Review

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Pharmacogenomics in pain treatment

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Abstract: The experience of chronic pain is one of the commonest reasons for seeking medical attention, being a major issue in clinical practice. While pain is a universal experience, only a small proportion of people who felt pain develop pain syndromes. In addition, painkillers are associated with wide inter-individual variability in the analgesic response. This may be partly explained by the presence of single nucleotide polymorphisms in genes encoding molecular entities involved in pharmacodynamics and pharmacokinetics. However, uptake of this information has been slow due in large part to the lack of robust evidences demonstrating clinical utility. Furthermore, novel therapies, including targeting of epigenetic changes and gene therapy-based approaches are further broadening future options for the treatment of chronic pain. The aim of this article is to review the evidences behind pharmacogenetics (PGx) to individualize therapy (boosting the efficacy and minimizing potential toxicity) and genes implicated in pain medicine, in two parts: (i) genetic variability with pain sensitivity and analgesic response; and (ii) pharmacological concepts applied on PGx.

Keywords: acetaminophen; chronic pain; clinical translation; opioids; pharmacogenetics (PGx).

Introduction

Pain is the most common presenting physical symptom in primary care, accounting for an enormous burden of patient suffering, quality of life, work disability, health care and societal costs. According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [1]. If untreated, chronic pain is very common and, approximately, one in three Americans and one in five Canadians and Europeans, are reported to suffer from this problem [2].

From a genetic point of view, chronic pain is a typical gene x environment interaction, where the inherited genetic predisposition can influence greatly the development of pain syndromes from various painful experiences [3]. Different subtypes of pain can be described based on their neurophysiological basis and duration, including neuropathic, nociceptive, dysfunctional, acute and chronic. Treatment of pain-related suffering requires knowledge of how pain signals are initially interpreted and subsequently transmitted and perpetuated. In fact, the evolution and intensity of the painful experience shows great individual differences, even in response to the same stimulus in an experimental environment [4].

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The enormous variability in individual response to the many disparate treatments for chronic pain is clinically important and needs to be better understood. The notion that "one size fits all" has been replaced by the idea of patient-tailored healthcare prevention and therapy. This is the base of personalized medicine. Within this paradigm, the research community has turned to examine genetic predictors of disease and treatment responses. Pain researchers performed genetic studies over the last decade that evaluated the association between genetic variability and pain sensitivity or analgesic response. Simultaneously, there is an increased recognition regarding the complexity of pain research, acknowledging the additional role of epigenetic, transcriptomic, proteomic and metabolomic factors in the development, experience and treatment of pain [5].

Tools to personalize treatment of pain syndromes

The relatively high heritability rate and the assumed mechanisms behind transition from acute to chronic pain suggest that genetic research might provide useful target molecules for future drug development, as well as, could be used as a tool to personalize the treatment of pain syndromes [6].

Gene-association studies searching

Gene-association studies searching for common genetic variants modulating pain vulnerability produced confounding results, probably because only few genetic regions were examined and its replication is very rarely found between the studies. In addition, most of these studies ignored the gene x environment interaction effect of stressful life events on vulnerability to pain that may contribute to transition to chronic pain state by triggering negative mood [7]. Furthermore there are few meta-analyses in the field of pain genetics, and the only available considered the *OPRM1* functional polymorphism 118A>G, but it did not confirm the relevance of this polymorphism in pain, only found weak evidences of less nausea and increased opioid intake in GG carriers [8–10].

A large meta-analysis of microarray studies for pain-induced gene expression changes in animal models resulted in the identification of genes commonly regulated by painful states. Immune system-related gene clusters showed the best association with induced pain suggesting a pronounced effect of inflammatory mechanisms underlying painful conditions. However, extrapolation of these results even between rat and mouse species failed [8]. The differences in gene regulation observed in rat's dorsal root ganglia (DRG) were almost completely absent in mice, despite the fact that the painful stimulus was the same. Therefore, cautious extrapolation of these results is required in human studies [11]. Further research is required in order to assess the most pervasive factors in chronic pain development, and also to identify gene sets that shape the vulnerability profile toward those factors. With proper analgesic medication and concomitant personalized preventive therapy we can intervene the transition of the experienced pain into a chronic maladaptive state [12].

Genome-wide association studies

Genome-wide association studies (GWAS) have identified hundreds of genetic variants associated with complex human diseases and traits scanning markers across the complete sets of DNA. However, they rarely reported or even measured the experienced pain. This might be due to the lack of reliable and cheap pain level measurement tools, and, also, because of the fluctuations in the personal pain experience that makes very hard to detect true average pain intensity in cross-sectional studies [13].

Most variants identified so far confer relatively small increments in risk and explain only a small proportion of familial clustering, leading many to question how the remaining "missing" heritability could be explained. However, most of the studies compare the co-occurrence of the painful disease itself, and not the experienced pain states. Induced pain under laboratory circumstances can provide slightly better measurements of the heritability rate of pain-vulnerability, which is estimated among 22%–60% [14].

The rare exception of the multi-level GWAS study of chronic widespread pain resulted in the association of rheumatic pain with 5p12.2 chromosomal region [13]. These results might facilitate to other research groups to consider experienced pain as a worthy target for GWAS analyses. In addition, novel therapies, including targeting of epigenetic changes and gene therapy-based approaches are further broadening future options for the treatment of chronic pain [15].

Epigenetic modifications

Epigenetic modifications, such as DNA methylation and histone modifications (e.g. acetylation and

phosphorylation), are known to cause stable gene expression changes via chromatin remodeling. These mechanisms have a role not only in the determination of developmental cell fates, but also in the physiological and pathological processes in the nervous system. Alterations in DNA methylation, an enzymatic covalent modification of cytosine bases in the DNA, could serve as a "genomic" memory of pain in the adult cortex mediating the long-term consequences of painful experiences and embed them into the genome. DNA methylation is an epigenetic mechanism for long-term regulation of gene expression. Neuronal plasticity at the neuroanatomical, functional, morphological, physiological and molecular levels has been demonstrated throughout the neuroaxis in response to persistent pain, including in the adult prefrontal cortex. Importantly, there is emerging evidence that a variety of genes undergo epigenetic regulation via DNA methylation and histone modifications within peripheral and central nervous systems, thereby contributing to the alterations in both, pain sensitivity and pharmacological efficacy in neuropathic pain. It is discussed whether epigenetic mechanisms can serve as potential targets to treat neuropathic pain [16].

Neuroimaging with functional magnetic resonance imaging

Living with unrelenting pain is maladaptive and is thought to be associated with physiological and psychological modifications, yet there is a lack of knowledge regarding brain elements involved in such conditions. The era of neuroimaging with functional magnetic resonance imaging (MRI) studies provide us a completely new aspect of pain genetic research. The capability for recording real-time activation of human brain in reaction to painful stimulus provides system-based biological phenotypes which are more able to assess the effect of genetic and neurobiological variables than simple syndrome phenotypes [17].

In fact, sustained high pain of chronic back pain (CBP) resulted in increased activity in the medial prefrontal cortex (including rostral anterior cingulate), strongly related to intensity of CBP, and this region is known to be involved in negative emotions, response to conflict and detection of unfavorable outcomes, especially in relation to the self. Interestingly, spontaneous CBP involves specific spatiotemporal neuronal mechanisms, distinct from those observed for acute experimental pain, implicating a salient role for emotional brain concerning the self [18].

Also, with MRI technology we can distinguish between different components of pain processing, such cognitive, affective or sensory elements and seems to be useful to entangle the previously confounding results about genetic predictor variants. These results suggest that different kinds of exposure to pain can cause transition to chronic pain states in different allele carriers, and also they would respond to psychological pain-management therapy differently [11].

Pharmacogenomics in inflammatory pain treatment

In contrast to the wide variety of pain and painful syndromes, only a handful of pharmacological substances proved to be effective against pain. Benefit/risk ratio of all the analgesic drugs is unsatisfactory with either a limited efficacy or a high level of adverse effects and, sometimes, both.

Analgesic drugs

Acetaminophen: new targets

Acetaminophen is one of the most popular and widely used drugs for the treatment of pain and fever. It occupies a unique position among analgesic drugs. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), it is almost unanimously considered to have non-anti-inflammatory activity and does not produce gastrointestinal damage or untoward cardiorenal effects. Unlike opioids, it is almost ineffective in intense pain and has no depressant effect on respiration. A novel and original view of this molecule now proposes acetaminophen to be a pro-drug needed to be biotransformed to be analgesic [19] by (i) hepatic deacetylation of into para-aminophenol; (ii) conjugation by the cerebral fatty acid amide hydrolase enzyme into AM404 [20] involving the activation of TRPV1 receptors [19, 20], followed by the inhibition of Cav3.2 [21] and the modulation of CB1 receptors [22]. This complex mechanism disinhibits the periaqueductal grey matter output neurons, which could promote activation of the descending serotonergic inhibitory pathways as shown both in animals [23–25] and humans [26].

NSAIDs as COX inhibitors: balancing benefit/risk

The COX inhibitors are used most commonly in noncancer pain, however, in patients with severe pain they are often

proved to be ineffective, as well as, they present dangerous renal and gastrointestinal long-term side effects. In addition, they increase the risk of serious cardiovascular conditions, especially in patients with high risk for these conditions. The risks of these and other side effects increase in the elderly, when taken at higher doses, and with long-term use. As of April 2005, following recommendations by the US Food and Drug Administration issued a public health advisory stating that "NSAIDs should be administered at the lowest effective dose for the shortest duration consistent with individual patient treatment goals". It is recommended that patients consult with their treating physician to evaluate the relative benefits and risks, especially of COX-2 inhibitors, in order to come up with the best treatment plan for their individual clinical situation [27, 28].

Opioids: large inter-individual analgesic variations

Opioids with their central mechanisms of action are controversial drugs in noncancer pain treatment. Apart from the most-discussed abuse potential, the tolerance and dependence developed after chronic administration are also limiting the usage of opioids against pain [29]. Moreover, opioids suffer from invalidating adverse effects, which can alter the quality of life of patients and, in some rare cases, jeopardize the vital prognosis. They modulate nociception by stimulating μ opioid receptors (μOR), the major molecular gate for opioid analgesia [30]. None of the pharmacological activities of morphine, either its analgesic or adverse effects, could be detected in mutant mice lacking μOR [31]. This explains the difficulty to separate beneficial from adverse effects of μOR agonists. Recently, truncated μOR splice variants [32] have been proposed as targets to improve benefit/risk ratio of opiate analgesics [33]. Several other strategies have been developed to try to reduce opioids adverse effects, such as using agonists of other opioid receptors [34, 35] or peripheral μOR antagonists [36, 37]. However, the former ones produce a limited analgesia [38] and the latter ones need to be co-prescribed with opioids and prevent constipation, but not morphine central adverse effects such as respiratory depression [39].

Recently, using a different strategy, it has been demonstrated that the TREK-1 K^+ channel is a crucial contributor of morphine-induced analgesia in mice, while it is not involved in morphine-induced constipation, respiratory depression and/or dependence. These observations suggest that direct activation of the TREK-1 channel, acting downstream from the μOR, might have strong analgesic effects without opioids-like adverse effects [40, 41].

Empirically, it is well understood that large inter-individual variations exist with respect to the response to opioids [42]. With conventional drug dosing, some patients will experience toxicity whereas other patients will not receive adequate analgesia at the same dose. Variations in analgesic efficacy can vary as much as two- to 10-fold or even 100-fold among members of the same family [43, 44].

Pharmacogenetics

Pharmacogenetics (PGx) refers to the way in which genetic differences between individuals influence patient drug responses and drug disposition [9, 10, 45]. Generally, genes affecting outcome of treatment can be divided into two broad categories. On the one hand, genes affecting pharmacodynamics, based on variations in drug target receptors and downstream signal transduction (i.e. μ-opioid receptor, *OPRM1*; enzyme catecholamine methyltransferase, *COMT*, etc.) [46, 47]. On the other hand genes affecting pharmacokinetics (PK) that affect drug metabolism and/or elimination (i.e. cytochrome P450 family of enzymes, enzymes responsible for glucuronidation, drug transporter proteins, COX enzymes, etc.) altering the relationship between drug dose and steady state serum drug concentrations [48].

Pharmacodynamics

Some candidate genes are implied either directly (opioid receptors) or indirectly into the opioid transduction pathways when signal is transmitted to a variety of effectors (e.g. adenylate cyclase or calcium and potassium ion channels named Kir3.2, *KCNJ6*).

Opioid receptors

Opioid receptors belong to the family of G-protein-coupled receptors (GPCRs). There are three types of classical opioid receptors: mu (μ), kappa (κ) and delta (δ). They share a high degree of homology and are structurally similar, containing an extracellular N-terminus domain, seven transmembrane domains and an intracellular C-terminus domain. Most variations are found in the N-terminal domain and extracellular loops. The extracellular loops determine ligand binding and are, therefore, particularly important. Splice variations of opioid receptor mRNA have been shown to produce receptor subtypes which may be of functional importance [49].

Opioid receptor μ1 (*OPRM1*) gene

The μ-opioid receptor encoded by the opioid receptor μ1 (*OPRM1*) gene is the primary site of action for the most commonly used opioids. Therefore, it represents the first-line candidate for evaluating the role of polymorphisms in the clinical effects of morphine.

Studies in mice with targeted deletion of *OPRM1* gene established that this receptor is essential for morphine analgesia, physical dependence and reward [31, 50]. More than 100 single nucleotide polymorphisms (SNPs) localized in the C-terminal intracellular domain of the protein have been described, and could possibly participate in various transduction signaling pathways following agonist binding [51, 52].

The most common polymorphism C118A>G (rs1799971, A118G), leading to an asparagine to aspartate substitution (Asn40Asp), with an allelic frequency varying from 2% to 50% according to ethnic groups, has been extensively studied [53]. This polymorphism is responsible for the loss of a putative N-linked glycosylation site in the N-terminal domain of the receptor and is associated with modified response to opiates. Indeed, the variant protein exhibits a three-times greater binding affinity for the endopeptide β-endorphin, whereas binding to substances such as morphine, methadone and naloxone was unaffected *in vitro* [54]. Subjects carrying the variant G-allele were found to present reduced response to morphine treatment [9, 10, 55–57] and reduced analgesic response to alfentanil and morphine-6-glucuronide [46, 58, 59], requiring higher doses of morphine for pain relief [46, 60]. In addition, it is also associated with *MOR* expression, a variant associated with a decrease in both mRNA expression and translation into a functional protein [61]. Also, lower mRNA expression in human brain tissue and in transfected cells was found in G-allele carriers [57].

Other SNPs from *OPRM1* and the other classical opioid receptor genes, including *OPRK1* and *OPRD1*, have been tested, for example, in the European Pharmacogenetic Opioid Study (EPOS). EPOS is the largest genetic association study of opioid response to date, with 2294 patients taking opioids for cancer-related pain. A total of 112 SNPs in 25 genes, including *OPRM1, OPRK1* and *OPRD1*, were investigated for relationship to oral equivalent morphine dose requirements. However, no association was identified with any of the SNPs tested in both, development and validation analyses [60].

Opioid transduction pathways

β-Arrestin 2

β-Arrestin 2 is an intracellular protein that is integral to μOR inactivation and internalization [62–66]. On binding, opioid receptor agonists differentially trigger receptor phosphorylation and recruitment of β-arrestin. Knockout studies have shown that mice lacking β-arrestin 2 gene (*ARRB2*) exhibit prolonged analgesia from morphine treatment at lower doses [66]. It is worth noting that prolonged analgesia in mice lacking *ARRB2* may also be due to a combination of more complex effects transduced by multiple GPCRs in the knockout animal model [66]. Polymorphisms in *ARRB2* have been associated with overall response to morphine and opioid switching [67].

Pharmacokinetics

Other genes are implicated in the cellular transport of the molecules (such as *ABCB1*) or in their metabolism, which aims to convert lipophilic chemical compounds into more readily excreted hydrophilic products (mainly cytochrome isoforms *CYP2D6*, *CYP3A4* and *CYP2B6*, and a glucuronosyltransferase implied in morphine metabolism, *UGT2B7*).

Opioid metabolism

Different enzymes in phase 1 and/or phase 2 metabolisms are important for the metabolism of different opioids.

a) Phase 1 metabolism

a1) Cytochrome P450 2D6 (CYP2D26)

CYP2D26 is highly polymorphic and expression of different variants results in several phenotypes: poor metabolizers (PM) express two nonfunctional alleles (e.g. two of *4, *5, *6 or other alleles), intermediate metabolizers express at least one reduced functional allele (e.g. one of *9, *10, *41 or other alleles), extensive metabolizers (EM) express at least one functional allele, and ultrarapid metabolizers (UM) that present multiple copies of the functional allele. The prevalence of variant alleles exhibits considerable interethnic differences [68]. The frequencies of these phenotypes in Caucasians are: PM, 5%–10%; intermediate metabolizers, 10%–15%; EM, 65%–80% and UM, 5%–10%. Well-characterized SNPs in *CYP2D6* lead to the inability to convert codeine to morphine, thus making codeine ineffective as an analgesic for approximately 10% of the Caucasian population [69]. In UM, codeine is convert to morphine and high concentrations of morphine can be observed [70] inducing major adverse effects. Tramadol is also metabolized through *CYP2D6* and its analgesic effect may change according to the polymorphisms of this enzyme [71].

a2) Cytochrome P450 3A (*CYP3A4*) and 2B6 (*CYP2B6*)

The CYP3A4 enzyme is localized in the liver and small intestine and, thus, contributes to first-pass and systemic

metabolism of opiates. *CYP2B6* gene is a major isoform implied in methadone metabolism and clearance. However, although its activity is highly variable among individuals, no clear correlation between a genotype and a phenotype has yet been established [72].

b) Phase 2 metabolism

b1) *UGT2B7*

UGT2B7 insures the glucuronidation of morphine to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) metabolites [73]. M6G is approximately twice as potent as morphine in animal models and humans [74]. Even though, M3G has little affinity for opioid receptors, but may contribute to excitatory effects of morphine [75]. One frequent SNP, UGT2B7*2, has been studied (rs7439366, His268Tyr, 802C>T) that seems to be associated with a decreased activity [76].

Multi-drug resistance genes

P-glycoprotein 1 also known as multidrug resistance protein 1 or ATP-binding cassette sub-family B member 1 (ABCB1) is an important protein of the cell membrane involved in multidrug resistance. It is responsible for decreased drug accumulation in multidrug-resistant cells and also functions as a transporter in the blood-brain barrier. Mutations of the *ABCB1* gene (SNP 1236C>T) have been associated with higher methadone doses (>150 mg/day) in methadone-maintained heroin addicts [77].

There has been noted to be an association between the *ABCB1* and the *OPRM1* gene polymorphisms related to morphine pain relief; combining evaluation of the two genes allowed detection of three response groups, resulting in a sensitivity close to 100% and specificity of more than 70% in predicting morphine relief [78]. Also an association between *COMT* and *OPRM1* gene polymorphisms has been found in other studies [79, 80]. Carriers of both *COMT* Met/Met in Val158Met and *OPRM1* A/A in A118G polymorphisms required less morphine than other subjects, however, differences were not significant and further studies should evaluate this association [79].

There may be differences between male and female patients at this gene as well; men with the TT allele had higher beta-endorphin levels than men with the more common CC allele, while the opposite was true in women [81]. In addition, women with the TT allele presented a higher risk of postoperative pain 3 months after surgery [82]. Similarly, female G-allele carriers of *OPRM1* A118G SNP presented a slower recovery rate than male G-allele carriers after the disc herniation and increased pain intensity [83–85].

Modifying systems

a) Catechol-O-methyltransferase (*COMT*)

The involvement of catecholamines in pain modulation is known from both clinical and experimental studies [57]. *COMT* is a key modulator of dopaminergic and adrenergic neurotransmission, and, as a consequence, in the reward signaling response to opioids. The C472G>A SNP of *COMT* (rs4680, Val158Met) causes a valine to methionine substitution at codon 158 in the enzyme. The Met allele leads to an enzyme up to four-times less active than the Val allele [86].

b) Potassium channel, inwardly rectifying subfamily J, member 6

This gene encodes a member of the G protein-coupled inwardly rectifying potassium channel family of inward rectifier potassium channels. This type of potassium channel allows a greater flow of potassium into the cell than out of it. These proteins modulate many physiological processes, including circuit activity in neuronal cells, through G-protein coupled receptor stimulation and it has been shown to participate in the modulation of analgesic effects on postsynaptic transmission and miosis under opioid treatment [80].

c) Serotonin transporter

Preliminary work in pain research is now emerging, with published studies that examine genotypic influence *serotonin transporter* (*5HTT*) gene polymorphisms on opioid analgesia in healthy volunteers and clinical response to anti-depressants [87–89].

Translating pharmacogenomics discoveries into the clinic

In general, PGx studies thus far in pain management have failed to yield evidence of improved clinical outcomes associated with knowledge of patient genotypes when prescribing pain medications. Genetic factors are thought to be responsible for approximately 12%–60% of response variance in opioid treatment, as evaluated in twin studies [90]. Many genes have been studied in order to identify PGx markers in opioid treatment, including genes implied in opioids' pharmacodynamics and PK. In this review, we focus on those genes, although numerous genes have been implied in nociception and inflammation, and can participate in the analgesic dose requirement.

On an individual level, there is a difference in the analgesic response to a given opioid. Various factors such as gender, age and genetic variation can affect the

analgesic response. In fact, opioid analgesia can be predicted from activity of reward-responsive brain regions during pain as well as subjects trait-reward responsiveness ratings [91, 92]. Thus, studies have shown promising results regarding PGx as a diagnostic tool for predicting the individual response to a given opioid in experimental settings; however, in the clinic, it is a more complicated task to accomplish [93].

Pharmacogenomics in neuropathic pain treatment

Neuropathic pain is characterized by complicated combination of positive (e.g. hyperalgesia and allodynia) and negative (e.g. hypoesthesia and hypoalgesia) symptoms, and is refractory to conventional pharmacological agents, including morphine.

Recently, Finnerup et al. [94] proposed a revision of the NeuPSIG (Special Interest Group on Neuropathic Pain, from the International Association for the Study of Pain) recommendations for the pharmacotherapy of neuropathic pain as follows: first-line treatment for tricyclic antidepressants, serotonin-noradrenalin reuptake inhibitors, pregabalin and gabapentin; second line for lidocaine patches, capsaicin high concentration patches and tramadol; third line for strong opioids and botulinum toxin A [94]. They also stated that topical agents and botulinum toxin A are recommended only for peripheral neuropathic pain.

In recent years, it has begun to be appreciated that the pathobiology of various neuropathic pain subtypes may differ [95]. As an example, chemotherapy-induced peripheral neuropathy (CIPN) is a common secondary toxicity to neurotoxic anticancer drugs. The type of anticancer drug and the cumulative dose may impact in the incidence (possibly until 90% of patients for oxaliplatin), the symptoms and the severity/grade of neuropathy [96]. Recent meta-analysis demonstrated that among 31 studies (4179 patients), 68% (57.7–78.4) of patients suffered of CIPN 1 month after chemotherapy, 60% (36.4–81.6) after 3 months and 30% (6.4–53.5) at 6 months or more [97]. In the case of oxaliplatin, which is probably the most neurotoxic anticancer drug, neuropathy symptoms can last until several years after the end of the chemotherapy cycles (2 years in the study by André et al. [98] and 8 years in the study of Yothers et al. [99]). Neurotoxicity mechanisms of anticancer drugs are not fully understood, but they may result from interactions with DNA, mitochondria, ion channels, glutamate neurotransmission and/or kinases, at various levels such as DRG (sensory neurons, Schwann cells, satellite cells) and spinal cord (neurons, glial cells) (for review, see Carozzi et al. [100]). CIPN is thus relatively distinct from other forms of neuropathic pain, including pathophysiology and symptomatology [101, 102]. After a systematic literature search identifying randomized controlled trials for the treatment of CIPN, it has been concluded on the poor efficacy of these drugs in CIPN. Genetic factors may be important in predisposing patients to this adverse effect.

Pharmacodynamics

Chemotherapy-induced peripheral neuropathy and drug-induced peripheral neuropathies (DIPNs) are encountered, including small-fiber involvement. The introduction of new diagnostic techniques, such as excitability studies, skin laser Doppler flowmetry, and PGx, holds promise for early detection and elucidation of underlying mechanisms. New approaches to improve functions and quality of life in CIPN patients are discussed. Apart from developing less neurotoxic anticancer therapies, there is still hope to identify chemoprotective agents, such as erythropoietin and substances involved in the endocannabinoid system, able to prevent or correct painful CIPNs [103].

Increased susceptibility to peripheral neurotoxicity after exposure to offending agents has been associated with polymorphisms in genes involved in the following pathways: chemotherapy-induced DNA adducts repair [104], immune function (cytotoxic T-lymphocyte-associated protein 4), also known as CD152 (cluster of differentiation 152), CTLA4 and compatible time-sharing system, reflexive coupling within Schwann cells (Gap Junction Protein, Epsilon 1, GJE1), drug binding (proteasome subunit beta 1, PSMB1) and neuron function (Transcription Factor, 4TCF4 and dynein cytoplasmic 1 intermediate chain 1, DYNC1I1) [105], apoptosis [106], mitochondrial dysfunction, inflammation [107] and oxidative stress scavengers such as glutathione S-transferase 1 (GST1) [108].

Pharmacokinetics

Chemotherapy-induced peripheral neuropathy has been associated with variations in genes encoding for drug transporters, detoxification enzymes, genes involved in DNA repair mechanisms and integrin B3 Leu33Pro polymorphism [109].

For instance, polymorphisms of the gene encoding *ABCB1*, have been suggested to partially explain the variability of taxane-induced DIPN [110]. It should be noted

that several other studies have been unable to identify relevant associations [111, 112]. Similarly, genetic variants of proteins involved in the metabolism of xenobiotics, for example, cytochrome 3A5, have been linked to increased risk of DIPN in children receiving vincristine [113]. A range of polymorphisms have also been identified with GWAS in association with oxaliplatin [114], paclitaxel, bortezomib, thalidomide and vincristine [107, 108].

Voltage-gated sodium channels

While the use of pharmacogenetic techniques to identify genetic polymorphisms has enabled further identification of potential differences in susceptibility to neurotoxicity between individual patients, it remains a lack of consensus on the association between genetic variants and the risk of neurotoxicity. Further studies with standardized objective measures of neuropathy, the choice of the good primary outcome and larger patient numbers will be required to fully assess the involvement of genetic polymorphisms in the risk of neurotoxicity.

A recently published collaborative international study attempted to overcome those limitations, thoroughly investigating a series of SNPs in genes coding for neurologically relevant targets, such as the voltage-gated sodium channels (SCNA), in an adequately powered, prospective cohort of well-characterized patients. SCNAs are fundamental to facilitate the initiation and propagation of action potentials in neurons. These membrane proteins are encoded by >10 genes in mammals, and mutations in SCNAs are associated with diseases of both, the central and peripheral nervous system [115]. The results of this study provided evidences to support a causal relationship between *SCN4A-rs2302237* and *SCN10A-rs1263292* polymorphisms and increased incidence and/or severity of oxaliplatin-induced peripheral neuropathy [116]. Further *SCNA* SNPs, such as the *SCN2A* R19K polymorphism, have been previously investigated with negative results [117]. These results illustrate the difficulty to choose potential genetic biomarkers. Mutations in genes encoding SCNAs have emerged as the most clinically relevant genes associated with several pathologies. This is the case for *SCN10A* regarding peripheral pain disorders. However, *SCN4A* has not been associated with pain syndromes [118].

Looking for new genetic biomarkers

A better understanding of the pathophysiology of CIPN will certainly lead to identify new molecular targets for the prevention of this particular neuropathy. For example, mechanistically, oxaliplatin promotes neuronal over-excitability by drastically lowering the expression of distinct potassium channels (*TREK, TRAAK*) and by increasing the expression of pro-excitatory channels such as the hyperpolarization-activated channels (HCNs). These findings are corroborated by the analysis of TREK-TRAAK null mice and the use of the specific HCN inhibitor ivabradine, which abolishes the oxaliplatin-induced cold hypersensibility [119, 120].

These results suggest that oxaliplatin exacerbates cold perception by modulating the transcription of distinct ionic conductance that together shape sensory neuron response to cold. The translational and clinical implication of these findings would be that ivabradine, a nonspecific HCN blocker, or TREK and TREK agonists, may represent tailored treatment for oxaliplatin-induced neuropathy. Ivabradine, which has been developed to treat stable angina pectoris, is able to selectively and strongly attenuate the cold sensitization effects of oxaliplatin in mice. Therefore, as a drug already used in the clinic, it could rapidly become a new potential preventive analgesic treatment in patients undergoing oxaliplatin chemotherapy [119]. Moreover, unpublished data from A. Eschalier's group suggest the involvement of epigenetics in the transcriptional changes observed after oxaliplatin administration in mice, which opens to new pharmacological prevention strategies opportunities in this pathology.

Conclusions

Ideally, PGx studies aim to aid in the selection and dosing of an optimal drug therapy for a specific patient. Choosing the optimal therapy should lead to maximize therapeutic benefit, improved patient adherence and reduction in adverse drug reactions. However, patients are very commonly prescribed several medications for multiple comorbidities and genetics can only partially explain the variability in patient responses to analgesic drugs.

Regardless that, one of the major challenges facing researchers working in this field, is translating their discoveries into clinical practice. As an emerging field, PGx confronts new challenges such as ensuring its correct standardization and its correct translation into routine clinical practise. The need to standardize how PGx information in order to translate it into routine clinical practices, to ensure dissemination of knowledge and education of clinicians and patients, need different multidisciplinary consortiums as the European Society of Pharmacogenomics and Personalised Therapy (ESPT). Furthermore,

concerted efforts and open and active cooperation with industry, are required in order to facilitate translation and commercialization, avoiding to stuck PGx biomarkers in the discovery phase. Additionally, the knowledge and acceptance of new approaches to determine drug targets by clinicians, regulators, patients, and the public will be important in determining future success.

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