the generation and conduction of actions potentials [12]. Three transmembrane voltage-gated sodium channels are strongly expressed in nociceptors, Nav1.7, Nav1.8, and Nav1.9. Because of their expression patterns and electrophysiological characteristics, all are considered likely to have important roles in pain detection (Figure 1) [13]. In support, dominant activating mutations in each cause paroxysmal excess pain diseases [5,14,15], and inactivating mutations of Nav1.7 as well as an unusual activating mutation of Nav1.9 cause painlessness [11,16].

CIP and SCN9A/Nav1.7

Initial case reports of CIP outlined an inability to feel any type of pain, and also **anosmia** (of which many patients are unaware). Some, however, doubted the phenotype because there were no neurological deficits to explain the lack of pain-sensing, including normal findings of peripheral nerve biopsies. This view shifted when three studies described families with CIP caused by bi-allelic mutations in the gene *SCN9A* [16–18]. *SCN9A* encodes the voltage-gated sodium channel Nav1.7. All of the familial mutations characterized in one study lead to a complete loss of Nav1.7 activity, and were thus nulls [16].

The pain-less phenotype caused by Nav1.7 loss of function has been confirmed and extended in further human and mouse studies. To date, adults with *SCN9A*-CIP have not been found to experience acute, inflammatory, nor, very significantly, **neuropathic pain** [19]. Chemotherapy and cancer bone pain may persist because these are reported to be non-SCN9A-dependent [20]. It is not yet possible, because of the limited numbers of *SCN9A* mutant pain-less people identified, to say conclusively that WT Nav1.7 is essential for neuropathic pain. While it remains to be proven that Nav1.7 blockade can cause complete analgesia, this channel remains an exciting target for treating acute and chronic pain [21]. In *Scn9a* knockout mice, anosmia leads to weaning failure and early postnatal death, which force-feeding can rescue, confirming the greater role played by smell in rodents than in humans [22,23]. Clinicians who treat pain have long known that some suffering can only be alleviated by blockage of the sympathetic nervous system. Independent evidence for this was shown in mice where complete replication of human *SCN9A*-CIP was only produced by knocking-out *Scn9a* in the dorsal root ganglia, spinal cord, and the sympathetic ganglia [23,24]. Finally, although *SCN9A* is expressed in β cells of the Islets of Langerhans (the primary insulin-producing cells), diabetes develops in neither *SCN9A*-CIP human or mouse – suggesting that Nav1.7 is redundant in this cell type [25]. Of clinical

Glossary

Analgesic: any member of a group of drugs used to achieve relief from pain.
Anosmia: the loss of the sense of smell.
Chronic pain: pain that lasts longer than 6 months.
Congenital insensitivity to pain (CIP, also known as congenital analgesia): a rare conditions in which a person cannot feel (and has never felt) physical pain.
Epigenetic: the control of the expression of genetic information being modified at a molecular level without a change to the DNA sequence – for example, promoter methylation silencing gene expression.
Hypomorphic mutation: a mutation that causes a partial loss of gene function.
Mechanoreceptor: a sensory receptor which responds to mechanical stimuli.
Mendelian Inheritance: inheritance pattern defined by Mendel's laws of segregation, independent assortment, and dominance. A trait inherited according to these laws is one that is controlled by a single locus. In such cases, a mutation in a single gene is responsible for a given disease. Multifactorial disease, for example autism, is thought to be caused by many genetic contributors and environmental effects, and is hence not inherited in a Mendelian pattern.
Neuropathic pain: pain caused by damage or disease of the somatosensory nervous system.
Neurotrophin: one of a family of secreted, neural growth factors that induce the survival, differentiation and growth of neurons.
Nociceptor: a sensory neuron that responds to noxious, potentially damaging stimuli, and relays this information to the central nervous system.
Triskelion: the functional unit of clathrin composed of three clathrin heavy chains and three light chains.